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CODEX COMMITTEE ON PESTICIDE RESIDUES

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DISCUSSION PAPER ON MONITORING THE PURITY AND STABILITY OF CERTIFIED REFERENCE MATERIAL OF MULTI-CLASS PESTICIDES DURING PROLONGED STORAGE

(Prepared by Argentina and India)

Background

1. CCPR51 (2019) considered a request related to the shelf-life of reference materials raised by some delegations that certified reference material (CRM) were used for many purposes e.g. good agricultural practice (GAP) supervised field trial data, monitoring of import/export samples etc. Noting the limitation of the use of the CRM after the expiry date which led to recurring high costs for laboratories, consideration should be given to including guidance on monitoring of purity and stability of CRM of multi-class pesticides during prolonged storage. CCPR51 noted that the issue of CRM was important and should be further considered at its next Session.

2. CCPR51 further agreed to request Argentina and India to prepare a discussion paper regarding monitoring of purity and stability of CRM of multi-class pesticides during prolonged storage for consideration at CCPR52.[1]

3. Argentina and India have prepared a discussion paper as contained in the Annex to this document which provides conclusions and recommendations for consideration by CCPR.

Recommendations

4. CCPR is invited to consider the conclusions and recommendations of the discussion paper as provided in the Appendix to this document.

[1] REP19/PR, paras. 182-184, 186

APPENDIX

DISCUSSION PAPER ON GUIDELINES FOR MONITORING THE PURITY AND STABILITY OF CERTIFIED REFERENCE MATERIALS OF PESTICIDES DURING PROLONGED STORAGE

Background

0. Following discussion at the 51st Session of the Committee on Pesticide Residues (CCPR51 – April 2019), the Committee agreed to the preparation of a discussion paper on monitoring the purity and stability of certified reference materials (CRM) of multi-class pesticides during prolonged storage for consideration at CCPR 52 in 2020.

1. The Committee noted that 'purity and stability of the CRM of multiclass pesticides' may or may not remain the same during and after prolonged storage up to 10-15 years. Since this new area lacked internationally harmonized guidelines and in view of their increasing use globally in analytical laboratories, it merited an elaborative discussion among the stakeholders on effective and sustainable use of CRMs for reliable analysis of pesticide residues in food and related matrices and to ensure food and the environment safety.

2. Based on the information received from different experts, and stakeholders, Argentina and India prepared the current discussion paper for consideration of CCPR52.

3. The discussion paper has been drafted based on various ISO Guides/EURACHEM.CITAC Guide/SANTE guidance documents and other literature reports on CRMs.

Objective

4. To develop a discussion paper on 'Monitoring the Purity and Stability of CRMs of Pesticides during Prolonged Storage' for the harmonization of concepts and criteria for the recognition of the expired/expiring CRMs with valid purity and stability for continuance of their use in analysis of multi-class pesticides, and pesticide residues in different food commodities and the environment (soil, air, water) samples. Thus use of expired RMs/CRMs with duly certified values of purity and stability as mentioned in CoA, in the measurement systems will not only ensure continuity of their use in the laboratories but also have economic impact by saving the purchasing cost of fresh CRMs.

Relevance for the strategic objectives of Codex

5. The discussion paper is in consonance with the scope of the Codex Committee on Pesticide Residues (CCPR) mandate of considering new proposals and discussion papers justifying the significance of the new discussion papers.

Introduction

6. Pesticide residues in food commodities have become a worldwide agricultural trade-concern which has led to enforcement of strict pesticide regulations. Analyses of multi-class pesticides in the food chain with reliable measurement and accuracy require CRMs of known chemical purity and stability to ensure food safety, food quality and the safe environment (Reenie, 2015). The reference materials (RMs) are prepared by chemical synthesis and purified through various chromatographic and spectroscopic procedures, elemental analysis, and X–ray structure analysis, among others.

7. A CRM is a specific class of RM whose property values (purity, concentration, etc) are established and certified in accordance with metrological principles using international best practice protocols established as per ISO Guidelines.

8. CRMs are certified before bottling and packaging by a metrologically valid procedure for one or more specified properties, associated uncertainty, and a statement of metrological traceability. After certification, the RM is referred to as CRM.

9. Unlike the RM, the CRM has metrological traceability and is accompanied by a certificate, which documents the property values and the uncertainty, issued by the reference material producer (RMP) in accordance with international standards and best practice protocols (ISO 17034 (2016) and ISO Guides 30 (2015), 31 (2015), 33 (2015) and 35 (2017). ISO Guide 17034 (2016) outlines the general requirements to be met by an RMP to demonstrate its competence. The certification is carried out in accordance with the requirements of ISO Guides which are published by ISO REMCO (Reference Material Committee of the International Standardization Organization) to produce and certify RMs. ISO Guide 34:2009 defines RM as material that is sufficiently homogenous and stable with respect to one or more specified properties, and which has been established to be fit for its intended use in a measurement process [ISO Guide 35:2017; ISO Guide 30:2015].

10. CRMs are required for purity assessment and accurate qualitative and quantitative analysis (trueness and/or precision) of pesticide active ingredient(s) in technical materials and formulations, stock solutions, working solutions, and for the analysis of pesticide residues in food commodities and the environmental samples.

11. Commercial suppliers of pesticide standards sell CRM standards with 2-3-5 years short-term expiry dates, though there is no requirement to find maximum shelf life. This forces laboratories to buy new standards and prepare new stock solutions more frequently than strictly necessary. This leads to: insurmountable extra work, especially for compounds for which stability is normally not questionable; increased laboratory costs; and impeded implementation of Codex standards and guidelines.

12. It has been observed that several stable CRMs even after expiry continue to retain their valid purity as per Certificate of Analysis (CoA) and therefore entitled for continuous use as CRMs up to 3 years after expiration.

13. Additionally, shipping by the suppliers (most of the them for example TRC, NMI, Sigma, LGC, UPS are from Europe, Canada, Australia and USA) to laboratories in developing countries increase too much the acquisition (cost and time) of references materials required to perform a sustainable pesticide residue control program. Many times, laboratories get material close to the expiration date. Sometimes the availability of references materials from thesuppliers are limited.

Purity and stability of CRMs during prolonged storage

14. High purity CRMs are indispensable to the accuracy and reliability of the analysis (Guimarães et al., 2014). Accuracy of data is reliant on accuracy in sample preparation, of calibrators used, as well as the method of analysis (Rettinger et al., 2010). Inadequacies during preparation, packaging, storage, as well as cross-contamination during improper handling of RM/CRM may affect accuracy of concentration, stability, and uncertainty in the overall process of establishing CRM purity during short– and long–term storage (Rettinger et al., 2010).

15. CRMs are utilized in the calibration and assessment of a measurement system and procedure, that includes method development, validation, quality control and assurance, root-cause analysis, assignment of values to specified properties, proficiency testing (PT), inter-laboratory comparison, and metrological traceability (ISO Guide 35, 2017).

16. As a result of the impact of temperature, light, oxygen, humidity etc, the CRMs are liable to degradation during prolonged shipping and storage during transit. Effective storage methods are thus needed to ensure the stability and purity of CRMs within and beyond their expiry date.

17. Since CRMs are susceptible to degradation by temperature, light, oxygen, humidity etc., it is therefore necessary to investigate their short– and long–term stability and purity under controlled storage conditions (Lamberty et al., 1998). Particularly for the expired CRMs, it is pre–requisite to re–certify/re–verify its purity and stability for subsequent use to achieve reliable analytical results.

18. Short– and long–term stability studies of the CRM include different storage conditions of temperature and time (ISO Guide 35, 2017). For long-term (isochronous) stability studies, the CRMs are stored in a deep freezer at sub–zero temperature (≤ –20 °C) for a period of 2 or more years (WHO, 2006 a,b; Tahlan et al., 2005) and analysed initially at the time of procurement and thereafter proposed monitoring at regular intervals until expiration and 3-5 years after expiration.

19. Studies conducted in different laboratories indicated that when CRMs were stored at sub–zero temperature for longer period, most of the CRMs remained optimally stable up to 15 years with respect to their observed purity (WHO, 2006 a,b; Tahlan et al., 2005). This is because at sub–zero temperature, the adverse effects of thermal degradation, photo-degradation, oxygen, humidity, transpiration, etc. are minimized thereby prolonging the shelf life of the CRMs.

20. The purity of CRMs whose validity had expired as per CoA should be compared with the purity of the freshly procured valid CRMs by HPLC/GC/LC-MS/GC-MS in terms of retention time (RT in minutes), peak area at the respective UV maxima and the characteristic mass fragment ion peaks. If its purity level after re-verification in the ISO accredited lab is found within the limits prescribed in the certificate of analysis, it implies that the analyte level(s) in the CRM are unchanged and therefore should be considered for continued use as CRMs.

21. According to international guidelines, if a laboratory maintains the CRM at storage conditions better than those recommended by the manufacturer (i.e. temperature lower than recommended without exposure to light and moisture), the rate of degradation of the CRM is significantly minimized. Under such conditions, the expiry date as recommended by the RMPs may be extended as appropriate for a CRM by a date allowing for storage up to 10 years or as long as certified property values mentioned in CoA hold good (≤ ±10%) (SANTE, 2017).

Inter-laboratory comparison and verification of purity by participation in the PT programme

22. An inter–laboratory comparison and re–verification of purity may be conducted in different ISO/IEC 17025 accredited laboratories at different places, at different times, by different people, and using different equipment (Armishaw, 2016) to verify the % purity of the expired and valid CRMs in different laboratories.

23. International and national PT programmes may be conducted by the international PT sample providers which are accredited with ISO/IEC 17025 (2005) quality system and are competent under the terms of ISO/IEC 17043 (2010) to carry out PT programmes in different food commodities.

24. Purity and stability of the valid and expired CRMs can be verified through z–scores acquired in the international and national PT programmes conducted by the international PT sample providers in ISO/IEC 17025 accredited laboratories competent under the terms of ISO/IEC 17043 (2010). Use of z–scores obtained through PT programme is a globally accepted procedure to verify the % purity and validity of the expired CRMs, and for demonstrating quality of results (Thompson, 2016; ISO 13528, 2015).

25. The criteria of z–score has been successfully utilized by US FDA in one of its exercises to re–verify non–certified RMs including expired RMs/CRMs of elements. According to US FDA, if z–score obtained in a PT programme with respect to the targeted analyte is in an acceptable range, then both non–certified RM as well as expired RM/CRM of that analyte is still fit for the purpose (Cunningham and Capar, 2014). A z–score of 2 or less is considered acceptable, a z–score between 2 and 3 is questionable, and beyond 3 is unacceptable (National Measurement Institute, 2016, Thompson, 2016).

Long-term intra-laboratory and inter-laboratory validation experiments conducted at ICAR-IARI, New Delhi, India

26. The long-term intra-lab and inter-lab validation experiments were performed to assess the storage stability of standards and stock solutions of LC-pesticides. Isochronous stability study of 89 CRMs of multi-class pesticides, stored at ≤ –25 °C, conducted at the Pesticide Residue Laboratory (PRL) at ICAR-IARI, New Delhi, India to assess their purity beyond their expiry date revealed that when CRMs were stored in conditions better than those recommended by RMPs for longer period of 3 years, most of the CRMs remained optimally stable with respect to their observed purity and stability (Sharma et. al. 2019).

27. The performance of the valid and expired CRMs was evaluated through 44 z-scores for 15 expired and 29 valid CRMs obtained in 14 international and national PT programmes conducted by the international PT sample providers such as EUPT- European Union Referral Laboratory, Spain; FAPAS- Food Analysis Performance Assessment Scheme, UK; APLAC- Asia Pacific Laboratory Accreditation Cooperation, Australia. Inter–laboratory comparison of 6 randomly selected expired and valid CRMs was tested by liquid chromatography-mass spectroscopy (LC-MS/MS) at three different ISO 17025 accredited laboratories and the average % deviation between % purity ranged from –2.35 to +0.95 %.

28. During 2013–2017, more than 96 % of the CRMs remained optimally stable with respect to their observed purity even after their expiry date as per certificate of analysis (CoA). Percentage deviations in purity of expired and valid CRMs posited well below 7 % and were in acceptable range (≤ ±10%) as recommended by the SANTE.

29. It was concluded that by harmonization and maintaining proper storage conditions and regular monitoring of % purity before and after their expiry, the expired CRMs retain their purity levels prescribed in their CoA. Such expired CRMs can continue to be used as valid CRMs by the laboratories as standard reference materials for testing, calibration, method validation, quality control, quality assurance, and other applications of measurements.

The long-term intra-laboratory and inter-laboratory validation experiments conducted at NVWA laboratory, Amsterdam, the Netherlands

30. Dorweiler et al (2016) conducted simulated accelerated aging study of multicomponent CRM mixes of 528 pesticides and their metabolites/ degradation products in solution phase at stressed temperature of 50 °C, and the samples analyzed at 0, 1.5, 3, and 6- day time period which simulated 0, 6, 12 and 24 months storage time. Study indicated that 65% of the CRMs remained stable up to 24 months, 19% exhibited borderline stability, and about 16% were significantly unstable. Thus, even in the solution phase, most of the CRMs retained their stability up to 24 months.

31. The long-term intra-laboratory and inter-laboratory validation experiments were performed at the NVWA laboratory, Amsterdam, the Netherlands to assess the storage stability of standards and stock solutions of LC-pesticides (André de Kok et. al. PO 006 pdf). The stability of CRM standards was assessed by continuously measuring old against new stock and calibration-mixture solutions, on a long-term basis.

32. The study revealed that the stability of the pesticide reference standards is up to 15 years, and in stock solutions (in toluene or MeOH), at -18°C, is up to 10 years. Based on these experiments, it is reasonable to assume that reference standards of pesticides in stock solutions, which are proven to be stable for at least 2 years, are also stable for at least 10 years if stored under appropriate conditions.

Conclusions

33. The above mentioned studies conducted in India and the Netherlands conclude that the pesticide residue laboratories may continue to use the expired RM/CRMs as valid RM/EncourageCRMs even after their expiry date provided that after re–verification or re–certification, the purity level is found within the limits prescribed in the CoA, or within the values recommended by the CRM manufacturer. It was further recommended that accreditation bodies of different countries should accept the transferability of stability data from one laboratory to another, provided that each laboratory ensures the exact storage conditions through temperature logging and traceability.

Recommendations for consideration by CCPR

34. CCPR52 may consider the following recommendation:

1.To establish an electronic working group to further develop the discussion paper on the use of reference material, such as harmonization of concepts and criteria, for consideration by the next session of CCPR.

2. Encourage technical exchange of information between countries, especially developing countries, through work in this EWG.

Annex

DEFINITIONS (More definitions can be added)

Pesticide

Pesticide means any substance intended for preventing, destroying, attracting, repelling, or controlling any pest including unwanted species of plants or animal during the production, storage, transport, distribution and processing of food, agricultural commodities, or animal feeds or which may be administered to animals for the control of ectoparasites. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant, fruit thinning agent, or sprouting inhibitor and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport. They include, inter alia, insecticides, fungicides, herbicides, acaricides, growth regulators, pheromones, semiochemicals and repellents.

Biochemical pesticides

Biochemical pesticides include substances that interfere with mating, such as insect sex pheromones, as well as semiochemicals that influence insect behavior such as attracting, repelling, and aggregating. In addition, plant extracts, oils and minerals can also manage pests, and are naturally occurring substances that control pests by indirect, or non-toxic mechanisms. Conventional pesticides, by contrast, are generally synthetic materials that directly kill or inactivate the pest.

Pesticide active ingredient

The bioactive component of the pesticide product (technical material or formulation) that provides the pesticide action.

Pest

Any species, strain or biotype of plant, animal or pathogenic agent injurious to plants or plant products.

Pesticide Residue

Pesticide Residue means any specified substance in food, agricultural commodities, or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products, and impurities considered to be of toxicological significance.

Reference Material

Reference material (RM) is a primary material which is sufficiently homogenous and stable with respect to one or more specified properties, and which has been established to be fit for its intended use in a measurement process

Certified Reference Material

A certified reference material (CRM) is a specific class of RM whose property values (purity, concentration etc) are established and certified in accordance with metrological principles using international best practice protocols established as per ISO Guidelines.

Reference Material Producer (RMP)

Company, organization or the agency that produces certified reference materials as per ISO Guide 34:2009 which specifies general requirements in accordance with which a reference material producer has to demonstrate that it operates

Proficiency Testing

Proficiency Testing is inter-laboratory comparison that enables labs to monitor the quality of their analytical results. It determines the performance of individual laboratories for specific tests or measurements, and is used to evaluate laboratories' continuing performance. An unknown sample(s) is received and analyzed by the laboratory, the lab results are returned to the PT provider, a statistical analysis of the all labs' results is performed, and the individual laboratory receives data on their performance compared to all other laboratories.

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