CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

Agenda item 7

CRD27
June 2024
ORIGINAL LANGUAGE ONLY

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON PESTICIDE RESIDUES

55th Session
Chengdu, Sichuan province, P.R. China
3-8 June 2024

REPORT OF THE IN-SESSION WORKING GROUP ON GUIDELINES FOR MONITORING THE STABILITY AND PURITY OF REFERENCE MATERIALS AND RELATED STOCK SOLUTIONS OF PESTICIDES DURING PROLONGED STORAGE (AT STEP 4)

(Prepared by India as Chair, ~~of the Electronic Working Group assisted by~~ Singapore and Argentina ~~and Singapore~~ as co-Chairs of the Electronic Working Group)

BACKGROUND

1. In addition to the background provided in CX/PR 55/24/6, India, as Chair of the EWG, with the assistance of ~~Argentina and~~ Singapore and Argentina as Co-Chairs of the EWG, have revised the guidelines based on comments submitted in reply to CL 2024/45-PR as presented in CX/PR 24/55/6-Add.1 and additional comments provided in CRDs i.e. Brazil, Burundi, China, European Union (EU), Ghana, Japan, Nigeria, Philippines, ~~European Union (EU),~~ Thailand, Uganda and Uruguay, ~~Uganda, Burundi, Japan, China, Nigeria~~ and ~~Ghana~~. In addition to those points raised in CX/PR 24/55/6, paragraph 11, key points of discussion arising from comments in reply to CL45 are as follows:

2. Based on the comments received from Argentina, Brazil, Burundi, Canada, Chile, China, Colombia, Egypt, EU, Ghana, Indonesia, Japan, Iraq, Nigeria, Peru, Philippines, Saudi Arabia, United Arab Emirates (UAE), United States of America (USA), Thailand, Uganda, Uruguay and International Commission for Uniform Methods of Sugar Analysis (ICUMSA) on the circular CL 2024/45-PR, the document has been refined and following changes have been incorporated in the document:

    1) Formula for calculating the percent deviation (in peak area or % purity) between the old (or expired)~~old~~ and new (or unexpired) standards have been included.
    2) The concentration terms have been provided in SI units.
    3) The use of internal standard has been suggested in Approach 1 for determination of stability as well as mitigation of other sources of variation.
    4) Definitions for %RSD, standard solution and internal standard have been included in the document.
    5) qNMR has been included as one of the ~~detectors~~ measurement techniques for determining purity of RMs
    6) The %RSD criterion for replicate measurements has been modified from "%RSD ≤ 10%" to "%RSD ≤ 10%, preferably <5%".
    7) The guidelines may be applied to mixture of standards provided the storage conditions are maintained as per the guidelines as long as these conditions do not contradict those indicated by the RMPs and they show acceptable stability. ~~as determined using Approach 1.~~ This scope of mixture of standards was however not included in the TOR of EWG established at CCPR54 ~~This point~~ and is therefore open for discussion at the plenary.

3. To facilitate discussion and identify key points which would require further deliberation during the plenary session, a virtual meeting of working group was held on 29 May, 2024. The Chair of EWG introduced the item, presented the background, work done and the changes made in the guidance document following two rounds of comments in the EWG and subsequent comments received on the CL 2024/45-PR. The Chair then presented the Appendix I in CRD03 and informed that further request had been received from few members to extend the scope of the guidelines to cover mixture of pesticides. She then invited the participants to provide general and specific comments related to the guidance document or any section thereof. The major points that were discussed during the meeting included ~~were~~ possible extension of the scope of guidelines to mixture of pesticides and suitability of Approaches I and II for monitoring the stability and purity of individual reference materials of pesticides and their related stock solutions, ~~mixture of standards,~~ use of internal standard in Approach I, criterion for %RSD for replicate measurements, inclusion of control charts in Approach I, formula for calculation of % deviation in purity and the possibility of including prediction of shelf-life of RMs. A few editorial changes were also suggested by the participating members.

4. The following are the outcomes of the meeting:

   1) There was a general support for extending the scope of the guidelines to mixture of pesticide~~s~~ standards. The Chair opined that while the guidelines could be extended to pesticide mixtures, keeping in mind that mixtures of pesticides were not included in the TOR of EWG on RM established during CCPR54. Considering the potential technical challenges that may be encountered by pesticide residues laboratories, a revised analytical protocol needed to be worked out accordingly so that the guidelines could be applied to pesticide mixtures. It was also observed by the participants that while Approach II was more suitable for individual pesticides, Approach I could be applicable to pesticide mixtures.
   2) The Chair clarified that the inclusion of internal standard in Approach I required further deliberations and that the suggested changes required to be studied critically to ensure that the purpose of the guidelines was not diluted.
   3) Regarding the setting of criterion for %RSD for replicate measurements as < 10% or <5%, it was decided that it would be taken up for discussion in the plenary.
   4) The formula for calculation of % deviation in peak area or purity were modified based on the suggestions received.
   5) Plotting of control charts have been included as one of the continuous monitoring ~~quality~~ parameters in Approach I.
   6) The suggestion related to stability study of pesticide as per the current ISO ~~35~~ guide was included in general criterion.
   7) The suggested editorial changes including replacement of ‘product information sheet’ with ‘reference material document’ have been incorporated in the guidance document.

5. These comments do not alter the conclusions and recommendations as presented in CX/PR 24/55/6 which are shown here below for convenience.

CONCLUSIONS

6. The EWG observed that there is a general support for the guidance document. Based on the discussions held at CCPR54 and comments received from the EWG & forum members, circular CL 2024/45-PR, CRD03 ~~and~~ as well as during the virtual meeting of working group the guidance document has been revised.

7. Two approaches (analytical protocols) have been proposed for monitoring the stability and purity of RMs and extending their use beyond the expiry date. If the stability and purity of RMs continues to meet the acceptability criteria, they may be considered suitable for use up to a maximum period of 10 years provided these are stored under conditions specified in the ~~g~~Guidelines.

RECOMMENDATIONS

8. CCPR is invited to:

i. consider the draft Guidelines for Monitoring the Stability and Purity of Reference Materials and Related Stock Solutions of Pesticides during Prolonged Storage as presented in CRD04 and agreed to advance it to step 5 for adoption by the Commission;

ii. agree for the expansion of scope of the guidelines to cover the mixtures of pesticide standards; and

iii. re-establish the EWG, chaired by India and co-chaired by Singapore and Iran to include the provisions for monitoring the stability and purity of mixed pesticide standard solutions and to refine the relevant sections in the document, and to submit the revised draft Guidelines for consideration at CCPR56.

~~i. consider the proposed guidelines as set out in Appendix I and provide general and specific comments on the document including its readiness for advancement in the Step Procedure, and~~

~~ii. identify key issues or sections in the document that may need further consideration or development in order to progress with the finalization of the guidance document.~~

~~iii. Possible establishment of EWG to address key issues identified in the virtual working group meeting (VWG) i.e. extension of scope to mixture of pesticides~~

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 ~~3~~4)

INTRODUCTION

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 level in the food chain requires 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 pesticide MRLs 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 for performing regular pesticide residue analysis. These problems are magnified for multi-pesticide residue analysis by testing laboratories ~~situated~~ in developing countries as they are required to allocate a large part of their funds for~~to the~~ frequent procurement of expensive RMs. Furthermore, use of RMs is restricted by the expiry dates specified by the RMPs in the reference material document (e.g. ~~either~~ certificate of analysis (CoA) or product information sheet) which provides the value for purity, expiry date and measurement uncertainty of the RMs. Many times, laboratories cannot afford frequent purchase of high-cost RMs for their pesticide residue control work.

3. ~~Furthermore~~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 insurmountable extra work and increased laboratory costs, especially for compounds for which stability is well-understood. Additionally, shipping of RMs by the suppliers to laboratories increase the acquisition time for procurement (few weeks to months), creating hurdles in sustainable pesticide residue control program.

4. There are RMs that remain stable even after the expiry dates stated in the reference material document with no significant change in the purity. Some studies[1,2,3] 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 lack of data on the stability and purity of RMs during prolonged storage and absence of guidance procedures for monitoring prevents their use beyond the expiry dates.

5. This document represents a crucial~~first~~ step towards developing comprehensive harmonized guidance which would enable the laboratories to monitor the stability and purity of the pesticide RMs and their stock solutions during prolonged storage. The document aims to~~would~~ provide guidance to the laboratories to monitor the stability and purity of RMs for their possible use beyond their expiry dates as well as for continued use of stock solutions which retain their stability and purity.

---

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.

SCOPE AND OBJECTIVE

6. The purpose of this document is to furnish a framework which would assist the laboratories in monitoring the stability and purity of individual reference material (RM) of pesticides during prolonged storage and identify expired RMs with continued stability and purity. The general criterion of the proposed new work is to monitor and verify the stability and purity of individual RMs~~/ mixture of standards~~[4] before and after expiration 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 which continue to be valid can be used for the accurate and reliable determination of pesticide residue levels.

7. This document is applicable to reference materials (RMs) of pesticides and their individual stock standard solutions~~/ mixture of standards~~ of known purity specified by a reference material producer (RMP).

8. These guidelines will enable the pesticide residue laboratories to overcome the ~~shortcomings~~ 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 ~~should~~ 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 ~~should~~ shall be maintained, and quantitative measurements that ~~should~~ 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 ~~should~~ shall be conducted in laboratories in compliance with the general criteria for testing laboratories laid down in ISO/IEC 17025:2017, with the scope relevant to the measurement concerned.

11. The RMs ~~should~~ shall be procured from a RMP who is accredited as per ISO 17034 to ensure analytical traceability or from a National Metrology Institute recognized by peers or designated by countries.

12. For ensuring metrological traceability, the analytical balances used shall ~~should~~ be calibrated with weights traceable to the national/international standards.

13. Calibrated class A glassware or appropriate electronic pipettes, traceable to national/international standards, ~~should~~ shall be used for volumetric measurements.

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

15. The equipment used for storage and monitoring of RMs according to the reference material document should ~~must~~ be traceable to national/international standards.

16. In case a laboratory is predicting the shelf-life of an RM, current ISO Guide[5] ~~35:2017~~ may be referred.

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

17. The storage conditions of RMs are specified by RMPs in the reference material documents as these are susceptible to degradation at high temperature and other unfavourable environmental conditions~~factors~~. Environmental conditions (~~humidity and/or~~ temperature and humidity, as appropriate) ~~must~~ shall be recorded, monitored and controlled by the laboratory.

~~[4] If analytical techniques allow for the inclusion of the mixture~~

[5] ISO 33405:2024 -Reference materials — Approaches for characterization and assessment of homogeneity and stability

18. If a laboratory maintains the RMs at storage conditions which are better 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 a RM by a date allowing for storage up to 10 years or as long as the purity mentioned in the reference material document holds good (≤ ±10%) (SANTE[6], 2024). Another study revealed the stability of pesticide reference standard up to 15 years or in stock solution up to 10 years[1,2].

19. To avoid any cross contamination or degradation of RMs, the vials can ~~could~~ be placed in 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. Storage conditions shall ~~should~~ be monitored with appropriately calibrated equipment and ~~should~~ shall be 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

20. Two analytical approaches may be considered for monitoring the stability and purity of RMs and their stock solutions and for extending their use beyond the expiry date provided their purity ~~of RM~~ is proven to be acceptable.

21. In Approach 1, the stability of new (or unexpired) and old (or expired) RMs~~/ new and old (or expired)old stock solutions/new and old mixtures of pesticides~~ is determined simultaneously, and it is applicable for neat standards and their related stock solutions ~~and mixtures~~. The comparisons of peak area or concentration ~~should~~ shall be run under repeatab~~ili~~le~~ility~~ conditions, and mitigate other sources of variation in instrument response, such as use of internal standard, if applicable. If the deviation (in peak area/purity) after expiration is found 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 purity remains acceptable[1,2,7]. Here new (or unexpired) RM would be required for the comparison purpose.

22. As per Approach 2, whenever a new (or unexpired) ~~fresh~~ 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 internal standard ~~can~~ is to be used to account for any change in the response of the equipment. This approach is applicable only for the neat RMs accompanied by reference material document.

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

23. Prepare fresh stock solution of the old (or expired) and ~~newly acquired RM~~ new (or unexpired) RM standard of appropriate concentration. Appropriate concentration will depend on the response of the RM in the detector. Generally, for HPLC-DAD/GC-FID, good response is obtained between 10 mg L^{-1} to 100 mg L^{-1}. ~~while~~ F~~f~~or single quadrupole GC-MS or /LC-MS, 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. ~~a good response is obtained between 1 to 5 mg L^{-1}. Higher concentration of the RM may lead to saturation of the detector.~~

6 SANTE/11312/2021 V2, Implemented by 01/01/ 2024, European Commission Directorate General for Health and Food Safety.
7 EURL DataPool, https://www.eurl-pesticides-datapool.eu/

24. ~~Inject~~ Analyse the standard solution of the old (or expired) and new (or unexpired) RM prepared from the stock solution at an appropriate concentration ~~into~~ on appropriate~~the~~ instrument (HPLC[8]-DAD[9], ~~/~~HPLC-UV[10], ~~/~~GC[11]-FID[12], ~~/~~LC[13]-MS[14] or GC-MS, LC-MS/MS, ~~or~~ GC-MS/MS~~,~~ or ~~-~~qNMR[15]) and record the peak area. ~~Perform a minimum of five replicate measurements to obtain an acceptable level of variation (% RSD ≤ 10%).~~ An internal standard may be used to reduce measurement variation. Two methods described below can be employed. ~~The mean value of the peak area for the new stock solution is taken to be 100% and is also used as a basis for the calculation of the percentage difference.~~

25. Method 1 (Peak Area Comparison): Inject standard solutions of the old (expired) and new (unexpired) ~~standard solution~~ RMs prepared from the stock solution at ~~the~~ approximately the same ~~same~~ concentration ~~as the new RM~~ into the instrument and record the peak area. It is recommended that the injection sequence of the five replicates of new (or unexpired) and old (or expired) standards should be randomized to minimize the drifting of signal response in the course of measurement. ~~Perform a minimum of five replicate measurements to Calculate~~~~obtain~~ the ~~a~~ 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%.~~standard with %RSD ≤ 10%, preferably < 5%~~.

26. Method 2 (Peak Area Ratio Comparison): Spike a different RM (unexpired) as an internal standard into the standard solutions of the old (or expired) and new (or unexpired) RMs. Inject the solutions and record the peak area of the RM and the internal standard, and perform a minimum of five replicate measurements and calculate the average ratio of RM area to internal standard area for the old and new RMs with %RSD ≤ 10%. The internal standard peak should have a similar abundance to the RM being verified and it should not interfere with the analysis of the target RM in either retention time or molecular weight (m/z).

27. ~~It is recommended that the injection sequence of the five replicate new and old standards should be randomized to minimize the drifting of signal response.~~ If the means from at least five replicate measurements for each of two standard solutions ~~(old~~ old (or expired) and new (or unexpired) ~~do not differ by more~~show deviation of no more than ~~≤than ±~~ 10%, the old (or expired) standard may be considered suitable for continuing use. The mean value from the new (or unexpired) solution is taken to be 100% and is also used as a basis for the calculation of the percentage-difference.

28. The ~~-~~% deviation can be calculated using the formula:

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

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

30. To monitor the stability of the RM over time, a plot of the measured purity/concentration vs time of monitoring may be made which would help ~~in~~ identify~~ing~~ the deviation in stability of RM with time.

31. To ensure the validity of the above-described stability and purity testing protocols, t~~T~~he gravimetric records shall ~~should~~ 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 ~~be allowed to~~ attain room temperature/ambient temperature and be wiped to remove any adhering moisture. The exposure of RM and stock solutions to ambient~~high~~ temperatures and light must ~~should~~ be kept as short as absolutely necessary.

---

8 High-performance liquid chromatography
9 Diode-Array Detection
10 Ultra-violet spectroscopy
11 Gas chromatography
12 Flame ionization Detector
13 Liquid Chromatography
14 Mass Spectrometry
15 Quantitative Nuclear Magnetic Resonance

32. The ~~daily~~ 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 ~~should~~ be maintained. Also, the temperature at which the RMs and their stock solutions are opened for use shall ~~should~~ be recorded.

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

33. To verify the purity of the RM, chromatographic assay shall ~~should~~ be performed preferably as per the analytical conditions mentioned in the reference material document by the RMP. The verification of RM purity is performed by considering the purity (in terms of percent peak area) mentioned in the reference material document as the reference value.

34. Prepare fresh stock solution of the new (or unexpired)~~ly acquired~~ neat standards of RMs and internal standard (a different unexpired RM) of appropriate concentration in a suitable ~~organic~~ solvent. For appropriate concentration which will depend on the response of the RM in the detector, paragraph 22 of Approach I may be referred. ~~to section -will depend on the response of the RM in the detector.-Appropriate concentration will depend on the response of the RM in the detector. Generally, for HPLC-DAD/GC-FID, good response is obtained between 10 mg L^{-1} to 100 mg L^{-1} while for GC/LC-MS, a good response is obtained between 1 to 5 mg L^{-1}. Higher concentration of the RM may lead to saturation of the detector.~~

35. The standard solution of the RM prepared at an appropriate concentration from the stock solution is ~~is injected into~~analysed by the instrument (HPLC-DAD, ~~/~~HPLC-UV, ~~/~~GC-FID,~~/~~ LC-MS, ~~or~~ GC-MS in full scan mode, or qNMR) as per the analytical conditions mentioned in the reference material document and the percent peak area so obtained 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~~impurities~~ that may be present. A minimum of five replicate measurements ~~should~~ shall be performed to obtain a mean value of percent purity and the %RSD of the replicates should be ≤ 10%~~, preferably < 5%~~. The instrument ~~should~~ shall be calibrated as per the conditions recommended by the manufacturer.

36. Compare the mean value of verified purity obtained from the laboratory analysis with the reference value of purity provided in the reference material document. The % purity mentioned in the reference material document is considered as the purity reference value while calculating % deviation in purity.

37. Spike a different RM (unexpired) as an internal standard into the standard solution of the RM. Inject the solution and record the peak area of the RM and the internal standard, and calculate the average ratio of RM area to internal standard area. The internal standard peak should have a similar abundance to the RM being verified and it should not interfere with the analysis of the target RM in either retention time or molecular weight (m/z).

38. Repeat the same procedure at regular intervals of at least once a ~~e~~ year using a new stock solution of the RM, particularly before and after expiry of the RM to monitor its stability and purity during prolonged storage.

39. After 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 % (% deviation of less than or equal to 10%) and 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. ~~The mean value from the reference value is taken to be 100 % and is used as a basis for the calculation of the percentage difference.~~

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

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

41. To ensure the validity of the above-described stability and purity testing protocols, ~~T~~he gravimetric records shall ~~should~~ be maintained for RMs (opened or unopened), both solid and liquid during storage before and after use. Before recording the weight, the container must ~~should be allowed to~~ attain room temperature/ambient temperature and be wiped to remove any adhering moisture. The exposure of RM and stock solutions to ~~high~~ room temperatures and light must ~~should~~ be kept as short as absolutely necessary.

42. The ~~daily~~ record of the storage conditions (e.g., temperature and humidity) as well as the date of use of the RMs shall ~~should~~ be maintained. Also, the temperature at which the RMs are opened for use shall ~~should~~ be recorded.

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: ~~(CXG90)~~A chemical added at a known amount to samples and/or standards in a 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. ~~An internal standard (IS) is a chemical compound added to the sample test portion or sample extract in a known quantity at a specified stage of the analysis, in order to check the correct execution of (part of) the analytical method. The IS should be chemically stable and/or typically show the same behaviour as of the target analyte.~~

~~**Multi-class Pesticides**: Multi-class pesticides include insecticides, fungicides, bactericides, nematicides, herbicides, etc. belonging to different chemical groups.~~

Reference Material Document~~**Product Information Sheet or Certificate of Analysis (CoA)**~~: A document that provides the relevant information about certified purity, concentration, date of expiry, and measurement uncertainty of an RM which in compliance with the requirement in the ISO 17034 and ISO Guide 31. Reference material document can be in the form of 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. The purity is typically expressed in percentage 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 Document**: Document containing all the information that is essential for using any RM~~

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): ~~Also called coefficient of variation, l~~It is expressed as sample standard deviation divided by the sample mean.

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: Chemical solution which 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~~reagent~~, of high concentration, from which appropriate dilutions can be made at the time of use.