CODEX ALIMENTARIUS COMMISSION

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GUIDELINES FOR MONITORING THE STABILITY AND PURITY OF REFERENCE MATERIALS AND RELATED STOCK SOLUTIONS OF PESTICIDES DURING PROLONGED STORAGE

(At Step 7)

(Prepared by the Electronic Working Group chaired by India and co-chaired by Canada, Iran (Islamic Republic of) and Singapore)

Codex Members and Observers wishing to submit comments at Step 6 on the guidelines as presented in Appendix I should do so as instructed in CL 2025/38-PR available on the Codex webpage[1]

BACKGROUND

1. The 51st Session of the Codex Committee on Pesticide Residues (CCPR51, 2019) considered a request related to the shelf-life of Certified Reference Materials (CRMs) and their use beyond expiry date was considered in CCPR51 (2019). Following this, a discussion paper was drafted by Argentina and India on "Guidelines for monitoring the purity and stability of certified reference materials of pesticides during prolonged storage" for consideration by CCPR52 (2021). During the 52nd (2021)[2], 53rd[3] (2022) and 54th[4] (2023) sessions of CCPR, the discussion paper and proposal for new work underwent series of revisions incorporating the suggestions made by electronic working group (EWG) members related to scope, acceptability criteria and analytical protocol of the guidelines.

2. During CCPR55 (2024)[5], India, as Chair of the EWG, revised the guidelines based on comments submitted in reply to CL 2024/45-PR. The revised guidelines were considered by a Virtual Working Group (VWG) meeting convened prior to CCPR55, and by an in-Session Working Group (ISWG) convened by CCPR55 in the margins of the plenary session. India, also speaking on behalf of the co-Chairs Argentina and Singapore, presented the guidelines and the revisions made by the EWG, VWG, and ISWG to the plenary session.

3. Based on the revisions made in the EWG, VWG, and ISWG, CCPR55 agreed to advance the guidelines to Step 5, noting that sufficient progress had been made to advance the document in the Step Procedure while recognizing that some refinements may still be needed, including incorporating provisions to cover mixed pesticide standards solutions.

4. The 47th Session of the Codex Alimentarius Commission (CAC47, 2024) adopted the guidelines at Step 5, as proposed by CCPR 55, and advanced the document to Step 6, for comments, and further consideration by CCPR56.[6]

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1 Codex webpage/Circular Letters: http://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/.
Codex webpage/CCPR/Circular Letters: https://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/jp/?committee=CCPR

2 REP21/PR52, paras. 198-201

3 REP22/PR53, paras. 235-242

4 REP23/PR54, paras. 254-259

5 REP24/PR55, paras. 223-230

6 REP24/CAC47, Appendix II

5. Following the detailed discussions held during CCPR55 on the proposed guidelines, it was agreed to:

   (i) forward the Guidelines for Monitoring the Stability and Purity of Reference Materials and Related Stock Solutions of Pesticides during Prolonged Storage to CAC47 for adoption Step 5;
   (ii) expand the scope of the guidelines to cover mixtures of pesticides and to inform CCEXEC and CAC accordingly; and
   (iii) re-establish the EWG, chaired by India, and co-chaired by Canada, Iran, and Singapore, working in English to:
      a. include provisions for monitoring the stability and purity of mixed pesticide standard solutions;
      b. refine relevant sections in the document as necessary; and
      c. submit the revised guidelines for consideration at CCPR56

WORK PROCESS

6. During the first round of the EWG, the draft guidance document adopted by CAC47 at Step 5 was uploaded on the EWG forum inviting comments from EWG members regarding the provisions to be included in the guidelines for monitoring the stability and purity of mixed pesticide standard solutions and the sections of the document which require further refinement. Comments were received from Chile, Colombia, Costa Rica, South Africa and Uruguay. The EWG members suggested rearrangements in the text of the analytical protocol for better clarity and inclusion of an additional/new approach for monitoring the stability and purity of pesticide mixtures.

7. The relevant sections of Approach 1 and 2 in the guidance document for monitoring the purity and stability of individual pesticides were revised based on the comments received and an additional approach was included for monitoring the stability and purity of pesticide mixtures. The document was uploaded by the EWG Chair inviting second round of comments from the EWG members. In the second round Chile, Colombia, EU, Germany, Thailand, Uruguay and USA provided their comments on the forum which were mainly focussed on Approach 3 for monitoring the stability and purity of reference materials (RMs) of pesticide mixtures and further refinement of Approaches I and II.

8. The document as revised by the EWG is presented in Appendix I: Guidelines for monitoring the stability and purity of reference materials and related stock solutions of pesticides during prolonged storage; and the Annex for definitions. Appendix II contains the references for the development of the guidelines. Appendix III provides the list of participants.

KEY POINTS OF DISCUSSION

9. The following are the key points of discussion based on the comments received in CCPR55 and during two rounds of circulation of the document in EWG.

   1. Extension of the scope of guidelines to include mixtures of pesticide standards in the guidance document and inclusion of Approach 3 in the analytical protocol for verification of stability of reference materials of pesticide mixtures during prolonged storage. Approach 3 is applicable to mixture of RMs procured from a Reference Material Provider (RMP) accredited as per ISO 17034.

   2. The use of internal standard (IS) (unexpired) in Approach 1 is optional while in Approach 2, the use of IS is required to eliminate the requirement of new (or unexpired) RM to determine the purity and stability of the old (or expired) RM. In Approach 3, the use of IS is required to determine the stability of RM of mixture of pesticides by comparing the ratio of the mean peak area of old (or expired) RM and IS to the mean peak area of new (or unexpired) RM and IS.

   3. Reference value of purity in the reference material document or Certificate of Analysis (CoA) will be used for the calculation of % deviation in percent purity in Approach 2.

   4. References to the ISO guides have been updated to their latest editions.

   5. An additional practical approach as proposed by the European Union wherein the laboratories may extend the shelf life of a RM by a default factor if the material is stored at a lower temperature than recommended by the RMP. The proposed extension in shelf life depending on the storage temperature conditions as specified by the RMP and those maintained by the laboratories are summarized below for discussion.

	The max. shelf life for neat standards recommended by the RMP for a RM or CRM may be multiplied by the following FACTORS by default if kept under controlled storage conditions around the following temperatures:		
RMP recommendation regarding storage	Storage at Room temperature	Storage in Fridge (~4°C)	Storage in Freezer (~-18°C)
Room temperature	As indicated by RMP unless demonstrated otherwise	x3	x6
Fridge (~4°C)	Not foreseen	As indicated by RMP unless demonstrated otherwise	x2
Freezer [~-18°C)	Not foreseen	Not foreseen	As indicated by RMP unless demonstrated otherwise
Storage Ceiling (i.e. standards stored at this temperature should not be used more than …)	e.g. 4 years	e.g. 8 years	e.g. 12 years

CONCLUSIONS

10. The EWG observed that there is a general support for the guidance document. Based on the discussions held at CCPR55 and comments received from the EWG and forum members, the guidance document has been revised.

11. Apart from the two approaches (analytical protocols) for monitoring the stability and purity of individual RMs, an additional approach for verification of stability of RMs of mixture of pesticides and their use beyond the expiry date has been included. If the stability and purity of RMs continues to meet the acceptability criteria, they may be considered suitable for use beyond their expiry provided these are stored under conditions specified in the guidelines.

RECOMMENDATIONS

12. CCPR is invited to consider the proposed guidelines as set out in Appendix I and provide general and specific comments on the document including its readiness for advancement to Step 8 for final adoption by CAC48 (November 2025).

APPENDIX I

GUIDELINES FOR MONITORING THE STABILITY AND PURITY OF REFERENCE MATERIALS AND RELATED STOCK SOLUTIONS OF PESTICIDES DURING PROLONGED STORAGE

(For comments at Step 6)

PREFACE

1. Pesticide residues in food commodities have become a worldwide agricultural trade-concern, which has led to enforcement of strict pesticide regulations. More than 1200 pesticides are available globally to control the pests on different food commodities. Analyses of pesticides at trace levels in the food chain require the use of specific Reference Materials (RMs) of known chemical purity manufactured by the Reference Material Producers (RMPs) to ensure the reliability of the test results. Accurate determination of pesticide residues in food commodities is important for food safety control and fixation of Maximum Residue Limits (MRLs) of pesticides, thereby overcoming the related trade barriers. RMs with specified purity are also required for accurate qualitative and quantitative analysis of pesticide active ingredient(s) in technical products, formulations, and stock solutions.

2. Limited shelf life, diminishing purity, and high recurring cost of RMs act as major impediments to performing regular pesticide residue analysis. These problems are magnified for multi-pesticide residue analysis by testing laboratories in developing countries as they are required to allocate a large part of their funds for frequent procurement of expensive RMs. Furthermore, the use of RMs is restricted by the expiry dates specified by the RMPs in the reference material document (e.g., certificate of analysis (CoA) or product information sheet), which provides the value for purity, expiry date, and measurement uncertainty of the RMs as per ISO 33401. Many times, laboratories cannot afford the frequent purchase of high-cost RMs for their pesticide residue control work.

3. Moreover, due to supply chain constraints, some laboratories may receive RMs close to their expiry date, as mentioned in the reference material document. In such situations, the laboratories are forced to buy new standards and prepare new stock solutions more frequently than necessary. This leads to enormous amount of work and increased laboratory costs, especially for compounds for which stability is well understood. Additionally, shipping RMs by the suppliers to laboratories increases the acquisition time for procurement (a few weeks to months), creating hurdles in sustainable pesticide residue control programs.

4. There are RMs that remain stable even after the expiry dates stated in the reference material document with no significant change in purity. Some studies[1-3] have also reported that if RMs are stored at better storage conditions than recommended by the manufacturer, provided that these conditions do not contradict those indicated by the RMP in the reference material document, the RMs are stable for much longer than the expiry dates indicated by the RMPs. Such RMs may technically be allowed to be used beyond their expiry dates if laboratory checks are in place to demonstrate that they are stable and continue meeting the purity requirements. However, the absence of guidance procedures for monitoring the stability and purity of RMs prevents their use beyond the expiry dates.

5. This document represents a crucial step towards developing comprehensive harmonized guidance enabling the laboratories to monitor the stability and purity of the pesticide RMs and their stock solutions during prolonged storage. The document aims to guide the laboratories in monitoring the stability and purity of RMs for their possible use beyond their expiry dates and for continued use of stock solutions that retain their stability and purity.

SCOPE AND OBJECTIVE

6. The purpose of this document is to furnish a framework that would assist the laboratories in monitoring the stability and purity of reference materials (RMs) of pesticides during prolonged storage and identifying expired RMs with continued stability and purity through robust analytical protocols so that such materials that retain their purity as per the reference material document even after expiry can continue to be used as valid RMs. Another aspect of the proposed work is to monitor the stability of the stock solutions used for pesticide residue analysis so that those solutions that continue to be valid can be used for the accurate and reliable determination of pesticide residue levels.

7. This document applies to RMs of pesticide standards of known purity specified by a RMP, including individual RMs, stock solutions of individual RMs, and RMs purchased as mixtures.

8. These guidelines will enable the pesticide residue laboratories to overcome the constraints associated with short expiry periods of RMs and use them beyond their expiry dates mentioned in the reference material document. After the expiration date, the RMs retaining the purity specified in the reference material document can be used as RMs or as quality control materials (QCM) for the analysis of pesticides, provided that these are stored under conditions specified in the guidelines and according to the manufacturer's instructions. RMs that do not remain stable and do not show acceptable purity during prolonged storage shall not be used by laboratories for pesticide residue testing/quantitative purposes, as accurate results may not be obtained.

9. The guidelines cover the storage conditions that shall be maintained and quantitative measurements that shall be performed to monitor the stability and purity of RMs and their stock solutions before and beyond their expiration period.

GENERAL CRITERIA

10. The analysis shall be conducted in laboratories in compliance with the general criteria for testing laboratories laid down in ISO/IEC 17025, with the scope relevant to the measurement concerned.

11. The stability of mixtures of RMs may be evaluated under these guidelines only if the mixture is purchased from the RMP, who can certify the purity and stability of each of the individual components.

12. The RMs shall be procured from an RMP accredited as per ISO 17034 to ensure analytical traceability or from a National Metrology Institute recognized by peers or designated by countries.

13. To ensure metrological traceability, the analytical balances used shall be calibrated with weights traceable to the national/international standards.

14. Calibrated class A glassware or appropriate electronic/automatic pipettes traceable to national/international standards shall be used for volumetric measurements.

15. The instrumentation used in purity tests should have comparable or greater sensitivity/specificity to those used in the reference material document of the RM.

16. According to the reference material document, the equipment used for storing and monitoring RMs should be traceable to national/international standards.

17. ISO Guide[4] may be referred for assessing the shelf-life of an RM

18. To ensure the validity of the stability and purity testing protocols provided below, the gravimetric records shall be maintained for RMs (opened or unopened), both solid and liquid, and their respective stock solutions during storage before and after use at each time. Before recording the weight, the container should attain room temperature/ambient temperature and be wiped to remove any adhering moisture. The exposure of RM and stock solutions to ambient temperatures and light must be kept as short as absolutely necessary.

19. The record of the storage conditions (e.g., temperature and humidity) as well as the date of use of the RM and their stock solutions shall be maintained. Also, the temperature at which the RMs and their stock solutions are opened for use shall be recorded.

CRITERIA FOR STORAGE CONDITIONS FOR PESTICIDE REFERENCE MATERIALS AND THEIR STOCK SOLUTIONS

20. The storage conditions of RMs are specified by RMPs in the reference material documents, as these are susceptible to degradation at high temperatures and other unfavorable environmental conditions. Environmental conditions (temperature and humidity, as appropriate) shall be recorded, monitored and controlled by the laboratory.

21. If a laboratory maintains the RMs at better storage conditions, i.e., more protective than those recommended by the RMPs (i.e., temperature lower than recommended without exposure to light and moisture, etc.), the rate of degradation of the RMs is significantly minimized as long as these conditions do not contradict those indicated in the reference material document by the RMP. Under such conditions, the expiry date as recommended by the RMPs may be extended as appropriate for an RM by a date allowing for storage of up to 10 years or as long as the purity mentioned in the reference material document holds good (≤ ±10%) (SANTE[5], 2024). Another study revealed the stability of pesticide reference standards for up to 15 years or in-stock solutions for up to 10 years[1,2].

22. To avoid any cross-contamination or degradation of RMs, the vials can be placed in an airtight capped tube/sealed pouch (made of suitable polypropylene or high-quality plastic material) and immediately stored in the freezer/refrigerator at conditions more protective than those recommended by RMPs, preferably at subzero temperature. The stock solutions must also be stored in airtight capped glassware or any other suitable material as specified by the RMP. Storage conditions shall be monitored with appropriately calibrated equipment and controlled and recorded. Exposing glassware to extreme temperatures should be avoided.

ANALYTICAL PROTOCOL FOR MONITORING THE STABILITY AND PURITY OF PESTICIDE REFERENCE MATERIALS AND INDIVIDUAL STOCK SOLUTIONS

23. Three analytical approaches may be considered for monitoring the stability and purity of individual RMs and their stock solutions and mixed pesticide RM standards and extending their use beyond the expiry date, provided their purity is proven acceptable.

24. In Approach 1, the stability of new (or unexpired) and old (or expired) RMs is determined simultaneously, and it is applicable for individual neat standards and their related stock solutions. The comparisons of peak area shall be run under repeatability conditions and mitigate other sources of variation in instrument response, by averaging the values of replicate measurements. Alternatively, an internal standard (IS) may be used to compare the peak area ratio of new (or unexpired) and old (or expired) RMs. If the deviation (in peak area) after expiration is found within ±10%, or alternatively the peak area ratio deviation is within ±10%, the analyte in the RM is acceptable and, therefore, can be considered for continued use as a RM. For neat standards and stock solutions, monitoring of stability & purity may be continued regularly up to a maximum of 10 years (SANTE) provided the deviation in purity remains acceptable[1,2,6]. Here, new (or unexpired) RM would be required for comparison.

25. In Approach 2, whenever a new (or unexpired) RM is procured by any laboratory, its purity is monitored periodically before and after expiry using the same analytical conditions as mentioned in the reference material document. Here, new (or unexpired) RM need not be procured. An unexpired IS of any pesticide RM, appropriate for the method is used to account for any change in the response of the equipment. This approach applies only to neat RMs accompanied by reference material documents. As the analyte is spiked with the IS, the selection of the IS should be based on previous experience that shows a good stability over the expected storage time. The IS should further show a good measurement behavior and should not interfere with the measurement of the tested analyte.

26. Approach 3 is similar to Approach 1 wherein the stability of new (or unexpired) and old (or expired) RM is determined simultaneously and is applicable to mixed pesticide RM standards. As in approach 1, the comparisons of peak area of each pesticide RM in the mixture shall be run under repeatability conditions and mitigate other sources of variation in instrument response, by averaging the values of replicate measurements. Alternatively, an internal standard (IS) may be used to compare the peak area ratio of each RM pesticide in new (or unexpired) and old (or expired) mixture. If the deviation (in peak area) after expiration is found within ±10%, or alternatively the peak area ratio deviation is within ±10%, for each pesticide RM in the mixture, the analyte in the RM is acceptable and, therefore, can be considered for continued use as a RM.

Approach 1: Comparing the stability of old (or expired) and new (or unexpired) pesticide reference standards; applicable to neat standards of reference materials and related stock solutions

27. Prepare a fresh stock solution of the old (or expired) and new (or unexpired) RM standard of the appropriate concentration. Appropriate concentration will depend on the response of the RM in the detector. Generally, for HPLC[1]-DAD[2]/GC[3]-FID[4], a good response is obtained between 10 mg L^{-1} to 100 mg L^{-1}. For single quadrupole GC-MS[5] or LC[6]-MS, the appropriate concentration typically ranges from 1 to 5 mg L^{-1}, while for triple quadrupole GC-MS/MS or LC-MS/MS, 0.1 to 0.5 mg L^{-1} or lower concentration may be more appropriate to avoid signal saturation.

1 High-performance liquid chromatography
2 Diode-Array Detection
3 Gas chromatography
4 Flame ionization Detector
5 Mass Spectrometry
6 Liquid Chromatography

28. Analyze the standard solution of the old (or expired) and new (or unexpired) RM on a proper instrument (HPLC-DAD, HPLC-UV[7], GC-FID, LC-MS or GC-MS, LC-MS/MS, GC-MS/MS, or qNMR[8]) and record the peak area. Either of the two methods described below can be employed.

29. Method 1 (Peak Area Comparison): Inject standard solutions of the old (or expired) and new (or unexpired) individual RMs prepared from the stock solution at the same concentration into the instrument and record the peak area. It is recommended that the injection sequence contain at least five replicates of new (or unexpired) and old (or expired) standards and should be alternating to minimize the drifting of signal response in the course of measurement. Calculate the mean value of the peak area for the old (or expired) and new (or unexpired) RM of the five replicates. The %RSD of the replicate measurements should be ≤ ±10%. Calculate the % deviation in average peak area of the old (or expired) and new (or unexpired) standard solutions using the formula below given. The mean value from the new (or unexpired) solution is taken to be 100% and is also used as a basis for calculating the percentage difference.

$$\%\ deviation = \frac{\left|(Mean\ peak\ area\ for\ old\ (or\ expired)\ standard\ - Mean\ peak\ area\ for\ new\ (or\ unexpired)\ standard)\right|}{Mean\ peak\ area\ for\ new\ (or\ unexpired)\ standard}\ x\ 100$$

30. Method 2 (Peak Area Ratio Comparison): Spike a different RM (inert and unexpired) as an IS into the standard solutions of the old (or expired) and new (or unexpired) RMs prepared from the stock solution at the same concentration. Inject the solutions and record the peak area of the RM and the IS, perform a minimum of five replicate measurements, and calculate the average ratio of RM area to IS area for the old (or expired) and new (or unexpired) RMs with %RSD ≤ 10%. The IS peak should have a similar abundance to the RM being verified, and it should not interfere with the analysis of the target RM in terms of either retention time or molecular weight (m/z). Calculate the % deviation using the below given formula:

$$\%\ deviation = \frac{\left|(Mean\ peak\ area\ ratio\ of\ old\ (or\ expired)\ and\ internal\ standard\ - Mean\ peak\ area\ ratio\ of\ new\ (or\ unexpired)\ and\ internal\ standard)\right|}{Mean\ peak\ area\ ratio\ of\ new\ (or\ unexpired) and\ internal\ standard}\ x\ 100$$

31. If the % deviation (as obtained from the above Method 1 or Method 2) shows a deviation of ≤ ±10%, the old (or expired) standard may be considered suitable for continuing use.

32. The old (or expired) standard shall be compared with the new (or unexpired) standard at regular intervals of at least once a year, provided the recommended storage conditions are maintained.

33. To monitor the stability of the RM over time, a plot of the % deviation vs. time of monitoring may be made, which would help identify the deviation in stability of RM with time.

Approach 2: Verification of purity of neat standards of pesticide reference materials during prolonged storage (not suitable for verification of stock solutions)

34. To verify the purity of the RM, a chromatographic assay shall be performed, preferably as per the analytical conditions mentioned in the reference material document by the RMP. If it is not feasible to match the exact conditions of the RMP, deviations should be documented and justified. Furthermore, if the deviation comes from the use of a different technique, the laboratory must guarantee that the technique has an equivalent or better sensitivity. RM purity is verified by comparing the purity (in terms of percent peak area) obtained through analysis with the purity mentioned in the reference material document.

35. Prepare a fresh stock solution of the new (or unexpired) neat standards of RMs and IS (a different unexpired RM) of appropriate concentration in a suitable solvent. The IS solution should be prepared in the same solvent in which the stock solution is prepared to consider any background interference that may be present. Appropriate concentration will depend on the response of the RM using the selected detection method; please see paragraph 27 of Approach 1 for suggested concentration ranges.

7 Ultra-violet spectroscopy

8 Quantitative Nuclear Magnetic Resonance

36. Prepare the standard solution of the RM from the stock solution and analyze it through the instrument (HPLC-DAD, HPLC-UV, GC-FID, LC-MS, GC-MS in full scan mode, or qNMR) as per the analytical conditions mentioned in the reference material document. The percent peak area obtained through the software of the instrument while carrying out the analysis is recorded as percent purity. Inject a blank solution of the same solvent in which the stock solution is prepared prior to this to consider any background interference that may be present. A minimum of five replicate measurements shall be performed to obtain a mean value of percent purity, and the %RSD of the replicates should be ≤ 10%. The instrument shall be calibrated as per the conditions recommended by the manufacturer.

37. Compare the mean value of verified purity (percent purity) obtained from the laboratory analysis with the reference value of purity provided in the reference material document. The certified value (reference value) listed in the reference material document is considered as the purity reference value while calculating % deviation in purity.

38. The % deviation in percent purity can be calculated as:

$$\%\ deviation = \frac{\left|\left(Mean\ peak\ percent\ area\ for\ neat\ standard\ -\ \%\ Purity\ reference\ value\right)\right|}{\%\ Purity\ reference\ value}\ x\ 100$$

39. To determine changes in the response of the equipment with time, spike the solution of an unexpired IS of the same concentration as RM in the standard solution of RM. Inject the solution and record the peak area of the RM and the IS and calculate the average ratio of the RM area to the IS area. The IS peak should have a similar abundance to the RM being verified, and it should not interfere with the analysis of the target RM in terms of either retention time or molecular weight (m/z). Monitoring the signal of the RM with respect to IS helps to take into account the signals that may not be visible but contribute to the percent share of the analyte on the summed area of the chromatogram.

40. Repeat the same procedure at regular intervals of at least once a year using a freshly prepared solution of the RM and compare with the freshly prepared solution of the unexpired IS, particularly before and after the RM's expiry, to monitor its stability and purity during prolonged storage and obtain % deviation in the ratio of peak area.

$$\%\ deviation = \frac{\left|\left(Mean\ peak\ area\ ratio\ of\ RM\ before\ expiry\ and\ IS\ -\ Mean\ peak\ area\ ratio\ of\ RM\ after\ expiry\ and\ IS\right)\right|}{Mean\ peak\ area\ ratio\ of\ RM\ after\ expiry\ and\ IS}\ x\ 100$$

41. After the expiry of the RM, if the mean value of percent purity in terms of percent peak area obtained for the RM and the reference value (as obtained from reference material document) do not differ by more than ±10% (the % deviation of less than or equal to ±10%) and the deviation (%) in the ratio of peak area for the RM compared to the internal standard is ≤ ±10%, the RM may be considered suitable for continuing use in the laboratory.

Approach 3: Verification of stability of mixed pesticide RM standard solutions during prolonged storage.

42. This approach has been aligned with Approach 1. Prepare a fresh stock solution of the new (or unexpired) and old (or expired) mixed pesticide RM standard of appropriate concentration in a suitable solvent. Appropriate concentration will depend on the response of the RM using the selected detection method; please see paragraph 27 of Approach 1 for suggested concentration ranges.

43. Analyze the standard solution of the old (or expired) and new (or unexpired) RM mixture on a proper instrument (HPLC-DAD, HPLC-UV, GC-FID, LC-MS, GC-MS in full scan mode or qNMR) as per the analytical conditions mentioned in the reference material document and record the peak area. Either of the two methods described below can be employed.

44. Method 1 (Peak Area Comparison): Inject standard solutions of the old (or expired) and new (or unexpired) mixed pesticide RM prepared from the stock solution at the same concentration into the instrument and record the peak area of each pesticide RM in the mixture. It is recommended that the injection sequence contain at least five replicates of new (or unexpired) and old (or expired) standards and should be alternating to minimize the drifting of signal response in the course of measurement. Calculate the mean value of the peak area of the five replicates for the old (or expired) and new (or unexpired) RM. The same will be calculated for all the pesticide RMs in the mixture. The %RSD of the replicate measurements should be $\leqslant$ 10%. Calculate the % deviation in average peak area of each pesticide RM in the old (or expired) and new (or unexpired) standard solutions of the mixture using the formula below given:

$$\%\ deviation\ (for\ each\ pesticide\ RM) = \frac{\left|\left(Mean\ peak\ area\ for\ old\ (or\ expired)\ standard\ -\ Mean\ peak\ area\ for\ new\ (or\ unexpired)\ standard\right)\right|}{Mean\ peak\ area\ for\ new\ (or\ unexpired)\ standard}\ x\ 100$$

45. Method 2 (Peak Area Ratio Comparison): Spike a different RM (inert and unexpired) as an IS into the standard solution of the old (or expired) and new (or unexpired) mixed pesticide RM prepared from the stock solution at same concentration. Inject the solutions and record the peak area of each pesticide RM in the old (or expired) and new (or unexpired) mixture as well as the IS by performing a minimum of five replicate measurements with %RSD ≤ 10%. Calculate the average area ratio of each pesticide RM in the old (or expired) and new (or unexpired) RM mixture to the IS. The IS peak should have a similar abundance to the RM being verified, and it should not interfere with the analysis of the target RM in terms of either retention time or molecular weight (m/z). Calculate the % deviation of each pesticide RM in the mixture using the below given formula:

$$\%\ deviation\ (for\ each\ pesticide\ RM) = \frac{\left|(Mean\ peak\ area\ ratio\ of\ old\ (or\ expired)\ and\ internal\ standard\ - Mean\ peak\ area\ ratio\ of\ new\ (or\ unexpired)\ and\ internal\ standard)\right|}{Mean\ peak\ area\ ratio\ of\ new\ (or\ unexpired)\ and\ internal\ standard}\ x\ 100$$

46. If the % deviation for every pesticide RM in the mixture (as obtained from the above Method 1 or Method 2) shows a deviation of ≤ ±10%, the old (or expired) pesticide RM mixture may be considered suitable for continuing use.

47. The old (or expired) mixed pesticide RM standard shall be compared with the new (or unexpired) mixed pesticide RM standard at regular intervals of at least twice a year, provided the recommended storage conditions are maintained.

48. To monitor the stability of the mixed pesticide RM standard over time, a plot of % deviation vs. time of monitoring may be made, which would help identify and predict the deviation in stability with time.

ANNEX

DEFINITIONS

Certified Reference Material (CRM): Reference material (RM) characterized by a metrologically valid procedure for one or more specified properties, accompanied by an RM certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

Internal standard: A chemical added at a known amount to samples and/or standards in chemical analysis, including the blank and calibration standards. This substance can then be used for calibration by plotting the ratio of the analyte signal to the internal standard signal as a function of the concentrations. This ratio for the samples is then used to obtain the analyte concentrations. The internal standard used needs to provide a signal that is similar to the analyte signal in most ways but sufficiently different so that the two signals are readily distinguishable from each other.

Mixture of Reference Material: Reference standard of pesticide containing multiple compounds procured from a Reference Material Producer (RMP) accredited as per ISO 17034 to ensure analytical traceability or from a National Metrology Institute recognized by peers or designated by countries

Reference Material Document: A document that provides the relevant information about certified purity, concentration, date of expiry, and measurement uncertainty of an RM, which is in compliance with the requirement in ISO 17034 and ISO 33401. Reference material documents can be in the form of a Product Information Sheet or Certificate of Analysis (CoA).

Purity: Characteristic of a reference material which indicates the proportion of the stated component of interest in relation to the total substance. Purity is typically expressed in percentages and should be considered when preparing standard solutions.

Quality Control Material (QCM): Reference material used for quality control of a measurement.

Reference Material (RM): Material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process.

Reference Material Producer (RMP): Body (organization or company, public or private) that is fully responsible for project planning and management; assignment of, and decision on property values and relevant uncertainties; authorization of property values; and issuance of a reference material certificate or other statements for the reference materials it produces.

Relative Standard Deviation (%RSD): It is expressed as the sample standard deviation divided by the sample mean multiplied by 100.

Stability: Characteristic of a reference material, when stored under specified conditions, to maintain a specified property value within specified limits for a specified period of time.

Standard solution: A chemical solution that has a precisely known concentration. Standard solutions are generally prepared by dissolving a solute of known mass into a solvent to a precise volume or by diluting a solution of known concentration with more solvent.

Stock Solution: A solution of a reference material or standard of high concentration from which appropriate dilutions can be made at the time of use.

Traceability: Metrological traceability, property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.

Uncertainty: measurement uncertainty, non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used.

APPENDIX II

(For information)

ORIGINAL LANGUAGE ONLY

Reference Documents

1) de Kok, A., de Kroon, M. and Kiedrowska, B. (PO 005 pdf, 2019). Stability of pesticides reference standards and stock solutions Part 1 GC-pesticides NVWA - Netherlands Food and Consumer Product Safety Authority, Laboratory of Food and Feed Safety-Chemistry Laboratory, National Reference Laboratory (NRL) for Pesticide Residues in Food and Feed, Wageningen, The Netherlands.

2) de Kok, A., de Kroon, M. and Scholten, J. (PO 006 pdf, 2019). Stability of pesticides reference standards and stock solutions Part 2. LC-pesticides NVWA - Netherlands Food and Consumer Product Safety Authority, Laboratory of Food and Feed Safety-Chemistry Laboratory, National Reference Laboratory (NRL) for Pesticide Residues in Food and Feed, Wageningen, The Netherlands.

3) Sharma, K. K., Tripathy, V., Gautam, R., Gupta, R., Tayade, A., Sharma, K., Yadav, R., Shukla, P., Devi, S., Pandey, P., Singh, G., Kalra, S., Walia, S. (2020). Monitoring of purity of CRMs of multi-class pesticides during prolonged storage before and after expiration. Accreditation Qual. Assur., 25 (10), 89-97. 10.1007/s00769-019-01411-w.

4) ISO 33405:2024-Reference Materials- Approaches for characterization and assessment of homogeneity and stability

5) SANTE/11312/2021 V2, Implemented by 01/01/2024, European Commission Directorate General for Health and Food Safety.

6) EURL DataPool, https://www.eurl-pesticides-datapool.eu/

7) ISO 33401:2024- Reference materials — Contents of certificates, labels and accompanying documentation

8) ISO/IEC 17025: 2017- General requirements for the competence of testing and calibration laboratories

APPENDIX III

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