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Proficiency testing as a tool to assess quality of data: the experience of the EU Reference Laboratory for chemical elements in food of animal origin

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Abstract: Quality and reliability of analytical results are, in general, key issues for all laboratories but become a top priority for laboratories accredited according to ISO/IEC 17025:2005. In this international standard the proficiency testing (PT) is regarded as a means to assure the validity of results. Nowadays, the proved competence of laboratories is an essential requirement especially for that structures that are involved in the official controls aimed at ensuring the safety of EU food products and the public health. To guarantee the EU consumers, the Council and the Commission have designated 28 European Union Reference Laboratories (EURLs) for food and feed, whose main role is to contribute to the standardization of analytical methods and to the harmonization of performance among the EU National Reference Laboratories (NRLs) to reach a comparable level of quality in the analytical data among all Member States. With this aim, the organization of PTs is a task that each EURL has to accomplish. Over the last 15 years, the EURL for chemical elements in food of animal origin (EURL-CEFAO) have organized 32 PTs on determination of total As, Cd, Pb and total Hg in meat, milk, fish and offal for the benefit of its network of NRLs. Some specific aspects of this activity will be discussed (e.g. preparation and characterization of PT materials, statistical evaluation of data, follow-up actions). Finally, based on the EURL-CEFAO experience, it will be demonstrated that the participation into PTs on a regular basis can result in an improvement of the laboratory's performance as well as in the harmonization of the results submitted by participants.

Keywords: chemical elements; Eurasia 2018; European Union Reference Laboratory; interlaboratory comparisons; maximum level; proficiency testing.

Introduction

Nowadays, the concept of quality is increasingly widespread in the most varied analytical fields (e.g. chemical, clinical, microbiological analyses) [1–6]. As a consequence, laboratories have to put in place different strategies to ensure the quality and reliability of their results in order to be competitive in the eyes of potential customers. In this perspective, an increasing number of laboratories choose to accredit their methods in compliance with specific international standards. In particular, accreditation according to ISO/IEC 17025 [7] can be considered essential to ensure the competence of testing and calibration laboratories. Within this

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standard, great importance is given to the participation of accredited organizations in interlaboratory comparisons (ILCs) on regular basis. An ILC consists in “organization, performance and evaluation of measurements or tests on the same or similar items by two or more laboratories in accordance with predetermined conditions”. Proficiency testings (PTs) are one of the best way of assessing the quality of results as they are based on the evaluation of participant performance against pre-established criteria by means of ILCs. Therefore, each laboratory can compare its results with those from other participants thus having an objective and independent assessment of the quality of its analyses. In fact, especially in medical area, PTs are regarded as an external quality assessment (EQA) scheme since laboratories can externally validate measurement or testing process. As a result, the demand of specific schemes has increased over the last years, though the supply has not increased accordingly in all fields.

This is such a hot topic that a specific international standard (ISO/IEC 17043:2010) has been issued with the aim of stating the general requirements for the competence of PT providers (PTPs) and for the conduction of the scheme [8].

Over the last years, many organizations have focused their activity on the development of PT schemes but, although most followed international standards, only a few of them were accredited as PT providers.

The new revision of ISO/IEC 17025 specifically refers to ISO 17043 accreditation for the suppliers of interlaboratory comparisons. Therefore, the afore mentioned picture is changing as the number of PT providers applying for this specific accreditation is raising so as to be competitive by offering the laboratories schemes that can be better considered by the Accreditation Bodies.

Determination of chemical elements in food is an example where the availability of commercial PTs is quite inadequate to meet the demand. This kind of analytes/matrices combination is of particular interest as the main route of human exposure to this chemicals is through the food chain [9–15]. That is the reason of their inclusion in the EU official controls aimed at guaranteeing the safety of foodstuffs. In fact, protection of public health is the goal of all EU laws and regulations in the sectors of agriculture, animal husbandry and food production sectors. A large body of rules at EU level governs the entire food production and processing chain within the European Union, but also imported and exported goods [16, 17]. EU countries implement these harmonized standards and establish controls to enforce them. The task of ensuring the effectiveness of the control systems is delegated to the Directorate General for Health and Food Safety (DG SANTE) that is responsible for EU food safety and health policy and for monitoring the implementation of legislation in this sector.

The EU control network is organized like a pyramid at the top of which there are the EURLs, at the base there are the official laboratories (OLs) and in the middle there are the National Reference Laboratories (NRLs). Official laboratories are laboratories designated by the competent authority of a Member State (MS), responsible for organizing official controls, to perform analysis, tests or diagnosis of samples that have been taken for official control purposes. Furthermore, each MS appoints one or more NRLs to collaborate with the respective EURL and to coordinate and support the activities of OLs by organizing and planning experimental technical activities (methods of analysis, organization, implementation of PT activities) and training. Finally, the EURLs ensure that NRLs and OLs have up-to-date information on available methods, organize PTs, perform follow-up activities and offer training courses for NRLs.

This complex pyramidal organization has the ultimate aim of harmonizing activities and performances between the different MSs of the European Union to better guarantee public health and food safety in each country.

This manuscript deals with the activity (period 2004–2018) of the EURL for Chemical Elements in Food of Animal Origin (EURL-CEFAO) that, in compliance with its duties, has focused on the activity of PTP to cover this particular area and to fill the gap caused by the scare availability of this kind of exercises.

The EURL-CEFAO scheme was intended for those EU National Reference Laboratories (NRLs) appointed as outstanding laboratories in their respective EU Member States.

Compliance with international standards, accreditation of the PT scheme, experience of PTP in the organization of inter-laboratory comparisons, high level of technical competence of the organizer and reliability of the assigned values are the prominent requirements for a well-qualified scheme. In order to provide participants with PTs which are highly valued by accreditation bodies, the EURL-CEFAO has been accredited as PTP since 2009 (according to ISO Guide 43-1 and ISO/IEC 17043:2010), though exercises have been organized by the laboratory since 2006. Over time, the EURL-CEFAO has developed and optimized a number of internal procedures with the view to produce adequate PT test items with the matrices of interest (milk, meat, fish, offal, honey, infant formula) in different forms (liquid, frozen and freeze-dried). So it has gained a great experience in the evaluation of the materials adequacy for PT purposes (i.e. stability, homogeneity) as well as in the statistical analysis of the results. The scheme is also conceived to monitor the long-term performance of participants by periodical repetition of the same matrix/analytes combination. This general strategy has continuously improved the laboratories participating in the exercises in terms of performance and harmonization of results. In fact, though the success/failure of the participants is evaluated by a more restrictive criterion than the one commonly used in the food sector, the percentage of satisfactory results has increased over the PTs.

Likewise, the results submitted by participants have reached a good level of agreement, the parameters related to data dispersion becoming more and more narrow. Last but not least, the use of control charts for z-scores allowed most laboratories to monitor their ability to produce reliable results and reach a steady performance.

Proficiency testing scheme of the EU reference laboratory for chemical elements in food of animal origin

Rationale

Participation in PTs organized by the EURLs is mandatory for laboratories that are designated as a reference in each Member State of the EU. As part of this institutional task, the EURL-CEFAO organized 30 exercises in the period 2006–2018 (Table 1). They were primarily planned as a long-term program to promote harmonization of performance within the network of the NRLs. In particular, the objectives pursued were the following:

- monitor and improve the performance of their analytical methods;
- verify the effectiveness of the corrective actions taken (when necessary) by repeating the same matrix;
- provide long-term follow-up of their performance;
- promote the improvement of the quality control system

The PTs were focused on chemical elements and foods for which a maximum level (ML) is set in relevant regulations [18–22] but, starting from 2012, new combinations of analytes/matrix were considered as well. These combinations were selected on the basis of information received from the European Commission (e.g. discussion on the introduction of new limits in relevant regulations; emerging topics) as well as following specific demands from the NRLs.

Thirty PTs were conducted as of 2006 following the procedure schematized in Fig. 1: production and characterization of materials were carried out by the EURL staff as well as the statistical evaluation of results (including the evaluation of participants' performance and issuing of reports).

After an adequate planning, the management of a PT was articulated in some fundamental steps: preparation of PT material; evaluation of its adequacy; statistical evaluation of the participants' results; assessment of the participants' performance.

Production of material and assessment of its suitability for PT

Over the years the EURL-CEFAO produced about 4000 PT test items based on different kinds of matrices [23–25]. Therefore, proper procedures were developed and optimized in order to produce materials adequate for PTs purposes and in a physical form as similar as possible to the samples analyzed by laboratories during

Table 1: Scheme of the PTs conducted by the EURL-CEFAO from 2005 to 2018.

Year	PT code	Matrix	Chemical elements	Physical form
2005	9th PT	Fish	As, Cd, Cr, Cu, Fe, Hg, Pb, Zn	Freeze-dried
2006	10th PT-1A/1B	Meat	As, Cd, Pb	Freeze-dried
	10th PT-2	Milk	As, Cd, Pb	Freeze-dried
2007	11th PT-1	Milk	As, Cd, Pb	Liquid
	11th PT-2	Meat	As, Cd, Pb	Freeze-dried
	11th PT-3	Fish	As, Cd, Pb, Hg	Freeze-dried
2008	12th PT-1	Milk	As, Cd, Pb	Liquid
	12th PT-2	Liver	As, Cd, Pb	Freeze-dried
	12th PT-3	Meat	As, Cd, Pb	Freeze-dried
2009	13th PT-1	Milk	As, Cd, Pb	Liquid
	13th PT-2	Fish	As, Cd, Pb, Hg	Freeze-dried
2010	14th PT-1	Meat	As, Cd, Pb, Hg	Frozen
	14th PT-2	Milk	As, Cd, Pb	Liquid
	14th PT-3	Fish	As, Cd, Pb, Hg	Frozen
2011	15th PT-1	Liver	As, Cd, Pb	Frozen
	15th PT-2	Meat	As, Cd, Pb	Freeze-dried
2012	16th PT	Milk	As, Cd, Pb	Liquid
	17th PT	Infant formula	Cd, Pb	Powdered
2013	18th PT	Meat	Cd, Pb, Hg	Frozen
	19th PT	Honey	Cd, Pb	Liquid
2014	20th PT	Kidney	Cd, Pb, Hg, Cu	Frozen
	21st PT	Mussels	As, Cd, Pb, Hg	Freeze-dried
2015	22nd PT	Infant formula	Cd, Pb, Mo	Powdered
	23rd PT	Fish	As, Cd, Pb, Hg	Freeze-dried
2016	24th PT	Honey	Cd, Pb	Liquid
	25th PT	Milk	As, Cd, Pb	Liquid
2017	26th PT	Meat	Cd, Pb, Cu, Hg	Freeze-dried
	27th PT-PIF	Infant formula	As, Cd, Pb, Ni	Powdered
	27th PT-LIF	Infant formula	As, Cd, Pb, Ni	Liquid
2018	28th PT	Mussels	Cd, Pb, Ni, As, Hg	Frozen
	29th PT	Processed meat	Ca, Cd, Pb, Sn, Hg	Frozen

For the 10th PT-1 on meat (year 2006) two levels of concentration were proposed (level A and level B).

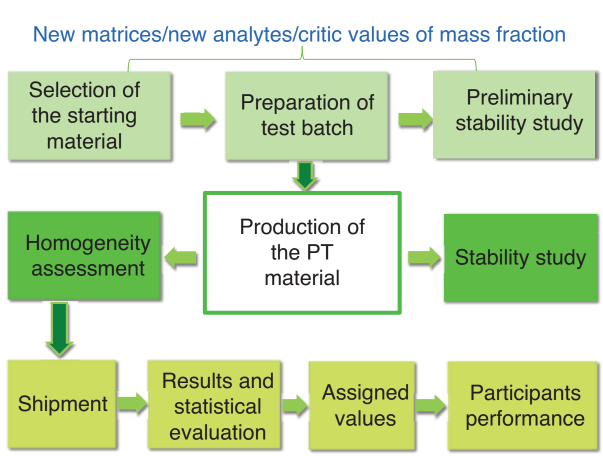

Fig. 1: Scheme of the approach followed by the EURL-CEFAO to conduct PTs.

their routine work. Liquid samples (e.g. milk), partially liquid samples (e.g. honey), freeze-dried material (e.g. meat, fish, offal, milk) and frozen samples (e.g. meat, fish, offal) were prepared as PT test items. The analytes concentration was often adjusted around MLs or other values of interest. This adjustment was performed either spiking the starting material, purchased at retail stores, with standard solutions of chemical elements or diluting it with a suitable similar matrix. The former was used if the basal content of analytes was lower than the concentration value planned for PT, the latter was used if the basal content was greater than the concentration value foreseen in the final material (e.g. mercury in fish).

Freeze-dried samples were periodically included in the exercises so as to supply the NRLs with samples easy to handle and store that they could use for their internal scope as well.

Once PT test items were prepared, their adequacy for PT purpose had to be assessed by testing stability and homogeneity. In particular, stability had to be guaranteed at least for the duration of PT and the level of homogeneity had to be enough to be confident that differences among test items would not significantly affect the evaluation of participants' performance. As for the homogeneity, it was evaluated against restrictive criteria using precise analytical methods making the participant feel more confident about the quality of the samples. In fact, the sufficient homogeneity of the PT material was evaluated following an internal procedure based on the International Harmonized Protocol (IHP). The procedure fixes a criterion on the precision of the analytical method to apply: the criterion to be compliant with is that the ratio between the analytical standard deviation (σ_{an}) and the standard deviation for proficiency assessment (σ_{pt}) has to be lower than 0.5. The fulfillment of this criterion is recommended to avoid that possible differences among the samples (different test items) are covered up by the analytical variability of the analytical method used. Obviously, the lower σ_{pt}, the lower σ_{an} must be to comply with the criterion. As the σ_{pt} used by the EURL-CEFAO is more restrictive than Horwitz (used for PT in food sector), σ_{an} must be low enough. Furthermore, the data collected by the EURL-CEFAO over the years showed that this ratio was usually lower than 0.2 so the methods for evaluating the homogeneity were more precise than methods commonly used by the EURL-CEFAO.

As discussed below, all the assigned values were derived by using the consensus from participants. This approach could lead to a biased value but its reliability could be considered a strength point of the EURL-CEFAO scheme that further assured participants about the value of the scheme. In fact, the laboratories belonging to the network had a high level of competence as they were the outstanding ones of the EU. This aspect combined with the strong analytical background of the experts performing the statistical evaluation of results assured the reliability of the assigned values, which was confirmed by the comparability of assigned values (x_{pt}), values of homogeneity (x_{hom}) test and expected values (x_{exp}). The expected value was the value of concentration calculated taking into account the basal content of analytes in the sample and the known spiking.

In addition, some studies were conducted to derive x_{pt} from a calibration against the reference value of suitable certified reference materials (CRMs). The values assigned using this procedure resulted comparable to the values obtained from consensus, demonstrating the adequacy of the statistical procedure applied to derive the assigned value.

As an example, the expected value (based on the gravimetric spiking), the assigned value, the value from homogeneity test and the value assigned against CRMs are compared in Table 2 for two PTs on milk (14th PT-2 and 16th PT). CRMs used for deriving the assigned value ($x_{pt\text{-}CRM}$) were BCR063R (certified only for Pb) and ERM-BD 150 (certified for both Cd and Pb) for the 14th PT and the 16th PT, respectively.

Table 2: Comparison among expected value (x_{exp}), value from homogeneity test (x_{hom}), assigned value (x_{pt}) and value assigned against CRM ($x_{pt\text{-}CRM}$).

Analyte/PT	x_{exp}	x_{hom}	x_{pt}	$x_{pt\text{-}CRM}$
Cd/14th PT-2	6.00 ± 0.04	6.4 ± 0.6	6.0 ± 0.4	n.e.
Pb/14th PT-2	24.0 ± 0.2	27.0 ± 2.2	25.2 ± 1.0	26.5 ± 2.8
Cd/16th PT	4.98 ± 0.04	4.90 ± 0.43	5.15 ± 0.28	5.3 ± 1.5
Pb/16th PT	27.3 ± 0.3	28.6 ± 2.3	28.0 ± 1.2	31.0 ± 2.0

Each value is reported with the expanded uncertainty (k = 2) and all values are expressed in $\mu g\ kg^{-1}$.

Statistical evaluation of the results

Before starting a PT it is necessary to set the standard deviation for proficiency assessment (σ_{pt}) as well as to define the procedure for deriving the assigned value. These "reference values" are key to evaluating the performance of the participants. Among the possible approaches, the EURL-CEFAO chose the consensus from participants to derive the assigned value and the fitness for purpose to set σ_{pt}. The "consensus" is a commonly used approach but the organizers of PTs should be aware of some disadvantages such as the possibility of assigning a biased value. As for the EURL-CEFAO, the probability that a bias occurred in the assigned value was minimized. Firstly, because the results were considered also from an analytical point of view and rejected a priori in case of doubts about how they were obtained. Secondly, because the possible presence of statistical subpopulations, linked to the analytical techniques used, was thoroughly investigated and adequately evaluated.

The σ_{pt} most commonly used in food sector is derived from Horwitz–Thompson equation (σ_H) that is exclusively based on the concentration value without taking the analyte and/or matrix into consideration. The EURL-CEFAO adopted more restrictive values set according to specific algorithms that were developed taking into account the analyte, the matrix and the level of concentration. This approach was followed because the NRLs were required to perform better than ordinary laboratories. Therefore, the resulting values of σ_{pt} corresponded to the level of performance that the participants in the PT were expected to achieve. Furthermore, these value were also conceived to correspond to low enough values taking into account the expertise and the role of the NRLs. Both x_{pt} and σ_{pt} were usually set by applying robust statistics following a procedure compliant with ISO 13528:2015 [26].

Evaluation of the participants performance

The participant's performance was evaluated as z-score (z_i) that is calculated according to formula (1).

$$z_i = \frac{(x_i - x_{pt})}{\sigma_{pt}} \tag{1}$$

where x_i is the PT result submitted by the participant. The performance was acceptable for $|z| \leq 2.0$, questionable for $2.0 < |z| < 3.0$ or unacceptable for $|z| \geq 3.0$.

The participation of the NRLs to the PTs organized by the EURL-CEFAO and the constant follow-up action led to a general improvement of the network performance as the percentage of laboratories satisfactorily performing increased till to reach a steady good performance for almost all analytes/matrix combinations.

As an example, in Fig. 2 the results of similar exercises organized over the years are reported. The PTs and chemical elements used for comparison were selected in order to compare exercises with a similar difficulty.

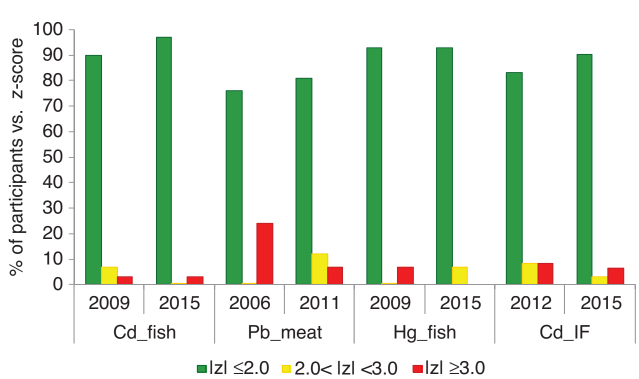

Fig. 2: Comparison of the network performance for Cd, Pb and Hg between PTs on the same matrix and similar values of concentration. The color of the bars represents the performance: green for satisfactory, yellow for questionable and red for unsatisfactory.

Therefore, the same matrix in the same physical form (e.g. freeze-dried bovine meat vs. freeze-dried bovine meat) as well as similar assigned values of chemical elements were compared.

In terms of z-score the percentage of satisfactory results (green) significantly increased, whilst the number of unsatisfactory (red) or questionable (yellow) data decreased.

The EURL-CEFAO used Shewhart control charts as a graphical means to combine performance scores over several PTs [27]. In general terms, this visual presentation is far more explicative than the interpretation of a single numeric score as it allows participants to check their performance over the time and the PTP to monitor the general performance of the network, also pointing out possible crucial points of the exercises. The charts were updated after each PT and distributed to participants so they could promptly evaluate their performances for a specific matrix/analyte combination. An example of this kind of chart, related to PTs on meat, offal, fish and processed food, is reported in Fig. 3. It is evident that the participant has never had problems to analyse arsenic in these matrices whilst its performance for cadmium and lead has been improved over the exercises.

The improvement of the EURL-CEFAO network was not only proved by the increased percentage of satisfactory z-scores but it was also demonstrated by the harmonization of the submitted results. In fact, the indicators of data dispersion calculated by the participants' results, namely standard deviation of the mean (SD) and robust standard deviation (s*), decreased over the PTs confirming that data dispersion became more and more narrow. In particular, since 2010 SD resulted lower than σ_{pt} and close s*. This trend is clarified in Fig. 4 where the following ratio are reported as percentage: SD/x_{pt}, σ_{pt}/x_{pt} and s*/x_{pt}.

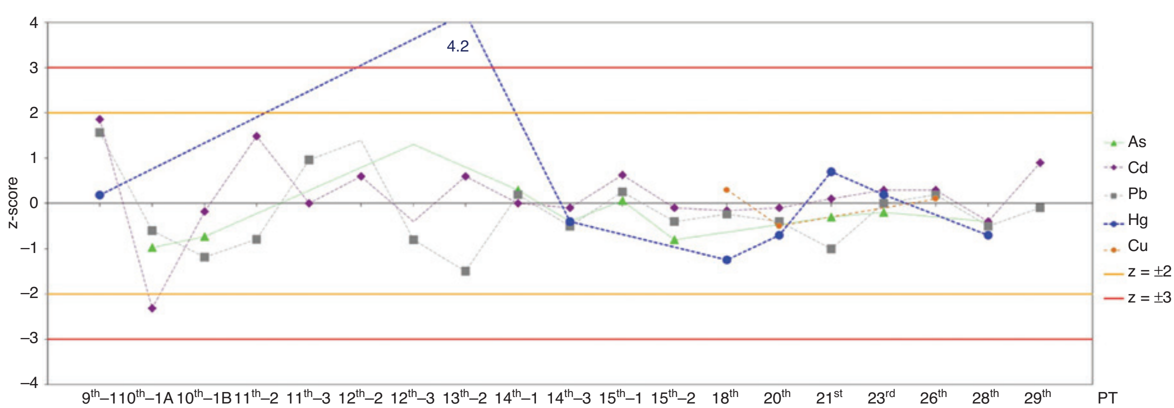

Fig. 3: Shewhart control chart of z-scores for As, Cd, Pb, Hg and Cu in meat, fish and offal from a single participant (period from 2005 to 2018).

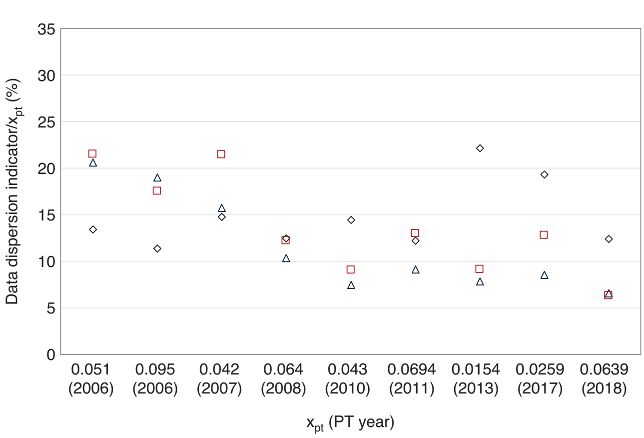

Fig. 4: Comparison of data dispersion indicators over PTs on meat: SD/x_{pt} (open square); σ_{pt}/x_{pt} (open diamond) and s*/x_{pt} (open triangle).

Conclusions

Based on the EURL-CEFAO experience, it is demonstrated that the high level of competence of the participants in PTs as well as the effectiveness of the procedures used by the Provider to prepare PT test items and to treat the results account for setting reliable assigned values. Furthermore, the organization of recurrent PTs on the same matrix/analyte combination enables participants to monitor the performance of their analytical methods on a regular basis and the PTP to constantly check the quality of the network. In addition, a thorough activity of follow-up (e.g. control charts of z-scores) leads to an improvement of the network's general performance as well as to the harmonization of the results submitted by participants. In particular, the harmonization of results among laboratories dealing with official controls within the EU is a further guarantee for the consumer safety.

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