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Review

A historical review of the use of pesticides in Colombia agriculture.

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Abstract: The role that Colombia will play in terms of food supply in the coming years has generated a discussion on the agricultural practices implemented, specifically in the use of pesticides. Therefore, this article aims to provide a comprehensive and complete review of the status of pesticide use in the agricultural sector, highlighting the agri-food industry in Colombia. Currently, the use of pesticides has intensified throughout the world, generating a call for attention by governmental entities in terms of regulation. Colombia for the year 2019 presented a rate of use of 7.8 kg/ha of pesticides, placing it among the twenty countries with the highest rate. On the other hand, the quantities and economic benefits of exports and imports are growing steadily. Several organizations have focused their efforts on determining the health consequences that people exposed to chronic and/or acute intoxication may suffer. This has led to cases of cytogenetic, neurocognitive and physical effects, prompting governmental organizations to regulate the use of pesticides. Finally, the need to design pesticide management and handling systems that respond to the needs of producers and the sector, integrating international food safety guidelines, is identified.

Keywords: Agriculture; agri-food sector; analytical methods; Colombia; pesticides residues, toxicology effects.

1. Introduction

Agri-food systems have had the capacity to respond to the growing demand for agricultural products, which has led most countries to strengthen this primary sector [1]. Directly favouring economic development in the territories dedicated to this type of activities [1], facilitating the production of goods and services that contribute to the generation of employment, the improvement of the quality of life of farmers, the opening of import and/or export trade relations, among other socioeconomic factors relevant to today's economies [1, 2]. That said, agricultural systems produce an average of 11 billion tons annually between food (wheat, rice, coarse grains, oilseed crops and roots, tubers and bananas) and non-food products (natural fibers and wood) [3]. On the other hand, it is estimated that the gross value of agricultural production exceeds 3.5 billion dollars, being one of the sectors with the greatest monetary movement in developed and developing countries, untying in the perception of economic, social, environmental and political value throughout the life cycle chain of agricultural products [1-3].

However, the growing pressure on this sector to meet the food needs of an ever-increasing population has made agri-food systems environmentally unsustainable [1, 2].

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Consequently, modern agriculture is based on conventional practices that implement the use of chemical fertilizers and pesticides in large proportions, the implementation of monoculture practices, genetic modification for high-yield crops, the use of machinery that resorts to the use of fossil fuels, the lack of guidelines to delimit the agricultural frontier, and the few opportunities for technological implementation and process innovation [4-6]. These intensive and not very resilient practices generate a high level of impact in the use of natural resources, especially in the contamination of surface and subway water bodies, pollution, compaction, alteration in the structure and loss of fertility of soil horizons, loss of biodiversity, increase in production costs for the farmer, affectation of human and plant health, among other things [1-7].

In view of the above, the unfortunate management of the consumption of chemically synthesized phytosanitary substances such as herbicides, pesticides, pesticides, among others, has led to a significant increase in the use of pesticides [3-6], has aggravated the perceived consequences of conventional practices [4, 7]. Unfortunately, the traditional agricultural model visualizes the application of these products as a solution for the control of diseases originating from vertebrates, invertebrates and pathogenic organisms that can affect food production [8]. Since between 20% and 40% of crops are lost due to diseases caused by these organisms [9]. Resulting in the use of 2.56 kg of pesticides per arable hectare globally by 2019, with the American (3.7 kg/ha) and Asian (3.6 kg/ha) regions having the highest amount of pesticide application; compared to the African (0.39 kg) and European (1.66 kg) regions [9]. The agrochemical industry had a total of 36.54 billion dollars in imports and 35.51 billion dollars in exports worldwide for the same year, resulting in a total of 36.54 billion dollars in imports and 35.51 billion dollars in exports for the same year [9]. These products are so widely used nowadays that the market has a classification system taking into account their application function, target organism and active substances [8, 10].

In addition to the unbridled use of pesticides, the lack of regulatory processes, product counterfeiting, resistance mechanisms by pathogenic organisms and the impact on the environment and human health [4, 7, 8, 10, 11], have caused a strong discussion due to the costs associated with the use of substances from chemical synthesis processes and used in the pesticide sector. [10]. Currently, a large number of academic papers developed in conjunction with regulatory organizations, public and private organizations, and non-government organization (ONG) are investigating the impact of chronic and/or acute pesticide exposure on humans and ecosystems [8, 12, 13]. This has made it possible to count on work such as that led by the ONG Environmental Working Group (EWG), which annually issues the 12 food products with the highest pesticide content, highlighting fruits and vegetables such as strawberries, spinach, kale, collard and mustard greens, nectarines, apple, among others [14]. Having said that, the objective of this article is to provide a comprehensive and thorough review of the status of the use of pesticides in the agricultural sector, identifying the evolution, the implementation of instrumental techniques for the identification and possible toxicological effects associated with this type of substances, highlighting their use in the Colombian agricultural sector.

2. Pesticides

2.1. Pesticides history.

The agrochemical industry has evolved strongly in response to the increase in demand for food and non-food agricultural products, thus avoiding high rates of plant mortality throughout the life cycle of the species planted. [12]. This phytosanitary practice has been implemented since the earliest vestiges of agriculture, using sulphur (S) incineration strategies as a fumigation technique [15, 16]. The production of the first generation of pesticides based on lead (Pb), copper (Cu), mercury (Hg) and nicotine ($C_{10}H_{14}N_2$) was carried out at the beginning of the 19th century in Europe, perceiving a low rate of phytosanitary

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control efficiency and a high rate of bioaccumulation in the environment [15]. Subsequently, the green revolution, industrialization and the development of World War I and II led to the exploration of new forms and varieties of pesticide production [15–17]. As a result, the manufacture of the second generation of pesticides, which had made up for the lack of low effectiveness of the first generation, but with much higher levels of contamination and ecosystemic and human deterioration. [17, 18]. This trend of sintering new pesticides continues to grow with products such as, triazolopyridine ($C_6H_5N_3$), spinosyn A ($C_{41}H_{65}NO_{10}$), strobilurin ($C_{25}H_{30}O_7$), glyphosate ($C_3H_8NO_5P$), among others, the latter being the most sold and marketed pesticide since its introduction to the market in the 70s and 80s [15], [16]. This increase in the production and use of this type of substances was the beginning of routine instrumental analysis of pesticide residues in different agri-food, environmental and human matrices in the 1960s to the present day [17,18].

2.2. Classification, toxicology and regulation of pesticides.

Regulatory organizations classified pesticides according to their specific function, toxicity, specific action and chemical family [15, 18, 19]. The Environmental Protection Agency (EPA) classified pesticides according to their specific function as algicide (plant protection control to kill and/or retard algae growth), antimicrobials (plant protection control to kill germs and microbes), disinfectants (plant protection control to control germs and microbes), nematicides (plant protection control to control and/or kill plant pests), fungicides (plant protection control to kill fungal problems such as: mould and rust), herbicides (phytosanitary control to eliminate or inhibit unwanted plant growth), insecticides (phytosanitary control to kill and control insects), among others [19]. On the other hand, the World Health Organization (WHO) catalogues them taking into account the degree of toxicity (see Table 1) according to the median lethal dose (LD_{50} in mg/kg) and the tolerant median lethal concentration (LC_{50}) in organisms and in relation to their body weight. [20, 21].

Table 1. WHO recommended classification of pesticides by hazard.

Toxicological category	Dangerousness	DL_{50} for rats (mg/kg) body weight)	
		Oral	**Dermal**
Ia	Extremely hazardous	<5	<50
Ib	Highly hazardous	5–50	50–200
II	Moderately hazardous	50–200	200–2000
III	Slightly hazardous	Over 2000	Over 2000
U	Unlikely to present acute hazard	5000 or higher	

Source: World Health Organization (WHO), (2019).

From a commercial point of view, their regulation and classification are provided from two major segments; the first, the environment of use (domestic, agriculture, livestock, food processing industry and personal hygiene), while the second considers their presentation and method of use (gases or liquefied gases, fumigants and aerosols, powders with a particle diameter of less than 50 μm, solids and preparations in the form of tablets, liquids or baits) [19]. Similarly, pesticides are classified according to their synthesis and chemical composition (see Table 2), allowing the identification of Carbamates, Coumarin derivatives, Urea derivatives, Organochlorine (OCPs), Organophosphorus (OPPs), Pyrethroids and Triazines [22].

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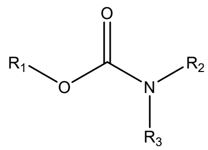
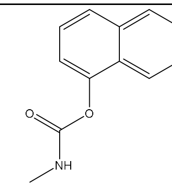
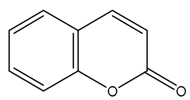
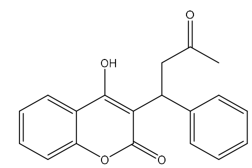
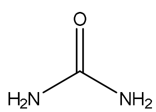
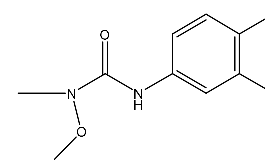
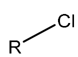
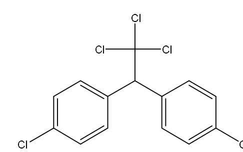
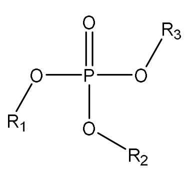
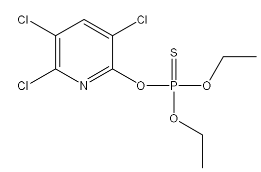
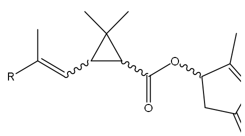
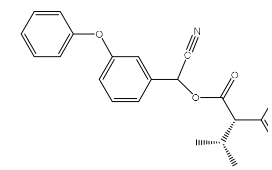
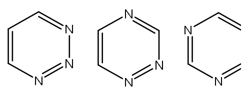
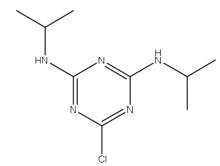
Table 2. Classification of pesticides, according to chemical family [19, 22–27].

Family	General structure	Description	Agricultural use	Example	Structure
Carbamates		Organic compounds derived from carbamic acid NH_2COOH. It is widely used for its interference in the nervous system of insects by cholinesterase enzymes.	High precision inhibitory agent for the biological control of mites and nematodes that affect the growth of plant species.	Carbaryl	
Coumarin derivatives		It is a major secondary metabolite present in the seeds, roots and leaves of several plant species. They are currently synthesized into derivatives to enhance their plant protection potential.	This type of compound plays an important role in the phytosanitary control that can be provided to plants, as it has a high spectrum of bactericidal, fungicidal and insecticidal action.	Warfarin	
Urea derivatives		Ureas are compounds that commonly a nitrogen has cyclic group substituents such as an aryl. These products are currently still under development and high spectrum of use.	A widely used herbicide that interferes with the physiological and photosynthetic activities of plants leading to the death of the target individual.	Linuron	
OCPs		It corresponds to the first generation of halogenated organic pesticides. It has a high spectrum of action and promoted the development of many chlorinated organic compounds.	Thanks to their broad spectrum of action, organochlorine pesticides are used as insecticide, fungicide, herbicide, acaricide, etc.	DDT	
OPPs		They constitute a large group of chemically synthesized compounds. Their success is related to their ability to phosphorylate the cholinesterase enzyme that regulates the transmission of nerve impulses.	Mainly used as a phytosanitary control tool to prevent the proliferation of insects and mites. With a high spectrum of action and effectiveness.	Chlorpyriphos	

Pyrethroids		They are defining as acid esters derived from cyclopropane. They are slightly toxic to mammals, decompose in soil, are soluble in water and slightly soluble in the atmosphere.	Their agricultural use is condition to insect control, with different application techniques such as spraying, vaporisation by electrical instruments, mosquito nets, among others.	Esfenvalerate	
Triazines		It is a heterocyclic compound and is among the first-generation pesticides. They are poorly soluble in water, not very selective and easily degraded in the soil by the action of plants and microorganisms.	They are a series of compounds widely used in the agricultural sector. They are currently used as herbicides due to their high spectrum of action by blocking photosynthesis.	Atrazine	

OCPs: Organochlorine Pesticides; OPPs: Organophosphorus Pesticides

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As the development and use of pesticides progressed, studies related to their impact on ecosystems and human health similarly increased [15, 18]. As a result, regulatory and academic organizations have expressed their concern about the consequences identified by chronic and/or acute exposure to this type of substances in different study matrices. [15, 18]. One of the first toxicological works compiled was entitled *"Silent Spring"* (1962), which identified the behavior of pesticides from the synthesis of chlorinated hydrocarbon-bides throughout the life cycle of agri-food products [15]. It showed an accumulation rate of 3 ppm of chlordane, heptachlor, dieldrin, aldrin, en-drin and dichloro diphenyl trichloroethane (DDT) in different products, which could increase (≥ 65 ppm) when transforming goods such as milk into butter [28]. One of the most worrying results was the bioaccumulation of pesticides in pregnant mothers and their subsequent passage to babies, since these compounds had the capacity to cross the placental barrier. [15, 19]. This study resulted in a ban on the use of DDT by EPA in 1972 in a response marked by controversy and divided opinion. [15].

That said, in order to protect consumers, regulatory organizations and countries have taken steps to standardize the amount of pesticide residues identified in agri-food products distributed for human consumption. [29]. These limits are called "maximum residue limits (MRLs)" and are related to good agricultural practices [30]. As a consequence, WHO and FAO defined MRLs in the Codex Alimentarius, evaluating the results obtained in different supervised trials on agri-food products contaminated with pesticide residues and these as they could affect humans in a possible episode of chronic and/or acute intoxication. [30, 31]. It should be mentioned that MRLs are not toxicological limits or that they are established considering their tolerable daily intake. This value refers to a threshold limit of pesticide identification that is not likely to be harmful to the consumer but clarifying that occasional consumption of products contaminated with pesticide concentrations higher than the MRL may cause chronic and/or acute toxicological effects in humans [28, 29].

This proposal has gained importance in the international context due to its recognition within the Agreement on Sanitary and Phytosanitary Measures of the World Trade Organization [30], [31], so it should be taken as a reference when analyzing pesticide residues in any agricultural product. In general, MRLs are not unique for each pesticide or commodity, with maximum thresholds between 0.01 and 10 mg/kg [30]. For example, bulb vegetables have maximum residue limits depending on the type of pesticide used (aldrin and dieldrin 0.05 mg/kg, azoxystrobin 10 mg/kg, boscalid 5 mg/kg, cyhakothrin includes lambda-cyhalothrin 0.2 mg/kg and myclobutanil 0.06 mg/kg); This same mechanism applies to most agricultural products, including grain cereals, citrus fruits, fruit vegetables, cucurbits, shelled peas, leafy vegetables, legumes, pome fruits, roots and tubers, among others [31]. These levels are constantly studied and, if necessary, modified or prohibited, especially when children are involved as a vulnerable population [30].

2.3. Analytical methods for the analysis of pesticide residues in agri-foods.

Separation and identification techniques is one of the most important aspects of any analytical method. Therefore, the conditions of the analytes, the sample pre-treatment methods and the instrumentation must be considered in order to obtain the adequate limits of detection (LODs) and quantification (LOQs) according to the current legislation and to reach the levels of reliability and reproducibility of the analysis [32, 33]. For pesticide residues, the most commonly used techniques in laboratories worldwide are gas chromatography (GC) and liquid chromatography (LC), while capillary electrophoresis (CE) has been applied to a much lesser extent [32, 33]. In fact, the first two are frequently encountered in any analytical laboratory engaged in routine pesticide analysis. With the instrumental developments of GC over time, this technique has positioned itself as one of the most widely used techniques for the analysis of thermally stable and low polarity

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pesticides due to the relatively high volatility of many pesticides, the relatively low cost of the instrumentation compared to LC or CE and the easy maintenance of the equipment [32, 33].

As for conventional detectors, they have been widely used, especially for the analysis of specific groups of pesticides. Examples are the nitrogen-phosphorus detector (NPD) and the flame photometric detector (FPD) for the analysis of OPPs and ONPs [34, 35] respectively, and the electron capture detector (ECD) for OCP due to its high level of sensitivity and selectivity that minimizes matrix interference. The flame ionization detector (FID) has also been widely used, but less frequently, due to its almost negligible selectivity [36, 37]. On the contrary, GC coupled to mass spectrometry (MS) soon gained prominence in the identification and quantification of pesticides due to its much desired confirmatory capability, as well as its higher selectivity and higher or comparable sensitivity, which are essential, especially when it comes to the analysis of highly complex matrices [38]. A detailed description of the instrumental techniques implemented for the identification of pesticide residues can be found in Table 3.

Table 3. Instrumental techniques to identify pesticide residues in agri-food products [39–48].

Instrumental technique	Description	Detectors	Benefits	Limitants	some examples of pesticides analyzed
GC	The most widely used separation technique for low polar and thermally stable pesticides due to the relatively high volatility of many pesticides	NPD, FPD, for the analysis of OPPs, ONPs ECD for OCPs, FID, MS and MS/MS.	Relatively low cost of the instrumentation compared to LC or CE and easy maintenance of the equipment	High molecular weight, highly polar, and/or thermally labile compounds	Chlorpyriphos-methyl, Chlorpyriphos, Alachlor, Triadimefon
Fast gas chromatography	Fast multiresidue analysis, achieving a better resolution and at the lowest possible cost	NPD, FPD, for the analysis of OPPs, ONPs ECD for OCPs, FID, MS and MS/MS.	Time reduction, optimizes lab capacity, implementation of standardized workflows	Separation power is very low compared to conventional capillary GC.	Pirimiphos-ethyl, Heptachlor, Aldrin
MD-GC	Detailed analysis of complex matrices.	NPD, FPD, for the analysis of OPPs, ONPs ECD for OCPs, FID, MS and MS/MS.	Multiplication of the chromatographic resolution, selectivity, sensitivity and the information obtained on the identification of the analytes	Time required for optimization and separation, as well as the complex coupling of instrumentation	Myclobutanil, Dieldrin, Oxyfluorfen.
LC	Complementary separation technique to GC, also for the analysis of pesticides. The use LC is recommended for the analysis of high molecular weight, highly polar, and/or thermally labile compounds	UV, DAD, MS and MS/MS	Analysis of high molecular weight, polar and/or thermally labile compounds.	Reagent consumption in the mobile phase is higher than in GC. Use of large amounts of organic solvents and the long analysis time.	Carbaryl, Carbofuran, Lindane
MD-LC	Analyze extremely complex samples as well as a large number of compounds	UV, DAD, MS and MS/MS	Improved sample throughput and minimize sample loss or contamination	Requires adjustment of many parameters to achieve successful separation: type of stationary phases, compatibility of mobile phases, temperature and solvent gradients, coincidence of column dimensions and flow rates, and volume of transferred fraction	Diphenylamine, Chlorpropham, Dichloran

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Capillary electrophoresis (CE)	Separation technique based on the differential migration of charged species under the action of an electric field or potential gradient that is set for that purpose	LIF, UV-VIS, DAD, MS, electrochemistry.	Provides high analysis speed, high efficiencies, ease of automation, is applicable to a wide range of compounds, requires small sample volumes and minimal reagent consumption	Low detection limits	Pirimetanil, Ciprodinil Ciromazina, Pirimicarb, Pirifenox

DAD: diode-array detection; ECD: electron capture detector; FID: flame ionization detector; FPD: flame-photometric detector; GC: gas chromatography; LC: liquid chromatography; LIF: laser-induced fluorescence; MD-GC: multidimensional gas chromatography; MD-LC: multidimensional liquid chromatography; NPD: nitrogen-phosphorus detector; MS: mass spectrometry; MS/MS: Tandem mass spectrometry; OCPs: organochlorine pesticides; ONPs: organonitrogen pesticides; OPPs: organophosphate pesticides; UV: ultraviolet.

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3. Agriculture in Colombia.

Colombia is a country located in the northwest corner of South America, with a continental shelf extension of 1,141,748 km^2 and 988,000 km^2 of maritime continental shelf; it is the fourth largest country in the region and the twenty-sixth largest in the world [49]. The neighbouring countries and regions are Panama (northwest), Antilles Sea (north), Venezuela and Brazil (east), Pacific Ocean (west) and Peru and Ecuador (south) [49, 50]. Its administrative division is made up of 32 departments, 1 capital district (Bogota) and 1,122 local administrative entities (1,103 municipalities, 18 non-municipalized areas and the island of San Andres and Providencia). [49]. Geographically, the country is in the intertropical zone of the equator and is crossed by the Andes Mountains and the Amazon plain. In addition, its relief includes landscapes of valleys and plains, peripheral mountain systems and central mountain systems [49–51]. This results in varied climatic zones, depending on the altitude at which it is located and the behaviour of rainfall. [49]. On the other hand, according to the Departamento Nacional de Estadistica (DANE), in the last population census conducted in 2018, the country has a population of approximately 48,258,494 inhabitants (inhabit); which represents a population density of 42 inhabit/km^2 and a population growth rate of 6.5%. [52]. Internally, Colombia is experiencing a phenomenon of massive displacement to urban places. As a result, 77.1% of the population is located in urban places and municipal capitals, while 7.1% in populated site and 15.8% in dispersed rural areas [52].

The agriculture has played an important role in the economic development of nations [3] and Colombia is no exception to this trend. Currently, the privileged geographical location, water resources, availability of natural resources and the variety of climates have contributed to the development of the agricultural sector as an important player in the country's economy [53]. As a result, the state is positioned among the seven nations with high agricultural potential, as well as its potential role in being catalogued as the global pantry that will respond to the increase in demand for agricultural products [53–55]. For this reason, the country has focused the efforts of multiple governmental portfolios on the design and implementation of strategies and activities that dynamize this economic sector to meet national and globalized expectations [78]. For this reason, the different social, economic and political sectors have established objectives of equity, poverty reduction, economic growth, redefinition of the rural sector, provision of environmental services and the fight against hunger [53, 54].

Now, according to data collected in the national agricultural survey conducted in 2019 by DANE, the production of agricultural goods is made up of agribusiness and agrifood derivatives with a production rate of 63,248,462 tonnes (t) and 42,208,363 tonnes (t) respectively, among which we can highlight coffee, oil palm, sugar cane, cocoa, soybeans and cotton [56]. In addition, fruit products, tubers, cereals, vegetables and legumes and forest plantations produced 6,712,167 t, 6,404,514 t, 4,423,183 t, 3,051,481 t and 448,154 t, respectively [56]. The country has excelled in export operations of exotic fruits of agrifood production, including tropical fruits such as pineapple, papaya, mango and avocado, the latter being known worldwide for being healthy and contributing to a balanced diet. [56].

3.1. Pesticides in Colombia.

As mentioned above, the role of agriculture in the Colombian economy is of vital importance; therefore, the use of pesticides has become a daily practice in most of the productive areas of the country. [57, 58]. As a result, there are a total of 530 chemical pesticide marketers for agricultural use, the use of more than 100 active agents, the authorization of use of 3064 types of pesticides and the qualified registration of 97 technical

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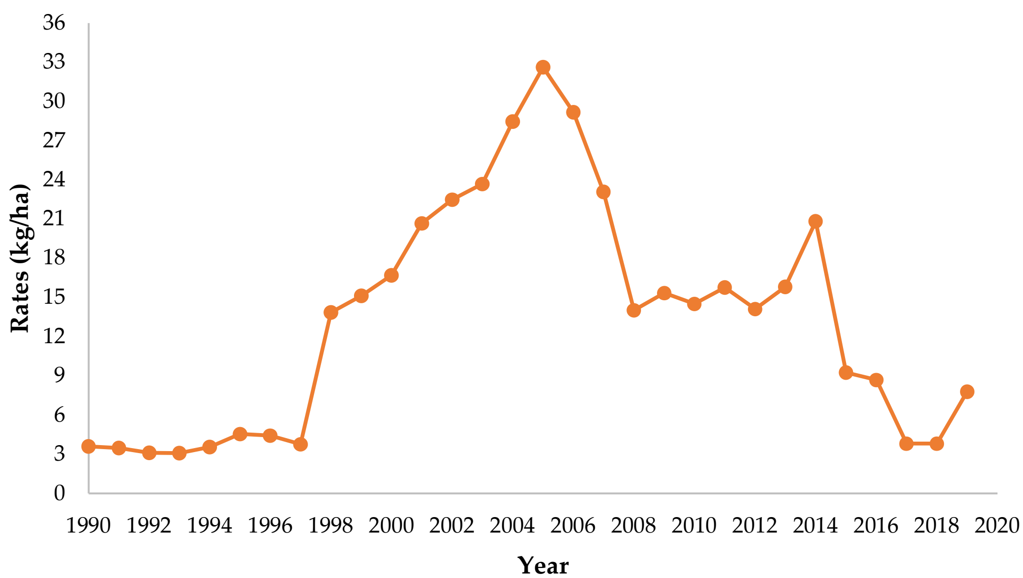
departments. [59–61]. However, the implementation of bad agricultural practices, the counterfeiting of products, the lack of knowledge on the part of producers and the lack of accurate information have set off the alarm bells of national governmental organizations [57, 58]. Emphasizing its concern for the toxicological effects related to cases of chronic and/or acute exposure that may be evidenced in humans and ecosystems, the bioaccumulation of pesticide residues in the food produced and the increase in associated production costs, considering that about 14% of total costs are related to the purchase of phytosanitary inputs for small and medium farmers [57, 58, 62, 63].

The use of pesticides in Colombia dates back to the 1970s when demand for products such as corn, cotton, potatoes, rice and coffee intensified worldwide [64, 65]. Generating an increase in the use, production, export and import of pesticides of different chemical families, mainly organochlorines and organophosphates such as dieldrin, aldrin, endrin, heptachlor, hexachlorobenzene, toxaphene and DDT [64, 65]. Currently, Colombia has a consumption of 7.8 kg/ha of pesticides for the year 2019 with a minimum of 3.1 kg/ha in 1993 and a maximum of 32.63 kg/ha in 2005 (see graph 1) [9]. Positioning it as the sixth country with the highest rate of pesticide use per hectare in the American region for the year 2019; being surpassed by Suriname (24.96 kg/ha), Saint Lucia (19.6 kg/ha), Ecuador (14.03 kg/ha), Belize (11.3 kg/ha) and Uruguay (8.03 kg/ha) [9]. On the other hand, Colombia is surpassed in the use of pesticides by countries such as: China Taiwan province (13.35 kg/ha), Hong Kong (13.75 kg/ha), Israel (12.75 kg/ha), Mainland (13.07 kg/ha), Republic of Korea (10.59 kg/ha) located in the Asian continent (3.6 kg/ha); Cyprus (9.98 kg/ha), Netherlands (8.80 kg/ha) located on the European continent (1.66 kg/ha); Mauritius (10.03 kg/ha), Seychelles (12.26 kg/ha) located on the African continent (0.39 kg/ha) and New Zealand (8.2 kg/ha) located on the oceanic continent (2.1 kg/ha) [9].

Graph 1. Pesticide use rate in Colombia 1990 to 2019.



For the year 2005, the maximum use of pesticides per hectare in Colombia is evidenced, this growth trend responds to the governmental strategies that are implemented for the constant improvement of the agricultural sector. As a result, the licit sector grew by 3.42%, which represents 71 percentage points above the previous year [66, 67]. Similarly, there has been a 7.01% decrease in the number of hectares under illicit crops, encouraging farmers to harvest products such as fruits, leafy vegetables, aromatic herbs and flowers [66, 68]. Exports grew, increasing the stock of products shipped abroad, mainly

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bananas, flowers, palm, sugar, coffee, among others [66–68]. Similarly, the reduction of unemployment, the growth of rural employment and the performance of agricultural credit boosted the development of the sector and, consequently, the increase in the use of materials required in the field, such as substances for phytosanitary control. [66].

Colombia for the year 2019 imported a total of 50,854 tons of pesticides being salt of pentachlorophend, clofenotane (INN) and antimalarial insecticides those of greater contribution; with an approximate economic value of 351,893 million dollars, being salt of pentachlorophend, oxirane (ethylene oxide) and mercury compounds, excluding amalgams those of greater contribution [9]. The country's exports are marked by the shipment of 74,472 tons of pesticides abroad, being the antimalarial insecticides, oxirane (ethylene oxide) and salt of pentachlorophend, with a total economic value of approximately 405,777 million dollars [9]. Between 1990 and 2019 there is evidence of a constant growth in the quantities and monetary value of import and export operations, which allows us to deduce the high impact of the agrochemical sector in the Colombian economy and the growth of the agri-food sector to demand more quantities of pesticides and thus ensure food safety conditions in products for national and international consumption [9].

The use of pesticides has been widespread in many regions of the country and in high-value crops such as vegetables, tubers, cereals, fruits, among others [58, 62, 63]. Data provided by the Ministerio de Agricultura y Desarrollo Rural, mentions that corn, rice, potato, cocoa, strawberry, mango, onion, Hass avocado, pineapple, among other products, present aptitudes for the commercial development of the country, with vast extensions of land for their cultivation (from 1.9 million ha to 22.2 million ha) [69]. However, the harvesting of this type of species requires a high content of phytosanitary products; this need is of concern and has attracted the attention of organizations and academia, generating case studies that focus their efforts on the identification of pesticide residues in agri-foods [58, 62, 63].

Implementing multiple analysis techniques in which we can highlight the gas chromatography, being a more economical tool, with high yield rates, a much shorter waiting time and with the ability to analyze multiple types of residues. In the same way, research seeks to have limits of detection (LOD) and quantification (LOQ) that allow the typing of pesticide residues in multiple matrices, considering the MRLs established at a global level. As a result, studies concluded a high number of pesticides in samples of junca onion, tropical fruits and vegetables, coffee, annona, cherimola and gulupa with SPME and QuEChERS sample preparation techniques and with limits of quantification 0.11-7.15 μg/kg, 0.1-1 μg/kg, 0.7-5 μg/kg, 5 μg/kg, 1 μg/kg, respectively (see table 4) [70–74]. Cabe aclarar que, en cada caso de estudio estos límites de cuantificación estaban calibrados a los límites máximos de residuos (LMR) establecidos [30]. Por ejemplo para las matrices vegetales contemplaron los LMR establecidos para pesticidas como aldrin and dieldrin (0,05 mg/kg), boscalid (40 mg/kg), clothianidin (2 mg/kg), paraquat (0,07 mg/kg), entre otros [30].

Table 4. Some examples of the application of GC-MS and GC-MS/MS and LC-MS and LC-MS/MS for the determination of pesticides in food samples from Colombia.

Number of multiclass pesticides	Matrix	Sample preparation	Analysis technique	Analyser	LOQ	References
21	Junca Onion	SPME	GC-MS	NPD	0.11-7.15 μg/kg	[70]
201	Tropical fruits and vegetables	QuEChERS	LC-HRMS	QqQ	0.1−1 μg/kg	[71]
13	Coffee	SPME	GC-MS	Q	0.7−5 μg/kg	[72]

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48	Annona cherimola and gulupa	QuEChERS	GC-MS/MS	QqQ	5 µg/kg	[73]
50	Exotic fruits	QuEChERS	GC-MS	Q	1 µg/kg	[74]

GC-MS: Cromatografía de gases espectrometría de masas; GC-MS/MS: Cromatografía de gases espectrometría de masas en tándem; LC-HRMS: Cromatografía líquida de alta resolución espectrometría de masas; NPD: Detector de fósforo de nitrógeno SPME: Microextracción en fase sólida; P: Cuadrupolo simple; QqQ: Triple cuadrupolo; QuEChERS: Rápido, fácil, barato, eficaz, robusto y seguro; LOQ: limite de cuantificación.

Likewise, several studies seek the identification of pesticide residues in agri-foods and their correlations with health effects, resulting in the implementation of quantitative and qualitative methodologies that allow correlating public health indexes and intoxication scenarios due to chronic and/or acute exposure to pesticides (see Table 5). The results of the analysis of human tissue samples such as hair, nails, blood, among others, which were analyzed by analytical techniques, identified the presence of pesticides resulting from chronic and/or acute exposure by inhalation, ingestion or dermal contact and how these episodes could generate health effects (see Table 5). One of the most alarming results is the identification of pesticides banned in Colombian territory such as dieldrin and endrin since 1974 [75].

Tabla 5. Case studies on the determination of pesticides in agricultural products in Colombia.

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Matrix	Analysis area	Tecnica instrumental	Example of pesticides analyzed	Crops used	Restriction in colombia	Affections	Comments
Blood and urine samples.	Rural areas of the department of Córdoba.	Gas chromatography (GC)	Atrazine	Sorghum, corn, sugar cane y pineapple	Not restricted	It generates DNA damage, chromosomal mutation, adenocarcinoma, asthenozoospermia, fetal resorption, fetal weight, hypertrophy, fibroadenoma, etc.	Study conducted in a population exposed to pesticides due to the development and consumption of contaminated agri-food products [57, 59, 75, 76]
Correlational analysis of symptomatically in humans.	Urban and rural areas of the Colombian Caribbean	-	Chlorpyrifos	Vegetables, rice, corn, potato, banana, rice, sorghum, cocoa, oranges, papaya, tangerine, coffee, fruit trees, pompon, ornamentals, etc.	Not restricted	It generates ataxia anhedonia, anophthalmos, Anemia hypochromic, abnormalities multiple, asthenozoospermia, brain injuries, etc.	Study correlating clinical histories with cases of chronic and/or acute pesticide poisoning. About 92% of the cases are related to situations of oral ingestion of the substances [59, 75–77].

Passionflower (granadilla, gulupa, passion fruit)	Rural areas of the department of Huila.	Gas chromatography (GC)	Carbofuran	corn, cotton, cucurbits, potatoes, soybeans, sugarcane, sunflowers, tobacco and exotic fruits.	Not restricted	It generates edema Agricultural workers' diseases, Bronchitis chronic, cardiomyopathies, colonic neoplasms, etc.	Many pesticides were found in the different fruits analysed. Some samples exceeded the maximum residue limits (MRL) [59, 75, 76, 78].
Dried fruits (strawberry, blackberry, passion fruit, pineapple and grapes)	Local food stores in Bogota.	Gas chromatography (GC)	Dieldrin	It was used in multiple types of crops, however, in many regions of the world it is prohibited, so its use is not detailed at present.	Restricted	It generates breast neoplasms, cryptorchidism, depressive disorder, infertility female, Neoplasms, paralysis, seizures, Parkinson Disease, etc.	Identification of multi-classes of residues, highlighting fruits contaminated with pesticide residues that have been banned since 1974 [59, 75, 76, 79].
			Malathion	Bulb and long onion, Chinese onion, bean, tomato, eggplant, avocado, potato, coffee, pineapple, papaya, tree tomato, cotton and rose.	Not restricted	It generates asthma, autism spectrum disorder, arrhythmias cardiac, acute kidney injury, chemical and drug induced liver injury, gliosis, etc.	
			Endrin	It was used in multiple types crops, however, in	Restricted	It generates DNA damage and chromosomal mutation,	

				many regions of the world it is prohibited, so its use is not detailed at present.			
Minor tropical fruits (Rose apple/pomarrosa, starfruit/carambola, yoyomo and papayuela)	Local food stores in Bogota.	Gas chromatography (GC)	Carbaryl	Corn, rice, potato, avocado, cassava, melon, pineapple, sugar cane, cocoa, guanabana, mango, guava, citrus and coffee.	No restricted	It generates asthma, agranulocytosis, burns chemical, eczema, cognition disorders, leukopenia, lymphoma non-Hodgkin, neurotoxicity syndromes, etc.	Analysis that managed to identify 35 multiclass pesticides in tropical fruits in local stores in Bogota by means of an optimized QuEChERS AOAC 2007.1 method [59, 75, 76, 80].
			Dicloran	Lettuce	No restricted	It generates prenatal exposure delayed effects	
Strawberry fruits	Rural areas of the department of Cundinamarca.	Gas chromatography (GC)	Methamidophos	Brassica crops, cotton, head lettuce, potatoes, cutworms, broccoli, brussels sprouts, and cabbage	No restricted	It generates ataxia, chromosome breakage, depressive disorder, miosis, muscle weakness, foodborne diseases, poisoning, etc.	Analysis that managed to identify 32 multiclass pesticides. a lack of integrated management of the application of these substances is evident [59, 75, 76, 81].
			Clorfenapir	Tomate	Its use is restricted in coffee crops.	Agricultural workers' diseases, fatigue and poisoning.	

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2.2. Toxicological and regulatory aspects in Colombia.

Currently, public and private organizations have expressed their concern about the effects that may be observed in the population, due to cases of acute and/or chronic intoxication with pesticides, due to the high volume of pesticide application on crops [81–83]. Studies such as *"Cytogenetic damage in peripheral blood lymphocytes of children exposed to pesticides in agricultural areas of the department of Cordoba, Colombia"* had the objective of establishing genetic damage in children exposed to pesticides in agricultural areas. The result was the identification of multiple pesticide residues in urine and blood samples and their correlation in cytogenetic damage observed in the samples [57]. Another clear example of this type of situation is found in the rural area of the country's capital (Usme and Sumapaz), where neurocognitive disorders were evaluated in children exposed to pesticides in prenatal and postnatal stages [84]. As a result, 13% of the mothers surveyed reported having applied pesticides during pregnancy and postnatal exposure figures were approximately 65% of exposure to pesticides in their homes and 55.5% exposed to pesticides from crops grown near schools [84]. In addition to the identification of low rates of working memory, verbal comprehension and processing speed in the sample (boys and girls between 7 and 10 years of age) [84], it should be remembered that pesticides are neurotoxic compounds that act mainly on the nervous system. [85].

In the study entitled *"Intoxicación por plaguicidas: Casuística del Hospital Universitario del Caribe y la Clínica Universitaria San Juan de Dios de Cartagena"*, through the historical analysis of quantitative and qualitative data on hospital behaviour, a high number of patients intoxicated by pesticides due to episodes of oral ingestion, dermal contact or inhalation were recorded. The pesticides most related to cases of poisoning in the first healthcare were chlorpyrifos (14%), while propoxur (17.7%) were the most recurrent pesticides in the second healthcare [77]. We could continue referencing a greater number of studies that relate pesticide exposure to intoxication processes through oral ingestion, dermal contact or inhalation, which shows the serious situation that Colombia is experiencing due to the uncontrolled use of these phytosanitary substances and how its repercussions will be felt over the years and in different segments of the population.

As a result, governmental organizations have responded to the call to regulate, manage and monitor activities related to the use of pesticides in multiple sectors. As a result, Colombia is one of the countries that has adopted the guidelines of the Codex Alimentarius and the Stockholm Convention, which prohibits the use of 17 pesticides classified as persistent organic pollutants (POPs), including aldrin, chlordecone, DDT, endrin, lindane, Sulfluramid, among others, by means of Resolution 447 of 1974 of the Ministerio de Agricultura [75, 85]. In the same year, the registration of fungicide products for agricultural use based on mercury compounds (Hg) was cancelled by resolution 2189 of 1974 of the Instituto Colombiano Agropecuario (ICA) [75]. This regulatory behaviour continues to be constantly updated, thus generating not only total prohibition guidelines, but also partial prohibition depending on the type of crops, such as the prohibition of parathion only for cotton crops and technician pastures and methyl parathion for cotton pests and technician rice stipulated in resolution 2471 of 1991 of the ICA. [75]. Likewise, the authorization to import, commercialize and use compounds such as methyl bromide for the quarantine treatment of exotic pests in plant tissue at ports and border crossings was granted by resolution 02152 of 1996 of the Ministerio de Salud [75]. The last decision is taken by resolution 092101 of March 02, 2021, which stipulates the temporary suspension of phytosanitary control products containing fipronil as active ingredient in avocado, coffee, citrus and passionflower crops [75].

Taking into account the sanctioning processes in Colombia, the consolidation of an inventory of persistent organic pesticides has been carried out, expressing concern about the storage and final disposal systems for this type of substances. [64, 85]. For 2007, it is estimated that about 21,920, 1,890, 135,402 and 600 kg of DDT are stored in Bogotá,

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Cartagena, Honda and Puerto Inirida, respectively. Similarly, it is estimated that about 2,378.7 m3 of soils are contaminated with persistent organic pesticides in the departments of Cesar, Bolivar, Tolima and Atlántico [64]. In addition, the Política Ambiental para la Gestión Integral de Residuos Peligrosos y Plan de Acción 2022-2030, highlights the problems being experienced in the five geographic regions (Caribbean, Eje Cafetero and Antioquia, South Pacific and Amazonia, Orinoquia and Central Andean) with respect to the disposal of pesticide waste. Mentioning the high volume of domestic and agricultural pesticide residues disposed of in the different municipalities of the territory [86]. For this reason, governmental entities have sought mechanisms for the management and handling of this type of substances, issuing labelling systems depending on the categories of acute toxicity according to the Globally Harmonized System (GHS) [85]. In the same way, it has been sought to implement disposal techniques such as thermal utilization, hydrolysis and advanced oxidation processes [87].

However, in international terms, Colombia lags in the regulatory process of pesticide use. Currently, countries belonging to the European Union strictly prohibit the use of parathion, DDT, paraquat, among other substances currently used in the country or found in multiple studies aimed at identifying pesticide residues in different matrices (see table 5) [57]. For these three types of substances, MRLs have been stipulated between 0.1 to 0.2 mg/kg adopted in 2005, 0.1 to 10 mg/kg adopted between 1997 and 2003 and 0.01 to 10 mg/kg adopted in 2006, respectively. [30]. This situation hinders possible export operations since the minimum required food safety conditions are not met in continents such as Europe. Where they promote the transition to resilient and organic agricultural processes, avoiding the massive consumption of pesticides in food, thus minimizing the impact on the health and ecosystems of European territories [88].

4. Conclusiones

The identification of pesticide residues in different matrices that contemplate relationship with the consumption, inhalation and/or dermal contact of pesticides or contaminated products has caused the concern of governmental organizations. In the future, Colombia will play a vital role in terms of food supply worldwide and requires improving and strengthening the sanctioning processes that encourage the improvement in the integral management of this type of substances. Keeping in mind the appropriate interpretation of the needs of the sector and the products. This type of improvement will result in the optimization of the safety of harvested foods that will be consumed nationally and internationally. Currently, these regulatory processes must be aligned with international prohibitions, considering MRLs established in the Codex Alimentarius and additional guidelines such as SANTE.

Finally, the country perceives a high tendency in the number of studies that seek to evaluate the impact on health and ecosystems due to chronic or acute intoxication events, implementing techniques of analysis of qualitative and quantitative variables. The conclusion is that there is a lack of agricultural practices implemented throughout the agricultural sector. Therefore, governmental and academic entities need to design plans that allow the transition to sustainable agricultural practices, encouraging the producer the correct sizing in the use of this type of substances and how with minimal strategies such as the implementation of personal protective equipment, health effects can be avoided, such as genetic, neurocognitive and physical mutations that affect the present and future generation of farmers. Also, the importance of implementing organic phytosanitary products and processes to reduce the concentration and exposure rates of pesticides in food and non-food agricultural products.

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References

1. García, Z.; Nyberg, J.; Owaise Saadat. *Agricultura, expansión del comercio y equidad de género*, 1st ed.; Food and Agriculture Organization of the United Nations (FAO) (FAO): Roma, Italy, 2006; pp. 1-59.
2. Food and Agriculture Organization of the United Nations (FAO). *Agricultura mundial: hacia los años 2015/2030*. 1st ed.; Food and Agriculture Organization of the United Nations (FAO): Roma, Italy, 2002; pp. 1-106.
3. ood and Agriculture Organization of the United Nations (FAO). *El estado mundial de la agricultura y la alimentación 2021*. 1st ed.; Food and Agriculture Organization of the United Nations (FAO): Roma, Italy, 2021; pp. 1-198.
4. Lykogianni, M.; Bempelou, E.; Karamaouna, F.; Aliferis, K. A. Do pesticides promote or hinder sustainability in agriculture? The challenge of sustainable use of pesticides in modern agriculture. *Sci. Total Environ.*, **2021**, *vol. 795*, p. 148625
5. Le Campion, A.; Oury, F. X.; Heumez, E.; Rolland, B. Conventional versus organic farming systems: dissecting comparisons to improve cereal organic breeding strategies. *Org. Agric.*, **2020**, *vol. 10*, pp. 63–74.
6. Redlichová, R.; Chmelíková, G.; Blažková, I.; Svobodová, E.; Vanderpuje, I. N. Organic food needs more land and direct energy to be produced compared to food from conventional farming: Empirical evidence from the Czech Republic. *Agric.*, **2021,** *vol. 11*, pp. 813 .
7. Tudi, M.; Ruan, H. D; Wang, L.; Lyu, J.; Sadler, R.; Connell, D.; Chu, C.; Phung, D. T. Agriculture development, pesticide application and its impact on the environment. *Int. J. Environ. Res. Public Health*, **2021**, *vol. 18*, pp. 1–24.
8. Rani, L.; Thapa, K.; Kanojia, N.; Sjarma, N.; Singh, S.; Grewal, S.A.; Srivastav, L.A.; Kaushal, J. An extensive review on the consequences of chemical pesticides on human health and environment. *J. Clean. Prod.*, **2021**, *vol. 283*, p. 124657.
9. FAOSTAT. Available online: https://www.fao.org/faostat/en/#data/EP (accessed May 13, 2022).
10. Gomiero, T.; Pimentel, D.; Paoletti, M. G. Is there a need for a more sustainable agriculture? *CRC. Crit. Rev. Plant Sci.*, **2011**, *vol. 30* pp. 6–23.
11. Deknock, A.; De Troyer, N.; Houbraken, M.; Dominguez, G. L.; Nolivos, I.; Van Echelpoel, W.; Eurie, M. A.; Spanoghe, P.; Goethals, P. Distribution of agricultural pesticides in the freshwater environment of the Guayas river basin (Ecuador). *Sci. Total Environ.*, **2019**, *vol. 646*, pp. 996–1008.
12. Dhananjayan, V.; Jayanthi, P.; Jayakumar, S.; Ravichandran, B. Agrochemicals impact on ecosystem and bio-monitoring. In *Resources Use Efficiency in Agriculture*. 1er ed.; Kumar, S.; Meena, R. S.; Jhariya, M. K., Eds. Springer: The Gateway, Singapore, 2020, vol. 1, pp. 349–389.
13. Kumar, V.; Kumar, R.; Singh, J.; Kumar, P. *Contaminants in agriculture and environment: health risks and remediation*, 1st ed.; Agro. Environ. Media, Publication Cell, Agriculture and Environmental Science Academy (AESA): Gurubakhs Vihar, India, 2019; pp. 1-276.
14. Environmental Working Group (EWG). EWG's 2022 Shopper's Guide to Pesticides in Produce. Washington, D.C.
15. Davis, F. R. Pesticides and the perils of synecdoche in the history of science and environmental history. *Hist. Sci.*, **2019**, *vol. 57*, pp. 469–492.
16. Matthews, G. A. *A history of pesticides*, 1st ed.; Centre for Agricultural Bioscience International (CABI): Boston: United States, 2018; pp. 1-288.
17. Buttermore, E. N.; Cope, W. G.; Kwak, T. J.; Cooney, P. B.; Shea, D.; Lazaro, P. R. Contaminants in tropical island streams and their biota. *Environ. Res.*, **2017**, *vol. 161*, pp. 615–623.
18. Patton. D. E. Legal aspects of pesticides and toxic substances testing requirements. *J. Environ. Sci. Heal. Part B*, **1980**, *vol. 15*

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pp. 645–663.

19. Información básica sobre pesticidas. Available online: https://espanol.epa.gov/espanol/informacion-basica-sobre-pesticidas#pesticida (accessed Mar. 17, 2021).
20. World Health Organization (WHO). Guidance document on safe use of pesticide: classification of pesticides according to hazard. Ginebra, 1974.
21. World Health Organization (WHO). Safe use of pesticides: classification of pesticides according to hazard. Ginebra, 1975.
22. Bond, E.J, *Manual of fumigation for insect control*, 54th ed.; Food and Agriculture Organization of the United Nations: Roma:, Italy, 1984; pp. 1-333.
23. Isern, M. D. *La química de los pesticidas y su metodología analítica*, 1st ed. Cerider: Centro Regional de Investigación y Desarrollo de Rosario: Santa Fe, Argentina, 2002; pp. 1-61.
24. Doménech, J. Plaguicidas: Sus efectos en la salud humana. *Elsevier*, **2004,** *vol. 23*, pp. 108–114.
25. Cherin, P. *Recognition and management of pesticide poisonings*, 6th ed.; Enviromental Protection Agency (EPA): Washington, United States, 1997; pp. 1-257.
26. Jin, Y.; hao Ding, Y.; jing Dong, J.; Wei, Y.; hong Hao, S.; cheng Feng, B. Design, synthesis and agricultural evaluation of derivatives of N-Acyl-N-(m-fluoro-benzyl)-6-amino-coumarin. *Nat. Prod. Res.*, **2022**, *vol. 36*, pp. 798–804.
27. Espinosa, J. L. Análisis de pesticidas en muestras de alimentos: tratamiento de la muestra y determinación por LC y GC acopladas a MS. Master, Universidad Nacional de Educación a Distancia, Cuenca, Ecuadro, 2018.
28. Carson, R. Silent Spring. In *Historical Perspectives on preventive conservation*, 1st ed;, Staniforth, S. Ed.; The Getty Conservation Institute: Los Angeles, United States ,1962; pp. 254–257.
29. Residuos de plaguicidas en los alimentos. Available online: https://www.who.int/es/news-room/fact-sheets/detail/pesticide-residues-in-food (accessed Mar. 28, 2022).
30. Maximum Residue Limits (MRLs). Available online: https://www.fao.org/fao-who-codexalimentarius/codex-texts/maximum-residue-limits/en. (accessed Mar. 28, 2022).
31. Food and Agriculture Organization of the United Nations (FAO); and World Health Organization (WHO). *Comisión del Codex Alimentarius: Manual de procedimiento*, 15th ed.; Food and Agriculture Organization of the United Nations (FAO); and World Health Organization (WHO): Roma, Italy, 2016; pp. 1-222.
32. Pico, Y.; Alfarhan, A. H.; Barcelo, D. How recent innovations in gas chromatography-mass spectrometry have improved pesticide residue determination: An alternative technique to be in your radar. *TrAC - Trends Anal. Chem.*, **2019**, *vol. 122*, p. 115720.
33. Musarurwa, H.; Chimuka, L.; Pakade, V. E.; Tavengwa, N. T. Recent developments and applications of QuEChERS based techniques on food samples during pesticide analysis. *J. Food Compos. Anal.*, **2019**, *vol. 84*, p. 103314.
34. Dąbrowski, Ł. Multidetector systems in gas chromatography. *TrAC - Trends Anal. Chem.*, **2018**, *vol. 102*, pp. 185–193.
35. de Castro, I. M.; dos Anjos, M. R.; dos S. de Oliveira, E. Determination of benzyl isothiocyanate in Carica papaya using gas chromatography with selectives detectors. *Quim. Nova*, **2018**, *vol. 31*, pp. 1953–1959.
36. Madej, K.; Kalenik, T. K.; Piekoszewski, W. Sample preparation and determination of pesticides in fat-containing foods. *Food Chem.*, **2018**, *vol. 269*, pp. 527–541.
37. Muir D.; Sverko, E. Analytical methods for PCBs and organochlorine pesticides in environmental monitoring and surveillance: A critical appraisal. *Anal. Bioanal. Chem.*, **2006**, *vol. 386*, pp. 769–789.
38 Domínguez, I ; Frenich, A. G.; Romero-González, R. Mass spectrometry approaches to ensure food safety. *Anal. Methods.*, **2020,** *vol. 12*, pp. 1148–1162.
39 Lawal, A.; Wong, R. C. S.; Tan, G. H.; Abdulra'Uf, L. B.; Alsharif, A. M. A. Recent modifications and validation of QuEChERS-dSPE coupled to LC-MS and GC-MS instruments for determination of pesticide/agrochemical residues in fruits and vegetables: Review. *J. Chromatogr. Sci.*, **2018**, *vol. 56*, pp. 656–669.
40 Mezcua, M.; Ferrer, C.; García-Reyes, J. F.; Martínez-Bueno, M. J.; Sigrist, M.; Fernández-Alba, A. R. Analyses of selected non-authorized insecticides in peppers by gas chromatography/mass spectrometry and gas chromatography/tandem mass spectrometry. *Food Chem.*, **2009**, *vol. 112*, pp. 221–225.
41. Sapozhnikova, Y.; Lehotay, S. J. Multi-class, multi-residue analysis of pesticides, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers and novel flame retardants in fish using fast, low-pressure gas chromatography-tandem mass spectrometry. *Anal. Chim. Acta*, **2013**, *vol. 758*, pp. 80–92.
42. Golge, O.; Kabak, B. Evaluation of QuEChERS sample preparation and liquid chromatography-triple-quadrupole mass spectrometry method for the determination of 109 pesticide residues in tomatoes. *Food Chem.*, **2015**, *vol. 176*, pp. 319–332.
43. López-Ruiz, R.; Romero-González, R.; Garrido Frenich, A. Ultrahigh-pressure liquid chromatography-mass spectrometry: An overview of the last decade. *TrAC - Trends Anal. Chem.*, **2019**, *vol. 118*, pp. 170–181.
44. Fanali, C.; Dugo, L.; Dugo P.; Mondello, L. Capillary-liquid chromatography (CLC) and nano-LC in food analysis. *TrAC - Trends Anal. Chem.*, **2013**, *vol. 52*, pp. 226–238.
45. Frenich, A. G.; Romero-González, R.; del Mar Aguilera-Luiz, M. Comprehensive analysis of toxics (pesticides, veterinary drugs and mycotoxins) in food by UHPLC-MS. *TrAC - Trends Anal. Chem.*, **2014**, *vol. 63,* pp. 158–169.

46. Jiang, X.; Wang, W.; Xu, L.; Lu, L.; Zhou, H.; Chen, H. Review on rapid detection of pesticide residues in agricultural and food products. *Nongye Gongcheng Xuebao/Transactions Chinese Soc. Agric. Eng.*, **2016**, *vol. 32*, pp. 267–274.
47. Knoll, S.; Rösch, T.; Huhn, C. Trends in sample preparation and separation methods for the analysis of very polar and ionic compounds in environmental water and biota samples. *Anal. Bioanal. Chem.*, **2020**, *vol. 412*, pp. 6149–6165.
48. Che, Q.; Liu, Q.; Shen, L.; Xue, Y.; Wang, Y.; Yan, C. Simultaneous chiral separation of three triazole pesticide enantiomers with submicron C18 bonded silica stationary phase by pressurized capillary electrochromatography. *Chinese J. Chromatogr.*, **2018**, *vol. 36*, pp. 388–394.
49. Ficha tecnica Colombia: Available: http://www.exteriores.gob.es/documents/fichaspais/colombia_ficha pais.pdf (accessed: Jan. 04, 2022).
50. Bell, P. L. Geografía, topografía y clima. In *Colombia a Commercial and Industrial Handbook*, 1st ed.; Banco de la Republica: Bogotá D.C, Colombia, 2011, vol. 1, pp. 37–50.
51. Cabrera leal, M; Duarte Ortega M.; Lamprea Quiroga, P. S.; Lozano Picón, R. J. Renzoni, G. Circunstancias Nacionales. 1999.
52. Departamento Nacional Administrativo de Estadistica (DANE). Censo demografico 2018. Bogotá, 2018.
53. Junguito, R.; Perfetii, J. J.; Becerra, A. Desarrollo de la agricultura colombiana. Bogotá D.C. Available online: https://repository.fedesarrollo.org.co/bitstream/handle/11445/151/CDF_No_48_Marzo_2014.pdf (accessed: Jan. 05, 2022).
54. Perfetti, J. J.; Balcázar, Á.; Hernández, A.; Leibovich, J. Políticas para el desarrollo de la agricultura en Colombia. Bogotá D.C, 2013.
55. Organización de las Naciones Unidas para la Alimentación y la Agricultura - en Colombia. Available online: https://www.fao.org/colombia/es/ (accessed Mar. 14, 2022).
56. Departamento de Nacional de Estadisitica (DANE). Censo Nacional Agropecuario - 2019. Available online: https://www.datos.gov.co/Estad-sticas-Nacionales/Censo-Nacional-Agropecuario-CNA-/6pmq-2i7c (accessed Mar. 16, 2022).
57. Ruiz-Guzmán, J. A.; Gómez-Corrales, P.; Cruz-Esquivel, Á.; Marrugo-Negrete, J. L. Cytogenetic damage in peripheral blood lymphocytes of children exposed to pesticides in agricultural areas of the department of Cordoba, Colombia. *Mutat. Res. - Genet. Toxicol. Environ. Mutagen.*, **2017**, *vol. 824*, pp. 25–31.
58. Feola, G.; Binder, C. R. Identifying and investigating pesticide application types to promote a more sustainable pesticide use. The case of smallholders in Boyacá, Colombia. *Crop Prot.*, **2010**, *vol. 29*, pp. 612–622, 2010.
59. Instituto Colombiano Agropecuario (ICA). Registro nacional de plaguicidas. Bogotá D.C, pp. 1–176, 2022.
60. Instituto Colombiano Agropecuario (ICA), Empresas comercializadoras de plaguicidas quimicos de uso agricola. Bogotá D.C, pp. 1–24, 2022.
61. Instituto Colombiano Agropecuario (ICA). Departamentos tecnicos para insumos agricolas registrados. Bogotá D.C, pp. 1–5, 2022.
62. Bojacá, C. R.; Arias, L. A.; Ahumada, D. A.; Casilimas, H. A.; Schrevens, E. Evaluation of pesticide residues in open field and greenhouse tomatoes from Colombia. *Food Control*, **2013**, *vol. 30*, pp. 400–403.
63. Hernández, F.; Portolés, T.; Ibáñez, M.; Bustos-López, M. C; Díaz, R.; Botero-Coy, A. M.; Fuentes, C. L.; Peñuela, G. Use of time-of-flight mass spectrometry for large screening of organic pollutants in surface waters and soils from a rice production area in Colombia. *Sci. Total Environ.*, **2012**, *vol. 439*, pp. 249–259.
64. Ministerio de Ambiente y Desarrollo Sostenible, Global Environmental Facility (GEF); Programa de las Naciones Unidas para el Desarrollo; World Bank, *Inventario nacional de existencias de plagucidas - COP*, 1st ed. Ministerio de Ambiente y Desarrollo Sostenible: Bogotá D.C, Colombia, 2007; pp. 1-36.
65. Sanint, L. R. Crop biotechology and sustainability: a case study of Colombia. 1995.
66. Portafolio. Los resultados del sector agropecuario en el 2005. Bogotá D.C, 2005.
67. Sector agricultura 2005. Available online: https://www.dane.gov.co/index.php/estadisticas-por-tema/gobierno/encuesta-sobre-ambiente-y-desempeno-institucional-nacional-edi/edi-nacional-2005/sector-agricultura-2005 (accessed May 18, 2022).
68. Martínez, A. M.; Tordecilla, L.; Rodriguez, M.; Grandett, L. M. Analysis of the performance of the Colombian agricultural sector: Period 2005-2020. *Rev. Investig. e Innovación Agropecu. y Recur. Natruales*, **2022**, *vol. 9*, pp. 42–51.
69. Ministerio de Agricultura y Desarrollo Rural. Cadena de agroalimentos 2021. Bogotá D.C, 2021.
70. Arrubla Vélez, J. P.; Villa Pulgarín, N.; Grisales Betancur, E. A.; Grisales Bedoya, J. M.; Gómez Benitez, M. A.; Guerrero Álvarez, G. E.; Paredes Cuervo, D. Pesticide residues in Junca Onion (Allium fistulosum) cultivated in Risaralda, Colombia. *Semin. Agrar.*, **2020**, *vol. 41*, pp. 1875–1896.
71. Huérfano Barco, I. M.; España Amórtegui, J. C.; Guerrero Dallos, J. A. Development and validation of qualitative screening, quantitative determination and post-targeted pesticide analysis in tropical fruits and vegetables by LC-HRMS. *Food Chem.*, **2022**, *vol. 367*, pp. 130714.
72. Moreno, A. A.; Machado, P. B. Producción de café en Colombia. 2019.
73. Varela-Martínez, D. A.; González-Curbelo, M. Á.; González-Sálamo, J.; Hernández-Borges, J. Analysis of pesticides in cherimoya and gulupa minor tropical fruits using AOAC 2007.1 and ammonium formate QuEChERS versions: A comparative study. *Microchem. J.*, **2020**, *vol. 157*, p. 104950.
74. España Amórtegui, J. C. Guerrero Dallos, J. A. Practical aspects in gas chromatography-mass spectrometry for the analysis

 doi:10.20944/preprints202204.0277.v2

of pesticide residues in exotic fruits. *Food Chem.*, **2015**, *vol. 182*, pp. 14–22.
75. Ministerio de Agricultura y Desarrollo Rural and Instituto Colombiano Agropecuario (ICA). Restricción, prohibiciones y suspensión de registros de plaguicidas de uso agrícola en Colombia. Bogotá D.C, pp. 1–6, 2022.
76. National Center for Biotechnology Information. PubChem Compound Summary. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Clomazone#section=Fire-Fighting (accessed May. 17, 2022).
77. González, G. Intoxicación por plaguicidas: casuística del hospital universitario del Caribe y de la clínica universitaria san Juan de Dios de Cartagena. Master, Universidad Nacional de Colombia, Bogotá. Colombia, 2011.
78. Bastidas, D. A.: Guerrero, J. A.; Wyckhuys, K. Peticide residues in passifloras crops in regions of high production in colombia. *Rev. Colomb. Quim.*, **2013,** *vol. 42*, pp. 263–281.
79. Varela-Martínez, D. A.; González-Curbelo, M. Á.; González-Sálamo, J.; Hernández-Borges, J. Analysis of multiclass pesticides in dried fruits using QuEChERS-gas chromatography tandem mass spectrometry. *Food Chem.*, **2018**, *vol. 297*, p. 124961.
80. Varela-Martínez, D. A. ; González-Curbelo, M. Á.; González-Sálamo, J.; Hernández-Borges, J. High-throughput analysis of pesticides in minor tropical fruits from Colombia. *Food Chem.*, **2019**, *vol. 280*, pp. 221–230.
81. Sánchez, M.; López V. D.; Fischer, G.; Acuña C. J. F., Darghan, A. E. Pesticide residues in strawberry fruits cultivated under integrated pest management and conventional systems in Cundinamarca (Colombia). *Rev. Colomb. Ciencias Hortícolas*, **2019**, *vol. 13*, pp. 35–45.
82. World Health Organization (WHO). *Clasificación recomendada por la OMS de los plaguicidas por el peligro que presentan y directrices para la clasificación*, 1st ed.; World Health Organization (WHO): Geneva, Switzerland, 2019; pp. 1-92.
83. Lesmes-Fabian, C.; García-Santos, G.; Leuenberger, F.; Nuyttens, D.; Binder, C. R. Dermal exposure assessment of pesticide use: The case of sprayers in potato farms in the Colombian highlands. *Sci. Total Environ.*, **2012**, *vol. 430*, pp. 202–208.
84. Benavides-Piracón, J. A.; Hernández-Bonilla, D.; menezes-Filho, j. A., de Joode, B. V. W.; Vásquez, Y. A.; Bahia, T. C.; Quintana, M. A.; Molina, n. J.; Moya, I. A.; Hernández, M. A. Prenatal and postnatal exposure to pesticides and school-age children's cognitive ability in rural Bogotá, Colombia. *Neurotoxicology*, **2022**, *vol. 90*, pp. 112–120.
85. Ministerio de Ambiente y Desarrollo Sostenible. Cartilla: Plaguicidas COP aspectos básicos. Bogotá D.C, pp. 1–15, 2017. Available: https://quimicos.minambiente.gov.co/wp-content/uploads/2021/05/Cartilla_Plaguicidas_COP_2017.pdf.
86. Ministerio de Ambiente y Desarrollo Sostenible. *Política ambiental para la gestión de residuos peligrosos, y Plan de Acción 2022-2030*, 1st ed.; Ministerio de Ambiente y Desarrollo Sostenible: Bogotá D.C, Colombia, 2022; .
87. Sánchez, N. P.; Rodríguez, M. S.; Sarria, V. M.; Pesticidas obsoletos en Colombia Situación actual y alternativas de tratamiento y disposición. *Rev. Ing.*,**2006**, *vol. 0*, pp. 13–22.
88. Geissen, V.; Silva, V.; Huerta, E.; Beriot, N.; Oostindie, K.; Bin, Z.; Pyne, E.; Zomer, P.; Mol, H.; Ritsema, C. J. Cocktails of pesticide residues in conventional and organic farming systems in Europe – Legacy of the past and turning point for the future," *Environ. Pollut.*, 2021, *vol. 278,* p. 116827.