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

OFFICE OF THE
SCIENCE ADVISOR

Mr. Michael Flournoy
Chair, Environmental Laboratory Advisory Board
Eurofins Frontier Global Sciences Inc.
11720 North Creek Parkway North, Suite 400
Bothell, WA 98011

Dear Mr. Flournoy,

Thank you for your letters of September 19, 2018 on user-generated mass libraries and tuning criteria and October 17, 2018 on minimum criteria for selected ion monitoring (SIM) methods. As noted in previous communications (dated November 16, 2018), the Office of the Science Advisor (OSA) shared your letters with representatives from all EPA Offices and Regions for their consideration. Agency regulatory programs have their own processes to address modifications to analytical methods and equipment parameters as part of Method Update Rules. ELAB members and other stakeholders should use these processes in the future to suggest specific analytical changes or clarifications. ELAB can provide advice and recommendations to the EPA Science Advisor. We do not have a direct role in the processes of regulatory programs.

The Office of Water (OW) and the Office of Land and Emergency Management (OLEM) have provided information (Attachments 1 & 2) related to ELAB's letter regarding instrument performance criteria. OW notes that revised methods 624.1 and 625.1 do allow for alternative instrument tuning criteria and the use of user-generated mass spectrometry libraries. In addition, OLEM states that updated methods 8260D and 8270E have revised tuning verification criteria that are flexible enough to allow the use of new mass spectrometry technologies and also allow instrument manufacturer's acceptance criteria. Methods 8260D and 8270E also allow the use of user-generated reference spectra. OLEM suggests review of these revised methods on the SW-846 website (references provided in Attachment 2).

OLEM has also provided information in Attachment 2 regarding criteria for Selected Ion Monitoring (SIM) methods. They note that revised methods 8260D and 8270E incorporate many of the categories of

quality controls and minimum suggested criteria noted in your October 17, 2018 letter. OLEM provides a detailed comparison between several minimum SIM QC criteria suggested by ELAB and those found in the revised methods. If individual members of ELAB have further clarifying questions or concerns regarding methods 8260 and 8270, they are encouraged to contact Christina Langlois-Miller, as noted in their memorandum to this Office.

Sincerely,

Tom Sinks

Tom Sinks, Ph.D.
Director
Office of the Science Advisor

CC: Adrian Hanley, Christina Langlois-Miller

Attachments

Attachment 1 – Comments provided from Adrian Hanley, Office of Water

It is unclear how the concerns raised in the letter apply to wastewater methods 624.1 and 625.1, which are specifically mentioned in the letter.

The ELAB letter states:

"The substitution of laboratory-generated libraries/relaxed tuning criteria could be applicable for quantitative analysis including; 624.1, 625.1, 8260 and 8270, and others that require verification against National Institute of Standards and Technology (NIST) library spectra or require strict instrument tuning rules."

Clean Water Act mass spectrometry methods have always used user-generated mass spec libraries (and calibrations) for quantifying analytes. The NIST library would only be used for library searches, and most 600-Series methods do not include searches, but focus on the regulated parameters. When we revised methods 624.1 and 625.1 in 2017 we added flexibility to the tuning requirements. This has been part of our ongoing effort to harmonize our methods, per the request of ELAB.

Below are relevant excerpts from methods 624.1 and 625.1:

Excerpt from 624.1 on tuning:

Table 4 – BFB Key m/z Abundance Criteria [1]	
m/z	**Abundance criteria**
50	15 - 40% of m/z 95.
75	30 - 60% of m/z 95.
95	Base Peak, 100% Relative Abundance.
96	5 - 9% of m/z 95.
173	<2% of m/z 174.
174	>50% of m/z 95.
175	5 - 9% of m/z 174.
176	>95% but <101% of m/z 174.
177	5 - 9% of m/z 176.

1 Abundance criteria are for a quadrupole mass spectrometer. Alternative tuning criteria from other published EPA reference methods may be used, provided method performance is not adversely affected. Alternative tuning criteria specified by an instrument manufacturer may also be used for another type of mass spectrometer, or for an alternative carrier gas, provided method performance is not adversely affected.

Excerpt from 625.1 on tuning:

Table 9A – DFTPP Key m/z's and Abundance Criteria for Quadrupole Instruments [1]	
m/z	**Abundance criteria**
51	30 - 60 percent of m/z 198
68	Less than 2 percent of m/z 69
70	Less than 2 percent of m/z 69
127	40 - 60 percent of base peak m/z 198
197	Less than 1 percent of m/z 198
198	Base peak, 100 percent relative abundance
199	5 - 9 percent of m/z 198
275	10 - 30 percent of m/z 198
365	Greater than 1 percent of m/z 198
441	Present but less than m/z 443
442	40 - 100 percent of m/z 198
443	17 - 23 percent of m/z 442

1 Criteria in these tables are for quadrupole and time-of-flight instruments. Alternative tuning criteria from other published EPA reference methods may be used provided method performance is not adversely affected. Alternative tuning criteria specified by an instrument manufacturer may also be used for another type of mass spectrometer, provided method performance is not adversely affected.

Table 9B – DFTPP Key m/z's and Abundance Criteria for Time-of-flight Instruments [1]	
m/z	**Abundance criteria**
51	10 - 85 percent of the base peak
68	Less than 2 percent of m/z 69
70	Less than 2 percent of m/z 69
127	10 - 80 percent of the base peak
197	Less than 2 percent of Mass 198
198	Base peak, or greater than 50% of m/z 442
199	5 - 9 percent of m/z 198
275	10 - 60 percent of the base peak
365	Greater than 0.5 percent of m/z 198
441	Less than 150 percent of m/z 443
442	Base peak or greater than 30 percent of m/z 198
443	15 - 24 percent of m/z 442

1 Criteria in these tables are for quadrupole and time-of-flight instruments. Alternative tuning criteria from other published EPA reference methods may be used provided method performance is not adversely affected. Alternative tuning criteria specified by an instrument manufacturer may also be used for another type of mass spectrometer, or for an alternative carrier gas, provided method performance is not adversely affected.

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SOLID WASTE AND
EMERGENCY RESPONSE
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EMERGENCY MANAGEMENT

MEMORANDUM

SUBJECT: ELAB Letters Regarding Mass Spectrometry Methods in EPA's SW-846 Compendium

FROM: Betsy Devlin, Director Ken Elliott for
Materials Recovery and Waste Management Division

TO: Tom Sinks, Ph.D., Director, Office of the Science Advisor

This memorandum provides information from EPA's Office of Resource Conservation and Recovery in response to two letters dated September 19, 2018 and October 17, 2018, from ELAB (Environmental Laboratory Advisory Board) regarding mass spectrometry methods in EPA's SW-846 Compendium. We appreciate learning of the ELAB committee's concerns, so that we can better align our methods program with industry standards and ensure that our methods continue to produce scientifically rigorous data. Barnes Johnson, director of EPA's Office of Resource Conservation and Recovery, requested that I refer to you the information below.

EPA believes that many of ELAB's concerns were addressed in SW-846 Update VI in July of 2018, which finalized Methods 8260D and 8270E. In general, EPA agrees that standardizing performance criteria across EPA mass spectrometry methods from different methods programs can help reduce confusion in testing laboratories and potentially enable them to provide better data and report fewer false positive and false negative results. However, we ask you to keep in mind that SW-846 methods are used for many applications, including monitoring, regulatory compliance, enforcement, site assessment, remediation, and emergency response, and the stakeholders involved may have very different data quality needs and concerns depending on the application. Also, as a result of the 2005 Methods Innovation Rule published in the June 14, 2005 Federal Register (70 FR 34538), most SW-846 methods are considered guidance, and labs can modify or substitute these methods as long as the modification or substitution is proven to work for the matrix and analyte and that it meets the project's data quality objectives.

Therefore, with the exception of certain methods the use of which is required in the RCRA regulations (referred to as "method-defined parameters") SW-846 methods allow project managers and laboratories the flexibility to tailor the data collection effort to their project-specific data quality objectives. Where SW-846 methods are guidance (i.e., not method-defined parameters), advance approval of method modifications by EPA is not required; however, EPA recommends that the data generator consult with

their regulatory authority before modifications are performed. EPA also encourages persons modifying a method to not only demonstrate but document method modifications.

ELAB's specific issues identified in the September 19, 2018 letter were 1) lack of flexibility in mass spectrometer tune verification criteria, and 2) user-generated mass spectral libraries as an alternative to the NIST library. The October 17, 2018 letter concerned selection of a minimum set of performance criteria for selected ion monitoring (SIM) methods. These concerns are briefly summarized and addressed below:

ELAB Concern #1: Tune verification criteria in SW-846 methods 8260 and 8270 are overly restrictive and limit innovation in mass spectrometry applications.

EPA Response: We agree that some aspects of the tune verification acceptance criteria in previous versions of these and other EPA gas chromatography/mass spectrometry (GC/MS) determinative methods were unnecessarily restrictive. The tune verification procedures and criteria in these previous versions were also not flexible enough to accommodate certain method applications and new technologies, including tandem mass spectrometry. To address these issues, the SW-846 Methods Workgroup revised the tune verification criteria in Methods 8260 and 8270 in the most recent SW-846 Update, which was finalized and published in July 2018 as SW-846 Update VI, Phase II: Methods 8260D and 8270E. The revised tune verification sections in these methods achieve the following:

- Minimize restrictions on low-to-high mass ion ratios;
- Harmonize acceptance criteria for p-bromofluorobenzene and decafluorotriphenylphosphine with the most recently published drinking water method revisions 524.4 and 525.3; and
- Allow alternative reference compounds, including perfluorotributylamine (internal calibrant commonly used to optimize GC/MS systems), and instrument manufacturers' own acceptance criteria to be used to demonstrate MS settings are appropriately optimized.

The revised tune verification criteria in these methods focus on evaluating mass assignments and mass resolution, which are of principal importance for quantitative analysis. These changes should enable Methods 8260D and 8270E to accommodate most types of unit mass resolution mass spectrometers in current commercial production and use, including those mentioned in ELAB's letter. Please review these method revisions, which can be found on the SW-846 website (References a. and b. below), particularly Sections 9 and 11, and relay any additional concerns you may have with the tune verification options and acceptance criteria presented therein.

ELAB Concern #2: User-generated instrument-specific mass spectral libraries would be more appropriate for quantitative analysis, and some testing laboratories would like to know whether EPA would approve of user-generated mass spectral libraries as an alternative to the NIST mass spectral reference library to support qualitative identification of chemicals in samples. EPA should accept a minimum set of scientifically rigorous validation criteria for user-generated libraries, potentially based on NIST's criteria for adding new spectra to their own mass spectral library.

EPA Response: Although EPA allows flexibility in many SW-846 methods, we recommend the use of user-generated reference spectra for Methods 8260D and 8270E, so the SW-846 Methods Team does not understand the need for EPA approval as you have described. Most EPA determinative mass spectrometry methods, including Methods 8260D and 8270E, rely on instrument-specific, user-generated reference spectra to support qualitative identification of specific target chemicals in field samples. In addition, Methods 8260D and 8270E include an allowance to search spectra against mass spectral libraries to aid in qualitative identification of target and non-target analytes, which provides the analyst an additional tool to limit false positive and false negative results. As identified in ELAB's letter, it would be difficult for a user-generated library to match the comprehensiveness of the Wiley/NIST mass spectral library database. While this database has its limitations, a less comprehensive database could result in a smaller likelihood of assigning the correct tentative identification to non-target mass spectra in samples or could lead to mistaken assumptions about uniqueness of matches to library spectra (References c. and d. below).

ELAB Concern #3: EPA methods that allow mass spectrometers to be operated in selected ion monitoring (SIM) mode for quantitative analysis should include a minimum set of standardized performance criteria for quantitative analysis (minimum SIM criteria listed under subheadings a.-g. in the 10/17/2018 ELAB letter).

EPA Response: EPA's Office of Land and Environmental Management responded to a similar inquiry from ELAB as part of a consolidated response through EPA's Forum on Environmental Measurements in December 2017 (Reference e. below). Since then, SW-846 Methods 8260D and 8270E were finalized and published, and many of the categories of quality controls and suggested minimum acceptance criteria that were raised in ELAB's October 2018 ELAB letter have been incorporated in these methods.

ELAB's October 2018 letter also mentions that the applicability of the proposed performance criteria should be limited to SIM. Except in limited circumstances, EPA's view is that the same set of minimum performance criteria provided in Methods 8260D and 8270E are appropriate for tandem mass spectrometry applications as well.

EPA compared the minimum SIM QC criteria suggestions in the October 2018 ELAB letter to the procedures or criteria in Methods 8260D and 8270E, and in some instances the criteria ELAB suggested are more comprehensive or more restrictive than the SW-846 reference methods; these are presented in the table below, followed by EPA's response to these ELAB suggestions:

Paragraph from October 2018 Letter	Quality Control Type	ELAB Suggestion	8260D/8270E Criterion
e.	Number of Scans Per Peak	8	5 (but preferably 10+)

f.	Number of Scan Descriptors Per Peak	3	2
h.	Identification / identification verification criteria (e.g., ion ratios)	Qualifier ion ratio (i.e., ratio of qualifier ion abundance to quantitation ion abundance) within ±20% of qualifier ion ratio in reference spectrum	Qualifier ion ratio within ±30% of qualifier ion ratio in reference spectrum

- ELAB's suggestion in paragraph e (Number of Scans Per Peak): Methods 8260D and 8270E recommend acquiring a minimum of 5 but preferably 10 or more spectra across each chromatographic peak. As part of our method development work, the EPA SW-846 Methods Workgroup determined a need for laboratories to acquire more spectra across peaks to better define peak shapes, therefore a recommendation to acquire 10 or more spectra across each peak was included in the methods. However, the lower minimum spectral acquisition rate published in previous versions of these methods was retained to acknowledge that, for some applications, laboratories and project managers have to balance dwell time, number of concurrent ions acquired, and spectral acquisition rate to meet their data needs.

- ELAB's suggestion in paragraph f (Number of Scan Descriptors): Methods 8260D and 8270E recommend acquiring a minimum of two ions per target analyte in SIM mode, one for quantitation and the other to aid in qualitative identification. Increasing the number of ions monitored per target analyte in SIM provides more information to support identification of target analytes, but the laboratory or data user may have to make the same trade-offs as described above. Acquiring a larger number of ions concurrently can decrease the spectral acquisition rate and the sensitivity of the mass spectrometer for monitored ions. It is worth noting that qualitative identification may not be the limiting consideration for data usability for some applications. For example, when many similar chemicals of the same class are monitored in a sample, like polycyclic aromatic hydrocarbons (PAHs), qualitative identification of an individual PAH may be supported by the presence of other PAHs in the same sample in addition to chromatographic retention times and qualifier ion abundances in individual target analyte mass spectra.

- ELAB's suggestion in paragraph g (Identification / identification verification criteria) (e.g., ion ratios): As part of our method development work, the EPA SW-846 Workgroup discussed using more restrictive qualifier ion ratio criteria than earlier versions of the methods, which would be consistent with EPA wastewater and drinking water methods (which both use maximum qualifier ion ratios of ±20%, although they may disagree on whether the ion ratio limits should be absolute or relative). The workgroup's concern about restricting the maximum ion ratio criteria was related to the increased potential to report false negative results in more difficult or complex sample matrices, especially for target analytes with prominent and common characteristic ions. Instead of restricting the qualifier ion ratio criteria, these method revisions emphasize that

qualifier ion ratio criteria are intended to be used as a guideline in conjunction with chromatographic retention time and the analyst's professional judgment to determine whether a target chemical is present.

We appreciate ELAB's comments and continued interest in SW-846. If you have additional questions or concerns regarding this response, please feel free to contact me, or Christina Langlois-Miller of my staff at langlois-miller.christina@epa.gov.

cc: Michael F. Delaney, Ph.D., Chair, Environmental Laboratory Advisory Board
Ross Elliott, Associate Director, Materials Recovery and Waste Management Division
Kim Kirkland, Chief, Waste Characterization Branch
Christina Langlois-Miller, Methods Team Lead
Thomas O'Farrell, ELAB Designated Federal Official

References:

a. EPA Method 8260D, June 2018. Found at: https://www.epa.gov/hw-sw846/sw-846-test-method-8260d-volatile-organic-compounds-gas-chromatographymass-spectrometry

b. EPA Method 8270E, June 2018. Found at: https://www.epa.gov/hw-sw846/sw-846-test-method-8270e-semivolatile-organic-compounds-gas-chromatographymass-spectrometry

c. NIST MS Search User's guide, V. 2.2. See p. 27. Found at: https://chemdata.nist.gov/mass-spc/ms-search/docs/Ver20Man.pdf

d. Stein, Stephen. Estimating probabilities of correct identification from results of mass spectral library searches. Journal of the American Society for Mass Spectrometry. Volume 5, Issue 4, April 1994, Pages 316-323. Found at: https://www.sciencedirect.com/science/article/pii/1044030594850224

e. Letter dated December 20, 2017, from Mike Shapiro, U.S. EPA (on behalf of the FEM) to Mr. Henry Leibovitz, ELAB, regarding standardizing Selected Ion Monitoring procedures and associated quality control criteria across EPA methods programs. Found at: https://www.epa.gov/sites/production/files/2018-06/documents/henry_leibovitz_sign_final_response_letter.pdf