ORIGINAL PAPER

PESTICIDE RESIDUE SCREENING IN CITRUS FRUITS BASED ON GAS CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY AND HEALTH RISK ASSESSMENT

BRADUT – BOGDAN MINEA[1], CRISTIANA RADULESCU[1,2,3*]

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Abstract. *Lately, there is maximum concern in most states, all over the world, regarding the levels of pesticide residues in food products, considering their chemical properties with direct implications on human health. Many studies have shown that the adverse effects of cumulative exposure to multiple pesticide residues are far more severe than any single exposure. Statistically, the number of food alerts generated by the presence of pesticide residues in fruits on the market, between 2017 and 2021, as well as the situation related to the number of imports and intra-EU trade that took place during the same period was highlighted. This study aims to analyze pesticide residue levels in citrus fruits (i.e., lemons, grapefruit, and orange) imported from non-EU and EU countries, comparative with maximum residue limits (MRLs) provided by Regulation 2005/396/EC, to assess if intake levels pose a long-term risk to human health. The citrus samples collected from ten markets (retail and storage areas) in Romania, were prepared according to the procedure provided by EN 15662:2008 standard. The concentration of pesticide residues from citrus samples was determined by Gas Chromatography-Tandem Mass Spectrometry (GC-MS/MS). The results obtained by GC-MS/MS showed that from 52 citrus samples, 41 samples contained pesticide residues with values between 0.005 and 2.700 mg/kg, and several samples contained forbidden active substances (e.g., spirodiclofen and o-phenylphenol). The pesticide detection rate of the samples was 78.84%. The most frequently detected pesticides according to obtained results were imazalil, thiabendazole, pyrimethanil, pyraclostrobin, fludioxonil, as well as spirodiclofen and o-phenylphenol. The samples with the most detected active substances are from imports outside of the European Union. In addition, in several samples, simultaneously occurred four or even five mixed pesticide residues, hazardous to human health. This study shows that the presence of pesticide residues is constant in citrus fruits due to phytosanitary treatments carried out on crops in the development phase as well as on fruits in the storage phase treatments (e.g. insecticides, fungicides, etc.).*

Keywords: *citrus; pesticide residue; GS-MS/MS; maximum residue limit; RASFF.*

1. INTRODUCTION

Recent research reported that common foods and beverages, vegetables, water, wine, fruit juices, snacks, milk, and meat, may contain pesticide residues [1-5]. These hazardous

[1] National University of Science and Technology Politehnica Bucharest, Doctoral School Chemical Engineering and Biotechnology, 060042 Bucharest, Romania. Email: ingbradut@yahoo.com.
[2] Valahia University of Targoviste, Institute of Multidisciplinary Research for Science and Technology, 130004 Targoviste, Romania.
[*] *Corresponding author: radulescucristiana@yahoo.com; cristiana.radulescu@valahia.ro.*
[3] Valahia University of Targoviste, Faculty of Sciences and Arts, 130004 Targoviste, Romania.

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chemicals can cause a whole series of diseases in humans through ingestion [6-10]. Pesticides in food can pose a risk to humans, especially for children, in terms of skin, gastrointestinal, respiratory, reproductive, endocrine, and neurological diseases [11-17]. Several studies revealed that exposure to dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DD), malathion, parathion, and dimethoate caused endocrine dysfunction and promote tumor growth [17-21].

Briefly, the term "pesticide" refers to any substance intended to prevent, destroy, attract, repel, or control any pest, including unwanted species of plants or animals, being used in the production, storage, transport, distribution, and processing of food, agricultural products or animal feed. The term covers chemical compounds applied to crops before or after harvest to prevent spoilage during storage and transport. On the other hand, the term pesticides is attributed to substances intended for use as a plant growth regulator, defoliant, desiccant, fruit thinning agent, or germination inhibitor [22-25]. Fertilizers, animal and plant nutrients, feed additives, and animal drugs are usually not included in this definition [23, 25]. "Pesticide residues" refer to any specific compounds remaining after the use of a pesticide on plants, in food, primary agricultural products, or animal feed. The term refers to all pesticide derivatives, including contaminants with health risks, as well as conversion products, metabolites, reaction products, and other by-products [26-31].

Pesticides can be classified according to (a) their source: organochlorines, organophosphorus, carbamates, pyrethrins and pyrethroids [24]; (b) controlled pests: insecticides, fungicides, herbicides, rodenticides, insect repellents, acaricides, ovicides, nematocides [23]; persistence in soil: very stable - persistence > 18 months (i.e., organochlorines, pesticides containing metals), stable - persistence < 18 months (i.e., urea compounds and triazines), moderately stable - persistence < 12 months (i.e., amide and benzoic acid derivatives), unstable - persistence < 6 months (i.e., phenoxyacetic herbicides, toluidines), pesticides that disappear quickly (carbamic herbicides) [32].

The toxicity class of pesticides is established according to the acute oral lethal dose (LD_{50}), expressed in mg/kg body. It is given by the degree of danger of the respective product in a simplified way. Depending on the toxicity of pesticides, they are classified as follows: Class I - ("T+") LD_{50} = <50 mg/kg body - extremely toxic; Class II - ("T") LD_{50} = 51-200 mg/kg b.w. - highly toxic; Class III - ("Xn") LD_{50} = 201-1000 mg/kg b.w. - moderately toxic; Class IV - ("Xi") LD_{50} = >1000 mg/kg b.w. - weakly toxic [23]. Considering the above, Romanian legislation provides a special regime for phytosanitary substances in toxicity classes I, II, and III according to Ord. no 41/2007, chapter II, art. 15 [33].

The highest amount of pesticide residue, which can legally be found in/on contact with food or feed, is known as the Maximum Residue Limit (MRL), according to EC Regulation no 396/2006. In this regard, any active chemical substance used in food/feed/plant protection must have approval from the European Commission through a rigorous evaluation process [29]. In addition, without prior authorization, plant protection products cannot be used or placed on the market. Therefore, two important rules such as EC no. 1107/2009 which serves as the main regulatory framework for plant protection products, and EC no. 396/2005 cover every aspect of the legal restrictions on the amount of pesticide residues that can be present in food and feed are widely respected/implemented at European level [34, 35]. The last rule includes guidelines for government oversight of pesticide residues that may result from their use for plant protection in food.

Given the comprehensive set of Regulations, Directives, and Decisions at the European level to ensure food and feed safety, the European Union has implemented one of the highest food safety systems in the world. The Rapid Alert System for Food and Feed (RASFF), one of the tools that guarantee food safety, was created to ensure the exchange of information between member countries and to help the rapid action of food safety authorities in the event of threats to public health, throughout the food chain. Article 50 of Regulation (EC) no. 178/2002, generally referred to as the General Food Law, serves as its legal basis [36]. According to Regulation (EC) number 1715/2019, RASFF must ensure, first of all, the prevention of entering in the food market that poses a risk to people's health, and ensure that they are removed as quickly as possible from the food chain by the competent authorities of the EU member states [37]. Between 2017 and 2021 in Romania, there was a worrying increase in food alerts based on pesticide residues in/on fruits and vegetables in terms of imports (Table 1). At the same time, it seems that there was a close correlation related to the increase in imports and intra-EU trade in the category of mentioned agri-food products.

Table 1. The import and intra-EU trade of vegetables and fruits, from 2017 to 2021 in Romania markets.

No.	The year	Imports number of fruits and vegetables*	Intra-EU trade number of fruits and vegetables*
1.	2021	23812	34889
2.	2020	25047	28631
3.	2019	21364	33759
4.	2018	19796	30971
5.	2017	16055	27552

**data provided by the National Sanitary Veterinary and Food Safety Authority (NSVFSA) on the 3rd of August 2022 (notification no 11763 from the 3rd of August 2022, which are the basis of the statements mentioned above*

Table 1 shows that the imports of vegetables and fruits increased in Romania by approximately 48%, respectively by approximately 27% of intra-EU trade. These values are closely related to the increase in the number of food alerts for fruits/vegetables imported from third countries or intra-community exchanges.

Table 2 highlighted that the main fruit exporting countries, especially Turkey, Ecuador, Poland, and Netherlands, were among through main suppliers of fruits and vegetables that had pesticide residues. The values of pesticide residues exceeded the maximum limits allowed by Regulation 2005/396/EC and generated a constant increase in the number of alerts in the RASFF system at the level of Romania (from 4 alerts in 2017 to 25 alerts in 2021, Table 2).

Table 2. RASFF notifications* regarding the number of alerts generated by pesticide residues in/on vegetables and fruits, from 2017 to 2021, in Romania.

No.	Year	Alert notifications number	Information notifications number	Incriminated products	Origin
1.	2021	25	16	Grapefruit, peppers, mangoes, tomatoes, lemons, pears, pomegranates, bananas, oranges, onions, scallions, potatoes, broccoli, apricots, cherries, parsley, quinces, apples and lettuce	EU (3) and non-EU (7)
2.	2020	4	10	Grapes, lettuce, peppers, bananas, grapefruit, lemons, limes, and oranges	Non-EU (3)

No.	Year	Alert notifications number	Information notifications number	Incriminated products	Origin
3.	2019	3	2	Pomegranates, tomatoes, apples and melons	EU (2) and non-EU (3)
4.	2018	8	2	Apples, goji berries, grapes, celery, lettuce, peppers and green onions	EU (4) and non-EU (3)
5.	2017	4	1	Apples, bell peppers, kapia peppers, grapes and goji	EU (3) and non-EU (1)

**Data provided by the National Sanitary Veterinary and Food Safety Authority (NSVFSA) on the 3rd of August 2022 (notification no 11763 from the 3rd of August 2022, which is the basis of the statements mentioned above)*

In addition, it was noted that some countries outside the European Union (i.e., non-EU) have different legislation from the European Community, which allows them to set values above the maximum limits allowed by Regulation 2005/396/EC [34]. Instead, EU countries including Romania should control primary production more closely in terms of phytosanitary treatments in vegetables and fruits, so as not to exceed the maximum residue limits (MRLs), according to Regulation 2005/396/EC [34].

Further, Fig. 1 shows an alarming increase in the number of alerts generated by pesticide residues in fruits and vegetables in the amount of approximately 600%, respectively of information notifications of approximately 1600%. It was also noticed by the European Food Safety Authority (EFSA) [38] that almost the same countries of origin of the incriminated products are found every year (i.e., from EU and non-EU countries).

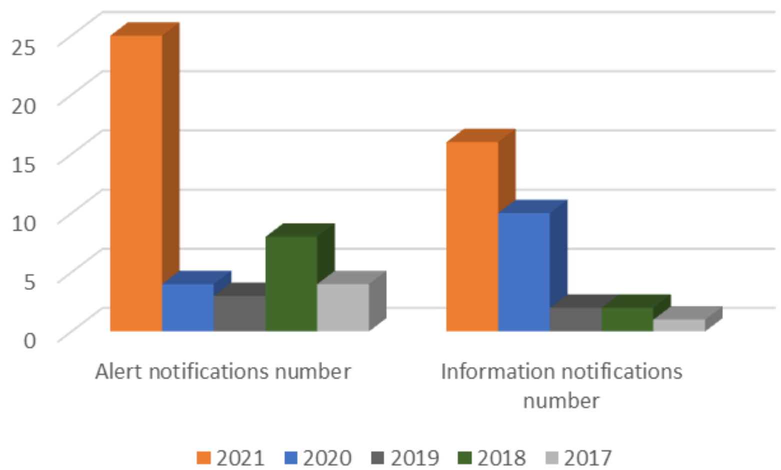


Figure 1. The number of alerts regarding pesticide residues between 2017 and 2021 in Romania.

Starting from the aforementioned data, this study aims (1) to analyze pesticide residue levels in citrus fruits (i.e., lemons, grapefruit, and orange) imported from non-EU and EU countries, (2) whether citrus residues comply with maximum residue limits (MRLs), (3) to assess if intake levels pose a long-term risk to human health. To achieve the objective (3), the obtained results related to the content of pesticides in citrus fruits were compared with toxicological reference values (generally the acceptable daily intake or acute reference dose, namely ADI value or AR_fD value).

2. MATERIALS AND METHODS

2.1. CHEMICALS AND REAGENTS

All the chemicals were of analytical-reagent grade (Sigma-Aldrich, NJ, USA). Pesticide reference standards, of 99% purity, of all analytes were purchased from Chem Service, Inc. (West Chester, PA, USA) and were stored in a freezer at −20 °C to minimize degradation. Milli-Q ultrapure water was used for dilution (Waters, Milford, MA, USA). The secondary amine sorbent (PSA, 40 μm, Bondesil) was purchased from Varian Inc., USA.

2.2. SAMPLING AND SAMPLE PREPARATION

Citrus fruit samples (Table 3) were collected from ten markets from two cities in Romania (i.e., Bucharest and Targoviste, Muntenia Region), of EU/non-EU countries origin.

Table 3. The coded citrus samples and the country from which they were imported.

Sample code	Citrus fruit sample	Provenience
L01-I	Lemon	Non-EU
L02-I	Lemon	Non-EU
L03-I	Lemon	Non-EU
L04-I	Lemon	Non-EU
L05-I	Lemon	Non-EU
L06-I	Lemon	Non-EU
L07-I	Lemon	Non-EU
L08-I	Lemon	Non-EU
L09-I	Lemon	Non-EU
L10-I	Lemon	Non-EU
L11-I	Lemon	Non-EU
L12-I	Lemon	Non-EU
L13-I	Lemon	Non-EU
L14-I	Lemon	Non-EU
L15-I	Lemon	Non-EU
L16-I	Lemon	Non-EU
L17-I	Lemon	Non-EU
L18-I	Lemon	Non-EU
L19-I	Lemon	Non-EU
L01-S	Lemon	EU
L02-S	Lemon	EU

Sample code	Citrus fruit sample	Provenience
P01-I	Orange	Non-EU
P02-I	Orange	Non-EU
P03-I	Orange	Non-EU
P04-I	Orange	Non-EU
P05-I	Orange	Non-EU
P06-I	Orange	Non-EU
P07-I	Orange	Non-EU
P08-I	Orange	Non-EU
P09-I	Orange	Non-EU
P10-I	Orange	Non-EU
P11-I	Orange	Non-EU
P01-S	Orange	EU
P02-S	Orange	EU
P03-S	Orange	EU
P04-S	Orange	EU
P05-S	Orange	EU
P06-S	Orange	EU
P07-S	Orange	EU
P08-S	Orange	EU
P09-S	Orange	EU
P10-S	Red orange	EU
G01-I	Grapefruit	Non-EU
G02-I	Red grapefruit	Non-EU
G03-I	Grapefruit	Non-EU
G04-I	Grapefruit	Non-EU
G05-I	Red Grapefruit	Non-EU
G06-I	Red Grapefruit	Non-EU
G07-I	Red Grapefruit	Non-EU
G08-I	Grapefruit	Non-EU
G09-I	Grapefruit	Non-EU
G10-I	Grapefruit	Non-EU

To achieve the first objective of this research, the prepared citrus samples were analyzed by GC-MS/MS in terms of pesticide residue content. The sampling procedure was performed according to Order 2004/147/RO [39]. Sample preparation stages involve the first preparation of the standard solution of 1000 mg/L. To obtain the desired concentration, weigh 10 mg of analytical standard, then pass quantitatively through a 1000 mL volumetric flask with isooctane:toluene (9:1 v/v), then bring to the mark. Further, a standard working solution of 5 mg/L was obtained from the standard solution of 1000 mg/L, using the isooctane:toluene mixture (9:1 v/v); finally, from the standard working solution, the calibration solutions were prepared. For pesticide extraction, a quantity of 7.5 g of sample is homogenized into a centrifuge tube and then stirred with 15 mL of acetone and 37.5 µL of TPP internal standard (concentration 10 mg/L) for 2 minutes. After 30 minutes of rest, 15 mL of methylene chloride and 15 mL of petroleum ether are added, and then the mixture is stirred once more for about 3 minutes. It is centrifuged for 10 minutes at 4000 rpm, and then 15 mL of the organic extract is evaporated in an RV3 proV Complete rotary evaporator (IKA-Werke GmbH & Co. KG Germany) until it is almost dry. At room temperature, it evaporates to a dry state. Finally, was added 3 mL of isooctane: toluene mixture (9:1 v/v) to resuspend the residue.

2.2. GAS CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY

The high sensitivity and selectivity of Gas Chromatography-Tandem Mass Spectrometry (GC-MS/MS) enable the identification and quantification of prohibited pesticide residues in various fruits, in compliance with the residue definitions, even in trace concentrations. In the GC-MS/MS technique, a tandem mass spectrometer is used, which allows to selection of specific analytes for individual fragmentation and thus, the complex mixtures, including pesticide residues, can be analyzed more readily. In addition, the GC-MS/MS method is successfully used for trace analysis of organic compounds but can also be used for quantitative workflows by comparison of signals to different standards. Taking into consideration these advantages, in this study, the pesticide residues analysis of 52 citrus samples was performed by 3800 Varian GC-MS/MS system (Varian Inc., USA). The mass spectrometer used for GC-MS/MS uses a beam of electrons to ionize analytes, which allows the decomposition of the analytes during ionization and, as well as more sensitive fragmentation during the MS/MS stages. Data were acquired, processed, and reported using Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) software. The performance of the method was tested following the SANTE/11813/2017 guidance document [41]. For each sample, residue results were calculated and expressed as mean values of three replicates. The following operating conditions are used: the thermostated enclosure is maintained at 50ºC for 1 minute then the temperature is gradually increased, 30 ºC/min up to 200 ºC, 2º C/min up to 215 ºC, 1ºC/min up to 230 ºC, 2ºC/min up to 260 ºC and 20 ºC/min up to 300 ºC. The following parameters are respected: the fragmentation gas is argon; injector = 270 ºC; the carrier gas is He with a flow rate of 1.5 mL/min; splitting flow rate is 20 mL/min; injection type is split; ionization energy = 70 eV; the temperature of the source is 175 °C; filament voltage is 50 µA; the temperature of the transfer line is 250 °C.

3. RESULTS AND DISCUSSION

Citrus fruits are part of the family *Rutaceae* and are grouped under the genus *Citrus* [42]. This genus has been divided into 159 species [43]. Ye X. revealed that precisely determining the number of species in citrus is very difficult, due to clonal variation, as well as the hybridization process [43]. On the other hand, citrus flavor is complex and difficult to characterize. According to the classification achieved by Richa et al, the most cultivated citrus species are: *Citrus sinensis* (sweet orange), *Citrus aurantium* (bitter orange), *Citrus limon* (lemon), *Citrus reticulata* (tangerine/clementine), and *Citrus paradisi* (grapefruit) [43].

Table 4. The bioactive compounds of the main citrus fruits and human health benefits [43, 45-53]

Citrus fruit	Group of compounds / Metabolites	Functional properties
Lemon - whole fruit (pulp, seed and peel) [43,48,50]	**Flavonoids**: *flavanones* (eriocitrin, eriodiktyol, hesperidin, naringin, neoeriocitrin, neohesperidin); *flavones (*apigenin, diosmetin, diosmin, homoorientin, luteolin, orientin, vitexin); *flavonols* (isoramnethin, quercetin, limocitrin, rutoside, spinacetin) **Phenolic acids**: ferulic acid, 3-(2-hydroxy-4-methoxyphenyl)propanoic acid, synaptic acid, *p*-hydroxybenzoic acid **Carboxylic acids**: citric acid, galacturonic acid, glucuronic acid, glutaric acid, homocitric acid, 3-hydroxymethyl glutaric acid, isocitric acid, malic acid, quinic acid **Carbohydrates**: monosaccharides: arabinose, fructose, β-fructofuranose, β-fructopyranose, galactose, glucose, mannose, myoinositol, rhamnose, scylloinositol, xylose **Amino acids**: L-alanine, L-arginine, L-asparagine, L-aspartic acid, dimethylglycine, glutamic acid, L-phenylalanine, DL-proline, L-tryptophan, L-tyrosine, L-valine **Coumarins:** citropten (5,7-dimethoxycoumarin), scopoletin), **Vitamins and their metabolites:** choline, pantothenic acid (vitamin B_5), trigonelline, vitamins C, A, B_1, B_2 **Macroelements:** calcium (Ca), magnesium (Mg), phosphorus (P), potassium (K), sodium (Na)	It helps digestion, improves immunity, prevents the accumulation of kidney stones, and improves the health of the epidermis. In addition, shows protection to the coronary, renal, and gastrointestinal systems
Orange (pulp, seed and peel) [43,47, 52]	**Flavonoids:** *flavanones* (hesperidin, naringenin, naringin); *flavones (*apigenin, luteolin); *flavonols* (quercetin, limocitrin) **Carotenoids:** β-carotene, lutein, β-cryptoxanthin **Carboxylic acids**: citric acid **Terpenes:** linalool, limonene, menthol **Amino acids:** L-alanine, L-leucine, isoleucine, L-aspartic acid, L-phenylalanine, threonine, cytidine, L-valine, L-adenosine, DL-lysine, L-proline betaine **Carbohydrates**: fructose, sucrose, galactose, glucose, limonin glucose **Vitamins and their metabolites:** vitamins C, A, E, B_6, thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (vitamin B_5), choline **Macroelements:** calcium (Ca), magnesium (Mg), phosphorus (P), potassium (K), zinc (Zn), manganese (Mn), iron (Fe) **Dietary Fiber**	Anti-cancer properties, boosting immunity due to increased intestinal absorption, lowering blood pressure, and reducing heart disease.
Grapefruit (pulp, seed and peel) [43,49, 53]	**Flavonoids:** *flavanones* (neohesperidin, hesperidin, poncirin, naringenin); *flavones (*rutin, narirutin); *flavonols* (quercetin, limocitrin) **Carotenoids:** β-carotene, α-carotene, lutein, lycopene, β-cryptoxanthin **Terpenes:** β-myrcene, α-pinene, sabinene; monoterpene oxide: carvone, cis-limonene oxide, trans-limonene oxide; sesquiterpene: caryophyllene, β-cubebene, α-copaene **Amino acids:** L-alanine, L-phenylalanine, threonine, cytidine, L-valine **Carbohydrates**: fructose, glucose, limonin glucose **Vitamins and their metabolites:** vitamins C, A, B_1, B_2, B_3 **Macroelements:** Ca, Mg, P, K, Zn, Na, Fe **Dietary Fiber**	Reduces blood pressure, prevents blockage of blood vessels, improves blood circulation, prevents cellular aging, increases immunity, regulates digestion, and prevents degenerative diseases such as Alzheimer's.

Citrus fruits, with their role as a valuable functional food and beneficial effect on human immunity, are included in the current diet of all age groups (from children to the elderly), due to their high content of flavonoids, vitamins, carbohydrates, phenolic acids, macroelements and (Table 4) [43, 45-53]. Several studies revealed that the *Citrus* genus can contain at least 100 unique volatile components [51, 52].

It can concluded that citrus fruits (i.e., lemon, orange, and grapefruit) contain high levels of ascorbic acid and flavonoid antioxidants including naringin and naringenin (Table 4) [51-53]. In addition, ascorbic acid (vitamin C) plays a key role in the formation of collagen, a primary component of much of the connective tissue in the body [43]. Considering the real health benefits of citrus bioactive compounds, it is understandable that any substance that can modify/destroy their structure and properties (mainly with the formation of stable clusters) represents a major risk for humans. The pesticides present in citrus fruits, regardless of the structure/class/dose, have a negative impact on the functional properties of the fruit. This research highlighted the fact that the presence of pesticide residues is constant in citrus fruits, and this fact is mainly due to the phytosanitary treatments carried out both on the crops in the development phase and on the fruits in the storage phase (e.g. insecticides, fungicides, etc.).

Ensuring and improving fruit quality in terms of safety involves the use of nano-pesticides in the future. Also, nano-fertilizers are a new solution for developing sustainable and modern agriculture. Thus, on hand the nano-pesticides have the properties of eco-friendly, target-specific, and controlled release, thus improving the utilization of pesticides and significantly reducing the level of pesticide residues and environmental pollution, on the other hand, nano-fertilizers improve the yield and nutrition of crops by slowly and target-specifically release of their into plants. The best example is the use of sodium and boron nano-fertilizer on pomegranate, which significantly improves the product quality, as shown by Davarpanah et al. (2016) in their study [54].

The use of nano-pesticides and nano-fertilizers is a valuable alternative, but the screening of pesticides in fruits must be continuously monitored, due to historical pollution and the long-term use of different pesticides in the context of climate change. Also, a more careful evaluation of imported fruits, especially from outside the EU, is necessary by establishing common rules regarding the use of forbidden pesticides in particular, but also the maximum limits allowed for pesticide residues.

The results obtained by GC-MS/MS technique showed that from 21 lemon samples, 18 samples (85.71%) contained pesticide residues with values between 0.005 and 2.700 mg/kg (Table 5). Several samples contained forbiddenactive substances, i.e., spirodiclofen (L02-I) and *o*-phenylphenol (L02-I, L06-I, and L10-I, from non-EU area), and the most dangerous sample turned out to be sample L02-I which contains both pesticides in a mixture, forbiddenby the Romanian rules, together with another dangerous pesticide, such as malathion (Table 6). Out of the 21 samples, three samples (4.41%) were found to be free of pesticides (i.e., L03-I, L14-I from non-EU and L02-S from EU). The most frequently detected pesticides according to results presented in Table 4 were imazalil (L04-I, L05-I, L07-I, L08-I, L09-I, L11-I, L12-I lemon samples from non-EU and L01-S from EU), thiabendazole (L04-I, L07-I, L09-I, L10-I, L11-I, L13-I samples from non-EU), pyrimethanil (L01-I, L08-I, L11-I, L12-I, L15-I, L16-I, L17-I, L18-I, L19-I samples from non-EU) pyraclostrobin (L17-I, L18-I, L19-I), fludioxonil (L08-I, L11-I, L12-I, L15-I, L16-I).

The samples with the most detected active substances were from outside the European Union; thus, some analyzed samples had pesticide residues from several categories, even four or five active substances/sample such as L08-I contains 1.400 mg/kg azoxystrobin, 1.300 mg/kg fludioxonil, 2.300 mg/kg imazalil, and 0.790 mg/kg pyrimethanil; L12-I contains 0.099 mg/kg azoxystrobin, 0.014 mg/kg fludioxonil, 0.700 mg/kg imazalil, and 0.480 mg/kg pyrimethanil; L11 - I contain 0.690 mg/kg azoxystrobin, 0.680 mg/kg fludioxonil, 1.560

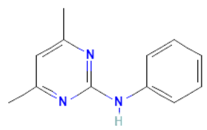
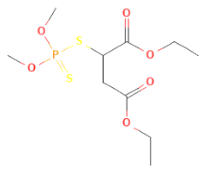
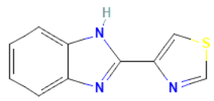
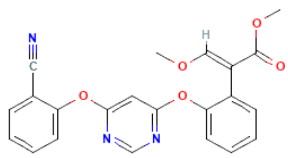
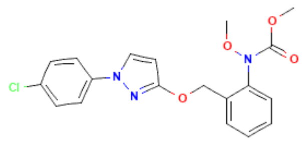
mg/kg imazalil, 1.320 mg/kg pyrimethanil, and 0.550 mg/kg thiabendazole (Table 5). For a better understanding, Table 6 shows the chemical structure, molecular formula, IUPAC name, and class of compounds/pesticides [55-57].

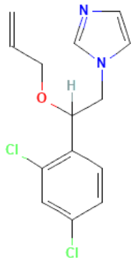
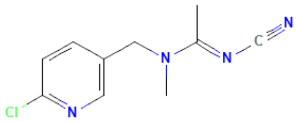
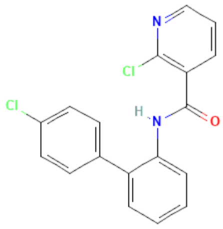
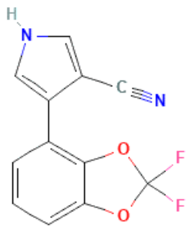
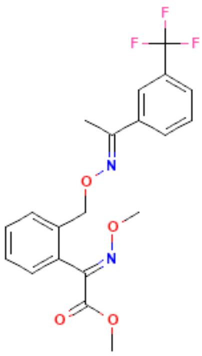
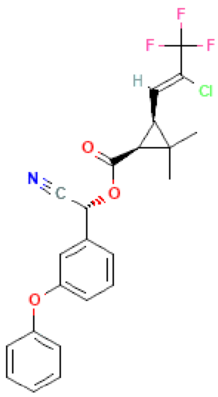
Table 5. The concentration of active substances in lemon samples.

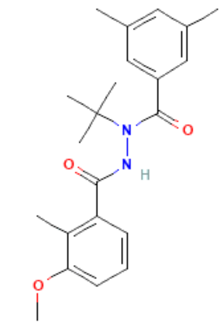
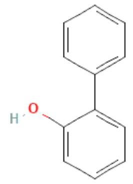
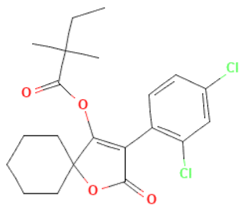
Sample code	Active substance	Concentration [mg/kg d.w.]
L01-I	Pyrimethanil	0.071±0.002
	Malathion	0.035±0.001
L02-I	Malathion	0.124±0.002
	o-Phenylphenol	0.014±0.001
	Spirodiclofen	0.015±0.001
L04-I	Imazalil	2.400±0.002
	Pyraclostrobin	0.015±0.001
	Thiabendazole	2.700±0.255
L05-I	Imazalil	0.650±0.025
L06-I	Malathion	0.127±0.008
	o-Phenylphenol	0.028±0.001
L07-I	Imazalil	0.420±0.028
	Thiabendazole	0.120±0.055
L08-I	Azoxystrobin	1.400±0.140
	Fludioxonil	1.300±0.550
	Imazalil	2.300±0.620
	Pyrimethanil	0.790±0.050
L09-I	Imazalil	1.900±0.250
	Thiabendazole	0.240±0.150
	Trifloxystrobin	0.014±0.001
L10-I	Lambda-cyhalothrin	0.063±0.002
	o-Phenylphenol	0.190±0.010
	Thiabendazole	0.340±0.050
L11-I	Azoxystrobin	0.690±0.050
	Fludioxonil	0.680±0.030
	Imazalil	1.560±0.150
	Pyrimethanil	1.320±0.120
	Thiabendazole	0.550±0.050
L12-I	Azoxystrobin	0.099±0.012
	Fludioxonil	0.014±0.001
	Imazalil	0.700±0.100
	Pyrimethanil	0.480±0.030

Sample code	Active substance	Concentration [mg/kg d.w.]
L13-I	Thiabendazole	0.760±0.050
L15-I	Azoxystrobin	0.120±0.010
	Fludioxonil	0.220±0.010
	Pyrimethanil	1.020±0.250
L16-I	Pyrimethanil	2.700±0.560
	Pyridaben	0.011±0.001
	Fludioxonil	0.570 ±0.050
L17-I	Pyrimethanil	1.200±0.350
	Pyraclostrobin	0.016±0.001
L18-I	Pyrimethanil	0.025±0.002
	Pyraclostrobin	0.005±0.001
L19-I	Pyrimethanil	0.230±0.020
	Pyraclostrobin	0.005±0.001
L01-S	Imazalil	0.700±0.100

Table 6. The chemical structure, IUPAC name, and class of pesticide [55-57].

Active substance	IUPAC name	Molecular formula	Chemical structure	Class of pesticide
Pyrimethanil	4,6-dimethyl-N-phenylpyrimidin-2-amine	$C_{12}H_{13}N_3$		Aminopyrimidine - fungicide
Malathion	diethyl 2-dimethoxyphosphinothioyl sulfanylbutanedioate	$C_{10}H_{19}O_6PS_2$		Parasympathomimetic organophosphate compound -insecticide
Thiabendazole	4-(1H-benzimidazol-2-yl)-1,3-thiazole	$C_{10}H_7N_3S$		Benzimidazole - fungicide
Azoxystrobin	methyl (E)-2-[2-[6-(2-cyanophenoxy) pyrimidin-4-yl]oxyphenyl]-3-methoxyprop-2-enoate	$C_{22}H_{17}N_3O_5$		Nitrile, aryloxypyrimidine - fungicide
Pyraclostrobin	methyl N-[2-[[1-(4-chlorophenyl)pyrazol-3-yl]oxymethyl]phenyl]-N-methoxycarbamate	$C_{19}H_{18}ClN_3O_4$		Carbamate ester - fungicide

Active substance	**IUPAC name**	**Molecular formula**	**Chemical structure**	**Class of pesticide**
Imazalil	1-[2-(2,4-dichlorophenyl)-2-prop-2-enoxyethyl]imidazole	$C_{14}H_{14}Cl_2N_2O$		Imidazoles - fungicide
Acetamiprid	N-[(6-chloropyridin-3-yl)methyl]-N'-cyano-N-methylethanimidamide	$C_{10}H_{11}ClN_4$		Carboxamidine - neonicotinoid insecticide
Boscalid	2-chloro-N-[2-(4-chlorophenyl)phenyl]pyridine-3-carboxamide	$C_{18}H_{12}Cl_2N_2O$		pyridinecarboxamide – fungicide
Fludioxonil	4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1H-pyrrole-3-carbonitrile	$C_{12}H_6F_2N_2O_2$		Benzodioxole - fungicide
Trifloxystrobin	methyl (2E)-2-methoxyimino-2-[2-[[(E)-1-[3-(trifluoromethyl) phenyl]ethylideneamino]oxymethyl] phenyl]acetate	$C_{20}H_{19}F_3N_2O_4$		Oxime O-ether, organofluorine compound – foliar fungicide
Lambda-cyhalothrin	[(R)-cyano-(3-phenoxyphenyl)methyl] (1S,3S)-3-[(Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate	$C_{23}H_{19}ClF_3NO_3$		Cyclopropanecarboxylate ester - insecticide

Active substance	IUPAC name	Molecular formula	Chemical structure	Class of pesticide
Metoxifenozide	N'-tert-butyl-N'-(3,5-dimethylbenzoyl)-3-methoxy-2-methylbenzohydrazide	$C_{22}H_{28}N_2O_3$		Carbohydrazide - insecticide
o-Phenylphenol	2-phenylphenol	$C_{12}H_{10}O$		Hydroxybiphenyls - fungicide
Spirodiclofen	[3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl] 2,2-dimethylbutanoate	$C_{21}H_{24}Cl_2O_4$		Dichlorobenzene - organochlorine acaricide

The data presented in Table 7 showed that from 21 orange samples analyzed by GC-MS/MS, 14 samples (66.66%) were found with pesticide residues with values between 0.024 and 1.060 mg/kg, several samples containing forbiddenactive substance, i.e., *o*-phenylphenol; out of the 21 samples, seven samples (33.33%) were found to be free of pesticides (i.e., P01-I, P02-I, P05-I, P07-I, P08-I from non-EU countries and P03-S, P05-S from EU countries). The samples with the most detected active substances are from outside of the European Union; two samples, P06-I and P10-I, among those analyzed, presented pesticide residues from several categories, with the same four active substances/sample, i.e., *o*-pheniphenol, imazalil, pyrimethanil, and thiabendazole (Tables 6 and 7).

Table 7. The concentration of active substances in orange samples.

Sample code	Active substance	Concentration [mg/kg d.w.]
P03-I	Azoxystrobin	0.086±0.020
	Imazalil	0.400±0.010
	Thiabendazole	0.067±0.001
P04-I	*o*-Phenylphenol	0.329±0.050
	Imazalil	0.370±0.020
	Pyrimethanil	0.300±0.010
P06-I	*o*-Phenylphenol	0.110±0.050
	Imazalil	0.720±0.020
	Pyrimethanil	0.320±0.010
	Thiabendazole	0.480±0.020
P09-I	Imazalil	0.098±0.001
P10-I	*o*-Phenylphenol	0.270±0.010
	Imazalil	0.560±0.020
	Pyrimethanil	0.140±0.010
	Thiabendazole	0.270±0.010
P11-I	*o*-Phenylphenol	0.300±0.020

Sample code	Active substance	Concentration [mg/kg d.w.]
P01-S	Fludioxonil	0.148±0.010
	Imazalil	0.154±0.010
	Thiabendazole	0.120±0.010
P02-S	Imazalil	0.200±0.020
P04-S	Imazalil	0.160±0.010
P06-S	Fludioxonil	0.024±0.001
	Thiabendazole	0.200±0.010
P07-S	*o*-Phenylphenol	0.109±0.001
P08-S	Pyraclostrobin	0.025±0.001
	Acetamiprid	0.024±0.001
P09-S	Imazalil	1.060±0.250
P10-S	Imazalil	0.390±0.010
	Pyrimethanil	0.200±0.010

The results presented in Table 8 showed that from 10 grapefruit samples analyzed by GC-MS/MS, 9 samples (90%) contained pesticide residues with values between 0.023 and 1.560 mg/kg, only one sample, G08-I, containing forbiddenactive substance, i.e., *o*-phenylphenol, and one sample (1.0%) revealed absence of pesticide residues (i.e., G01-I from non-EU countries). All analyzed samples originated from outside of the European Union, and only the G08-I sample among those analyzed, presented pesticide residues from several categories, with the same five active substances/sample, i.e., malathion, *o*-pheniphenol, imazalil, pyrimethanil, and thiabendazole (Tables 6 and 8).

Table 8. The concentration of active substances in grapefruit samples.

Sample code	Active sample	Concentration [mg/kg d.w.]
G02-I	Boscalid	0.036±0.001
G03-I	Imazalil	0.980±0.010
	Pyraclostrobin	0.013±0.001
	Thiabendazole	1.560±0.250
G04-I	Pyrimethanil	0.065±0.001
	Thiabendazole	1.190±0.520
G05-I	Pyrimethanil	0.580±0.050
	Thiabendazole	0.660±0.020
G06-I	Imazalil	0.340±0.010
	Pyrimethanil	0.750±0.020
	Thiabendazole	0.340±0.010
G07-I	Acetamiprid	0.017±0.001
G08-I	Malathion	0.024±0.001
	o-Phenylphenol	0.100±0.010
	Imazalil	0.500±0.010
	Pyrimethanil	0.130±0.001
	Thiabendazole	0.920±0.025
G09-I	Malathion	0.023±0.001
	Imazalil	0.830±0.020
	Thiabendazole	1.160±0.050
G10-I	Acetamiprid	0.060±0.001
	Metoxifenozid	0.330±0.010
	Pyraclostrobin	0.077±0.001

The European Commission has recently committed to reducing the total amount of chemical pesticides used and the associated risks, as well as the amount of more dangerous pesticides used, by 50% by 2030. These are plant protection products (PPPs) which, in accordance with Regulation 1107/2009/EC, contain active ingredients that either meet the limit criteria or are recognized as potential substitutes. This choice is a component of the European Commission's Farm to Fork strategy, which is a special initiative of the European Green Deal [58]. The requirements for the authorization of new active substances and the periodic renewal of those that have already been authorized are becoming increasingly rigorous, according to the provisions of Regulation 1107/2009/EC and Regulation 396/2005/EC respectively. Taking into account that the maximum residue limits are established according to the existing toxicological information, regarding the maximum residue limit for imazalil in lemons (5.0 mg/kg d.w.) and the maximum residue limit for oranges/grapefruit (4.0 mg/kg d.w.) European Safety Authority Food Authority (EFSA) found that some information on the toxicity and stability of metabolites during storage is missing. In this regard, according to Regulation 2005/396/EC two active substances such as *o*-phenylphenol and spirodiclofen (Table 6) are no longer approved at the level of the European Union from 2023 and 2020 respectively (Table 9), and in Romania *o*-phenylphenol it is forbidden to be used as fungicide.

Regarding the maximum residue levels, no exceeding of the values according to Regulation 396/2005/EC was found, but, taking into account the toxicological parameters (ADI, ARfD and AOEL), it can be said that there are health risks for those people who consume daily larger quantities than the usual average or other categories of consumers (e.g. vulnerable consumers, elderly and sick people, as well as children).

Table 9. Active substances - maximum residual limits, toxicological information, approved substances (EU PESTICIDES DATABASE according to Regulation 2005/396/EC).

Nr.crt.	Active substance	Approval date	Approval expiry date	MRLs* value [mg/kg bw]	Toxicological information (Data taken from EU - PESTICIDE DATABASE on 19th November 2023 according to Regulation 2005/396/EC)		
					ADI*/ [mg/kg b.w./day]	ArfD* [mg/kg b.w.]	AOEL* [mg/kg b.w./day]
1	Pyrimethanil	01.06.2007	15.03.2025	8.0	0.17	-	0.12
2	Malation	01.05.2010	31.07.2026	2.0	0.03	0.30	0.03
3	Thiabendazole	01.01.2002	31.03.2032	7.0	0.10	0.10	0.07
4	*o*-Phenylphenol	01.01.2010	31.12.2023	10.0	0.40	-	0.40
5	Spirodiclofen	01.08.2010	31.07.2020	0.5	0.015	-	0.009
6	Azoxistrobin	01.01.2012	31.12.2024	15.0	0.20	-	0.20
7	Pyraclostrobin	01.06.2004	31.01.2024	2.0	0.03	0.003	0.015
9	Imazalil	01.01.2012	31.12.2024	4.0	0.025	0.05	0.05
10	Acetamiprid	01.01.2005	20.02.2033	0.9	0.025	0.025	0.025
11	Boscalid	01.08.2008	15.04.2026	2.0	0.04	-	0.10
12	Fludioxonil	01.11.2008	15.06.2025	10	0.37	-	0.59
13	Trifloxystrobin	01.10.2003	31.07.2033	0.5	0.10	0.50	0.06
14	Lambda-cyhalothrin	01.01.2002	31.03.2024	0.2	0.0025	0.005	0.00063
16	Metoxifenozide	01.04.2019	31.03.2026	2.0	0.10	0.10	0.060

MRL - Maximum residue level; ADI - Acceptable daily intake; ARfD - Acute reference dose; AOEL - Acceptable operator exposure level.

4. CONCLUSIONS

Considering that citrus fruits and juices are considered beneficial for human health, with multiple nutritional, functional and medicinal effects, the results from this research show that most fruits on the market from Romania, especially imported ones, contain pesticide residues. Analyzing the statistical data it is observed in that period from 2017 to 2021, at the level of Romania, the number of food alerts generated by the presence of pesticide residues or forbiddenpesticides in/on fruits and vegetables has increased considerably (more than six times for alerts and sixteen times for the informative notifications); it reported that most of the agri-food products that were the basis for the generation of food alerts came from imports (third countries) and less from intra-EU trade or domestic production.

Fruit samples collected from the random ten markets from two cities of Romania contain pesticide residues in variable quantities, in a very high percentage, 85.7% of the total analyzed samples. The fact is the presence of pesticide residues in food products means a major risk due to their mutagenic potential the intake of food containing pesticide residues can lead to numerous disorders, such as dyslipidemia, diabetes, liver, kidney, and cardiovascular diseases, warrants special attention on this topic.

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