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An Overview on Steps of Pesticide Residue Analysis and Contribution of the Individual Steps to the Measurement Uncertainty

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Abstract To facilitate the international food trade as well as to protect consumers from exposure to unacceptable pesticide residue levels, Codex Alimentarius Commission, European Union, and National Authorities set maximum residue limits for different food commodities. The control of pesticide residues at national and international level requires reliable and comparable analytical data that can be obtained by applying validated methods and implementing an effective internal quality control and quality assurance system in the testing laboratories. For the correct interpretation of the analytical results, measurement uncertainty should be estimated. Pesticide residue analysis includes two main steps: sampling performed outside of the laboratory and laboratory operations comprising of sample preparation, sample size reduction, sample processing, extraction, clean-up, and chromatographic determination. By taking into consideration the contribution of the individual steps to the overall uncertainty of the results, the analytical procedures can be optimized to fit for the purpose of the analysis with minimum cost. The scope of this paper is to review major steps of pesticide residue analysis in the light of current developments, to highlight the importance of identification and estimation of the uncertainties associated with the results, to describe suitable methods for their estimation, and to summarize the contribution of each step to the combined uncertainty.

Keywords Pesticide · Pesticide residue analysis · Uncertainty

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Introduction

Infestation caused by pests can significantly reduce the yield of agricultural and horticultural crops. In order to protect crops, plant protection products are used. The use of pesticides dates back to 1,000 BC when Chinese used sulfur as a pesticide to control powdery mildew on fruit (Winter 2001). The value of worldwide agricultural production increased from $1,115,933 to $1,543,783 between the years 1993 and 2007 (http://www.fao.org). The use of pesticides in the agricultural production increases the yield of crops; on the other hand, uncontrolled and abusive application of pesticides can cause health problems and contaminates the environment. The adverse effects depend on the toxicities, application rates of pesticides, and consumption of treated

food. The use of these chemicals is regulated in order to protect consumers from exposure to unacceptable levels of pesticide residues in food and feed (http://ec.europa.eu).

To facilitate the international food trade and to protect consumers' health, the Codex Alimentarius Commission (CAC), European Union, and National Authorities set maximum residue limits (MRLs) based on good agricultural practice (CAC 2009a; EC 2005). Pesticide residue analysis of food commodities is generally required for registration of pesticides, checking compliance with MRLs in foods, and to provide data for protection of the environment and risk assessment, as well as verification of organic food labeling. For these purposes, each year many thousands of food and environmental samples are analyzed worldwide. In the European Union, more than 70,000 samples of nearly 200 different types of food were analyzed for pesticide residues in 2008 (EFSA 2010). In order to assist laboratories producing reliable and reproducible analytical results, guidelines have been developed on good laboratory practice in residue analysis (CAC 2003) and method validation and analytical quality control requirements (SANCO 2011). Reliable and comparable analytical data can be obtained by applying validated methods and implementing an effective internal quality control and quality assurance system in the testing laboratories. For the correct interpretation of the results, the uncertainty of the whole measurement process should be taken into account as required by the International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) Standard 17025 (ISO/IEC 2005).

The scope of this paper is to review the major steps of pesticide residue analysis in the light of current developments, to highlight the importance of identification and estimation of the uncertainties associated with the results, to describe suitable methods for their estimation, and to summarize the contribution of each step to the combined uncertainty.

Pesticide Residue Analysis

Steps in Pesticide Residue Analysis

Determination of pesticide residues was generally performed in seven steps: sampling, sample preparation, sample size reduction, sample processing, extraction and cleanup, and instrumental determination (Fig. 1).

Sampling

Sample is defined as one or more units selected from a population of units, or a portion of material selected from a larger quantity of material (IUPAC 1990; CAC 1999; EC 2002). If a representative sample reflecting the properties of the sampled object in adequate manner can be provided, reliable results can be reported to an end user (Thompson and Ramsey 1995).

CAC set sampling methods for the determination of pesticide residues for compliance with MRLs. A Codex MRL for meat and poultry is applied to a bulk sample derived from a single primary sample, while MRLs for plant products, eggs, and dairy products are applied to a composite bulk sample derived from one to ten primary samples. The primary samples must be taken randomly and should consist of sufficient material to provide laboratory sample(s) required from a single lot. If the bulk sample is larger than the required laboratory sample, it should be divided to obtain a representative portion. If mixing is inappropriate to form the bulk, the units should be allocated randomly to replicate laboratory samples at the time of taking primary samples. In this case, the replicate laboratory samples should be considered independent and their residue content interpreted accordingly. The minimum sizes of laboratory sample are defined, and these change according to food commodity. Samples of large-sized fresh fruits and vegetables (e.g., cabbages and cucumbers) with a unit generally larger than 250 g should contain a minimum of five crop units (2 kg), whereas samples of medium-sized commodities (e.g., apples and oranges) with unit weight between 25 and 250 g should contain ten fruits (1 kg). The European Community together with many countries applies the Codex sampling method (CAC 1999; EC 2002).

Sample Preparation

A sample received at laboratory not including package is known as laboratory sample. Conversion of laboratory sample into analytical sample may need sample preparation which includes removal of parts such as soil, stones, bones, withered leaves, etc. Sample preparation may be subject to systematic and random errors and it cannot be validated (Hill et al. 2000) Therefore, the analysts should exactly follow the Codex standard procedure (CAC 1999).

Sample Size Reduction

Pesticide residues are not homogenously distributed within the laboratory sample. Therefore, it is mandatory to process the whole laboratory sample to obtain a representative portion for extraction. The whole laboratory sample of large crops will be too big for the processing equipment, since, for instance, one cabbage, jackfruit, and papaya can weigh 2–3, 4–50, and 1–2 kg, respectively. Therefore, the size of the laboratory sample should be reduced by selecting one longitudinal segment from each fruit composing of the laboratory sample.

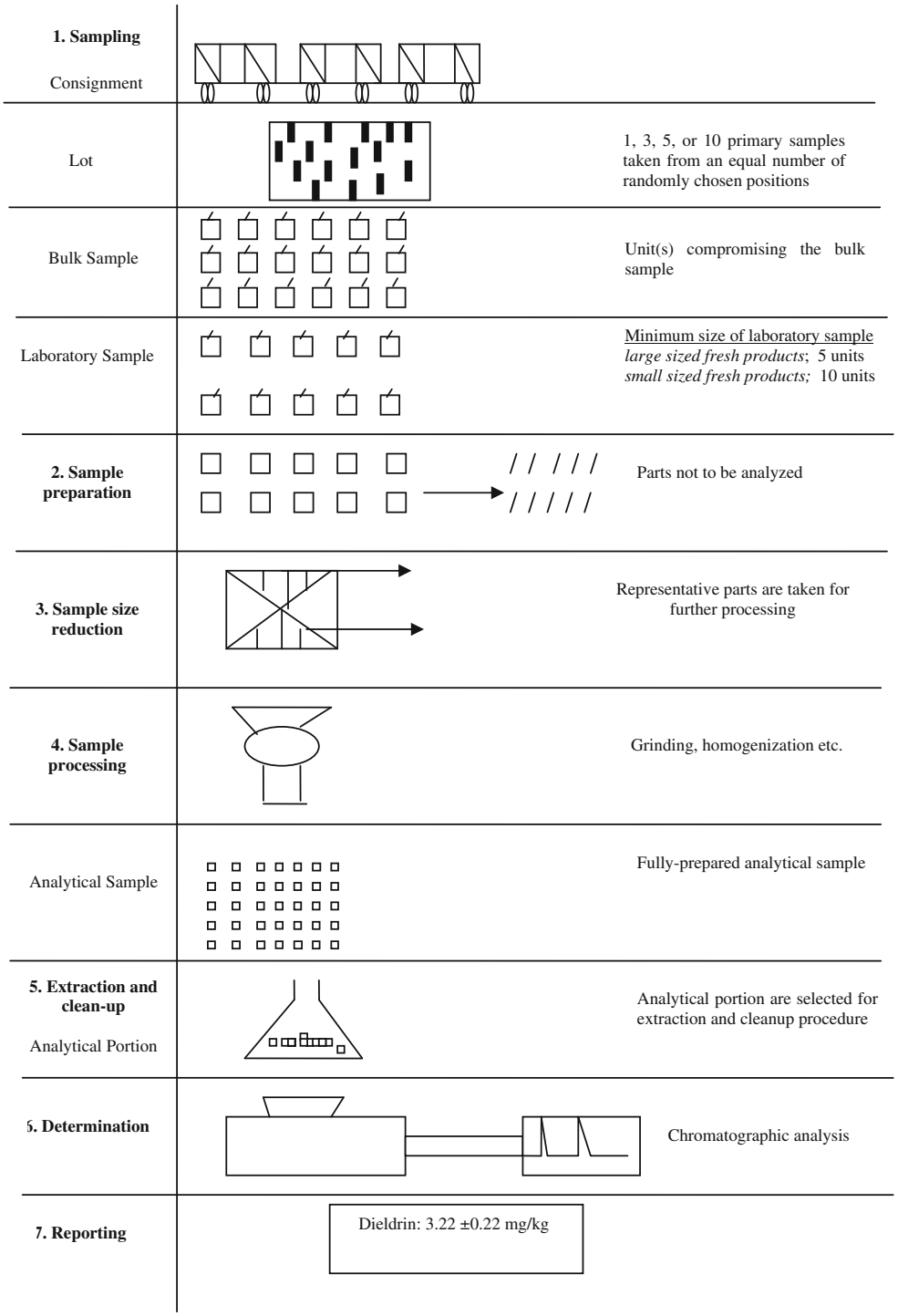

Fig. 1 Steps in pesticide residue analysis (CAC 2003)

Sample Processing

The sample processing may include cutting, grinding, and mixing to make the analytical sample acceptably homogeneous with respect to the analyte distribution, prior to removal of the analytical portion. Sample processing must be designed to avoid inducing changes in the concentration of the analyte. Sample processing and preparation are often used equivalently, though they should be clearly distinguished.

The following categories of equipment are mostly used for sample processing of food commodities (FDA 1999): (a) Blenders and homogenizer, the most popular equipment used in routine laboratories, generally consist of blades that are capable of high-speed movement. Blenders and homogenizers are most effective with liquids or samples that liquefy easily when blended (Kovalczuk et al. 2008). (b) Choppers and food processors have large capacities to comminute solid raw agricultural commodities, such as fruits

and vegetables (Paya et al. 2007). (c) Grinders are effective equipment for homogenization of raw meat and fish; (d) Mills are used for comminuting dry, hard commodities, such as grains (Mastovska et al. 2010).

Sample processing can be performed with the equipment explained as above either at ambient temperature or with the presence of dry ice. Homogenization time and speed of the equipment are adjusted to get pieces of peel ≤2–3 mm in size. This particle size was found as the minimum requirement for getting a well-homogenized analytical portion of ≥30 g (Maestroni et al. 2000a, b). If smaller portions (2–10 g) are extracted, the particles in the homogenized material must be much smaller.

Extraction

During extraction, pesticide residues and relevant metabolites are separated from the matrix and transferred into a liquid phase. The undissolved materials can be separated with filtration and centrifugation. Extraction efficiency of the analytical methods has been studied by some researcher so far (Senseman et al. 2003; Riley et al. 2005; Riedel et al. 2010). It was reported that the main parameters that affect the efficiency of extraction and consequently its uncertainty include sample matrix, particle size distribution, pH, extraction solvents, water content, temperature, and sample: solvent ratio, extraction method, time of extraction, types and amount of salt added, pressure, etc. (Lehotay and Mastovska 2007).

The extraction of a solid sample using a liquid (solvent) is typically applied in pesticide residue analysis (Krynitsky and Lehotay 2002). Some blenders and homogenizers can be used to disintegrate the matrix. The extraction solvents are chosen according to nature of the compounds to be determined and on the matrix under investigation. Ethyl acetate, acetonitrile, acetone, hexane, and methanol are the other commonly used solvents for sample extraction, depending on the commodity extracted (Pang et al. 1995; Klein and Alder 2003; Lehotay and Mastovska 2007; Schenk and Wong 2007). In recent years, more sophisticated equipment such as liquid-phase microextraction, microwave-assisted extraction, and supercritical fluid extraction have been developed as alternative methods to solvent-based extractions. Unfortunately, the equipment are costly and need specialized servicing (Lehotay and Eller 1995; Eskilsson and Björklund 2000; Lambropoulou and Albanis 2007).

Cleanup

Extraction cannot remove easily co-extractives such as oils, fats, waxes, and plant pigments, which can interfere significantly with the determination step. The removal of the extraneous co-extractives from the extract is known as sample clean up. Cleanup procedures depend on the differences in the physicochemical properties of the analytes from co-extracted matrix components (Krynitsky and Lehotay 2002).

There are various cleanup methods used in pesticide residue analysis. One of them is gel permeation chromatography (GPC) that allows the separation of compounds based on their molecular size (Tekel and Hatrik 1996). Solid-phase extraction (SPE) is a cleanup technique that uses high-performance liquid chromatography (HPLC) sorbents to separate analytes from the sample matrix. The sample is passed over a stationary phase. Florisil, alumina, aminopropil, and primary secondary amine (PSA) are common SPE sorbents. Polar organics such as sugars and fatty acids are strongly remained by PSA (Krynitsky and Lehotay 2002). The cleanup step of recently developed method, known as QuEChERS (quick, easy, cheap, effective, rugged, and safe), for pesticide residues in foods involves PSA (25 mg PSA for a 1-ml aliquot of 1 g sample equivalent) with anhydrous $MgSO_4$, and the approach was defined as "dispersive-solid phase extraction." The sorbents are simply mixed with acetonitrile extract on a vortex mixer to evenly distribute the SPE material (Anastassiades et al. 2003; Lehotay et al. 2005a, b, c; 2010).

Quantitative Determination

Gas chromatography (GC) with element-selective detectors [nitrogen phosphorus detector (NPD), FPD, and electron capture detector (ECD)] has been used for the determination of pesticides for many years. These systems are used for pesticides containing hetero-atoms such as halogens, phosphorus, sulfur, and nitrogen (Schenk and Wong 2007). Polar pesticides are not amenable to direct GC analysis. Therefore, they should be determined by HPLC. While element-selective detectors are still widely used (Aysal et al. 2004 and 2007; Georgakopoulos et al. 2009; Hernandez-Borges et al. 2009), they are being replaced or complemented by mass spectrometric (MS) detectors (Chen et al. 2009; SANCO 2011; Lehotay et al. 2010). Ultra-performance liquid chromatography with tandem quadruple mass spectrometry (UPLC-MS/MS) has been applied as a fast multi-residue method for determining polar pesticides (Kovalczuk et al. 2008; Pico et al. 2009). It was reported that the total time required for UPLC-MS/MS analysis of 64 pesticide residues and their toxic metabolites in fruit extracts was approximaely 8 min (Kovalczuk et al. 2008).

Measurement Uncertainty

Definition of Error and Uncertainty

Identification of the sources of errors is required to estimate their magnitude and to decrease them if possible in order to

optimize the procedures. There are three types of errors: gross or spurious, random, and systematic. Gross error is generally unintentionally occurred by analyst mistake or an instrumental malfunction when analytical result is generated. Therefore, it invalidates a measurement. Since it cannot be evaluated statistically, it is not included in the combined uncertainty. A sample that has been contaminated by poor handling can be given as an example to gross errors. Random errors which exist in all measurements cause variations in repeated observations of the measurand. As a result of random errors, replicate results can fall on either side of the mean value. Its magnitude can be decreased by increasing the number of observation. Systematic errors are also common in measurements. It is reported that systematic error always affects a series of measurements in the same sense; it means that all the data in a sample have values either too high or too low. In contradiction to random error, it cannot be reduced by increasing number of analysis (Miller and Ambrus 2000, EURACHEM/CITAC 2000; JCGM 2008a). Codex Guideline defines the most common random and systematic error in pesticide residue analysis. Some systematic errors include selection of analytical sample analyzed, decomposition of analyte during sample processing, incomplete recovery of analyte, and biases in calibration. Non-homogeneity of the analyte in single units of analytical sample, variation in composition of sample materials taken from a commodity, and precision and linearity of balances are examples of random errors in pesticide residue analysis (CAC 2006).

Uncertainty is defined as a non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used (JCGM 2008b). The parameter may be expressed as a standard deviation or half width of an interval with a given probability. Uncertainty is a different concept from measurement error, which can be defined as the difference between an individual result and the true value. Error is a single value; on the other hand, uncertainty is a range or an interval. The standard deviation of a repeated analysis results is not a measure of random error. Instead, it is the measure of the uncertainty of the mean value occurred by random effects (JCGM 2008a).

Approaches to Estimation of Measurement Uncertainty

It is a requirement under ISO/IEC 17025 that laboratories shall determine and make available the uncertainty associated with analytical results (ISO/IEC 2005). Therefore, laboratories should estimate the uncertainty of measurement results with an appropriate approach. To estimate uncertainty, measurand is firstly specified, possible sources of uncertainty are identified, uncertainty components are quantified, and finally combined uncertainty is calculated (EURACHEM/CITAC 2000).

There are basically two main approaches for estimating the uncertainty of analytical measurements. These are defined as bottom-up and top-down methods. Bottom-up approach is introduced by ISO (1993) and elaborated in 1995 by A focus for Analytical Chemistry in Europe/Cooperation on International Traceability in Analytical Chemistry (EURACHEM/CITAC) for analytical chemistry. In the bottom-up method, analytical procedures are divided into individual components or steps. Their standard uncertainties are estimated and summed up together to form the combined uncertainty. The bottom-up approach is very laborious and needs specific knowledge of the whole procedure. On the other hand, it is a useful approach that provides an understanding of the major components of measurement uncertainty. By taking into consideration the contribution of the individual procedures or steps to the overall uncertainty of the results, the analytical procedures can be optimized to fit for the purpose of the analysis with minimum cost (Ambrus 2004).

The top-down method is dependent on the results of inter-laboratory proficiency tests, collaborative trials, internal quality control data, and inter- or intra-laboratory validation studies (precision and trueness). If estimation is based on inter-laboratory studies, it takes into account the between-laboratory variability of the results. The second edition of EURACHEM Guide uses the validation and related data for obtaining uncertainty estimates (EURACHEM/CITAC 2000). Alder et al. (2001) estimated between laboratories' relative reproducibility standard deviation of 25% for pesticide residue analysis from proficiency test results in the concentration range of 1 μg/kg–10 mg/kg. This estimate naturally does not include sampling and sample processing. Furthermore, there are some more standard and guidelines, based on top-down method (Barwick and Ellison 2000, ISO 2004; Magnusson et al. 2004). Eurolab released a technical report on measurement of uncertainty. The report provides a summary of the current main approaches for uncertainty evaluation as well as outlines in detail the use of method validation and proficiency test results data for estimating measurement uncertainty (EUROLAB 2007).

Based on these background guidelines and standards, Codex Committee on Pesticide Residue is in the step of proposing a revised guideline on the uncertainty estimation of pesticide residue analysis from simplified top-down approach (CAC 2009b). Furthermore, Codex Committees on Methods of Analysis and Sampling (CCMAS) are working on the development of guidelines for estimation and interpretation of uncertainty of measurement results (CAC 2010). These guidelines are mostly concentrated on the analysis part, and they are not covering the estimation of uncertainty in individual steps of analysis such as sampling and sample processing.

Identification of Standard Uncertainties in Pesticide Residue Analysis

The uncertainty of analytical results obtained from pesticide residue analysis (S_R) can be calculated from the uncertainty of sampling, S_S, uncertainty of sample processing (S_{Sp}), and uncertainty of the analysis (extraction, cleanup, and instrumental determination) (S_A) with the application of the general law of error propagation. If sample size reduction is applied to a laboratory sample prior to sample processing, its uncertainty ($S_{\text{Size reduction}}$) should also be added.

$$S_R = \sqrt{(S_S)^2 + \left((S_{\text{Sizereduction}})^2 + (S_{Sp})^2 + (S_A)\right)^2}$$

$$S_R = \sqrt{(S_S)^2 + (S_L)^2}$$

where S_L refers to uncertainty arisen from laboratory phase.

If the whole sample is analyzed, the mean residue remains the same and the equation can be written as:

$$CV_R = \sqrt{(CV_S)^2 + (CV_L)^2}$$

where CV_R refers to relative uncertainty of analytical results obtained from pesticide residue analysis.

The relative uncertainty of results of the analysis of a laboratory sample (CV_L) is influenced by the random errors of sample size reduction ($CV_{\text{Sizereduction}}$), sample processing ($CV_{Sp}$), extraction ($CV_{ex}$), cleanup ($CV_{\text{cleanup}}$), and chromatographic determination (CV_{ch}). If the relative uncertainties of the individual steps are identified, the combined relative uncertainty of laboratory phase can be expressed as:

$$CV_L = \sqrt{(CV_{\text{Sizereduction}})^2 + (CV_{Sp})^2 + (CV_{Ex})^2 + (CV_{\text{Clean-up}})^2 + (CV_{ch})^2}$$

Estimation Methods of Standard Uncertainties in Pesticide Residue Analysis and Contribution of Individual Steps to Combined Uncertainty

Sampling

Variations, which are caused by heterogeneity as well as contamination, loss of analyte, or use of an incorrect sampling plan, may be observed between the compositions of random samples taken from a lot (Thompson 1998). These variations can lead to uncertainty in sampling step and should be taken into account (Ramsey et al. 1992; Ramsey et al. 1995; Glaeser 2002). However, in the past measurement uncertainty was generally considered only for laboratory phase (Zorzi et al. 2002). This conception has been changing, and sampling uncertainty is becoming increasingly recognized after the first edition of ISO/IEC 17025 released in 1999.

Various methods, which are dedicated to estimate sampling uncertainty for many contaminants and residues, have been published (Ambrus 1996; Ramsey 1997; Ramsey and Argyraki 1997; Ramsey et al. 1999; Squire et al. 2000; Gustavsson et al. 2006; Whitaker et al. 2006). One of them introduced by Ambrus (1996) and applied successfully in other studies (Hill 2000; Ambrus and Soboleva 2004; Caldas et al. 2006; Ambrus 2009) is based on the analysis of pesticide residues in crop units taken from a single field and drawing random samples of various sizes with replacement from them with a computer. The uncertainty of sampling, expressed as the standard deviation of the calculated residues in composite samples, could be calculated without error of sample processing and analyses and any additional costs. The results can be used for optimizing sampling protocols.

The methods used by Ramsey and Argyraki (1997) provided the basis for the recent international guideline elaborated by EURACHEM/EUROLAB/CITAC/Nordtest for estimation of uncertainty arising from sampling (Ramsey and Ellison 2007). After that, the Nordtest (Gron et al. 2007) group provided further case studies to complement the guideline.

The current international guideline defines the application of bottom-up and top-down approach in the estimation of sampling uncertainty. One of the methods based on top-down approach is defined as a duplicate method. In this method, a single sampler, a person carrying out the sampling procedures at the sampling point, should take duplicate samples from at least eight sampling targets (lot) (i.e., 10% of the total number of sampling target, but no less than eight targets). Target refers to a portion of material at a particular time that the sample is intended to represent. On the other hand, the ISO Standard 11648–1 (ISO 2003) for sampling bulk materials recommends that, for obtaining sufficient information about the variability of the analyte, ~20 lots should be sampled with preferably several pairs of samples taken from each lot. If duplicates are collected from the same sampling target, then sampling uncertainty just characterizes that target. However, if they are taken from different targets, then more rugged estimates can be obtained. All duplicate samples are prepared physically to obtain a test sample for further analysis. Replication can also be done in the sample preparation or in the other analytical steps to get more information on uncertainty (called as balanced design). Analysis of variance (ANOVA) is used as a statistical tool for estimating the random component of the uncertainty and it enables to separate sampling and analysis variances. Range statistics is also offered for calculations (Ramsey and Ellison 2007). Lyn et al. (2007)

reported that duplicate method is a simple and cost-effective procedure for estimating sampling uncertainty. CAC (2008) also recommended duplicate method as broadly applicable across the food sector.

The uncertainty of sampling in pesticide residue analysis may contribute to the 80–90% of the combined uncertainty of the results (Ambrus and Lantos 2002). Variability of residues within a field causes sampling uncertainty in pesticide residue analysis. Active ingredient application conditions, the agro-climatic and environmental conditions at the time of application, or delivery, size, shape, and density of plants have been claimed as significant factors influencing the distribution of residues within a field. On the other hand, physicochemical properties of some active substances did not appear to influence the variability. Besides the effect of pre-harvest, interval was considered insignificant for influencing the variability where the crop unit size did not change significantly during the period under consideration (Ambrus 2000; Harris 2000; Harris et al. 2000; Hamilton et al. 2004).

Variability of pesticide residues in composite samples has been related to the sample size. The relationship between the standard deviation of the residues in primary samples and composite samples of size can be described by the central limit theorem. According to the theorem, sampling uncertainty can be decreased by increasing sample size. Ambrus and Soboleva (2004) estimated typical relative standard uncertainties of sampling medium-sized crops for pesticide residue analysis in the cases of sample sizes of 1, 5, 10, and 25 as 81, 37, 25, and 16%, respectively. Ambrus (2009) conducted additional field trials to provide residue data for refining the estimated sampling uncertainty for small- and large-sized crops. It was concluded that the estimated typical relative uncertainties of taking composite samples according the Codex sampling procedure for determination of pesticide residues in small- and medium-sized and large-sized crops are 25 and 33%, respectively.

Between-fields variation of residues in composite samples is usually two to three times larger than the variation within field due to the differences in mean values of residue. The typical coefficient of variation (CV) values of between-fields variation of residues in composite samples ranged between 80 and 120% (Ambrus 2000). In a mixed consignment, a lot containing residues above the maximum residue limit can easily remain unobserved. Consequently, sampling of mixed lots should be avoided as far as practically possible (Hill 2000).

Sample Processing

It is generally assumed that sample processing procedure results in analytical portions that are representative of the analytical sample, even if 2–10-g portions are withdrawn from a large composite sample. Collaborative studies and proficiency tests are carried out with homogenized test materials. The recovery studies are usually performed with analytical portions spiked prior to extraction. Therefore, efficiency of sample processing cannot be estimated through such studies.

There are some reported methods on estimation of sample processing efficiency. Bettencourt da Silva et al. (2002, 2003) proposed a method for the estimation of sample processing and subsampling performance, based on comparisons of the experimental dispersion of results with the uncertainty estimated from developed models for the subsequent analytical steps. Lyn et al. (2003) applied a semi-balanced variant of staggered nested design. Data produced from the hierarchical design are treated with robust ANOVA to generate uncertainty estimates as standard uncertainties for sampling, physical sample preparation, and chemical analysis.

Another approach is to determine the sampling constant. Sampling constant concept was first applied by Ambrus et al. (1996) for estimating uncertainty of sample processing in pesticide residue analysis based on the work of Wallace and Kratochovil (1987). If a laboratory sample is statistically well mixed, the sampling constant, K_s, is defined as:

$$K_S = W \times CV_{Sp}^2$$

where, W is the weight of a single increment and CV_{Sp} refers to uncertainty of sample processing. The K_s is the weight of a single increment that must be withdrawn from a well-mixed material to hold the relative sampling uncertainty, CV%, to 1% at the 68% confidence level. This method was further used in case of various sample matrices in combination with ^{14}C-labeled compound which enabled direct and precise (CV=1–2%) determination of analyte concentration in the extracts of test portions (Maestroni et al. 2000a, b; 2003; Suszter et al. 2006; Tiryaki and Baysoyu 2006). The processing uncertainty depends on the nature of the sample, the heterogeneity of the pesticide residues in the sample, the processing equipment, as well as the sample processing procedure. The efficiency of different commercially available processing equipment can be substantially different. On the other hand, it is independent from the analyte, and its concentration provided that it is not volatile or decomposes during sample processing. It was recommended to use easily and reproducibly extractable, stable compounds for determining the K_s value. The use of ^{14}C-labeled compound is preferable, but unlabelled pesticides can also be used. In the latter case, the estimation of sample processing uncertainty takes longer especially where cleanup of the extract is required.

These studies revealed that random error of sample processing can be around 56, 23, and 18% respectively, when a kitchen blender is used in a usual manner for obtaining 5-,

30-, or 50-g analytical portions of apples. In several cases, even statistically well-mixed samples could not be prepared especially from tomato and soil. The extraction of a 5-g analytical portion has advantage in terms of solvent consumption and reduction of waste materials. The well-mixed status of homogenized analytical sample should always be verified before it is used; otherwise, reproducible analytical results may not be obtained. On the other hand, the analysis of 100- or 150-g analytical portions would only slightly improve the sample processing uncertainty compared to 30 g. Taking into account the typical uncertainty of analysis, the targeted sample processing uncertainty should be at or below 0.3 CV_A as in such cases it does not contribute significantly to the combined uncertainty of the results (Ambrus 2004).

Once the efficiency of sample processing is determined during method validation and verified by internal quality control procedures, the results obtained are valid for all pesticide residues except highly volatile and labile compounds, which can evaporate or degrade during the process to a various extent, depending on the conditions of the laboratory environment. The results underline the importance of applying appropriate internal quality control measures to confirm the effectiveness of the sample processing procedure.

Hill et al. (2000) reported that sample processing at ambient temperature can cause degradation for some pesticides such as chlorothalonil and folpet. Some pesticides such as bitertanol, heptenophos, isofenphos, and tolyfluanid decomposed partially at ambient temperature, but loss of residues did not occur at cryogenic processing (Fussell et al. 2002). In cryogenic milling, analytical samples are frozen usually at −20 °C and then they are disintegrated into a fine, free-flowing powder in the presence of dry ice (solid CO_2) or liquid nitrogen. Decreasing the temperature at sample processing, the potential reactions between any pesticide residues present in the samples and chemicals/enzymes released when plant cells are disrupted can be decreased. Studies revealed that cryogenic sample processing could improve sample processing uncertainty as well as decrease the pesticide decomposition (Fussell et al. 2007).

Extraction and Cleanup

It is reported that the major source of bias in extraction step is the efficiency of extraction. Ineffective cleanup can result in insufficient recovery of analyte, which is a source of systematic/random error, and matrix effects on GC (Ambrus 2000).

The compound's distribution coefficient between two solvents in liquid–liquid partitioning, solvent strength required for elution, and adsorbent used in column chromatography will affect the effectiveness of cleanup. The efficiency of both steps can be determined by adding known amounts of the analyte(s) concerned to the matrix blank and determining their concentrations by complete analysis (Ambrus 2000). On the other hand, such an experiment only gives an impression of the overall recovery of the method. Therefore, Tiryaki and Baysoyu (2008) spiked cucumbers with radiolabelled ^{14}C-Carbaryl prior to extraction and measure the radioactivity after each step to get separate recovery values for each step. Tiryaki and Baysoyu (2008) applied top-down and bottom-up approach to estimate uncertainties in both steps. It is reported that there was little difference between the two approaches, and relative uncertainties (CV) of EtAc extraction and GPC cleanup steps were 3 and 10.7%, respectively.

Chromatographic Determination

Determination of analyte by chromatographic methods is the last step in pesticide residue analysis. The quantification of pesticide residues is based on calibration curves constructed at each batch of analysis from injecting known amounts of the respective standard compounds at different concentration levels covering the concentration range in the analyzed samples.

It is reported that the uncertainty of GC and HPLC measurements of residues can be caused by different sources including (a) re-isomerization, decomposition, and transformation of the target analytes before and during sample preparation and processing; (b) bad separation or non-selective detection of the target analytes (from each other or from the matrix); (c) varying matrix blank response, and matrix effect; low or largely differing detection sensitivity for some of the analytes; (d) integration error; varying conversion rate of derivatisation; (e) standard preparation, injection, and calibration. The sources from a to d can be identified during method validation and can be controlled by daily internal quality control studies (Soboleva et al. 2004). The other point is the contribution of multi-component residues arising from the application of technical mixtures including structural and optical isomers, metabolites, and other breakdown products to the uncertainty of chromatographic determination (CAC 2006). Soboleva et al. (2004) explained the methods that can be used for identification of uncertainty of multi-components.

The uncertainty of standard preparation can be calculated using the bottom-up approach (EURACHEM/CITAC 2000). The relative uncertainty of replicate injections should be higher than the uncertainty of standard preparation to satisfy the linear regression precondition. The uncertainty of predicted concentration can be estimated from calibration data obtained either from weighted linear regression (WLR) or ordinary linear regression (ORL). Moreover, an Excel template was created to facilitate the complex calculations (Miller and Ambrus 2000).

The predicted analyte concentration based on multi-point calibration was studied by Ambrus et al. (2002) using 68 gas chromatography–electron capture detector (GC–ECD), GC–NPD, and HPLC–ultraviolet calibration data sets. It was found that, regardless of the actual concentration range of the calibration, the relative random error at the lowest calibrated level range in the case of ordinary linear regression was between 3 and 110% and for weighted linear regression, between 1 and 18%. At or above 1/3 of the calibrated range, it ranged between 1 and 7%, and there was no significant difference between the estimates obtained with WLR or ORL. Similarly, no difference was found in the uncertainty of the predicted concentration at the upper and of the calibrated range estimated with OLR or WLR when pesticide residues in apples were determined with GC–ECD.

Interpreting the Results of Measurements

Once combined standard uncertainty (S_R) is obtained from the contribution of individual steps in pesticide residue analysis, results can be provided with expanded uncertainty.

$$\text{Result} = x \pm U(\text{units})$$

The expanded uncertainty (U) can be calculated from the combined standard uncertainty (S_R) by multiplying with a coverage factor of 2 which gives a level of confidence of approximately 95%. Besides, if the combined uncertainty is based on statistical observation with relatively few degrees of freedom (less than 20), Student's t value can be used to calculate coverage factor (EURACHEM/CITAC 2000).

$$U = 2 \times S_R \text{ or } U = t_{\upsilon,\,95\%} \times S_R$$

Where, υ is the degrees of freedom and 95% represents the level of confidence.

The emerging practice of EU is to use the default expanded uncertainty figure of 50% (95% confidence level with 2 as coverage factor). It is recommended that if uncertainty estimation based on in-house method validation data is higher than the default value, the higher uncertainty figure must be considered on a case-by-case basis. In European Union, it is reported that in case of official food control by regulatory authorities, compliance with the MRL must be checked by assuming the lower limit of the uncertainty interval ($x-U$) to be the highest confirmed analyte concentration in the sample. It is emphasized that the MRL is exceeded if $x-U>$MRL (SANCO 2011).

The interpretation of analysis result related with compliance with MRL at national level is different from the compliance of a commodity to be exported. Since MRL for pesticide residues in commodities of plant origin refers to the average residue in the bulk sample of specified minimum size and mass, sampling uncertainty will not take into account at national level. On the other hand, for commodity to be exported, the laboratory has to certify that any composite sample of specified size will comply with the MRL. Therefore, the uncertainty of sampling should be taken into account and the compliance has to be stated at specified probability level with a given confidence level (Ambrus 2009).

Conclusion

The estimated typical relative uncertainties of taking composite samples according to the Codex sampling procedure for determination of pesticide residues in small- and medium-sized and large-sized crops can be 25 and 33%, respectively. Further studies would be valuable to estimate sampling uncertainty for dried products. Sampling uncertainty should be taken into account when commodities are exported. Sample processing uncertainty should be kept at or below 10%. Sample processing would be the major contributor to combined uncertainty if statistically well-mixed analytical samples cannot be prepared. Therefore, internal quality control measures should be established to confirm the effectiveness of the sample processing procedure during actual conditions of routine laboratories. Uncertainty arisen from sample size reduction should be taken into account during the sample processing of large-sized crops. The limited studies revealed that the relative uncertainties of EtAc extraction and GPC cleanup of cucumber for radio-labeled chlorphyrifos are 3 and 10.7%, respectively. Efficiency of extraction and cleanup step depends on the pesticide and matrix combination as well as salt and solvents. Therefore, further study can be performed for the other pesticides and extraction–cleanup techniques. Regardless of the actual concentration range of the calibration, the relative random error at the lowest calibrated level can range in the case of ordinary linear regression between 3 and 110% and for weighted linear regression, between 1 and 18%. At or above 1/3 of the calibrated range, uncertainty of calibration curve obtained from the two methods gives comparable results. Weighted linear regression can be selected to construct calibration curve in routine analysis.

The uncertainty of the results obtained from pesticide residue analysis is influenced by the performance of all individual steps. Once combined uncertainty is obtained from the contribution of individual steps in pesticide residue analysis, results can be provided with expanded uncertainty. Finally, decision on interpreting the results of measurements should be taken by related authorities.

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