

US EPA ARCHIVE DOCUMENT



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 20 2017

OFFICE OF
WATER

Mr. Henry Leibovitz, Chair
Environmental Laboratory Advisory Board
Rhode Island State Health Laboratories
50 Orms Street
Providence, Rhode Island 02904

Dear Dr. Leibovitz:

On behalf of the Forum on Environmental Measurements (FEM), I would like to thank the Environmental Laboratory Advisory Board (ELAB) for your letter providing detailed minimum criteria for selected ion monitoring (SIM) methods.

As noted in our September 26, 2017 letter, the FEM membership discussed minimum criteria for SIM methods during the October 24, 2017, FEM Quarterly meeting and shared ELAB's letter with key individuals involved in SIM gas chromatography/mass spectrometry (GC/MS) methods. In general, we are very supportive of having some minimum criteria for SIM methods, but the Agency's programs have differing needs, as you know.

Attached please find two items: a compilation of comments and clarifications from several of our programs; and an article offered as additional information to consider. The EPA is requesting ELAB review the information, comments, and clarifications offered and provide a revision to the minimum criteria for SIM methods offered. Once we have a final document, the FEM will ensure the dissemination of the document across the Agency's method community.

Thank you and the other members of ELAB for your assistance to the Agency for improving the EPA methods. Please continue to send us your comments and suggestions, as we believe that ELAB serves as an important mechanism for the FEM to keep abreast of important issues facing the measurement community. If you have any questions, please feel free to contact me at 202-564-5700 or shapiro.mike@epa.gov.

Sincerely,

A handwritten signature in black ink that reads "Michael Shapiro".

Michael H. Shapiro
Chair, FEM

Attachments

Cc: Lara Phelps, OSA
FEM Membership (individual names are available)

US EPA ARCHIVE DOCUMENT

ATTACHMENT 1: Comments Provided by Individuals, Listed by Office**OFFICE OF AIR (OAR) / OFFICE OF AIR QUALITY PLANNING AND STANDARDS (OAQPS)**

These comments are provided as they relate to stationary source air emissions measurements and ELAB's recommendations for measurement methods that include selected ion monitoring (SIM) low resolution mass spectrometry detectors.

ELAB notes that SIM mass spectrometry measurements are used to push an analysis to the highest sensitivity. ELAB should note that the target list and associated ions to monitor must be predetermined.

Under method flexibility ELAB limits changes in sample collection, preservation, and preparation to initial sample size and final extract volume, otherwise, initial demonstration of capability (IDC) must be performed to demonstrate the change are effective. OAQPS does not have IDC requirements prior to sample analysis, rather we choose to incorporate performance based requirements that are requirements to be met on each sample. The basic idea of demonstrating method performance is fundamental to analysis methods, however requiring IDC is, to us, only one way to show the laboratory delivered defensible data.

Regarding spiked samples as a means to determine QC acceptance, we prefer to carefully define the sample to be spike in addition to the spike components. Spiking clean matrix is just one type of spike application. To us, when possible, a matrix spike, matrix spike duplicate is a far more informative "spiked" sample. ELABs reference to spiked samples might benefit by defining the types of spiked samples that should or could be included to demonstrate capability or validity of sample analysis data.

The inference in "c. Type of MS" recommended by ELAB indirectly assumes the MS can perform full-scan analysis as well as SIM analysis. If that's the intent, it should be so stated.

The requirement for five scans per chromatographic peak would be qualified in our methods with the phrase, "or unless otherwise specified" since we may require more scans, especially for lower resolution chromatography applications.

The description in f. of the number of scan descriptors is not clear. Was it ELAB's intent to require one quantitation ion and two qualifying ions for a total of three ions per analyte? The convention that we use is two ions for the purpose of qualification and quantification. Also, ELAB should consider whether the requirement for 3 ions compromises the enhanced sensitivity if larger scan windows are required to gather data on ions that are markedly different in mass/charge ratio.

For "i. Retention time windows" ELAB recommends a specific 0.06 relative retention time compared to an authentic standard but stops short of making this a performance criterion. Rather, the recommendation is to rely on the experience of the analyst. In many cases, we find that the experience of the method development team is greater than the experience of the routine analyst and we would typically make this type of requirement pass/fail and expect the responsible laboratory QA report section to justify why the results should be accepted if the criteria have not been met.

For item "j. Identification/identification verification criteria" using ion ratios. We note that this recommendation would typically be a performance criterion in our methods. We prefer to refer to addition of confirmatory or isotopic standards rather than deuterium standards so as not to preclude carbon-labeled isotope standards.

OFFICE OF LAND AND EMERGENCY MANAGEMENT (OLEM) / OFFICE OF RESOURCE CONSERVATION AND RECOVERY (ORCR)

ORCR is updating two major organic methods for the analysis of volatiles and semi-volatiles in a variety of matrices using GC/MS. In these two updated methods we include the optional use of SIM, CI, and MS/MS. All “the minimum SIM criteria” listed in the ELAB letter, with the exceptions of different RT and Qualitative ion criteria (20% vs 30%), are already in the methods. Most of “these minimum SIM criteria” are current practices, although the old .06 min RRT criterion ELAB still uses for retention time has been dropped in the newer SW-846 methods in favor of an absolute RT measurement. That should be updated to reflect current use (i.e., delta RT).

One thing not included that has been important when we are looking at very low level analysis by SIM is to check to the specific matrix (using representative spiked and unspiked matrix samples) for the evaluation of positive and negative interferences. For example, IDCs performed in Ottawa sand do not provide sufficient evidence to determine whether the extracted material from a soil will obscure the characteristic ions monitored for a given target analyte.

We appreciate ELAB providing a list of minimum SIM criteria for our review and considerations. We are positive with most of ELAB’s proposed minimum SIM criteria for GC/MS methods. We also took a look at the ELAB letter, as well as, the current CLP requirements for SIM from SOMO2.4 and found some differences in the approach taken, from each of them and from our methods. Following lists some of the differences:

- 1) This document says a minimum of 1 quantitation ion and 2 qualifying ions should be acquired for each analyte, as minimum criteria. The latest drafts of 8260D and 8270E say at least 2 ions are monitored per analyte in SIM or SRM, and we suggest monitoring of additional ions (where possible) for more reliable qualitative identification when interferences are expected or observed. For analyses with a large number of target compounds, the 3 characteristic ions requirement may result in too few scans across the peaks. Having the flexibility to monitor ions that are not as affected by matrix interferences and are most diagnostic for the presence of a chemical in a given material may be more important than monitoring more ions. The ELAB letter also doesn’t mention using the molecular ion(s) for peak identification in SIM analysis, where practical, which tend to be more diagnostic of the presence of a chemical than fragment ions.
- 2) ELAB’s letter also says “Perform the tune check in full-scan mode if there is a need for SIM ion ratios to agree with full scan ion ratios or if the MS will alternate between full and SIM scans.” Verifying mass assignments and mass resolution has merit even when SIM ion ratios are not being compared to full mass range acquisition. Tune verification criteria in the soon to be published revisions of 8260D and 8270E may be based on acquisition of BFB or DFTPP mass spectra and comparing to the acceptance criteria in the methods, or on acquisition of PFTBA mass spectra and evaluating against instrument manufacturers’ acceptance criteria, and the BFB and DFTPP criteria are very flexible with respect to the low- to high- mass ion abundance checks, but these methods will require tune verification prior to initial calibration.
- 3) In addition to moving away from RRT, ELAB’s letter didn’t really address how retention time shifts can present a false negative potential risk for peaks that elute right at the end of a SIM or SRM acquisition segment (in our experience RT shifts are almost always to later RTs). A small retention time shift of a peak right at the end of a segment can push it past the window where the characteristic ions are acquired or cause a compound to be inaccurately quantitated.

- 4) One other concern we had with the letter was the requirement that qualifier ion responses maximize within 2 scans of the quantitation ion. While possibly a good measure of spectral quality, realistically this requirement is difficult to check for compliance without examining peaks in the data processing software.

OFFICE OF RESEARCH AND DEVELOPMENT (ORD) / NATIONAL EXPOSURE RESEARCH LABORATORY (NERL)

Overall, the description of SIM vs Scan modes is in good shape.

In background/assumptions, the text discusses SIM mode, which is another point that should be clarified. Assumption is this is meant for electron impact (EI), but with a few minor tweaks (particularly the +/- 20% abundance for qualifiers), it could also be appropriate for ECNI (electron capture negative ionization).

In part e., the text recommends that 5 points per peak is sufficient for quantitation. We disagree, it requires about 8 – 10 points to properly describe the difference between a normal and lognormal peak shape which affects the area under the curve, especially if there is slight tailing. Furthermore, when there are only 5 points, two define the baseline on either side, leaving only three to locate the maximum peak height; this introduces variability into retention time estimates.

In Part f., the text discusses the number of ions per analyte. This is a difficult issue for which to make rules. Some compounds do not need multiple ions; for example, the base peak for benzene is 78 which is unique within its time window. Other compounds may require multiple ions for identification; especially those that fragment similarly to hydrocarbons where the important ion is 43 or 85, but the identifier may be a much lower prevalence molecular ion. This section needs some work.

In part h., the text discusses multiple ions for identification – this is a difficult issue for which to make general rules. As mentioned above, low levels of compounds like benzene will not have identifier ions beyond 78. We suggest that peak shape be used as a secondary qualifier in such cases – which further bolsters the use of more than 5 scans per compound.

In part i., the text does not define internal standard and surrogate, which are often defined differently by different people. We recommend defining these terms to avoid confusion.

In part k, the text advocates for automated peak detection. This has intrinsic flaws, especially for smaller peaks or those near interfering peaks. The biggest skew in quantitation occurs when the automated software makes bad choices in setting the baseline. Also, it is difficult for the software to deal with larger peaks that may approach non-linear response and thus confuse where the peak actually is. We recommend that each chromatogram is at least checked by a subject matter expert when using automated integration.

In part l., the text speaks to various types of standards. Conspicuously absent is the use of isotopically labeled internal standards. We have found that this probably the best method for QA, especially for samples derived from liquids.

Summary:

Overall, this is a good description. However, we think that the recommendation for 5 scans/peak should be reconsidered. We looked into this in 1991 when we first developed SIM for method TO-14. We have attached the journal article for your entertainment.

Background/Assumptions.

Basic terminology - Masses are not monitored. It's the m/z that is monitored. It's OK to refer to the m/z as masses, but use something like "in which a range of mass to charge ratios (m/z) or masses, are monitored in each scan."

All masses are not monitored; a range is monitored. For example, 50-550 m/z . This is typically dependent on the instrument capabilities and the practical range of what is being measured since this range can be defined by the analyst. Full scan is scanning across this range where SIM is scanning across a series of defined m/z .

We would introduce the concept of cycle time and duty cycle in this section. The reason we use SIM is to increase the ratio of ions transmitted from the source to the detector for each m/z within a scan cycle (duty cycle). The number of scan cycles is limited by peak width (in seconds). To define a peak, you typically need 10 cycles across the peak. For a 2-second-wide peak, you have 200ms available per scan. If you define a SIM window or segment with 6 m/z monitored, you have a duty cycle of 30ms on each m/z . If you were scanning at a rate of 3 scans/second with a range of 50-550 m/z , you would only have a duty cycle of around 0.6ms for each m/z and only get 6 scans across the peak. The cycle times are further impacted by overhead time, which is the small amount of time the electronics take to switch between each m/z for the quadrupole mass filter or ion collection/ejection for an ion trap.

We would mention that duty cycle and scans across the peak are decreased for both SIM and scan when running both modes together. They are run in series and are not parallel processes.

"There is a tradeoff between excluding background interferences versus unambiguous identification." This section should say "There is a tradeoff between increasing sensitivity versus unambiguous identification."

Minimum SIM Criteria.

c. **Type of MS.** – Time of flight instruments do not use SIM or scan modes. We would also mention ionization mode somewhere and if this document applies to all modes.

e. **Number of scans per peak.** – Five would be an absolute minimum to measure peak area, but at least 10 scans across the peak are really needed to define the peak and noise. Again, we would mention that duty cycle and scans across the peak are decreased for both SIM and scan when running both modes together.

g. **SIM acquisition parameters.** We would suggest analyzing a high calibration standard up to 10x the highest concentration calibration standard for ion selection in scan mode due to the sensitivity difference. The ratios can be verified across the concentration range of the SIM analysis after selection. Sometimes it's very difficult to have two qualifier ions with enough sensitivity. Again, we think 10 scans across the peak are needed and peak width at low concentrations needs to be considered.

k. **Automated peak detection.** We would suggest adding that integration should be checked even though automated peak detection is being used.

OFFICE OF RESEARCH AND DEVELOPMENT (ORD) / NATIONAL RISK MANAGEMENT RESEARCH LABORATORY (NRMRL)

Not much more to add from my standpoint other than that these are definitely very basic ‘minimum criteria’.

k. made us wonder...is anyone not using automated methods for peak detection when using MS?

d. Tuning is usually practiced while considering manufacturer recommendations.

f. and g. The author may want to point out that the more ions used, the less sensitive the technique typically is. In complex mixtures, a factor of 2 increase in sensitivity with SIM can actually be pretty good. Not sure why one would want to select more than one ion to quantify while using SIM, but there may be such a scenario, but it is certainly not common.

OFFICE OF WATER (OW) / OFFICE OF GROUND WATER AND DRINKING WATER (OGWDW)

The Office of Groundwater and Drinking Water Technical Support Center has reviewed the ELAB document entitled “Minimum Criteria for Selected Ion Monitoring (SIM) Methods,” and generally agrees with the criteria presented. Our office has recently approved three methods for drinking water compliance that allow the use of selected ion monitoring for volatile organic compounds (EPA Methods 524.3 and 524.4) and synthetic organic compounds (EPA Method 525.3). Most of the criteria provided in the ELAB document is consistent with the criteria in the approved methods.

Relative to the overall document, there are a few items that need further clarification or revision in order to meet the needs of our program. Please consider the following:

- We appreciate the statement in the document indicating that method modifications ‘precluded by the applicable regulation should not be made’. But it should be further clarified to indicate that if a method does not make specific provision allowing for selected ion monitoring, it should not be used. This is an important point to make in regards to the drinking water program. Laboratories do not have the authority to change detectors or the detection modes defined in the approved drinking water analytical methods.
- As mentioned previously, our office has approved three newer methods that allow the use of SIM as an option for quantitative analysis. The methods for analyzing volatile organic compounds caution that if adequate sensitivity can be obtained using full scan, then only full scan should be used for quantitation. SIM should only be used if sensitivity cannot be achieved through full scan MS. As noted in the ELAB document, switching the detection mode to SIM comes at a price, namely improved sensitivity results in a loss of resolution. That’s why the presence of interferences can be problematic. Item (e) in the ELAB document suggests a minimum of five scans across each chromatographic peak. That can work in a clean matrix such as drinking water. However, an additional note should be added to indicate that in complex matrices, a lab should target 7-10 scans across each peak to obtain adequate resolution precision. Also, for instruments capable of alternating full scan and SIM modes, you want a minimum of 5 full MS scans and 5 SIM scans across each chromatographic peak.

- Item (j) in the ELAB document encourages the use of data qualifiers. Qualifying data for drinking water compliance, however, is not encouraged and considered an option of last resort. It is not appropriate to qualify data for the failure of any reagent-water prepared QC or calibration check standard. We have allowances in the newer drinking water methods to accommodate qualifying data if matrix effects bias the results. However, only a very small percentage of drinking water samples should ever be flagged or qualified for possible matrix effects. We advise revision of the statement in item (j).

OW / OFFICE OF SCIENCE AND TECHNOLOGY (OST)

This document is a good starting point for methods that do not have any SIM guidance. Some of these comments are merely informational for when SIM is used for NPDES (National Pollutant Discharge Elimination System) analysis, and fall under the authority of 40 CFR Part 136.

1. If an approved EPA method specifies how to run SIM, then the specifications of that method take precedence over a guidance document.
2. Clean Water Act (CWA) Methods allows SIM as a method flexibility in 40 CFR part 136.6(b)(2)(4)(xiv). This regulatory language takes precedence for methods that are used for NPDES compliance. 40 CFR part 136.6(b)(2)(4)(xiv) states:

“(xv) Use of selected ion monitoring (SIM) mode for analytes that cannot be effectively analyzed in full-scan mode and reach the required sensitivity. False positives are more of a concern when using SIM analysis, so at a minimum, one quantitation and two qualifying ions must be monitored for each analyte (unless fewer than three ions with intensity greater than 15% of the base peak are available). The ratio of each of the two qualifying ions to the quantitation ion must be evaluated and should agree with the ratio observed in an authentic standard within ± 20 percent. Analyst judgment must be applied to the evaluation of ion ratios because the ratios can be affected by co-eluting compounds present in the sample matrix. The signal-to-noise ratio of the least sensitive ion should be at least 3:1. Retention time in the sample should match within 0.05 minute of an authentic standard analyzed under identical conditions. Matrix interferences can cause minor shifts in retention time and may be evident as shifts in the retention times of the internal standards. The total scan time should be such that a minimum of eight scans are obtained per chromatographic peak.”

3. Generally speaking, this guidance should not override any method that has laboratory validation data for SIM. The SIM procedure in a validated method is known to work in real world data collected from actual sample matrices.
4. The data qualifier sections of the document are not appropriate for all method programs.
5. Overall this document works well as a general guidance for methods that allow SIM, but do not provide specifics. If the method does not allow SIM, then it should not be considered.
6. Recommend adding a note that suggests the analyst consult information from the instrument manufacturer, since most vendors have application notes on how to run SIM on their machine.
7. Agree with the overall point that the IDC needs to be done using SIM, but since the IDC is performed in reagent water or another reference matrix, it seems unlikely that "matrix specific co-eluting concomitant ions" are likely to exist in the IDC without an actual matrix.
8. Section I. covers retention time windows, but the use of retention time and relative retention time in the discussion is inconsistent. Recommend just using one criteria. Also, RT windows are often ± 3 standard deviations around the mean RT for the analyte. Later the section says that "Retention time in the sample should match within 0.06 relative retention time ... units ..." It

seems like retention time concepts are also being mixed and matched. If the two criteria are used because some methods may not have an internal standard for RRT, then state this and separate the criteria.

9. Section j uses a +/- 20% absolute window for ion abundances. The example states that if the base peak is used as the quant ion and has an abundance of 100% (by definition, if it is the base peak) and the secondary ion is at 45%, then the window is +/- 20% of the base peak, or 25 to 65 percent for the secondary ion. Most EPA methods that use SIM (admittedly often high res MS methods like 1613) use the 20% window around the RATIO, not the absolute abundance. For the previous example, if the theoretical ratio is 0.45 for the secondary ion or 2.22 for the primary ion (e.g., is it 45/100 or 100/45?), then the 20% is applied to that ratio and the windows would be 0.36 to 0.54, or 1.78 to 2.66.

REGIONAL OFFICE – 7

Only asking for 5 scans across the peak. This seems too low to properly define the peak and can lead to RT shifts and error in area integration. 8-10 scans would be better as a minimum guidance.

Section j. Disagreement with the ratios of the confirmatory ions should agree with the standards as a relative percentage rather than absolute percentage. For example, a secondary ion ratio in the standard = 45% versus the primary ion; then the acceptance window should be a relative 20% around 45% (i.e., 36% - 54%). For simplicity and for method harmonization, prefer the acceptance window to remain an absolute percentage (i.e. 25% - 65% using the same example).

ATTACHMENT 2: Separate File

Optimizing Sensitivity of SIM Mode of GC/MS Analysis for EPA's TO-14 Air Toxics Method

Joachim D. Pleil ^a, Teri L. Vossler ^a, William A. McClenny ^a & Karen D. Oliver ^b

- a. Atmospheric Research and Exposure Assessment Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA
- b. ManTech Environmental Technology, Inc., Research Triangle Park, North Carolina, USA
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DRAFT