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Advanced Chromatographic Techniques For Pesticide Determination In Biological Specimens: Precision Approaches In Analytical Toxicology

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ABSTRACT

Pesticides are crucial in preventing vector-borne diseases, protecting crops, and preserving food, thus playing a noteworthy role in sustaining global food production. The use of pesticides is expected to increase substantially, with projections indicating a rise to nearly 10 billion metric tons by 2050. Despite their benefits, pesticides raise concerns because of their potential effects on human health and the environment. Only around 1% of applied pesticides effectively reach the targeted pests, whereas the remaining 99% disperse into soil, water, and surrounding ecosystems, affecting non-target organisms. This widespread contamination has been associated with severe health risks, especially for agricultural workers and vulnerable populations like children. Chronic pesticide exposure often raises the threat of cancers, neurological disorders, and respiratory issues. Environmentally, pesticides harm biodiversity, degrade soil health, and cause a decline in pollinator populations, which are vital to ecosystem balance. To monitor and mitigate these risks, advanced chromatography techniques, particularly gas chromatography-mass spectrometry (GC-MS), liquid chromatography-tandem mass spectrometry (LC-MS/MS), and UHPLC-MS are widely used for the detection of pesticide residues in biological specimens, including blood and urine. These advanced techniques offer high sensitivity, specificity, and precision, making them essential for assessing human exposure, supporting public health studies, and meeting regulatory standards. This review delves into the complexities of pesticide exposure, recent advancements in chromatographic detection, and emerging strategies in residue analysis, emphasizing the need for ongoing innovation to enhance pesticide monitoring and safeguard the health and the environment.

Keywords: *Chromatography, Pesticide, Biological Samples, Toxicology, Innovation.*

1. INTRODUCTION

Pesticides are chemical agents widely utilized to control disease-spreading by vectors, protect crops, preserve food, and support various commercial and food-related industries, including agriculture, aquaculture, food processing, and storage [1]. These consist of plant growth regulators, molluscicides, rodenticides, fungicides, insecticides, herbicides, nematicides, and other substances [2], [3], [4]. It is globally accepted that pesticides can increase the affordable production and quality of food while lowering agricultural product losses [5], [6]. As a result, after World War II (1939–1945), the development of pesticides increased steadily and quickly. Approximately 4.19 million metric tons of pesticides were consumed worldwide in 2019, with China consuming the most (1.76 million metric tons), followed by the US (408 thousand tons) and Brazil (377 thousand tons) [7]. Annually, three billion kg of pesticides are used globally [8], when it comes to controlling insect pests on target plants, barely 1% of all insecticides are effective [9]. India is a leading pesticide producer, with an annual production of 90,000 tons of organochlorine pesticides (OCPs). Globally, agricultural pesticide consumption is projected to rise modestly in the coming years, increasing from approximately 4.3 million metric tons in 2023 to about 4.41 million metric tons by 2027 [10], and given the present growth rates, it is expected to reach 9.4–10 billion by 2050 [11] (Fig.1).

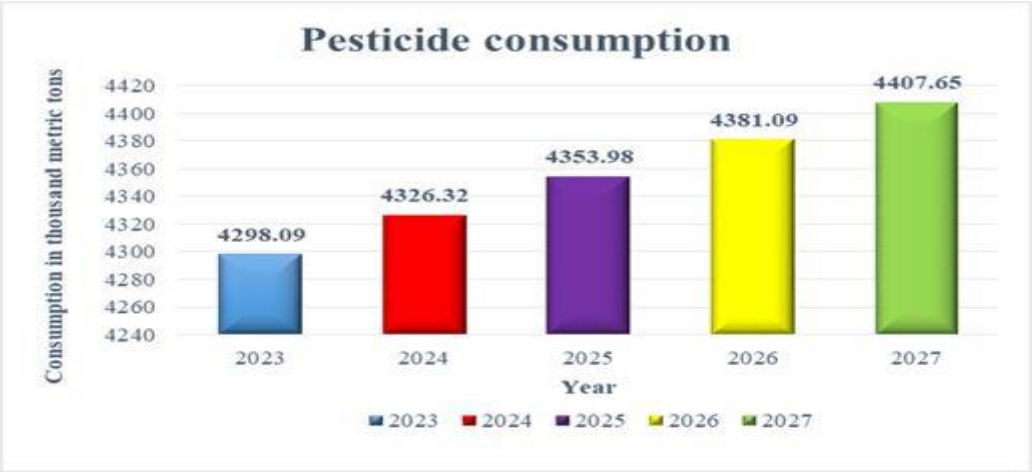


Figure 1: Worldwide expected pesticide consumption in thousand metric tons [11]

Thus, pesticides have significantly contributed to alleviating hunger and providing access to an abundant supply of high-quality food.

Although its exposure presents considerable hazards to both individuals and the ecosystem, with consequences ranging from acute toxicity to long-term ecological damage dependent on the pesticide category, level of exposure, and duration. Human exposure can occur through various routes, including ingesting contaminated food or water, inhaling airborne particles, and skin contact [12]. The World Health Organization (WHO) reports that 220,000 people die and around 3,000,000 cases of pesticide poisoning occur in underdeveloped nations annually [13]. Due to their weakened immune systems, kids are more vulnerable to pesticides than adults. Contact exposure to agricultural pesticides is highest among farm workers and their families. According to a team of academics, during the Green Revolution, low-income households started to store dangerous pesticides, which raised suicide rates and caused an estimated fourteen million premature deaths [14]. Additionally, it can result in several issues, including moderate skin irritation, birth deformities, tumors, genetic changes, neurological disorders, endocrine disturbance, and ultimately coma or death [15]. Certain pesticides, such as glyphosate—a commonly used herbicide—have been classified as "probably carcinogenic" by the International Agency for Research on Cancer (IARC). Long-term exposure to these pesticides has been linked to a higher risk of cancers, including non-Hodgkin lymphoma [16]. Pesticides like atrazine and dichlorodiphenyltrichloroethane (DDT) can disrupt hormone function, leading to reproductive and developmental issues. Studies have linked exposure to endocrine-disrupting pesticides with fertility problems, birth defects, and developmental disorders in children [17]. An OCP, including chlorpyrifos, are known neurotoxins that inhibit the enzyme acetylcholinesterase, leading to neurological disorders [18]. Pesticide exposure, particularly through inhalation, can exacerbate or alleviate respiratory illnesses including asthma and chronic obstructive pulmonary disease (COPD). Farm workers are particularly at threat due to constant exposure in poorly ventilated areas [19].

Pesticides can pollute turf, water, soil, and other vegetation if they are used excessively without any management. In addition to non-target plants and animals, it can be hazardous to beneficial insects, fish, birds, bees, and other creatures [20]. The U.S. Geological Survey (USGS) reports that studies have detected pesticide residues in over 90% of water samples from streams in agricultural areas of the United States (US). Fish populations can drop and aquatic food networks can be disrupted as a result of contaminated water harming aquatic organisms [21]. Pesticides may change the biochemical composition of soil, reducing its fertility and ability to support healthy plant growth. Such as OCP, can remain in the soil for years, disrupting microbial activity and harming beneficial organisms like earthworms and nitrogen-fixing bacteria [22]. Insecticides, particularly neonicotinoids, have been implicated in the decline of pollinators like honeybees and wild bees, which are crucial for crop pollination. The Food and Agriculture Organization (FAO) has reported a steady decline in global pollinator populations, which threatens food security. Pesticides can also affect non-target organisms [23]. Glyphosate has the potential to significantly lower seed quality and make plants more susceptible to disease [24]. Because pesticides promote colony collapse disorder, they can kill bees and reduce pollination [25]. Exposure to 2,4-D herbicides has been shown to impair the hatching ability of chicken eggs and induce sterility in pheasant chicks [26]. Tadpoles exposed to pesticides experienced lengthier metamorphosis, growth anomalies, and reduced capacity to evade predators and capture prey. Atrazine and other herbicides can cause male frogs to become hermaphrodites and decrease their capacity for reproduction [15].

Therefore, determining pesticide levels in biological specimens like blood, urine, and tissues is crucial. Human blood is the most accessible body fluid for determining pesticide residue levels and serves as a biomarker of exposure for assessing health effects at specific concentrations [27].

- Biological specimens help to quantify the internal dose of pesticides that individuals have been exposed to. This is essential for assessing potential health risks, particularly for those living in agricultural areas, workers handling pesticides, or consumers exposed through food [28].
- Monitoring pesticide levels helps identify both chronic and acute toxic effects as mentioned above [28].
- Measuring pesticide residues in populations allows for large-scale studies linking exposure levels to health outcomes, which can inform public health policies and regulations.
- Special populations such as youngsters, pregnant female, and the aged may be more susceptible to pesticide toxicity. Biomonitoring can provide data on the risks posed to these groups, guiding protective measures [29].
- In suspected cases of pesticide poisoning, determining the levels of pesticides can help in diagnosing the cause, allowing for timely treatment and intervention. It can also provide evidence in criminal or accidental poisoning cases, aiding forensic investigations.
- Preclinical changes or early detrimental metabolic health impacts caused by external pesticide exposure and/or absorption of certain pesticide compounds could also be documented by changes in biological markers [30].

To access the pesticide levels, chromatography techniques play a vital role owing to their distinct properties such as sensitivity, selectivity, precision, accuracy, and capability to separate complex mixtures. Its most commonly used types are based on either gas chromatography (GC), or high-performance liquid chromatography (HPLC), both coupled to mass spectrometry (MS) [31]. This method is used in toxicology to establish proof of the structure of unknown materials. Precision ensures consistent, reproducible results, while accuracy guarantees that the detected pesticide levels reflect the true concentrations present. Both are essential for reliable exposure assessment, regulatory compliance, risk evaluation, forensic investigations, environmental protection, food safety, and method validation [32].

The objective of this article is to explore pesticide exposure and its associated severe health complications, emphasizing the need for precise detection methods in biological samples. Over the years, chromatographic techniques have undergone significant advancements, with innovations like GC-MS/MS and LC-MS/MS enabling trace-level detection of both volatile and non-volatile pesticides. Emerging methods e.g., UHPLC, HPTLC, and multidimensional chromatography further enhance rapidity, sensitivity and promote eco-friendliness. This review aims to bridge the gaps between existing and emerging pesticide detection techniques, highlighting the potential of integrating advanced technologies with chromatographic methods to develop cost-effective, rapid, and highly sensitive analytical platforms.

Methodology

Related information was searched from the databases of PubMed, Medline, Web of Science, Scopus, Cochrane Library, and other official portals by combining the following keywords: "*Pesticide", "Chromatography", "Detection", "Biological sample", "Novel technologies", "Artificial intelligence", "Nanotechnology", "Green solvents", "Challenges and Limitations" and Innovation*".

The inclusion criteria: i) Articles related to the advancements in chromatography for pesticide analysis, including innovations in sample preparation techniques and novel chromatographic methods for detection. It also highlights the integration of advanced technologies with chromatographic systems and, the importance of their potential to enhance the sensitivity, accuracy, and efficiency of pesticide analysis. ii) The exclusion criteria: The articles do not specify different classes of pesticide, and or other pesticide detection techniques except chromatography.

2. HISTORICAL PERSPECTIVE OF CHROMATOGRAPHY IN PESTICIDE SAMPLE ANALYSIS (PSA)

The role of chromatography has advanced significantly over recent decades, as outlined in the following Table.

Table 1: Development of analytical methods as per decades.

Period	Key developments
Pre-2000	• Early use of GC for volatile pesticides • HPLC was introduced for non-volatile pesticide • GC-MS becomes the standard for sensitive pesticide detection since 1980 • Sample preparation advances (SPE, LLE) • Regulatory push for pesticide monitoring [33], [34].
2000–2010	• Fast GC and HPLC with capillary columns

	• Automated systems for high-throughput • Introduction of LC-MS/MS for multi-residue PSA • QuEChERS method simplifies preparation [9].
2010–2020	• UHPLC offers faster analysis and higher resolution • HRMS introduced for high selectivity • Multi-residue screening for hundreds of pesticides in one run • Stricter global regulatory compliance [35], [36].
2020–2024	• AI and machine learning integrated into chromatographic data analysis • Portable GC/LC devices for on-site testing Sustainable and eco-friendly methods • Nanotechnology-enhanced materials in GC/LC • Omics approaches for studying pesticide metabolites [37, p. 2], [38], [39].

Chromatography has long been a cornerstone of analytical chemistry, with **GC** emerging in the 1950s and quickly gaining traction for pesticide analysis (PA) by the 1960s. The technique became rapidly adopted due to the inherent feature to perform on a packed column multi-residue analysis. Capillary columns, combined with sensitive and selective detectors, offered high separation efficiency, enabling the simultaneous and efficient analysis of a significantly larger number of pesticides in a single run [33]. A GC operates by separating volatile analytes based on their distribution between a stationary liquid phase and a mobile gas phase. This made GC ideal for detecting volatile and semi-volatile pesticides, such as DDT, aldrin, and parathion [21]. GC proved crucial for detecting volatile pesticides, such as **organochlorines** and **organophosphates (OPP)** [40]. However, early GC instruments had limited sensitivity and selectivity, making it challenging to determine pesticide traces in intricate matrices like food or biological fluids. Around the same period, **LC** became an important tool, especially for non-volatile and thermally unstable pesticides that could not be assessed using GC. The LC separates analytes in a liquid mobile phase using different types of interactions (e.g., adsorption, partitioning) with the stationary phase. But it has also certain challenges in separating certain complex pesticide mixtures [41]. Reversed-phase liquid chromatography (RPLC) may effectively separate the majority of (very) polar pesticides without the need for a time-consuming prior derivatization step. To determine different classes of polar pesticides, RPLC with a suitable/robust UV or fluorescence detector was introduced in the field of PSA around 1980 [42], [43]. For regulatory purposes, the Netherlands uses a multi-residue method (MRM) that uses capillary GC with MS detection to identify about 300 pesticides in food, which accounts for roughly 60% of the pesticides listed in the Dutch Regulation on Pesticides in Foodstuffs [42]. Since these pesticides and their chemical families have poor volatility, strong polarity, and/or thermal instability, the GC cannot directly process them. Therefore GC-MS/LC-MS has emerged as a valuable tool in PSA as it provides simultaneous confirmation and quantification of several pesticides, obviating the need for multiple tests using various selective detectors [44].

2.1 Advances in sample preparation in PSA

Sample preparation techniques are fundamental in analytical chemistry. These techniques are essential to isolate, concentrate, or purify analytes. In liquid-liquid extraction (LLE), the dissolved solute is transferred between two immiscible liquid phases. Similarly, extractions involving a liquid and a solid phase are referred to as solid-liquid extraction (SLE). QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) is extensively utilized in food and agricultural samples, especially for complex matrixes. The LLE, compared with SPE works well for separating organic pesticide and herbicide chemicals from complex matrices and industrial effluent samples [34]. *de Pinho GP et al.* used LLE with low-temperature purification for PSA of λ-cyhalothrin, cypermethrin, chlorpyrifos, and deltamethrin in honey along with GC [45]. *Farajzadeh MA et al*. prepared a sample by LLE employing a GC–flame ionization detection (GC–FID) analysis and confirmed the presence of pyrethroids in oil samples [46]. The approach based on Florisil® SPE with LC-MS/MS detection and quantification of seven systemic insecticides in raw honey and pollen samples was developed and validated, owing to a different investigation [47]. *Alzaga et al*. investigated the stability of freeze-dried water samples containing eight agrochemicals (pesticides) to assess their appropriateness in water samples. Additionally, the separation and trace enrichment of target analytes from freeze-dried water samples were evaluated using two distinct extraction systems: LLE and supercritical fluid extraction [48].

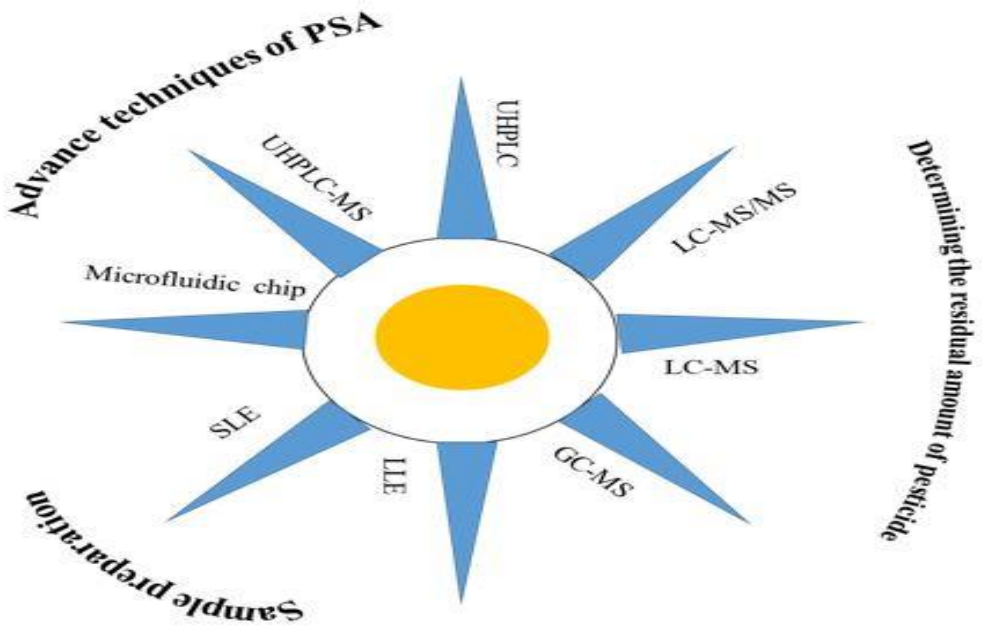


Figure 2: Techniques used in pesticide detection and sample preparations [33]

3. EVOLUTION OF CHROMATOGRAPHIC TECHNIQUES ALONG WITH TANDEM MASS SPECTROMETRY

3.1 Enhancement of GC-MS approaches for PA in biological samples

The increased use of GC-MS for PSA in biological matrices is especially important for studies related to toxicology and environmental health research. *Ramesh et al.* created a quick and accurate GC-Electron Ionization (EI)-MS technique to identify 13 pyrethroid pesticides in whole blood. He noted that the detection sensitivity of the selective ion monitoring mode is up to 0.05 ng/ml. The technique can identify various pyrethroid residues as low as 0.05–2 ng/ml [49]. *Corrion et al.* developed a GC-EI-MS process for measuring pesticides from numerous classes and their metabolites in maternal and umbilical cord blood. The study concluded that the method offers sensitivity and recovery comparable to other contemporary approaches. Additionally, it significantly reduces chromatographic analysis time while enabling the detection of a greater number of target analytes [50]. *Čajka et al.* quoted the performance characteristics obtained by GC–TOF MS reliable detection and accurate quantification of PSA even at very low concentration levels [51]. Even in baby food, the rapid GC-MS approach has offered an adequate limit of quantifications (LOQs) and good robustness for PSA [52]. *Kirchner* and colleagues remark on the same findings, i.e., good robustness for such a very complex PSA study in a plant matrix [53].

3.2 Introduction of HPLC in clinical toxicology

As previously mentioned, chromatographic techniques like GC and HPLC are frequently employed to identify polar pesticides in the environment. Both of these separation approaches are complementary to one another for certain applications, with neither offering a clear benefit [54]. However, HPLC works with polar and thermally labile chemicals. In one study, *Sandahl M et al.* used supported liquid membrane extraction and microporous membrane LLE with HPLC to identify thiophanate-methyl and its metabolites at trace levels in spiked natural water. This method gives low detection limits and greater selectivity [55]. To identify 19 carbamate pesticides in tea samples, *Wu et al.* created an MRM following with HPLC using a fluorescence detector. The study's findings demonstrated high linearity across all studies, with correlation values exceeding 0.9999 [56]. *Topuz et al.* established an appropriate technique for identifying four fungicides and one herbicide in fruit juices at the same time. C18-SLE cartridges are used in the procedure to preconcentrate 25 g fruit juice samples. RP-HPLC was used for the separation and quantification of the insecticides. According to the study's findings, the examined samples had good linearity and recoveries and no detectable residues [57].

3.3 Expansion of LC-MS/MS applications in pesticide analysis

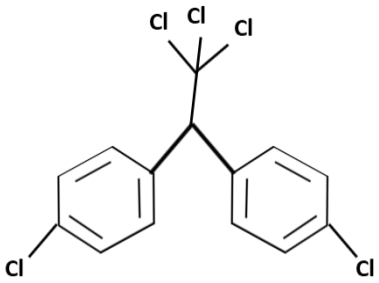
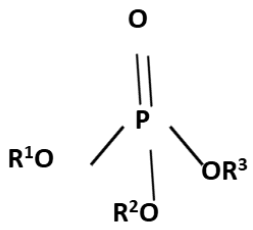
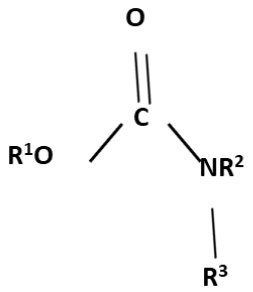
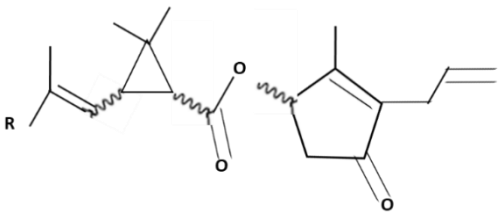
LC-MS/MS techniques utilizing atmospheric pressure ionization (API) interfaces, including atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI), are relatively expensive but deliver the high selectivity and sensitivity required for analyzing biological samples at trace and ultra-trace levels [58]. Because of its remarkable qualities, LC-MS/MS is being used more and more in clinical toxicology for multi-PSA [9]. A notable example of LC–MS/MS's application in biological monitoring of pesticide exposure comes from the National Centre for Environmental Health in Atlanta. In this laboratory, the technique is routinely used to detect up to 19 markers of commonly used pesticides in human urine. The

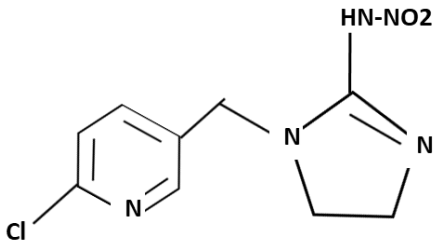
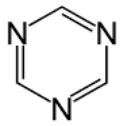
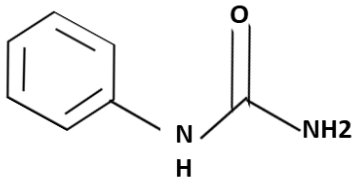
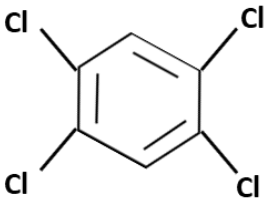
method's high throughput, exceptional sensitivity (with most LODs below 0.5 ng/mL), and ability to detect multiple residues highlight its effectiveness for biological monitoring of pesticide exposure [59]. Some pesticides, typically the most polarones—are eliminated rapidly from the body as free metabolites. A metabolite of ethylene bis dithiocarbamate fungicides, including maneb, mancozeb, and ziram, ethylene thiourea (ETU) has been identified in urine by LC-MS/MS with a detection limit of 0.5 ng/mL [60]. *Sancho et al.* used the OPP metabolites p-nitrophenol and 3-methyl-p-nitrophenol to thoroughly investigate several methods for quantifying xenobiotics in human urine by LC–(ESI)–MS/MS. This study demonstrated that the labeled p-nitrophenol IS was required for accurate quantification in the presence of strong ion suppression [61].

3.4 Comparison between GC-MS and LC-MS/MS for detecting several pesticide classes

Each mentioned technique has unique strengths and limitations. Their choice often relies on the chemical properties of the pesticides being examined. The comparison is mentioned in following Table 2 [62], [63]**.**

Table 2: Comparison of GC-MS and LC-MS/MS

Pesticide Class	**Structure**	**GC-MS**	**LC-MS/MS**
Organochlorine		Excellent choice for volatile, non-polar OCPs	Rarely used
Organophosphorus		Suitable for some OPPs, but thermal degradation	Preferred for a wider range of OPP
Carbamate		Poor, due to thermal instability	Ideal for polar, thermally unstable carbamates
Pyrethroid		Preferred due to volatility and stability	Sometimes used in complex matrices

Neonicotinoid		Poor, due to non-volatility	Method of choice for neonicotinoids
Triazine		Good for some, but derivatization needed	Preferred for sensitive, complex analyses
Phenylurea		Poor, due to poor volatility	Preferred for polar, thermally unstable compounds
Chlorinated Hydrocarbon		Excellent for volatile and stable compounds.	Rarely used.

4. EMERGENCE OF ULTRA-HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (UHPLC)

UHPLC has emerged as a more potent separation technique following HPLC's dominance of separation research. The first commercially accessible UHPLC system was developed by the Waters Corporation in 2004. Other significant manufacturers then began to follow the same technique. Practitioners choose UHPLCs because of their maximum efficiency, resolution, rapidity of analysis, robustness, reliability, and commercial availability of equipment and stationary phases based on sub-2-µm completely porous or sub-3-µm core-shell particles (Fig.3) [64]. *Nováková L et al.* reviewed the details of how UHPLC utilizes smaller particle columns and higher operating pressures to attain significantly improved resolution and faster analysis times compared to standard HPLC, making it particularly beneficial for complex pesticide mixtures [35]. In another paper, *Leandro et al.* compared the performance of UHPLC and HPLC [65]. This article emphasizes that the UHPLC improved sensitivity and selectivity due to its high separation efficiency, enabling better PSA even at low concentrations, while simultaneously reducing analysis time. Furthermore, it lowers the price of reagents with shorter run times [66]. The analysis of pesticide residues in fruits and vegetables, oil crops, olive oil and olives, salmon, beeswax, ginseng and its nutraceutical derivatives, tea leaves, and brewed tea has recently used UHPLC in conjunction with low-resolution MS/MS. These significant contributions were initiated from 2013 to March 2015 [67].

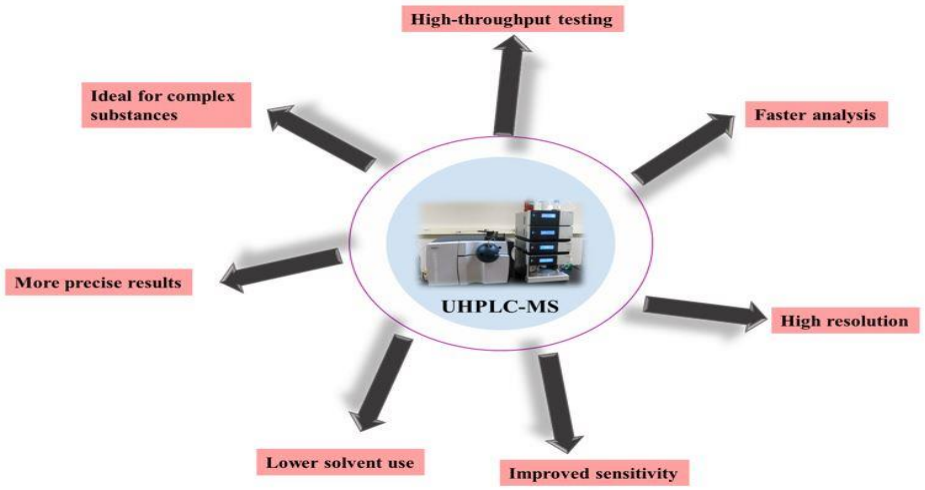


Figure 3: Advantages of UHPLC-MS [64]

When *López-Ruiz et al.* compared UHPLC–MS to traditional LC techniques, they discovered reduced limits of quantification (LOQs) [68]. *Petrovic et al.* have demonstrated the benefits of using UHPLC in conjunction with tandem MS for pharmaceutical environmental investigation; in only 10 minutes, 29 analytes in wastewater samples could be screened and confirmed. Another study employed the same combination to screen and measure 32 pesticides and metabolites in fruit samples [69]. *Pozo et al.* demonstrated exceptional separation efficiency, achieving very short sample runs (under 5 minutes per sample) to analyze 32 pesticides. This allows for high sample throughput [70]. *Walorczyk* used GC-MS/MS and UHPLC-MS with d-SPE integration to analyze 28 pesticides. For PSA with a high chlorophyll content that falls into the category of small crops, a technique was created. One significant finding was that, for a particular pesticide, relative constancy of matrix effects in both GC–MS/MS and UPLC–MS/MS analysis across multiple matrices allows for the quantification of pesticide residues in several matrices using a single matrix-matched calibration curve [71]. In recent years, there has been an upsurge in the use of high-resolution mass spectrometry (HRMS) coupled with LC using time-of-flight (TOF), Q-TOF, or Orbitrap analyzers. This is because HRMS has high resolution and accuracy in mass measurement are essential for the clear identification of analytes [36].

5. INNOVATIONS OF CHROMATOGRAPHIC TECHNIQUES IN PESTICIDE ANALYSIS IN CURRENT ERA

Recent developments in chromatographic techniques (2015-2024) in PSA is mentioned in following Table 3

Table 3: Current approaches in PSA using chromatography

Technology	Properties	Recent studies
Microfluidic chip technology	Reduced sample size, quick detection, ease of use, multifunctional integration, multiplex detection and portability, and high sensitivity [72].	• *Hossain et al.* used the inkjet printing technology to measure the activity of acetylcholinesterase on filter paper in order to create a paper chip for the detection of OPP residues in food and beverages [73]. • *Guo Yemin et al.* integrated the gold interdigital array microelectrode (IDAM) onto the PDMS microfluidic immunosensor chip to quickly identify pesticide residues in vegetable samples [54]. • To detect OPP, a plug-based microfluidics-based coulometric microdevice was generated [37].
Green solvent analysis	Strong chemical and thermal stability, tunable viscosity, eco-friendliness, and high pesticide extraction efficiency	• *Lu et al.* employed dispersive LLE to pre-concentrate OPP in ambient water using an ionic liquid based on imidazolium. They achieved good extraction recoveries and comparatively large enrichment factors (over 400) [74]. • *Wang et al.* pre-concentrated benzoylurea insecticides in honey using the same methods. Additionally, they

		employed the environmentally harmful acetonitrile to elute the herbicide residues. They did, however, achieve comparatively high extraction recoveries [75].
Nanomaterials incorporation along with Biosensors	Increasing sensitivity, and selectivity, improving accuracy, robustness, and field deployment capability, making analysis easier, faster, and more cost-effective [76].	• *Zhao* prepared silver NPs, and detected 11 OPP and Methomyl in apples and cabbage [77]. • *Thakkar* developed the MWCNT system, to analyze Paraoxon pesticide from potatoes [38]. • *Wang* prepared Fe3O4 and grapheme to analyze Chlorpyrifos pesticide cabbage and spinach [78].
Artificial intelligence (AI) and machine learning (ML) integration	Analyze large datasets of pesticide characteristics and toxicological information, allowing for predicting potential pesticide toxicity and optimal analytical methods for their detection, thereby contributing to safer and more efficient pesticide management practices.	• •Using ZnO-based photocatalysts, *Dashti et al.* constructed innovative machine-learning models that enhanced the estimation of the photocatalytic destruction of different pesticides [39]. • *Li F* employed six machine learning techniques to predict pesticide aquatic toxicity and nine molecular fingerprints to characterize them. This is a helpful instrument for assessing pesticide aquatic toxicity early on in environmental risk assessment [79].

6. APPLICATIONS OF ADVANCED CHROMATOGRAPHIC TECHNIQUES

Advanced chromatographic techniques are pivotal in various fields, including forensic science, clinical toxicology, pharmacokinetics, and toxicokinetics. The following Table 4 provides a summary of these techniques and their applications.

Table 4: Applications of chromatographic techniques

Chromatographic techniques	**Applications**	**Detection**	**Matrix**	**References**
HPLC–DAD	**Forensic toxicology**	Anticholinesterase pesticide	Animal stomach contents, liver, vitreous humor, and blood	*Fukushima*, [80]
QuEChERS extraction and LC/MS/MS system		Authentic 34 analytes	Liver tissue	*Cox et al.* [81]
HPLC-MS/MS		**9 insecticides, and fungicides**	**Blood, urine**	*Mouskeftara T* [82]
GC-MS		**Phorate pesticides**	**Blood, urine, bile**	*Simonelli A* [83]
ESI-HRMS and DART-HRMS		Terbufos and terbufos sulfoxide	Gastric content, hair, and nail samples	*Wurzler GT* [84]
LC-MS		Occupational and environmental pesticide exposure	Blood and hair samples	*Çelik, S* [85]

TD-ESI/MS/ MS	**Clinical toxicology**	Carbamate and organophosphate pesticides	Saliva, urine, and whole blood	*Su et al.* [86]
LC-MS/MS		Neonicotinoid insecticides	Urine, blood and hair	*Tu et al.* [87]
LC-MS/MS	**Pharmacokinetics and toxicokinetics**	OP pesticides	Blood sample	*Sinha* [88]
HPLC		Permethrin	Serum	*Bruce* [89]
HPLC		Chiral pesticide ethofumesate	Human liver microsomes.	*Perovani IS* [90]

7. CHALLENGES IN PESTICIDE DETERMINATION IN BIOLOGICAL SPECIMENS

Determining pesticide residues in biological specimens such as blood, urine, and tissues is essential for understanding human exposure and associated health hazards. However, this process presents unique challenges due to the complexity of biological matrices, the pesticide trace levels, the diversity of pesticide chemicals, and other factors [91]. Biological samples contain many endogenous compounds, including proteins, lipids, and enzymes, which can interfere with detecting and quantifying pesticides. The intricate matrix nature necessitates extensive sample preparation and clean-up steps, significantly increasing the time and cost required for accurate analysis [92]. Pesticides and their metabolites are often present in biological fluids at extremely low concentrations. Detecting these trace levels requires highly sensitive instrumentation, like LC-MS/MS or GC-MS/MS [93]. It often requires extensive sample preparation to remove matrix interferences, which can be time-consuming and labor-intensive. The cost of advanced chromatographic instruments, such as tandem technologies is high. Additionally, these methods rely on highly skilled operators and precise calibration to ensure accurate results. Furthermore, the use of hazardous solvents in some protocols raises environmental and safety concerns, highlighting the need for greener, more efficient approaches [94]. Additionally, each type of pesticide may have specific extraction, separation, and detection requirements, which complicates multi-residue screening methods when multiple pesticides need to be detected simultaneously.

Many pesticides are prone to degradation due to factors like temperature, pH, or prolonged storage. For instance, specimen handling and transport conditions must be carefully controlled to prevent the degradation of analytes, which could lead to inaccurate exposure assessments [95]. A lack of standardized methodologies for determining pesticide residues in biological samples also contributes to variability in test results across laboratories. Laboratories require significant funding to maintain the quality and precision of pesticide determinations, especially in routine testing environments [96].

Discussion: While previous literature or studies have extensively documented traditional chromatography methods, this review emphasizes the integration of novel technologies, such as artificial intelligence and nanotechnology, which are emerging as transformative tools in analytical toxicology. AI is playing an increasingly significant role in agriculture, driving advancements in areas such as agricultural robotics, pesticide detection, and crop and soil monitoring. With its continuous evolution, AI, combined with the Internet of Things (IoT), enables real-time monitoring of critical parameters like humidity, temperature, and soil health, optimizing resource usage. These technologies also enhance precision agriculture, smart greenhouse management, data analytics, agricultural drones (UAVs) deployment, and animal health monitoring. Furthermore, AI-driven machine learning algorithms process vast datasets to predict pest toxicity and assess human health risks, enabling precise pest detection and the formulation of effective remediation strategies [97]. Conventional techniques remain standard tools in pesticide detection and degradation studies. However, these methods are often time-consuming and costly. The integration of AI technologies with these conventional systems has gained popularity due to their ability to enhance accuracy, efficiency, and accessibility [77]. Meanwhile, the use of advanced sensors, such as electrochemical and biosensors, has grown due to their improved sensitivity and selectivity in pesticide detection. A promising development in this field is the application of NPs for pesticide detection and degradation. For instance, *Wang et al*. demonstrated a nanomaterial-based biosensor with high accuracy, reproducibility, and regeneration capabilities, which proved effective for trace detection of chlorpyrifos residues in vegetables [38]. These advancements highlight the evolving landscape of pesticide detection technologies [78]. Although there are some limitations of these techniques. AI models require large volumes of accurate and representative data to train effectively, and the availability of such data can be a significant constraint. Additionally, data biases can result in skewed predictions [98]. Also, the high cost of synthesizing and functionalizing NPs can restrict their widespread adoption, particularly in resource-limited settings. The scalability of nanomaterial production poses challenges, as maintaining consistent quality and functionality at larger scales is difficult. Additionally, the stability

and reproducibility of nanoparticle-based sensors may be affected by environmental factors [99]. Surface-enhanced Raman, fluorescence, chemiluminescence, photoacoustic spectroscopy, electrochemical, biosensors, and nanoparticle-based sensor techniques need to be investigated further. Microfluidics and lab-on-a-chip technologies, immunoassays, molecular diagnostics, and data-driven tools are complementary to chromatography and can be useful in pesticide analysis in the future. Combining these techniques with existing methodologies holds the potential to revolutionize pesticide detection systems. Collaborative efforts between researchers, policymakers, and industry stakeholders will be essential to foster responsible innovation and ensure the equitable application of these technologies in pesticide analysis and environmental monitoring.

8. CONCLUSION AND FUTURE DIRECTIONS

In conclusion, pesticides play a critical role in global food security by preserving food and protecting plants, but their widespread use poses significant health and environmental risks. Advanced chromatographic techniques like GC-MS and LC-MS/MS are instrumental in PSA with high accuracy, faster analysis, and high throughput testing which supports exposure assessments, public health research, and regulatory standards. However, with the increasing complexity of pesticide exposure, future research must focus on emerging technologies, such as personalized toxicology and AI/ML-based predictive models. Innovations such as personalized toxicology could provide more tailored approaches to understanding individual exposure risks, helping to identify vulnerable populations and optimize safety measures. While, AI/ML could revolutionize pesticide residue analysis by automating workflows, improving accuracy, and identifying previously unnoticed correlations in environmental and biological samples. Through the integration of these cutting-edge technologies into analytical methodologies, researchers can advance pesticide safety, safeguard vulnerable populations, and minimize ecological impact, ensuring a healthier and more sustainable future.

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