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Method validation using ^{14}c-chlorpyrifos as an internal standard analyte to determine the uncertainty and variability in multi-step processing of potato during pesticide residue analysis

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Abstract
Residue analysis of pesticides in the food matrices often includes multi-step and mass transfer protocols. According to the nature of the food matrix, these protocols are standardized. During the sample processing steps, mass transfer of food matrix is the primary source of not obtaining the precise results. The use of radioactivity for minimal loss of pesticide residues during sample processing makes the approach robust and sensitive enough to determine the sources of uncertainty. Factors that make the results uncertain lead to variability in the analysis outcomes from one analytical laboratory to another. In the present study, ^{14}C-chlorpyrifos was used to determine the amount of loss of the radioactivity at each step, indicating the amount of pesticide residue loss when following such protocols involving mass transfer procedure. After each transfer step, to recover the lost pesticide residues from the container where matrix samples were processed, the spiking solvent acetone was used. The amount of radioactivity determined on the Liquid Scintillation Counter after extraction and processing were added to the total amount of radioactivity obtained from surface run-off loss of radiolabeled pesticide and the loss due to spillage. The sampling constants (K_S) is the weight of the matrix withdrawn from a homogeneously processed sample with relative sampling uncertainty. Sample processing for potatoes as the food matrix in the present study showed better K_S values and hence $CV_{COMB.\ SP\%}$ values under the ambient conditions compared to those processed under dry ice conditions.

Keywords: chlorpyrifos, sampling constant (KS), liquid scintillation counter (LSC)

Introduction
Measurement of uncertainty is a different concept from the measurement of error. The uncertainty can occur due to random factors affecting the conduct of the experiment. It is the value within the range of defined probability level, therefore, stated as a difference between the individual result of an experiment and the actual value (EURACHEM/CITAC, 2000) [9]. These values help to regulate precisely the Maximum Residual Limits (Narenderan, and Meyyanathan, 2018). It is also to be noted that random error while conducting an analysis can never be smaller as compared to its other contributing source therefore the systematic error can be zero (Maestroni *et al*., 2000) [5, 13]. By increasing the number of observations, the effect of random errors can be reduced but in the other instance, systematic errors can be compensated completely (Ambrus A. and, Suszter G., 2019) [1]. Major sources of uncertainty highlighted are environmental conditions, matrix effects and interferences, the volumetric equipment, assumptions set during designing the protocol for experiments, sampling errors, and numerous random variations (Ellison S.L.R. and, Williams A., 2012) [7]. Uncertainty may additionally arise due to reasons like packaging, transportation, storage, setting an analytical portion for a test, and during a particular step of sample processing *viz.* extraction by using efficient solvent like ethyl acetate (Aysal, 2007) [4] , partitioning, cleanup, concentrating the extract, and instrumentation based. Appropriate solvent selection for extraction purpose is also considered one of the major factors for the recovery of the pesticide from the food matrix (Tiryaki, 2009) [25]. It is also emphasized by some residue analysts that during sample processing certain compounds get decomposed resulting in systematic errors hence leading to uncertainty in results (Hill *et al*., 2000 and Fussell, 2002) [11, 10]. Soliman in 2001, suggested the significance of the study on potatoes as it is the chief food matrix consumed worldwide in making home preparations as chips and french fries but a certain amount of pesticide residues are detected.

The uncertainty occurring during the analysis phase can be determined by using radiolabeled parent compound Carbon-14 (Bidaoui-El *et al*., 2000 and Suszter *et al*., 2006) [5, 13, 21], it precisely relates to the estimation of pesticide recoveries in totality thus gives the value of CV_A (uncertainty concerning analysis phase). Experiments involving analysis of the compound vulnerable to lose during its conduct can be taken into account by the use of radiolabel tracer techniques. In pesticide residue analysis the parent compound with appropriately labeled elements is used to precisely determine the recovery of the pesticide and its loss at any sample processing step (Tiryaki *et al*., 2008) [22, 24]. When a protocol involves the transfer of material containing an analyte into multiple locations then the chances of loss of that analyte becomes more. Consequently, the analysis does not yield reproducible results. The use of radiolabeled analyte in such experiments aids the analyst to precisely monitor the amount of recovery and loss of the analyte at various steps (Visi E., 2002) [26]. Bias is important for traceability; it indicates a reference value which can be computed as the difference between the mean measured

value and the true value. Bias is significant, as it accounts for analytical recovery and is indispensable while calculating uncertainty (Ambrus *et al*., 2020) [2]. Some biases that cause uncertainty are sampling bias, analyte characteristic or analytic bias and at spiking level the sample preparation bias (Quality control procedures for pesticide residues analysis, 2006). A "measurand" can be a concentration, mass, or volume as it refers to any quantity which is subjected to be measured (Omeroglu, 2012) [17]. The sampling constants (KS) demarcate the efficiency of sample processing (Ambrus *et al*., 1996) [3] and the homogeneity of analyte in the matrix (Suszter *et al*., 2006) [21]. It is referred to as the weight of matrix that is withdrawn from a homogeneously processed sample with relative sampling uncertainty to one percent at sixty-eight percent level of confidence (Wallace *et al*., 1987) [27].

The concept for determining the uncertainty in analytical measurements includes "Top-down" and "Bottom-up" approaches (Caudros-Rodr'ýguez *et al*., 2002) [6] and these approaches were compared by Stepan *et al*. in 2004 [19]. The former approach collectively sum-up all the sources of uncertainty whereas the latter approach highlights the most significant uncertainties. It is also suggested whenever a new method is implemented the bottom-up approach is implemented whereas the top-down approach is implemented when potent sources of uncertainty are well established (Tiryaki, and Baysoyu, 2008) [22, 24].

Mmaterials and Methods

Chemicals

Pesticide: The ^{14}C-Chlorpyrifos (supplied by IAEA), RPG life science limited, Sodium hydrogen carbonate ($NaHCO_3$), Sodium sulfate (Na_2SO_4), Dry ice, Liquid scintillation cocktail (Hydroflour, National Diagnostics; Atlanta; Georgia), Merck Ethyl acetate (Analytical grade), Acetone.

Equipment

A common laboratory chopper, Steel blades warring blender (Make: Khera Instruments), laboratory homogenizer machine, Centrifuge – Refrigerated (Make: Sigma), Beckman's Liquid Scintillation counter, Top load weighing balance, deep freezer (-80 ºC).

Glasswares required: 50 mL & 250 mL centrifuge tubes; 500 ml & 1L thick-walled Borosilicate glass beaker; 10 mL & 100mL measuring cylinder; Thermometer; Scintillation vials; 500 µl Hamilton's micro syringe; a stainless-steel spoon/ spatula; aluminium foil; 1 mL pipette; Whatman's filter papers (8 cm diameter).

Preparation of treating solution

The treating solution was prepared by dissolving ^{14}C-chlorpyrifos in solvent acetone in a pre-weighed vial. And added 1 µCi of ^{14}C-chlorpyriphos (specific activity of 26.8 mCi/ mmol) to the same vial.

Spiking of treating solution on the food matrix

Potatoes were taken and weighed around 1.5 kgs and individual unit of potato was cut into the longitudinal half. Then each unit was placed on a clean aluminium foil with a cut surface downward and the surface with peel was exposed upward for spiking the ^{14}C-Chlorpyrifos (with Hamilton's micro syringe). The potatoes where spiking was done were kept aside for 30 minutes for the absorption of pesticide. The residual run-off treating solution on aluminium foil was collected for radioactivity measurements as this loss of pesticide residue has also be taken into consideration while calculating and summing-up the total residue levels. The radioactivity was also measured in the vial used for preparing spiking solution of ^{14}C-Chlorpyrifos.

Preparation of homogenized analytical sample

Sample processing Potatoes under the ambient and dry ice conditions

The potato units on which spiking was done were added to the chopper and the chopping was continued for 6-7 minutes with an intermittent pause of 1 minute. To maintain the homogeneity and consistency the potatoes under processing were constantly mixed with the stainless-steel spoon. To ensure fine chopping the peel size of potatoes under chopping was monitored.

To accomplish fine grinding, in a warring blender 400g of chopped potatoes were transferred and 20 ml of distilled water was added which were then ground for around 3 minutes. At this level of sample processing size of the peel of potatoes was monitored which would ensure fine processing of the food matrix. Sample processing with dry ice or Cryogenic milling was carried out similarly as done for sample processing in ambient conditions. In this case, instead of adding water, the dry ice was added into the warring blender and grinder while chopping and grinding. The extent of chopping and grinding was determined by observing that the matrix so obtained after processing should be free-flow. The size of the peel was also monitored as earlier.

Preparation of Analytical portions

The larger analytical portions were prepared for analysis by withdrawing five replicates of 15g and 150g processed matrix in 250 mL thick-walled centrifuge tubes and 1L beakers respectively. In the same manner, smaller analytical portions were i.e., 5g and 50g analytical portions were prepared from the sample under process in the warring blender. These analytical portions were taken in 50 mL centrifuge tubes and 500 mL beakers respectively.

Extraction of Pesticide residues

Extraction of the ^{14}C-chlorpyrifos was done using Sodium bicarbonate. The analytical portions prepared were added with sodium bicarbonate in the ratio of 6:1 i.e., 25g, 2.5g, 8.33g, and 0.83g sodium bicarbonate was added to 5g, 15, 50g, and 150g analytical portion. Then this mixture was warmed at 27 ºC, constantly stirring with stainless-steel spatula. Analytical grade (Merck) ethyl acetate was then added in the ratio of 2:1 to each analytical portion and covered them with aluminium foil. Later, Sodium sulphate was added in each analytical portion in the ratio of 1:1 w/w. The small analytical portions (5g and 15g) mixtures were subjected to homogenizer for 1-2 minutes and centrifuged at 2500 rpm for 10 minutes whereas the larger analytical portions (50g and 150g) were kept aside, undisturbed. From these analytical portion extracts containing ^{14}C-Chlorpyrifos in the supernatant, 1 mL from each extract was collected in scintillation vials for radioactivity counting.

Radioactivity measurement on liquid scintillation counter

To each liquid scintillation vial, ^{14}C-chlorpyrifos containing matrix extract was collected and 19 ml of scintillation cocktail (Hydroflour, National Diagnostics) was added and gently vortexed. These vials were then placed in the Beckman's Liquid Scintillation counter.

Results and Discussion

Analysis and Calculations

To validate the methodology applied in the analysis of pesticide residues in any food commodity it is mandatory to determine uncertainty factors related to sample processing and calculate the efficiency of the procedure applied at each step (Tiryaki, 2006) [23]. Certain quadratic factors which influenced the experimental conditions were also described by Maestroni *et al*., 2018 [12] these include the extent of shaking & agitation, speed of centrifugation, etc. In the present scenario, two different temperature conditions were applied for pesticide residue detection in potatoes, which were efficient and repeatable (Suman, and Singh, 2011) [20].

To avoid tedious calculations, special statistical software (Meier, & Zund, 1993 and Miller, & Miller, 2000) [14, 15] is required to determine the uncertainty of predicted concentration based on approximations.

Sampling Constant (K_S) is the weight of a single increment that must be withdrawn from a well-mixed sample to hold the relative sampling uncertainty to 1% with a 68% level of confidence.

The calculations were done by applying the concept of sampling constant as follows:

$$K_S = W \times CV^2_{SP.} \quad \text{---------- 1}$$

W is the weight of the analytical portion withdrawn from processed sample or matrix

CV_{SP} is the coefficient of variance in sample processing which denotes the relative uncertainty of sample processing.

Homogeneity of the processed matrix determines the degree of extraction of residual pesticides. Value of sampling constant dictates the homogeneity of the sample processing hence the smaller analytical portion and larger analytical portion were compared.

$$K_{S\,(SM)} = K_{S\,(LG)} \quad \text{---------- 2}$$

$K_{S\,(SM)}$, sampling constant for small portion size of the processed matrix.

$K_{S\,(LG)}$, sampling constant for large portion size of the processed matrix.

Since R denotes the average residue concentration (R) of the small and large analytical portion is the same Hence for K_S, CV^2_{SP} can be substituted by S^2.

Now deducing the value of $K_{S\,(SM)}$ and $K_{S\,(LG)}$ from above

For small analytical portion, $K_{S\,(SM)} = W_{SM} \times S^2_{SM}$

For larger analytical portion, $K_{S\,(LG)} = W_{LG} \times S^2_{LG}$

And from equation 1 and 2

$S^2_{LG} \times W_{LG} = S^2_{SM} \times W_{SM}$

$S^2_{LG} = S^2_{SM} \times W_{SM} / W_{LG}$

$$V_{SP\,(LG)} = V_{SP\,(SM)} \times W_{SM} / W_{LG} \quad \text{---------- 3}$$

To check the homogeneity of chopping F-test was applied to compare the variance of sample processing of large versus small analytical portions.

After extraction, the average recovery (R) of replicates for each analytical portion was analyzed by calculating the value of V_A (Average of Variance of vial replicates of each sub-sample) and V_T (Average of Variance of each sub-sample of each analytical portion).

Further, one tail F-test$_{0.005}$ was applied to

$$F_{Calc.} = V_T / V_A$$

When $F_{Calc.} > F_{Tab.}$ It implies, $V_T >> V_A$

Then V_{SP} (Variance of sample processing) = $V_T - V_A$

And CV_A (Coefficient of Variance of sample processing) = $\sqrt{(V_{SP})}/R$

Where CV_A % signifies the reproducibility percent of the sample processing.

To verify the homogeneity of both the chopper and warring blender, two tail $F_{0.1}$ tests were applied.

$$\text{F-test} = W_{LG} / W_{SM} \times V_{SP\,LG} / V_{SP\,SM} \quad \text{(from Equation 3)}$$

$$F_{Tab.(0.1,4,4)} = 6.39$$

When $F_{Calc.} < F_{Tab.}$, it implies that the sample is well mixed, then sampling constant for each process i.e. K_S1 and K_S2 were calculated.

From the computed value of K_S1 and K_S2 the CV_1^2 and CV_2^2 were calculated by using the following formula:

$$CV_1^2 = K_S\,1 / W_{WB}$$

$$CV_2^2 = K_S\,2 / W_A$$

Where CV_1^2 – Coefficient of Variance for chopping.

CV_2^2 – Coefficient of Variance for blending.

W_{WB} – Weight of the chopped sample transferred to warring blender.

W_A– Weight of the analytical portion taken for the analysis.

Summing up the Combined Uncertainty during sample processing:

$$CV_{Comb.\,sp} = \sqrt{K_S1 / W_{WB} + K_S2 / W_A} \text{ Or } \sqrt{CV_1^2 + CV_2^2}$$

The I.A.E.A. guidelines suggest that difficulty in handling a large sample size leads to an increased value of reproducibility percentage whereas its reduced value can be obtained due to the segregation matrix with water. Hence regularly mixing of the matrix between the intervals is advised especially during sampling out the analytical portions. The values of reproducibility percentage obtained from sample processing and that obtained by CV_A% are approximately similar.

Homogeneity and Combined Uncertainty Estimation

The coefficient of variance during sample processing (CV_{SP} %) determines the value of the sampling constant (K_S). So, the value of CV_{SP} accounts for the efficiency of sample processing. Uncertainty in sample processing varies according to the K_S. In table 1 and figure 1, it is represented that the combined uncertainty value is varying according to sampling constants obtained after the first step i.e., blending (K_S1) and second step i.e., grinding (K_S2). The sampling

constants obtained for potato dry ice both after first and second processing were shown to be very high thereby the combined uncertainty (CV $_{COMB.\ SP\%}$) was also determined to be higher i.e., 11.11%. Whereas the sampling constants obtained for potato ambient i.e., 5.9%, are comparatively lesser so their combined uncertainty was also lesser (Table 1).

From table 1 it is quite evident that the values of the sampling constant obtained from grinding (K_S2) is lower as compared to those obtained from the first step grinding (K_S1) (figure 1). This finding suggests that two-step grinding considerably increases the efficiency of sample processing and leads to better recovery of pesticides from the food matrix. This shows that homogenous mixing of the pesticide in the matrix yields pesticide efficiently from the matrix.

Table 1: Sampling constant of both the food matrices processed under different temperature conditions and combined uncertainty of sample processing.

Matrix Conditions	KS_1	KS_2	CV $_{COMB.\ SP}$ %
Potato Ambient	6.46	5.24	5.9
Potato Dry Ice	69.02	31.94	11.11

KS_1-Sampling Constant of the matrix after Ist step processing.

KS_2-Sampling Constant of the matrix after IInd step processing.

CV $_{COMB.\ SP}$ - Combined Uncertainty in sample processing.

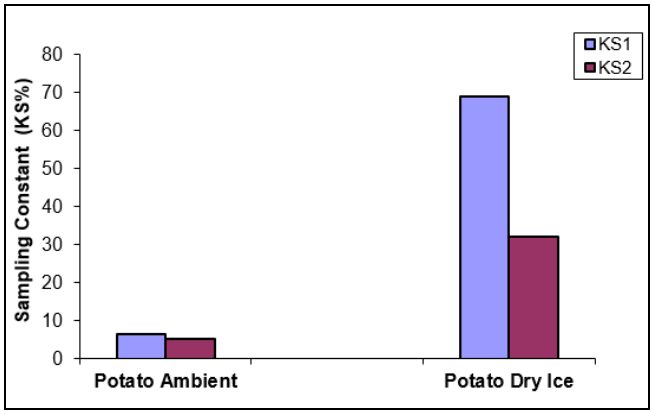

Fig 1: Comparison of sampling constant of Potato at different temperature conditions.

Percentage Recovery of ^{14}C labelled Chlorpyriphos

The graph shown in Figures 2 and 3 represents a comparative account of the percentage recovery obtained from a different analytical portion of potato and brinjal matrices processed at ambient and lower temperature conditions. It is evident from the graphs that recovery percentages obtained from analytical portions processed by two-step grinding are better than the single-step processing. The figure also represents that exceptionally, the recovery percentages of pesticide residues are comparatively higher for analytical portions sampled out from processed potatoes after the first step grinding under ambient temperature conditions. Whereas in rest of the samples processed under ambient conditions showed better recovery efficiency as compared to those processed under dry ice conditions. From table 2, it can be correlated that the percentage recoveries obtained from counting the amount of radioactive ^{14}C labeled Chlorpyrifos recovered from smaller and larger analytical portions of potato processed under similar conditions of temperature were in the ratio of 2:1.

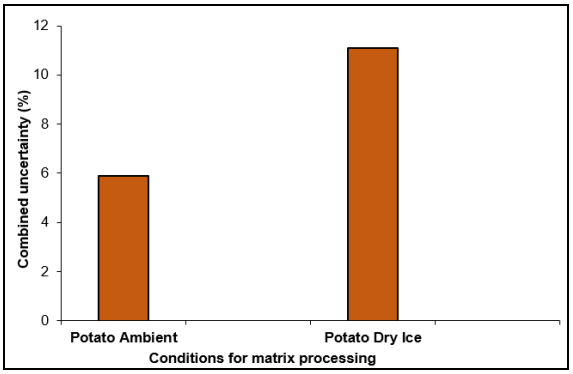

Fig 2: Comparison of combined uncertainty with Potato during their sample processing conditions.

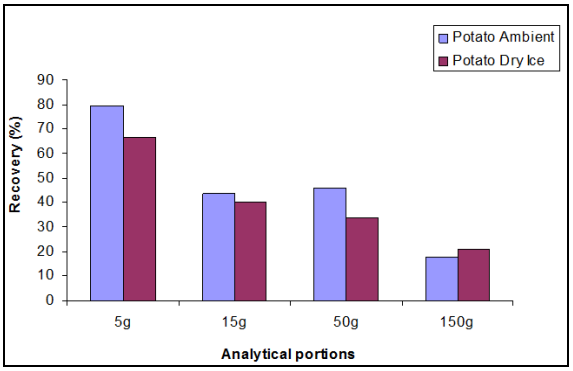

Fig 3: Comparison between Analytical portions and Percentage recovery of ^{14}C- Chlorpyriphos from Potato matrix.

Table 2: The average recovery of ^{14}C Chlorpyriphos in percentage for all the analytical portions of both the matrices processed under two different temperature conditions**.**

Analytical portions	Average Recovery of ^{14}C labeled pesticide (Chlorpyriphos) (in percentage)	
	Potato Ambient	Potato Dry Ice
5 g	79.55	66.59
15 g	43.74	40.08
50 g	46.15	33.97
150 g	17.58	20.89

Conclusion

To reduce the loss of pesticide during sample processing a procedure devised for sample processing should involve minimum transfer steps. The containers used for sample processing should be inert so the molecules of pesticides do not show any affinity towards the surface of the containers. Wholesome transfer of the food matrix from one container into another should be ensured with a negligible amount of left-over in it. The reproducible results are expected when there exists a minimum scope for uncertainty as well as least involvement of variability in the repeatably of the experiment. And the precision can be enhanced by

increasing the number of replicates taken in an experiment under consideration.

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