



## Optimization of QuEChERS method for determination of 315 pesticides residues: prelude to risk assessment using LC-ESI-MS/MS

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### Abstract

A residual analytical method for the determination of 315 pesticide compounds (including a wide range of physicochemical properties) in cereals was optimized and validated. The pesticide residues extraction was carried out using QuEChERS method and the determination was achieved using liquid chromatography tandem mass spectrometry (LC-MS/MS). Sample preparation efficiency was optimized by adding 10 ml water on 2g sample for hydration, before extracting with acetonitrile. The developed method was validated according to European Union guidelines (SANTE/2017/11813). The recovery tests were studied at three spiking levels of low concentration (0.01, 0.05, and 0.1 mg/kg). Most of the studied pesticides (301 compounds) have acceptable recovery between 70 and 120% with good precision. The developed method was successfully applied for the analysis of 60 collected cereals samples (wheat and maize) from Egyptian markets and grain storage silos. Twenty nine samples were free from any pesticide residues while 9 pesticides were found in 31 samples without exceed Codex and EU MRL limits. Finally, the residue data was used for estimation of dietary risk employing FAO/WHO approach.

**Keywords:** Pesticide residues; Grains; Wheat; Maize; LC-MS/MS; QuEChERS.

### Introduction

Wheat (*Triticum aestivum* L.) is one of the most essential cereal crops. Therefore, about 765 million tons of wheat grains were produced during 2019/2020<sup>[1]</sup>. Wheat, maize, and rice are considered staple grain, constituted as necessary food components for human health in Egypt<sup>[2]</sup>. Maize (*Zea mays*) is described as a common grain used worldwide as a dietary supplement for human food, and as both grain feed and fodder for livestock, due to its high content of carbohydrates and fibres. It is fed to the livestock<sup>[3]</sup>. Nevertheless, a good protein and oil content were found in maize with mineral compounds<sup>[4]</sup>. About 17% (1.3 billion) of the world population suffers from micronutrient deficiencies, while 11% (820 million) are undernourished in terms of energy intake<sup>[5]</sup>. However 35% of human population depend on wheat for their nutrition<sup>[5]</sup>. The high global population growth rates encouraged scientists to develop synthetic pesticides as an effective tool to protect agricultural products from pest attacks.

Therefore, it is necessary to control the application of these compounds using residue analysis Codex guidelines<sup>[6]</sup> and EU regulation<sup>[7]</sup>. The European Commission (2018) referenced that about 1000 pesticides can be used for crop protection<sup>[7,8]</sup>. The pest control program using chemical pesticides may have a potentially harmful effect on human health, and the environment. Therefore, maximum residue limits (MRLs) were established by many countries and governing organizations to control food risk, by regulating pesticide concentrations when used, and during trading operations<sup>[9,10]</sup>.

A referenced QuEChERS extraction procedure was developed and found to be significantly effective in the detection of pesticide multiresidues, including a wide range of polarities suitable for analysing dry herbal matrixes, by adapting the water amount added, and the hydration time<sup>[11]</sup>. Forbidden or restricted usage of pesticides needs an action plan to safeguard human health from the effects of these harmful substances<sup>[12]</sup>. Moreover, using the lowest limits in residue

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quantitation helps to monitor agricultural products in markets.

The aim of the study was to optimize and validate QuEChERS extraction method as an analytical procedure, using tandem mass spectrometry determination for 315 pesticide compounds in cereal samples. Wheat and maize are selected as representative matrix samples. Besides, an evaluation of the risk assessment is conducted for wheat and maize samples collected from Egyptian markets and grain storage silos.

## Experimental

### Monitoring area and sampling procedures

Sixty samples were collected from Egyptian markets, 30 wheat and 30 maize covering 5 different regions area (Cairo, Giza, Alexandria, Damietta and Beni-Suef). All samples were taken one kg from Egyptian markets (5 wheat and 5 corn samples from each regions) and one kg tacked from 50 kg packages from grain storage silos (2 samples from each regions) during September and October 2021. Risk assessment was carried out for all samples results in accordance to JMPR (FAO/WHO Joint Meeting of Pesticide Residue) using FAO evaluation model<sup>[13]</sup>.

### Chemicals and reagents

Solvents were qualified and purchased as follow: Methanol, Acetonitrile, HPLC grade, and Toluene,  $\geq$  99.9% Merck (Germany); Formic Acid 98-100%, and Ammonia Solution 33%, Riedel-de Haen; and de-ionized water generated by Millipore water-purification system (USA). QuEChERS extraction reagents, such as magnesium sulphate, sodium chloride, sodium citrate, and citric acid disodium salt were purchased already mixed in one package (Agilent Technologies). The final extract was filtered using Millipore syringe filter 0.45  $\mu$ m. Pesticide Reference Standards of Purity > 95% were prepared by Dr. Ehrensdorfer (Germany). Waring 7011HS 2-Speed Heavy-Duty Lab Blender (USA) was used for samples homogenizing.

### LC-MS/MS analysis

Liquid solid separation was done using Exion LC and API 6500+ Qtrap tandem mass from AB Sciex with electro-sprayer ionization (ESI) interface. Poroshell-C<sub>18</sub> column (3.0 x 50 mm, and 2.7  $\mu$ m particle sizes) was purchased from Agilent, USA. A mobile phase elution of 0.3 mL/min flow rate was adjusted for 16 minute in a gradient mixing as follow: 0 – 1 (A, 60%), 11.5 (A, 10%), 12 - 13 (A, 0%) and 14 – 16 (A, 60%), where A bottle was 10 mM pH4 ammonium formate buffer in methanol /water 1/9, and B bottle was methanol. LC-MS/MS ion source was in tune with an electrospray probe, and adjusted in the positive mode while the nebulizer, curtain, and collision gas were adjusted at 45 (G1, G2), 25 and 8 litre/min using nitrogen. Source temperature was set at 400°C, and

voltage at 5500 volt ion spray potential. Decluster potential, and collision energy were in tune for each analyte individually using direct infusion. Double MRM (Multiple Reaction Monitoring) was optimized for each pesticide, as quantitation and confirmation detection.

### Pesticide standards preparation

All the tested pesticides were individually prepared in Toluene at 1000  $\mu$ g/mL concentration as stock standard solution. A standard mixture from all analytes was collected and diluted in methanol at 5  $\mu$ g/mL. Instrument calibration solution mixtures were prepared in six levels (0.001, 0.002, 0.005, 0.01, 0.05, and 0.1)  $\mu$ g/mL in methanol. Individual pesticide solutions were stored at  $-18 \pm 2^\circ\text{C}$ , while other standard solutions were put in storage at  $4 \pm 2^\circ\text{C}$ .

### Extraction method

Two grams from the sample was weighed into 50 mL polyethylene (PFTE) tube before adding 10 ml of deionized water, and mixed for 5 sec by vortex. After 10 mins of sample hydration with water, 10 ml acetonitrile were added, then homogenized using geno/ grinder device (500 rpm) for 1 min. A second homogenization step was done after adding QuChERS reagent, and followed by 5 mins of centrifugation at 4000 rpm. The filtration of an aliquot was done by 0.45  $\mu$ m syringe filter before LC-MS/MS injection<sup>[11]</sup>.

### Calibration and matrixes matched standards

Any suppression or enhancement in analyte signal during the injection into the sample matrix was defined as matrix effect, since it is necessary for adjusting the results<sup>[14]</sup>. This phenomenon could be described as the reduction in the ionization efficiency of analytes produced by the remaining matrix components<sup>[15]</sup>. The final sample extract was injected into LC-MS/MS, and estimated using 6 calibrations levels diluted by acetonitrile. Moreover, matrix matched standards were prepared at 0.05 mg/ml to avoid matrix suppressions or enhancements during detection. One  $\mu$ l injection volume was also established to reduce matrix effects. A low amount of the injected volume enhanced sensitivity by reducing matrix effect, and improving chromatographic resolution<sup>[16,17]</sup>. Matrix effect when using ESI source was defined as the analyte ionization reduction found when injecting target analyte in extracted sample matrix<sup>[17]</sup>. An analytical study supported the use of 10mM pH4 as a buffer mobile phase with 315 wide-range polarity pesticides in dry samples, in order to grow the best possible sensitivity<sup>[11]</sup>.

## Results and discussion

### Method validation

Validation of the selected parameters, and accepted criteria were based on Eurachem guideline on method validation<sup>[18]</sup> and the guidance document on analytical

quality-control and method-validation procedures for pesticide residue analysis in food and feed<sup>[19]</sup>. The results of six replicates for 3 levels (0.01, 0.05, and 0.1 mg/kg) were used in performing the analytical method, using wheat and corn blank samples.

#### **Method linearity and limit of quantification**

Linearity estimation was evaluated using six standard concentrations (0.001, 0.002, 0.005, 0.01, 0.05, and 0.1 µg/ml) as shown in figure 1, including all analytes. Limit of detection (LOQ) was estimated using signal to noises ratio; Mevinphos pesticide was found the lowest analyte signal with value 4.8 signal/noise when using 0.001 µg/mL. Limit of quantification (LOQ) was found to be 0.01 mg/kg as the lowest possible amount detected with precise repeatability, for all the tested analytes.

#### **Extraction efficiency**

Recovery data show an accurate recovery (70-120%), and precise relative standard deviation (less than 20%) for 301 pesticides. On the other hand, 12 pesticides existed at 20% in their RSD, when 8 analytes were not enough to be covered with at least 70% in all replicates. Regarding these problematic compounds, it is clear that some of them, such as Acephate, Flonicamid, Monocrotophos, Omethoate, Oxydemeton methyl, Thiocyclam, and Dimethoate were found to be similar in their log octanol water (-0.89, 0.3, -0.22, 0.74, -0.74, -0.07, and 0.7, respectively), which refers to the effect of the high starch content in this sample (60-75%). Another observation revealed the effect of corn starch on reducing pesticide residues from the surface of basil leaves. This phenomenon could also be enhanced with a lower value of log octanol water<sup>[20]</sup>. Low signal should affect analyte sensitivity during analysis, due to the unstable accuracy. An amenable GC-MS/MS compound showed some incompatibility when using LC determination, such as Pymetrozine, Fenvalerate, Parathion methyl, Profluralin, T-Fluvalinate, and Fenitrothion. Low sensitivity was the compelling reason for the failure of some pesticides, such as Fenitrothion, Fenvalerate, Parathion-Ethyl, Parathion-Methyl, Profluralin, and Pymetrozine, to achieve a good recovery (70 to 120%), during the process of validating the method for multiresidue determination in dry herbal products<sup>[11]</sup>. Other factors played a big role in precision evaluation, such as analyte ionization during LC-MS/MS determination; insufficient ionization energy led to lower signal sensitivity. A relationship between these pesticides, such as parathion methyl and tebufenozide (pKa: 9.7 and 10.8), led to lower ionization power when using mobile phase pH = 4. A basic dissociation constant analyte suppressed the signal when injected into sample matrix using acid mobile phase pH<sup>[11]</sup>. Furthermore, the analyte could be already ionized in positive mode when using mobile phase of pH two units below the analyte pKa value<sup>[21]</sup>. The highest

pooled CV was found to be 20% for phorate, while the lowest mean recovery in Qtype was 73% for oxamyl, with SD 18.6, for 6 replicates. The relative standard uncertainty was found to be 10.4%, where t tab was 2.57, and t calc. was 3.56, for 5 degrees of freedom. The possible uncertainties due to reference standard preparation (volumetric flasks, balance, pipettes, pesticides standard purity, solvents, and micropipettes) were found to be 0.7%. Finally, UC (combined uncertainty) was found to be 22.7%, while the expanded uncertainty using a coverage factor (k =2) for a confidence level 95% was found to be ± 45%.

#### **Monitoring and dietary intake risk assessment**

Wheat and maize are the most important and the largest in food consumption. Therefore, pesticide residue determination should be conducted before and during their distribution. In the present study, 60 samples were collected, in order to investigate the possible risk on the Egyptian population. A validated method was used for 60 sample screenings of the tested pesticides. Figures 2, 3, 4 and 5 showed the total ion chromatogram with selected MRM for blank sample, calibration standards mixture 0.05 µg/mL, spiked sample 0.1 mg/kg and one from contaminated maize samples supported by found analytes. Results were evaluated under the EU and CODEX MRL regulation, as shown in table 1.

Table 2 shows that primiphos methyl was the most detectable pesticide in 18 samples while tetramethrin was detected in only one sample. Moreover, the highest risk was found due to the present of chlorpyrifos and chlorpyrifos methyl in samples while other contaminates represents no risk for short term evaluation. Focusing on the results of long term risk assessment deltamethrin represent the highest risk followed by profenfos than chlorpyrifos methyl (0.59, 0.19 and 0.1 respectively). All pesticides residues results were found in values less than EU and CODEX MRL limits except three pesticides Chlorpyrifos, chlorpyrifos methyl and profenfos which detected in two samples with values exceeded the EU MRL limits.

In India 2020 a pesticides residues monitoring was done for the determination of 72 LC-MS/MS and GC-MS/MS amenable pesticides, 150 rice samples were analyzed during this study. Only 2 pesticides compounds (carbendazim, acephate) were exceeded the EU-MRL in some samples. Moreover, this Indian screening resulted profenfos, deltamethrin and cypermethrin in 16, 2 and 5 % respectively from analyzed samples [22]. Also, primiphos methyl was found in 4 wheat samples in a south Brazil monitoring program 2015 [23].

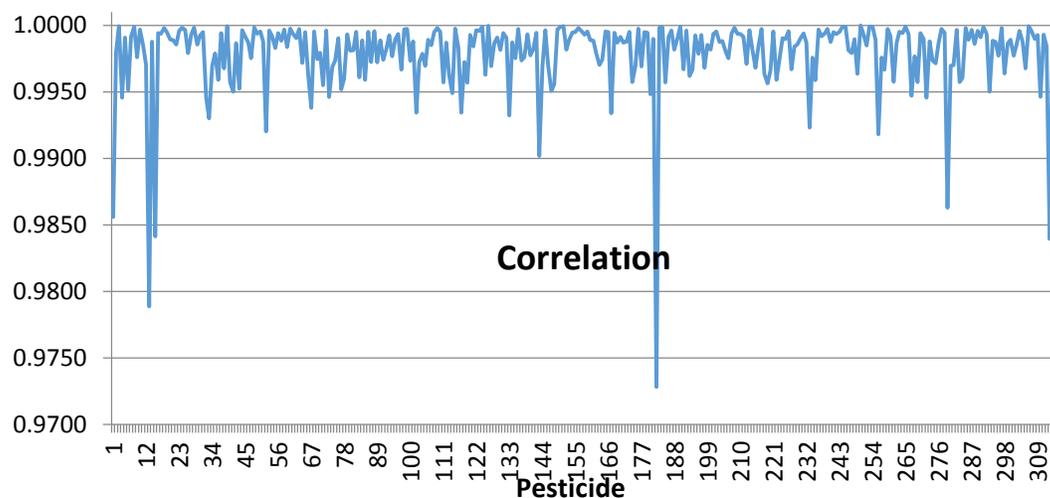


Figure 1. Pesticide Standards linearity calculated by correlation coefficient for all analytes using six levels of calibration.

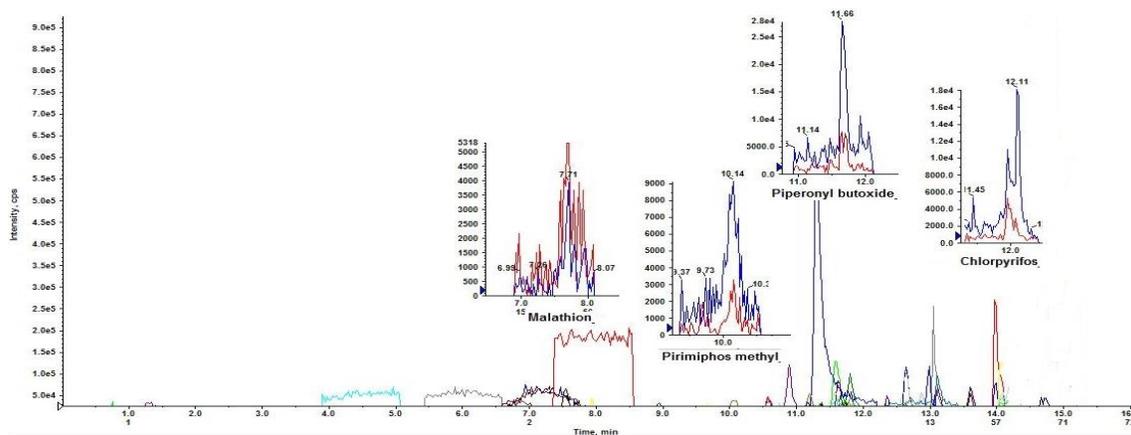


Figure 2. Total ion chromatogram supported by selected analyte peaks for founded pesticides in corn blank sample.

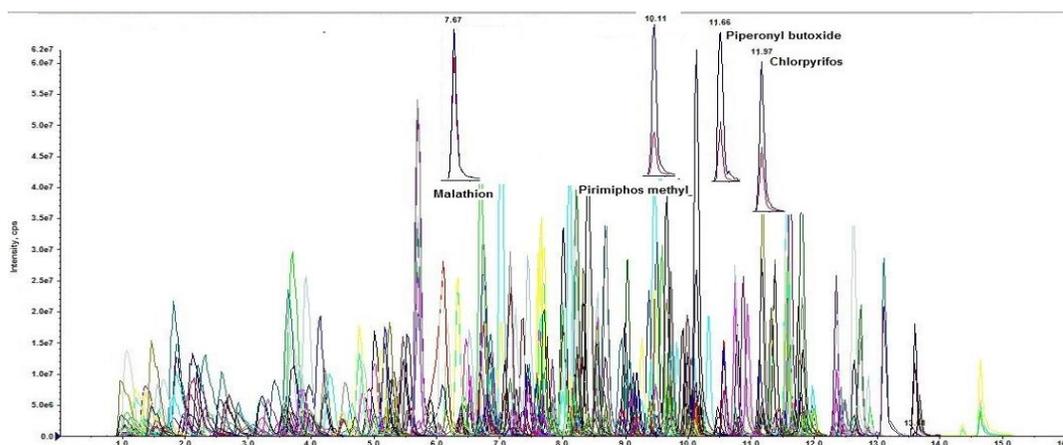
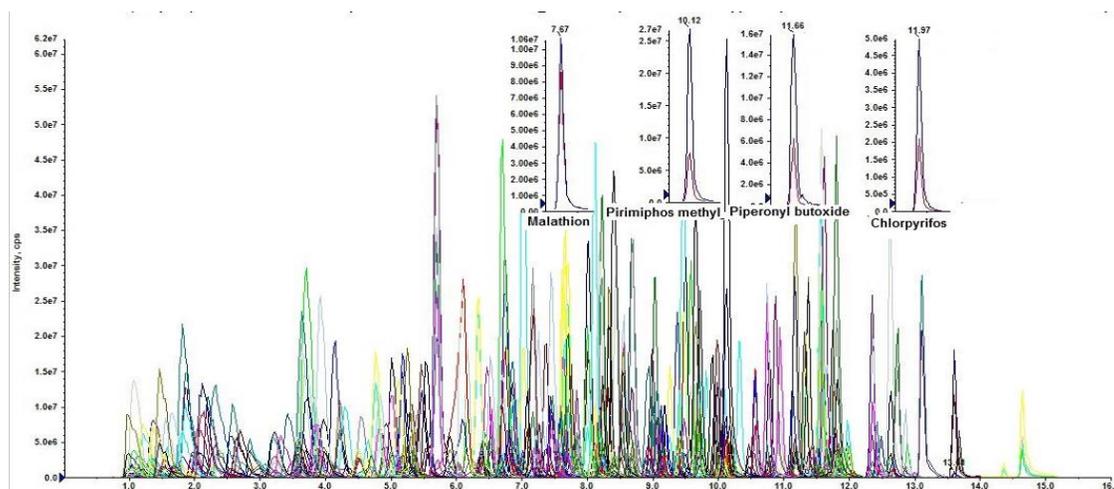
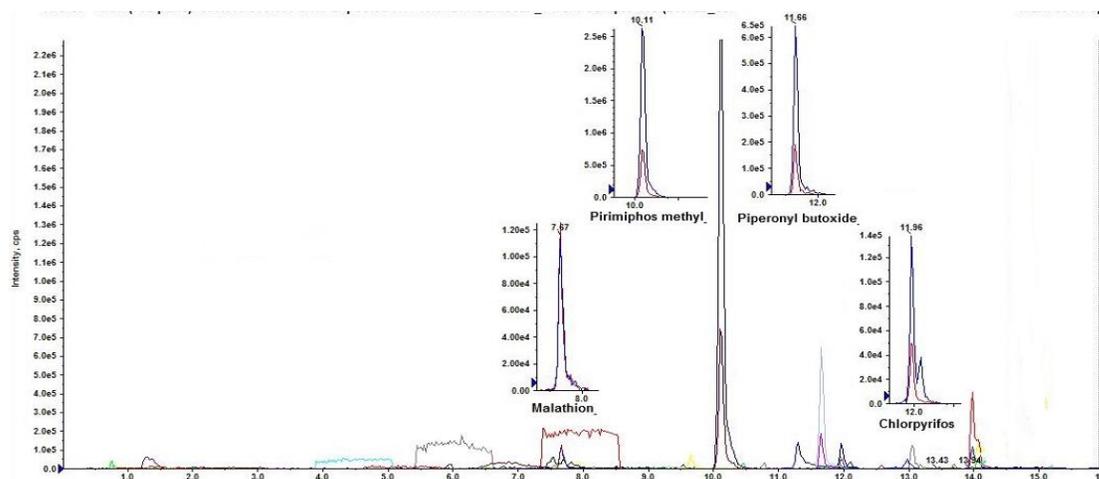


Figure 3. Total ion chromatogram of standards in solution (0.05 mg/kg) supported by 4 founded pesticides in a corn contaminated sample.



**Figure 4.** Total ion chromatogram of corn spiked sample (0.1 mg/kg) supported by 4 founded pesticides in a corn contaminated sample.



**Figure 5.** Total ion chromatogram of a corn contaminated sample supported by 4 founded pesticides.

All residue results were calculated before taking their medians, in order to assess the acceptable daily intakes (ADI) in accordance to JMPR (FAO/WHO Joint Meeting of Pesticide Residue) using FAO evaluation model. ADI and ARD values were found to be between 0.01 and 2 mg/kg bw, as shown in table 2, with regard to their dietary exposure, and risk quotient. The evaluated results revealed that the dietary risk of wheat and maize supported by 60 samples, using the tested method under the specific conditions, were insignificant and within the acceptable range, designating that they could be safely used for treatment of the tested grains. However, 9 out of the 315 tested pesticides were found in 60 samples, which indicated a low risk for the short-term and long-term evaluations. The highest estimated daily-intake value

was shown for deltamethrin (0.59 %), while when estimating the short-term risk, it was found for chlorpyrifos (2 %). On the other hand, 6 pesticides were found without any detected short-term risk, due to the detected low concentration, in comparison with their ARD. In addition, an exception in evaluation was done for tetramethrin, using unreferenced ADI value (0.01) to check for long-term risk, which resulted in a low risk (0.01 %) due to its presence in only one sample with LOQ result. Finally, there was no unacceptable risk found for the intake of raw wheat and maize in Egypt during this study.

**Table 1. Number of contaminated sample, Codex and EU MRL, median of residual results and risk study evaluation (short and long terms) using ADI and ARfD.**

Pesticides	Wheat			Maize			ADI	ARfD	L.T. Risk %	S.T. Risk %			
	N sample	MRL EU mg/kg	MRL Codex mg/kg	Median mg/kg	N sample	MRL EU mg/kg				MRL Codex mg/kg	Median mg/kg	M & K	W
Chlorpyrifos methyl	1	0.01	3	0.01	NF	0.01	NF	0.01	0.01	0.1	0.1	0	0.04
Chlorpyrifos	9	0.01	0.5	0.01	4	0.01	0.05	0.01	0.01	0.1	0.02	2	1
Cypermethrin	3	2	2	0.01	12	0.3	NF	0.01	0.02	0.04	0.01	0	0
Deltamethrin	5	1	NF	0.01	7	2	NF	0.01	0.01	0.05	0.59	0	0
Malathion	5	8	10	0.01	3	8	0.05	0.01	0.3	2	0.0007	0	0
Piperonyl butoxide	5	NF	NF	0.01	9	NF	NF	0.01	0.2	1.5	0.001	0	0
Pirimiphos methyl	6	5	NF	0.01	12	0.5	NF	0.01	0.03	0.2	0.007	0	0
Profenofos	4	0.01	NF	0.01	NF	0.01	NF	0.01	0.03	1	0.196	0	0
Tetramethrin NH4	1	0.01	NF	0.01	NF	0.01	NF	0.01	NF	N.F	0.01*	NF	NF

L.T: long term, S.T: short term, M: men, K: kids, W: women, N: number, MRL: maximum residue limit, ADI: acceptable daily intake, ARfD: acute reference dose, bw: body weight. \*: default MRL of 0.01 mg/kg according to art 18 (1)(b) regulation 396/2005.

**Table 2. Monitoring of 60 grain samples includes: founded pesticides and number of samples related to residual concentration.**

pesticides	Wheat, N of samples			Maize, N of samples				
	N.D	<LOQ (0.004-0.006) mg/kg	Low Value (0.010-0.190) mg/kg	High Value (0.20-1.310) mg/kg	N.D	<LOQ (0.004-0.006) mg/kg	Low Value (0.010-0.190) mg/kg	High Value (0.20-1.310) mg/kg
Chlorpyrifos-Me	29	-	-	1	30	-	-	-
Chlorpyrifos	21	-	9	-	26	2	2	-
Cypermethrin	27	-	3	-	18	2	10	-
Deltamethrin	25	3	1	1	23	1	2	4
Malathion	25	1	4	-	27	1	2	-
Piperonyl butoxide	25	-	4	1	21	2	2	5
Pirimiphos methyl	24	1	5	-	18	-	11	1
Profenofos	26	2	2	-	30	-	-	-
Tetramethrin	29	-	1	-	30	-	-	-

**N.D:** Residual concentration not detected or less than 0.004 mg/kg.

### Conclusion

The optimized analytical procedures were found to be effective in 315 pesticide compounds, resulting in good recoveries and accepted precision. The collected samples from Egyptian markets were found unviolated, as less pesticide residue concentrations were detected, in comparison with their EU and Codex MRL. The risk assessment achieved safe results when evaluated for long-term and short-term risks using FAO model.

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