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Review

Recent Advances in Chromatographic Analysis of Emerging Pollutants in Dairy Milk: A Review (2018-2023)

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Abstract: Emerging pollutants (EPs) encompass natural or synthetic substances in the environment that pose potential risks but have only recently been recognized or monitored. EPs consist of various categories including pesticides, pharmaceuticals, hormones, mycotoxins, and endocrine disrupting chemicals (EDCs). Through several pathways, EPs can access food, potentially leading to health impacts when their safe concentrations are exceeded. Milk, being a highly nutritious and a heavily consumed food product by many consumers of different ages, is a crucial food matrix where EPs should be regularly monitored. In literature, large number of studies was dedicated for the determination of different EPs in dairy milk, employing different analytical techniques. Chromatographic based techniques were the most prevalent means for analysis of EPs in milk, which demonstrated significant efficiency, sensitivity and accuracy for this specific purpose. Prior to chromatographic analysis, extraction of EPs from a complex matrix like milk, is essential. This review comprehensively covers relevant research papers on extraction and subsequent detection and determination of EPs in milk by chromatographic methods from 2018 and until 2023.

Keywords: emerging pollutants; dairy milk; gas chromatography; liquid chromatography; extraction

1. Introduction

In recent years, the global population has witnessed rapid growth, leading to a surge in consumer demand. This increase has resulted in the expansion of industrial manufacturing, agricultural activities, and technological developments. Consequently, both the environment and humans have been exposed to various new chemicals known as emerging pollutants (EPs) or contaminants of emerging concern (CECs)[1]. EPs are defined as synthetic or naturally occurring compounds found in the environment. They are generally not monitored but have the potential to cause adverse ecological effects and health consequences [2,3]. Broadly, EPs can be divided into three chemical categories: the first encompasses newly synthesized compounds, the second includes compounds that have long been present in the environment but have only recently been detected and recognized, and the third comprises compounds known for some time but whose detrimental effects on the environment and human health have been identified only recently [2,4] .

EPs consist of a wide array of organic and inorganic compounds commonly found in the environment, such as pesticides, perfluorinated compounds, pharmaceuticals, personal care products, endocrine disruptors, hormones, toxins, plasticizers, flame retardants, and more [1,4]. The majority of EPs stem from routine anthropogenic activities, including domestic, healthcare, agricultural and industrial processes [5]. These substances can infiltrate the environment, permeating various food sources and environmental matrices, such as water, soil, marine sediments, and both indoor and outdoor dust [1]. The global production of these pollutants is estimated to have surged from 1 million to 500 million tons annually [6]. EPs are recognized as potential environmental hazards due to their high toxicity and biochemical reactivity. They have adverse effects on the quality of natural resources and pose significant health risks to humans and other living organisms [7]. Many of these pollutants persist in the environment and tend to bioaccumulate in animal tissues [1]. Additionally, a significant number of them can be transported over long distances in the environment

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[8]. Consequently, assessing the health risks associated with human exposure to these contaminants becomes paramount. There are several pathways through which individuals can be exposed to EPs: inhalation of volatile EPs present in the air, direct skin contact, and ingestion. Factors such as the amount, frequency, and duration of exposure play a critical role in determining the risks associated with these pollutants. Furthermore, individual's factors such as diet, sex, age, lifestyle, and genetic makeup can significantly influence susceptibility to their effects [1,8].

EPs can pose a spectrum of health risks to humans, ranging from mild symptoms such as headache, dizziness, nausea, and skin irritation to severe conditions including cancer, reproductive disorders, heart diseases, nervous system disorders, liver damage, DNA mutation, among others [9]. For example, a study conducted by Bonefeld-Jorgensen et al. found compounds in serum and a strong correlation between the presence of perfluorinatedand an increased risk of breast cancer in Inuit women from Greenland [10]. In another research study, a significant relationship was identified between elevated levels of certain liver enzymes (alkaline phosphatase, gamma- glutamyltransferase, and lactate dehydrogenase) and bisphenol A, an endocrine disruptor, indicating a potential alteration in liver function [11].

Figure 1 is a graphical representation of some potential health risks posed by different types of EPs as demonstrated in literature.

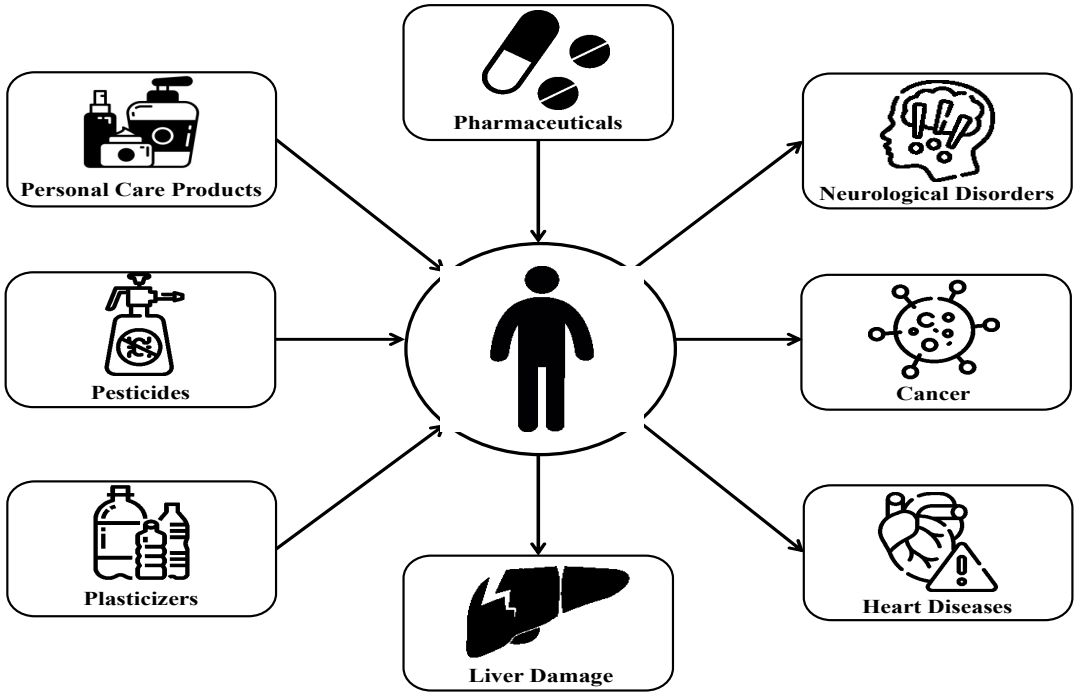

Figure 1. Health impacts of different types of EPs.

Notably, the adverse effects of EPs are not limited to humans. Evans *et al.* examined the impact of endocrine disruptors in Canada's Oldman River waters on the gene expression of the Longnose Dace fish species [12]. With approximately one-third of the 28,000 km2 watershed allocated to agricultural activities, particularly intensive livestock operations, runoff introduces significant amounts of endocrine disruptors into the river. Consequently, this has caused alterations in the fish's gene expression, notably leading to the feminization of male specimens. Given the potential risks posed by these pollutants to both humans and the environment, numerous studies are dedicated to providing comprehensive insights into their occurrence, potential impacts, fate, and analytical methods for detection in various food and environmental matrices [13–16].

2. Emerging Pollutants in Dairy Milk: A Concern for Public Health

Among various matrices containing EPs, dairy milk has emerged as a critical focal point. Renowned for its exceptional nutritional benefits, milk ranks among the most consumed food worldwide. It is a vital reservoir of protein, essential nutrients such as calcium, phosphorus,

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magnesium, zinc, iodine, potassium, and essential vitamins including A, D, B12, and B2 [17]. Due to its rich nutritional profile, milk plays a fundamental role in the diets of infants and young children. However, various EPs, including veterinary drugs, antibiotics, endocrine disruptors, phthalates, pesticides, and others, can contaminate milk [15,18–20]. Food and Agriculture Organization of the United Nations has reported a distribution of the average consumption of milk in different areas of the world. The data is based on per capita food supply at the consumer level. For the year 2020, they have reported some nations that consume less than 50 kg of milk per year, such as China, India, and Iran, and other nations consuming up to 290 kg of milk per year, such as Albania, Switzerland, and Kazakhstan. [21]

The presence of EPs in dairy milk can arise from multiple sources: contaminated cattle feed, polluted water sources, and residues from veterinary medicines. Notably, pesticide residues can find their way into animal feed due to improper application in agricultural practices. Moreover, milk's fat content makes an ideal medium for dissolving lipophilic pesticides [21,22]. Contamination may also occur when using polluted water for cleaning equipment involved in milk storage and processing or providing such water as drinking water for cattle [23]. Additionally, the use of veterinary drugs and antibiotics in cattle for disease prevention and treatment can introduce drug residues into milk [19,24]. Throughout the mechanical milking process, transportation from the farm's cooling tanks to the dairy factory's cooling tank, and packaging, phthalates might migrate into the milk [25].

While these contaminants may exist in minute quantities, they still pose serious health risks, especially if they exhibit persistence and bioaccumulative properties [1]. Regular or daily consumption of milk means that even trace amounts of these contaminants can accumulate significantly over time, posing a threat to consumer health. This concern is particularly critical for infants and children, given their heightened vulnerability due to their ongoing physiological development. Therefore, a thorough evaluation of milk quality is essential to ensure food safety and reduce health risks associated with these contaminants. Several studies have highlighted the detection of various EPs in milk, emphasizing the importance of comprehensive monitoring systems for animal feed, water, and medicines. These findings draw attention to concerns regarding milk's safety [15,26–28]. Numerous studies have developed analytical methods for evaluation of different types of EPs in milk and milk products. This review comprehensively covers all relevant research papers dedicated to the development of chromatographic-based analytical methods for determining different categories of EPs in dairy milk from 2018 to the present (2023). To maintain focus and coherence in this review, the scope excludes other dairy products, non-dairy or plant-based milk, and human milk due to the extensive volume of research studies available in these areas. Comprehensively covering all these areas in a single review would be impractical.

3. Chromatographic Techniques for EPs Analysis

Chromatography, in its fundamental concept, is based on the separation of sample components immobilized on a moving phase (mobile phase) over a fixed phase (stationary phase). Different sample components interact differently with the stationary phase and hence move slower or faster spending different times (retention time) until they elute from the column which enables for their separation. The mobile phase can be either gas or liquid, while the stationary phase can be solid or liquid.

Gas chromatography (GC), utilizing gas as the mobile phase, and liquid chromatography (LC), in which the mobile phase is a liquid, are the most popularly employed types of chromatography for analytical purposes. When combined with different types of detectors such as mass spectrometers (MS), ultraviolet detectors (UV), diode array detectors (DAD), fluorescence detectors (FLD), flame ionization detectors (FID) and electron capture detectors (ECD), GC and LC play a pivotal role in the analysis, identification and quantification of a wide variety of contaminants in food and environmental matrices, offering significant efficiency and sensitivity [14,29–31]. Delving into literature makes it evident that the most commonly employed methods for analyzing and quantifying residual contaminants in milk and dairy products generally rely on chromatographic techniques [13,32–34].

3.1. LC Based Techniques

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Paired with different detectors, typically FLD, UV, DAD and MS, LC based techniques emerge as a robust and powerful option for analysis of a wide range of compounds of different chemical and physical properties.

For decades, LC-MS have found applications for separation and determination of various contaminants in complex food and environmental matrices [32,35–37]. In this system, as the separated analytes elute from the column, they are introduced into the mass spectrometer, in which they are accelerated through magnetic and electric field that leads to their separation, based on their mass to charge ratio (m/z), providing information about their identity as well as their quantity. Moreover, the availability of different types of mass spectrometers, each differing in their ionization sources and/or mass analyzers, have further expanded the range of compounds that can accurately be detected. Those mass analyzers include time of flight (TOF), Orbitrap and tandem mass spectrometers.

Tandem mass spectrometry (MS/MS) or (MS2), which can be seen as an extension of MS, involves the use of two sequential mass spectrometry stages, allowing for detection of trace amounts of analytes with superior sensitivity. MS/MS in combination with LC techniques, such as high-performance liquid chromatography (HPLC) and ultra-high performance liquid chromatography (UHPLC), make up the most prevalent chromatographic method for analysis of residues of different categories of EPs in milk, those included veterinary drugs residues, pesticides, endocrine disrupting compounds (EDCs) and others [32,38–40]. For example, Nemati et al. have employed HPLC-MS/MS for the determination of residues of seven different pesticides in cow milk, with limit of detection (LOD) ranging between 0.09-0.27 ng/mL [41]. Moreover, an analysis method based on UHPLC-MS/MS was developed and validated by Macheka et al. for determination of compounds from the category of per- and polyfluoroalkyl substances (PFAs) in dairy milk and infant formula with a low LOD within the range of 0.005-0.05 ng/mL [42]. Guedes-Alonso et al. have also successfully applied another method based on UHPLC-MS/MS for the detection of fifteen steroid hormones in commercial raw milk achieving low LODs ranged between 0.047 to 1.242 ng/mL [27].

In recent years, the goal of shortening analysis times along with increasing sample throughput, sensitivity and resolution has driven the development of ultrafast separations and high-resolution MS (HRMS) detectors. Wu et al. have incorporated the separation capabilities of liquid chromatography with the accurate identification and detection of high-resolution mass spectrometry (LC-HRMS) for determination of eight peptide antibiotics in three different types of bovine milk with LODs ranging between 0.5 and 5.5 ng/g, which is far below the limits of concern for those types of antibiotics [43]. Similarly, LC-HRMS was also the technique of choice by Wang et al. for the selective and sensitive analysis of the two antibacterial drugs vancomycin and norvancomycin in milk samples with a LOD of 0.15 μg/kg for both [44].

In addition to MS, fluorescence detectors, at specific excitation and emission wavelength, offered high efficiency and precision that were in many cases comparable to that of MS. For naturally fluorescent analytes or analytes that can be derived to become fluorescent, HPLC coupled with fluorescence detector (HPLC-FLD) is particularly a valuable analysis tool. Badali et al. have proposed a method utilizing HPLC-FLD for determination of two types of poisonous mycotoxins, that are produced by certain molds, namely aflatoxin M1 (AFM1) and ochratoxin A (OTA) [45]. The developed method achieved a low LOD of 0.37 and 0.25 and ng/L for AFM1 and OTA, respectively. This method was applied for the detection of the two analytes in samples of cow milk. Similarly, Murshed has employed HPLC-FLD for determination of AFM1 in milk and milk products including powdered milk and yogurt, achieving a LOD of 0.002 μg/L [46]. While HPLC-FLD was the method of preference for analysis of mycotoxins in milk, it was rarely employed for determination of other types of EPs, such as veterinary drugs and pesticides.

Liquid chromatography in conjunction with UV detectors was of the earliest methods that have been used for different purposes such as detection and quantification of different categories of food and environmental pollutants residues [47–49]. However, UV-Vis detectors in which detection and identification of the eluants are based on their absorption in the UV or visible region of the electromagnetic spectrum, suffer from major drawbacks. Those include, avoiding the use of variety of solvents that strongly absorb in the UV region, such as ethyl ethers, chloroform, acetone, and benzene due to their interferences with the target analytes [50]. Even a common solvent like methanol, does absorb in the UV region, although being used in the mobile phase for HPLC-UV, but precautions

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steps and gradient elution are important to suppress its interference. This limitation of solvent options subsequently narrows and restricts the applicability of HPLC-UV systems. Moreover, compounds that don't contain chromophores (the functional groups that absorb in the UV-Vis region) will not be possible to assess by this system without a derivatization step, which in turn consumes large amount of sample, solvents and hazardous chemicals in addition to time lengthening, adding complexity to the analysis method and demonstrating another major drawback for HPLC-UV system.

Although being surpassed by MS and FLD detectors, UV combined with HPLC still finds applications in the analysis of many classes of pollutants in milk. For example, Al-Afy et al. have monitored tetracycline (TCN), oxytetracycline (OTC) and doxycycline (DC) antibiotics, that belong to the family of broad-spectrum tetracyclines (TCNs) antibiotics in bovine milk using an analytical method based on HPLC-UV for separation and detection [51]. The LOD was obtained in the range of 1.8–2.9 μg/L. HPLC with Diode Array Detection (HPLC-DAD) which is also referred to as photodiode array (PDA) detector (HPLC-PDA) in which absorbance of compounds is measured over a wide range of wavelengths in the UV-Vis region at one time (simultaneously) providing more detailed spectral information which allows for more precise and accurate compound identification, is also a powerful technique that was used in the context of EPs determination in milk. An example is the method provided by Vuran et al. for determination of the two antibiotics chloramphenicol and tetracycline in milk samples. LODs were 3.43 ng/mL and 3.55 ng/mL and the method was validated for its applicability for analysis of those compounds in complex matrices like milk [52].

While HPLC and UHPLC systems, coupled with the aforementioned detectors, currently dominating the analysis of EPs, recent efforts have been made to find alternative approaches that are less time consuming, less complex, more cost effective and more environmentally friendly [53,54]. Such approaches include the employment of capillary liquid chromatography (CLC) and micellar liquid chromatography (MLC) [54,55]. Tejada-Casado et al. have implemented CLC in conjunction with UV detector for determination of sixteen different anthelmintics drugs from benzimidazole group in milk [55]. This method achieved low LODs ranging between 1.0 and 2.8 μg/kg, providing an efficient and miniaturized chromatographic trial for the purpose of determination of EPs in milk. This technique was also reported to be simpler and greener, owing to the reduced solvent and sample consumption. Similarly, Prasad Pawar et al. have proposed a simple, cost effective and environmentally benign approach using MLC for determination of residues of mebendazole anthelmintic drug in samples of milk and dairy products as well as breeding waste from bovine animals [54]. This method demonstrated good sensitivity that was reflected in the low LOD ranging from 0.1–0.2 ppm. Those studies highlighted the potential of those simple liquid chromatographic techniques as alternatives for conventional HPLC and UHPLC based methods, that are although being powerful and sensitive, still require expertise, involve time consuming preconcentration steps and are comparatively much expensive.

3.2. GC Based Techniques

Chromatographic methods based on GC, including GC-MS, GC-FID and GC-ECD, have been reported by numerous studies to demonstrate high efficiency, sensitivity, selectivity and precision for determination of various categories of complex contaminants in milk [37,56,57] .

In most studies of EPs in milk samples, GC equipped with single MS provided better results than studies using GC with other detection systems such as FID and ECD. Yet, the use of tandem mass spectrometry (MS/MS) has been applied in recent years for achieving further better precision and sensitivity.

Using the high separation capability of GC in combination with the efficient detection of MS, Campos do Lago et al. have proposed a method for determination of four organophosphates pesticides with LOD ranging from 0.36 to 0.95 μg/L [58]. This method was efficiently applied for the detection of those pesticides in commercial bovine milk samples. Bisphenol A and five phthalate esters were targeted by Tang et al. who developed an analytical method also based on GC-MS that achieved low LODs in the range of 0.01 to 0.06 μg/L [59]. While Pan et al. has employed GC-MS/MS for developing a valid method for determination of six phthalate esters, achieving LODs ranged from 0.8 to 2.1 μg/L [60]. This method was suitable for investigation of the targeted phthalates in milk samples. GC-MS/MS was also the technique of selection by Hasan et al. who targeted a group of compounds under the two categories of polychlorinated biphenyls (PCBs) and polyaromatic

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hydrocarbons (PAHs) in a total of 100 cow milk samples [34]. This method achieved low values of LOD ranging from 0.016 to 0.031 ng/g for the targeted PCBs and 0.3 and 1.0 ng/g for PAHs.

Flame ionization detector (FID) is a unique type of detectors in which the sample is burned in a flame, which in turn generates electrically charged ions. The electrical current produced by those charged particles is what is measured in FID and proportionally related to the quantity of ions. J. Zhang et al. used FID coupled with GC for determination of eight phenolic compounds, achieving LODs within the range of 0.001-0.1 μg/L under optimum conditions [57]. The method was applied for determination of those analytes in five types of canned beverages including milk.

In addition to MS and FID, electron capture detector (ECD) is a highly sensitive type of detectors hyphenated with GC. ECD is a specialized tool for detection of electron absorbing analytes or electronegative compounds that have high affinity to electrons such as chlorinated pesticides, polychlorinated biphenyls (PCBs) and some types of drugs. Those type of compounds attract the emitted electrons by the radioactive source in ECD producing charged species (ions) their amount is directly proportional with the concentration of the target analyte. Rahman et al. have developed an analytical method based on GC-μECD for determination of an organochlorine pesticide (endrin) and its metabolite (δ-keto endrin) in five food products of animal origin (chicken, pork, beef, egg, and milk) with a LOD that reached 0.003 mg/kg [61].

It is worth mentioning that different chromatographic techniques coupled with different types of detectors are shown to be reliable for detection of different types of EPs either specifically or simultaneously. Although the majority of the studies provided methods for detection of compounds that belong to the same category of EPs, there are several studies that provided one chromatographic method that is valid for determination of multiclass residues of EPs. Jia et al. have developed an analytical method employing ultrahigh-performance liquid chromatography–hybrid quadrupole–linear ion trap mass spectrometry (UHPLC-Qtrap-MS) for simultaneous analysis of a total of two hundred and nine contaminants that belong to veterinary drugs, mycotoxins, and pesticides categories [13]. The developed method obtained a LOD that ranges from 0.01 to 1 μg.kg and was validated and applied for investigation of the contaminants in bovine milk samples.

Similarly, Izzo et al. have employed ultra-high-performance liquid chromatography/high-resolution mass spectrometry (UHPLC-Q-Orbitrap HRMS) for the analysis of a group of mycotoxins and pharmaceutically active compounds in milk with LOD within the range of 0.001 to 0.010 ng/mL [28].

4. Extraction of EPs from Milk

Prior to chromatographic analysis, sample treatment is a critical step that involves some preparation procedures including extraction, preconcentration of the compounds of interest, clean-up of impurities and homogenization.

In complex matrices like milk, analytes of interest are required to be selectively isolated, purified and extracted before introduction into the analysis technique. Especially that most of these analytes are present in low concentrations, extraction step is significantly useful and significantly affecting the overall performance of the analysis method.

4.1. SPE

Different extraction techniques used for this purpose include solid phase extraction (SPE), which since its introduction in 1980s, has been widely employed as a sample preparation approach [62]. SPE involves passing the sample over solid adsorbents/sorbents with a selective affinity to the target analyte usually packed in a cartridge or a column. Target contaminants adsorb to the solid phase whereas undesired components are washed away. SPE advantages include its simplicity, ease of automation and utilization of various types of adsorbents that are often readily available [63,64]. Since the solid adsorbent is the key factor in SPE approach, different types of adsorbents are being developed and enhanced over time. Those solid adsorbents include commercially available adsorbents as well as selectively synthesized adsorbents.

Decheng et al. have used a commercial SPE cartridge (PRiME HLB) for purification and extraction of the steroid hormone progesterone and twenty-one veterinary drugs under the class of progestins from milk samples, after solvent extraction and centrifugation [29]. Recoveries of the spiked milk samples were between 80.7% and 108.3%. In addition, bisphenol A (BPA) and bisphenol

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S (BPS) were extracted from milk samples by C18 SPE cartridges after their sonication and dilution reaching average recoveries of 86% ± 3 for BPA and 100% ± 7 for BPS [65]. Although commercial SPE adsorbents are frequently used, they often exhibit nonselective adsorption of target analytes which may in turn decrease the yield and efficiency of extraction. To address this issue, wide variety of SPE adsorbents are being specifically synthesized and tailored for selective recognition and extraction of the target analytes. In this context, molecularly imprinted polymers (MIPs) have become widely popular as solid adsorbents owing to their ease of preparation, structure predictability, cost effectiveness, specific recognition capability and broad applicability [64,66]. For extraction of lincomycin antibiotics from milk samples, Negarian et al. have utilized a selective lincomycin core-shell MIP, prior to its analysis by HPLC-UV, that yielded a recovery ranging from 80% to 89% [66]. additionally, MIP as a solid adsorbent was also applied by X.-C. Huang et al. for extraction of three endocrine disrupting chemicals, namely hexestrol, nonylphenol, and bisphenol A from lake water and milk samples, resulting in a recovery that ranged from 89.9 to 102.5% [35].

Moreover, Carbon nanomaterials have gained a great popularity as adsorbents in SPE due to their unique qualities, such as high surface area, excellent adsorption capacity, exceptional chemical activity, chemical stability and ease of surface modification or functionalization [67,68]. Those materials include carbon nanotubes (CNTs) including single-walled CNTs (SWCNTs) and multi-wall CNTs (MWCNTs), graphene oxide (GO) and graphene (G). In the context of EPs in milk, Jiang et al. have employed educed graphene oxide and gold nanoparticle (rGO/Au) for solid phase extraction of nine different mycotoxins from milk, the recoveries achieved were in the range of 70.2–111.2% [69]. whereas (N. Li, Qiu, et al.) have used magnetic MWCNTs modified with polyethyleneimine for selective extraction of ten different mycotoxins from milk samples, before introduction into HPLC–MS/MS system [70]. This approach obtained adequate recoveries ranging from 88.3 to 103.5%.

4.2. MSPE

Magnetic solid phase extraction (MSPE) is a type of SPE where magnetic sorbents are utilized for target compounds extraction and then easily separated along with the desired analytes from the sample by simply placing a magnet near the sample which eliminates the need for time-consuming traditional purification steps like filtration, decantation or centrifugation.

Many types of adsorbents used for MSPE of EPs from milk have been reported in literature. For instance, Guan et al. have synthesized core-shell composite of magnetic covalent organic framework (COF@Fe3O4) where the spherical Fe3O4 was the magnetic core and the COF that was synthesized by Schiff base reaction of 1,3,5-triformylphloroglucinol and p-phenylenediamine as the shell [71]. The synthesized COF@Fe3O4 was used as an adsorbent for six types of fluoroquinolone antibiotics (enoxacin, fleroxacin, ofloxacin, norfloxacin, pefloxacin, and lomefloxacin) from milk samples after their centrifugation and prior to their introduction into HPLC-UV, high recovery ranges from 90.4 to 101.2% of the spiked six fluoroquinolones in milk samples was reported.

4.3. SPME

Although classical SPE is still commonly applied for sample preparation in conjunction with chromatographic techniques, it has undergone substantial and ongoing advancements over time offering selective and precise separations at the same time shortening extraction time by using less steps and minimizing hazardous organic solvents, not only through development of different types of solid adsorbents but also through development of new variations of SPE that allowed for its operation in different modes and formats.

Solid phase microextraction (SPME), in which a solid microfiber such as silica rod is coated with an extraction phase selective to the target components, is one example of the advanced variations of SPE in which no or minimized solvents are utilized. SPME is particularly efficient for extraction of volatile and semi-volatile compounds. It can be carried out by either inserting the SPME fiber directly to the sample or in the headspace (HS) (the gas phase just above the sample). Jeong et al. have employed (HS-SPME) for extraction of the toxic organic compound furan from different food matrices including milk, peanut butter, tuna and peanut butter among others [72]. The extraction fiber was made of 75 μm carboxen/polydimethylsiloxane and the recovery ranged from 77.81−111.47% for furan in spiked food matrices.

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4.4. FPSE

Among the innovative variations of SPE is fabric phase sorptive extraction (FPSE), which involves the use of a natural or synthetic sorptive fabric that is treated or coated with a selective sorbent material integrating the principles of both SPE and SPME approaches [73]. The fabric support can be hydrophilic such as cotton cellulose or hydrophobic such as polyesters or combination of both depending on the polarity of the target analytes. Different types of sorbents can be bonded to the fabric substrate such as MIPs or sol-gel adsorbents depending on the properties of the target compounds which grants this technique high selectivity. Moreover, the fabric substrate as support for sorbent materials provides them with chemical stability and mechanical robustness [73].

For extraction of estrogenic endocrine disrupting chemicals and bisphenol A from milk samples, Mesa et al. have used commercial cotton fabric that was treated and coated with sol-gel adsorbents obtaining recoveries that ranged from 13.7 – 69.2% and observed that as the fat content of the milk decreases, the recovery values of the spiked samples increases [14].

4.5. IAC

In immunoaffinity columns (IACs), SPE principles are applied through selective antibody-antigen interactions. This extraction approach is commonly applied for extraction of mycotoxins from food samples prior to their analysis [46,74,75]. For instance, Mannani et al. have used IAC for purification and extraction of AFM1 from milk samples, obtaining mean recoveries ranged between 87% and 95% [75]. Despite the accuracy and selectivity demonstrated by this approach, as reflected in the adequate recovery values, it also suffers from some drawbacks including its relatively expensive costs and their limitation to single use [76] .

4.6. LLE

Liquid-liquid extraction (LLE) is a different type of extraction, which is also known as solvent extraction. LLE along with SPE represent the oldest extraction techniques that have been adopted for extraction of many contaminants from complex food and environmental matrices [63,77,78].

In LLE, compounds are partitioned between two immiscible aqueous and organic phases. Solvent selection is critical in this type of extraction. Choi et al. applied this technique using acetic acid in acetonitrile for the extraction of two types of pesticides (tebufenozide and indoxacarb) from different food matrices including milk followed by homogenization and centrifugation [79]. The recovery rate ranged between 73.22 and 114.93% in all the studied matrices. Although LLE extraction procedures are frequently applied, they come with several drawbacks including consumption of large sample and solvent volumes which contradicts the tide of green chemistry, low sensitivity, possible sample contamination, difficulty of automation as well as lengthy extraction times.

4.7. DLLME, ALLME and SALLE

To overcome those drawbacks, variations from LLE have been developed. Those include dispersive liquid-liquid microextraction (DLLME), salting out assisted liquid-liquid extraction (SALLE) and air assisted liquid-liquid microextraction (ALLME). In DLLME, the working mechanism involves a ternary solvent system that consists of a water-miscible solvent (dispersive solvent), water immiscible solvent (extraction solvent) and the aqueous sample with the target analytes. The extraction and dispersive solvents are mixed and rapidly injected into the aqueous sample forming a cloudy solution in which fine droplets of the extraction solvent are dispersed in the aqueous sample acting as highly efficient extractors for the target organic compounds. The large contact area between the extraction solvent microdroplets and the aqueous sample provides this extraction approach with high efficiency, rapidity, good recovery and high enrichment factor [77,80]. From milk, melamine was extracted via DLLME by Vaseghi Baba et al. before subsequent analysis by HPLC-UV, an extraction method that resulted in satisfactory relative recoveries ranged from 79.6 to 105.0% [49]. Additionally, a study conducted by Sharma et al. has revealed the applicability of DLLME for extraction of eight pesticides from milk, with a recovery within the range of 86.15 and 112.45% [81].

In SALLE, a water miscible organic solvent, such as acetonitrile or methanol, is mixed with the aqueous sample that contains the target compounds. A high concentration of salts, such as sodium

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chloride or magnesium sulfate, is added to the mixture. The addition of those salts reduces the solubility of polar compounds in the aqueous phase, so that they partition into the organic phase in a process known as “salting out”. This extraction technique offers multiple advantages including the possibility of employing polar or moderately polar solvents unlike most of the LLE techniques, which is especially valuable for compounds that have higher affinities to polar solvents, which in turn broadens its applicability to include wider ranges of compounds. For extraction of benzimidazole anthelmintic drugs from three types of milk from three types of milk (cow, sheep and goat), Tejada-Casado et al. have applied SALLE approach, obtaining recoveries that ranged from 79.1 to 99.6% [55].

In ALLME, a water immiscible (organic) solvent is mixed with the aqueous sample that contains the target analytes. Similar to the mechanism of DLLME, air is injected through a fine needle that produces fine bubbles in the sample solution leading to dispersion of the organic phase into microdroplets within the aqueous phase. ALLME also offers multiple advantages such as simplicity and improved efficiency due to large surface area provided by the extraction microdroplets [82] . Mogaddam et al. have applied ALLME for extraction of aflatoxin M1 from milk samples before their analysis by HPLC-FLD with an extraction recovery of 87% [83].

4.8. QuEChERS

QuEChERS, which stands for "Quick, Easy, Cheap, Effective, Rugged, and Safe," is another sample preparation method in which the sample is mixed with a solvent or a mixture of solvents (polar and nonpolar). Salts such as magnesium sulfate and sodium chloride are added to facilitate phase separation and concentrate analytes in either polar or nonpolar layer. The extract is further purified using an extraction solid phase combining aspects of SPE and LLE in a simplified form and smaller scale. QuEChERS extraction approach offers multiple advantages such as simplicity, selectivity, reduction of treatment steps and subsequently shortening extraction time, less solvent consumption and cost effectiveness [84].

As an example, Bang Ye et al. have used this extraction procedure to extract nineteen quinolone antibiotics from goat’s milk samples prior to their analysis by UPLC–MS/MS [32]. They used 5% formic acid in acetonitrile as the extracting solvent, anhydrous sodium sulphate, NaCl, sodium citrate, and disodium hydrogen citrate as the extraction powder and anhydrous sodium sulphate and C18 as the purification powder. This extraction process yielded recoveries in the range 73.4–114.2% for the target antibiotics. QuEChERS extraction method was chosen for extraction of different classes of EPs including pesticides, EDCs and pharmaceuticals from milk [31,85,86] .

4.9. MAE and UAE

Innovations in sample extraction and treatment techniques are continuous, not only by developing new types of sorbents and extraction devices but also by integrating different forms of energy such as microwave and ultrasound into extraction procedures.

Microwave-Assisted Extraction (MAE) is a nontraditional type of extraction in which microwave radiation is used to heat the sample matrix and the extraction solvent which in turn enhances and accelerates the extraction process by allowing for solvent penetration to the matrix. Microwave assisted solid phase extraction offers many advantages including the reduction of the required volume of both the sample and harmful organic solvents in addition to shorter extraction times due to the aid of the uniform heat effect, the automated nature of this technique and its ability to simultaneously instead of sequentially extract multiple samples [87,88].

The fact that MAE often requires less volumes of organic solvents and less extraction time compared to traditional extraction techniques subsequently lead to less waste generated and released to the environment which makes this type of techniques more environmentally friendly [87,88]. On the other hand, there are some limitations that should be considered before choosing MAE as the technique of extraction such as the tolerance of the sample to microwave radiation without being thermally degraded.

Although MAE is particularly well suited for solid samples, but it has shown to be efficiently adopted for extraction of analytes from liquid samples when combined with other types of extraction techniques such as LLE and SPE [87]. Although MAE approach was recently applied for analysis of different pollutants in food matrices [89–91], it was not reported for the extraction of EPs from milk within the time period covered in this review.

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Similar to MAE, in ultrasound assisted extraction (UAE), ultrasound waves are used to generate localized heat in the sample that facilitates extraction procedures. Kubica et al. have applied UA solvent extraction for extraction of nineteen phenolic compounds from powdered milk and infant and toddler ready to feed milk with recoveries ranging from 31% to 120%. This extraction approach was only seldom applied for the purpose of extraction of EPs from milk [36].

4.10. GDME

As time passes, advancements in extraction techniques continue. Among others, gas-diffusion microextraction (GDME) is a recent and innovative extraction technique in which microextraction process is combined with gas diffusion that assists in the adsorption of volatile and semi volatile analytes to microextraction fiber or syringe by creating a pressure difference that drives the target analytes from the liquid sample through the extraction device or membrane. Lobato et al. have employed GDME system for extraction of a group of organochlorine pesticides from milk samples prior to their analysis (GC-ECD) and (GC-MS) achieving recoveries above 90% [92]. Although this extraction approach offers multiple advantages such as low solvent consumption, shorter analysis time and high sensitivity, but sample type has to be taken into account while thinking of this approach for extraction, as GDME is well-suited for volatile samples and it may be not the optimal approach for extraction of complex matrices that contain wide range of volatile compounds.

4.11. EME

One of the recent advanced forms of extraction, is electro membrane extraction (EME). In EME, an electric field is applied to drive the migration of analytes through a supported liquid membrane (SLM), which is typically a porous membrane impregnated with an organic solvent that acts as an extraction phase. On one side of the SLM, the sample solution containing the target analytes is placed and considered as the donor solution. On the other side, an electrolyte solution is placed as a receiving or acceptor solution. Under the effect of the electric field the target charged analytes migrate from the sample solution towards the acceptor solution passing through the SLM. Huang et al. provided the most recent review that explains and covers EME fundamental aspects, advancements in device and operation modes as well as possible applications [93].

In the context of EPs and milk, Aghaei et al. used EME for extraction and preconcentration of ampicillin antibiotic residues in cow milk samples prior to their analysis by HPLC-UV [94]. The EME procedures involved optimization of SLM composition, which mainly composed of octan-1-ol, reduced graphene oxide and silver nanoparticles. A high enrichment factor of 295 was obtained corresponding to an extraction recovery of 37%.

5. Applications of Chromatographic Techniques for Analysis of Different EPs Categories in Milk

A massive body of literature has been devoted for analysis of EPs in milk by combinations of different extraction procedures and various subsequent chromatographic analytical techniques. Although different categories of EPs were analyzed in milk, but the major emphasis of the selected research studies was on four categories: pharmaceuticals, endocrine disrupting chemicals (EDCs), mycotoxins and pesticides. Residues of other categories of EPs were also determined in milk in number of studies, those included hormones, food preservatives, adulterants and per- and polyfluoroalkyl substances (PFAS).

5.1. Pharmaceuticals

Veterinary drugs and antibiotics are extensively used in veterinary medicine and livestock production because of their importance in treating and preventing various diseases, enhancing feed efficiency, and promoting growth rate [95,96]. They are commonly given to treat prevalent cattle ailments such as mastitis, endometritis, bronchopathies, pneumonia, lameness [15,19]. However, misuse of these drugs or not adhering to the recommended withdrawal periods post-treatment can result in the accumulation of their residues in the animal's body, animal's food, and the environment [15,24]. The remaining residues in the animal's body can contaminate food items like milk, egg, and meat [95]. Veterinary drug residues in milk not only directly impact human health but also affect the quality of dairy products consumed by humans [15]. Health risks associated with drug residues in milk encompass allergic reactions, cellular mutations, teeth hypoplasia, bone marrow aplasia, and

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imbalances in the intestinal microbiome [17,97]. Moreover, these residues can induce reproductive system abnormalities, elevate cancer risks, impair the immune system, and cause disruptions in the endocrine and nervous systems [97]. Consequently, to protect human health and ensure food safety, international regulatory agencies such as the People's Republic of China, the European Union (EU), and the Codex Alimentarius Commission (CAC) have established maximum residue limits (MRLs) for veterinary drug and antibiotic residues in milk. These limits act as precautionary benchmarks aimed at guaranteeing consumer safety [17]. To further illustrate the scope and depth of this concern, researchers have studied the presence of drug residues in dairy milk. Table 1 provides an overview of the most pertinent publications from 2018 until present on the detection and determination of veterinary drug and antibiotic residues in dairy milk using LC and GC methods coupled with different detection techniques. As reported in literature, different groups of antibiotics have been used in veterinary medicine and livestock industry and large number of research studies were devoted for their analysis using chromatographic based methods. The majority of selected research papers summarized in Table 1 have focused on determination of tetracyclines (TC) family of antibiotics. Owing to the antibiotic activity they exhibit against wide range of bacteria and microorganisms, TCs are excessively used as veterinary drugs [98,99]. Nonetheless, improper handling of TCs can lead to the existence of their residues in animal-based food products, creating a substantial risk to consumers. Such risks encompass allergic reactions in susceptible individuals, chronic toxicity, and the development of antimicrobial resistance [98–100].

Table 1. Overview of the performance of analytical methods for extraction and determination of pharmaceuticals residues in dairy milk.

Target EPs	Category	Extraction method	Analysis technique	Matrix	Analytical parameters	Conc. in real samples	Country	Ref
Tetracycline (TC), oxytetracycline (OTC), chlortetracycline (CTC), doxycycline (DC)	TCs Antibiotics	FPSE	HPLC-UV	Milk	LOD: 15 µg/kg LOQ: 50 µg/kg CCα:103.2 - 108.1 µg/kg CCβ:108.6 - 114.3 µg/kg R: 88.9 -122.4% RSD: ≤14.5%	ND	Greece	[101]
TC, OTC, CTC	TCs Antibiotics	MSPD	UHPLC–MS/MS	Milk powder	LOD: 0.217 - 0.318 ng/g LOQ: 0.723 – 1.060 ng/g LR: 1-100 ng/g R^2: 0.998-0.999 R: 84.7 - 93.9% RSD: <7.5%	ND	China	[102]
TC, OTC, DC	TCs antibiotics	MSPE-DLLME	HPLC-UV	Bovine milk	LOD: 1.8–2.9 µg/L LOQ: 6.1–9.7 µg/L LR: 10.0–200.0 µg/L R^2: > 0.9929 RSD: 2.5- 8.8% R: 70.6 - 121.5%	Spiked	Iran	[51]
OTC, CTC, TC	TCs Antibiotics	MSPE	HPLC-UV	Milk	LOD: 1.29 -2.31 ng/mL LOQ: 4.26 – 7.62 ng/mL LR: 5–250 ng/mL R: 79–109 % RSD: <7.25%	ND	China	[103]
TC, OTC, CTC, DC	TCs Antibiotics	MSPE	HPLC-UV	Milk	LOD: 1.03 - 1.31 µg/L LOQ: 3.46 - 4.41 µg/L LR: 5.0–700 µg/L R^2: 0.9991 - 0.9996 R: 86.7 - 98.6% RSD: 1.4–5.7%	ND	China	[100]
OTC, TC, CTC, DC	TCs Antibiotics	QuEChERS	HPLC-DAD	Milk	LOD: 15 µg/kg LOQ: 50 µg/kg CCα: 100.3-105.6 µg/kg CCβ: 100.6 -109.7 µg/kg R: 83.07% -106.3% RSD: <15.5%	ND	Greece	[104]
		SPME	HPLC-DAD	Milk	LOD: 0.077–0.350 µg/L	NS	Greece	[105]

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Sulfadiazine (SD), sulfapyridine (SP), sulfathiazole (SZ), sulfamethazine (SMZ), sulfamethoxypyridazine (SMP), sulfachloropyridazine (SCP), sulfamethoxazole (SMX), sulfisoxazole (SIX), sulfadimethoxine (SDM), sulfaquinoxaline (SQX)	SAs antibiotics				LOQ: 0.23-1.05 µg/L LR: 0.5–150 µg/L R^2: > 0.9964 R: 88 -97% RSD: <10% CCα:111.2 - 113.6 µg/L CCβ:122.6 -127.4 µg/L			
Sulfanilamide (SN), SD, SMZ, sulfamerazine (SM), SP, SZ, SMP, SMX, SDM	SAs Antibiotics	SPE	HPLC-UV	Milk	LOD: 3.0–12.3 µg/kg LOQ: 10–43 µg/kg LR:20–1000 µg/kg R: 80.7–101.3% RSD: <8.5%	ND	China	[106]
SN, SD, SZ, and sulfamethizole (SMT)	SAs antibiotics	CPME	HPLC-DAD	Milk	LOD: 16.7 µg/kg LOQ: 50 µg/kg LR: 50–2000 µg/L CCα: 104.5–111.4 µg/kg CCβ: 109.4–118.1 µg/kg Absolute R: 12.1–18.1% RSD: < 11.2%	ND	Greece	[107]
SZ, SME, SDM, Sulfamonomethoxine (SMM)	SAs Antibiotics	d-MSPE	HPLC-DAD	Milk	LOD: 2.5, 5.0 µg/kg LOQ: 7.5 – 10.0 µg/kg LR: 2.5 - 150.0 µg/kg R^2: > 0.997 R: 83.0 - 99.2% RSD: < 6%	SME: 15.1 µg/kg	Thailand	[108]
Ciprofloxacin (CIP), fleroxacin (FLE), and oxolinic acid (OXO), Danofloxacin (DAN), difloxacin (DIF), flumequine (FLU), lomefloxacin (LOM) marbofloxacin (MAR), nalidixic acid (NAL), norfloxacin (NOR), pefloxacin (PEF), pipemidic acid (PIP), sarafloxacin (SAR), enrofloxacin (ENR), levofloxacin (LEV), trovafloxacin (TRFX), orbifloxacin (ORB), ofloxacin (OFl), and cinoxacin (CIN)	Qs Antibiotics	QuEChERS	UPLC–MS/MS	goat's milk	LOQ: 5 ppb R^2: >0.9853 R: 73.4 –114.2% CV: <15%	ND	Taiwan	[32]
DIF, ORB, Sparfloxacin (SPA), SAR, FLE, MAR, OFL, ENR, DAN, LOM, PEF, CIP, ENO, NOR, PIP, CIN, OXO, NAL	Qs Antibiotics	MSPE	HPLC-MS/MS	Milk	LOD: 3.1- 13.3 ng/L LOQ: 10.4 - 44.2 ng/L LR: 0.05–10 µg/L R^2: 0.9975- 0.9996 R: 82.4 - 103.9% RSD: 2.9 –15.1%	CIP (2 µg/L), DAN (0.66 µg/L), (One sample)	China	[109]
OFL, NOR, CIP, ENR, DIF, PEF, DAN	Qs antibiotics	MSPE	HPLC–MS/MS	Milk	LOD: 0.35 - 1.5 µg/L LOQ: 1.2-4 µg/L LR: 1.5–200 µg/L R^2: > 0.99 R: 75 -88.3 % RSD: 5.3 -9.1%	ND	China	[110]
CIN, CIP, DAN, DIF, Enoxacin (ENO), ENR,		SBSE	UHPLC–MS/MS	Raw cow milk	LOD: 0.1-1.0 µg/kg LOQ: 0.5 – 4.0 µg/kg	CIP, ENR and MAR	Spain	[111]

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FLU LOM, MAR, Moxifloxacin (MOX), NAL, NOR, OFL, OXO, PIP, Piromidic acid (PIRO), SAR	Qs Antibiotics				LR: 0.5 – 150 µg/kg R^2: 0.99-0.999 R: 88.0–114.0% RSD: 2.0–14.0% CCα: 30.7–106.1 µg/kg CCβ: 31.3–122.0 µg/kg	2.7 - 35.3 µg/kg		
OFL, NOR, CIP	Qs antibiotics	SPE	HPLC-FLD	cow milk	LOD: 39, 30, 33 ng/L LOQ: 120, 92, 100 ng/L LR: 1.8–250 µg/L R: 60 - 70 % RSD: 4–13%	ND	Spain	[112]
CIP, ENR, NOR, LOM, ENO, SPA	Qs antibiotics	SPE	HPLC-UV	Milk	LOD: 2.8–5.1 ng/g LOQ: 9.5-17 ng/g LR: 10–2000 ng/g R^2: 0.9972 - 0.9997 R: 85.8% - 117.9% RSD: ≤ 9.4% CCα: 102.1-105.1 ng/g CCβ: 108.3 - 116.0 ng/g	ND	China	([47]
CIP, ENR, LOM, PEF, LEV gatifloxacin (GAT)	Qs Antibiotics	MSPE	HPLC-DAD	Milk	LOD: 0.25 - 0.5 ng/g LR: 2.5-1500 ng/g R^2: >0.9996 R: 81.05 - 98.75 RSD: 1.5 - 4.3%	ND	China	[113]
PEF, CIP, ENR, LOM, SAR	Qs Antibiotics	MSPE	HPLC-MS/MS	Milk	LOD: 0.04–0.10 ng/g LOQ: 0.1–0.2 ng/g LR: 0.1–200 ng/g r: 0.9991 - 0.9997 R: 78.1 - 95.2 % RSD: 1.2 - 7.9 %	Spiked	China	[114]
ENO, FLE, OFL, NOR, PEF, LOM	Qs Antibiotics	MSPE	HPLC-UV	Milk	LOD: 0.05 - 0.20 µg/L LOQ: 0.19 – 0.71 µg/L LR: 0.5 - 200 µg/L *r* : 0.9982- 0.9996 R: 90.4 - 101.2% RSD: 3.5 - 4.7%	ND	China	[71]
Ampicillin, benzylpenicillin, amoxicillin, oxacillin, and cloxacillin	β-lactams Antibiotics	D-m-SPE	UPLC–MS/MS	cow, goat and sheep milk	LOD: 0.03–0.20 µg/kg LOQ: 0.17 - 0.68 µg/kg LR: 0.1–300 µg/kg R^2: 0.9978- 0.9995 R: 87–107% RSD: ≤ 5.8% CCα: 4.1–31.0 µg/kg CCβ: 4.3 - 32.1 µg/kg	ND	Iran	[115]
Ampicillin	β-lactam Antibiotics	EME	HPLC-UV	Cow milk	LOD: 0.6 µg/L LR: 2–100 µg/L R^2: 0.995 R: 37–45% RSD: <7.1%	ND	Iran	[94]
32 antibiotics	β-lactam antibiotics	d-SPE	UHPLC-MS/MS	Bovine milk	LOD: 0.0090 - 1.5 µg/kg LOQ: 0.030 - 5.0 µg/kg $R^2 \geq 0.98$ R: 91 - 130% RSD: 1.4 -38.6% CCα: 2.1–133 µg/kg CCβ: 2.4 – 182 µg/kg	NS	Ireland	[116]
Ceftiofur	β-lactam Antibiotics	Online SPE	HPLC-MS/MS	bovine milk	LOD: 0.1 µg /L LOQ: 0.7 µg /L R^2: > 0.98 R: 73.4 - 111.3% RSD: < 15%	ND	Brazil	[117]
31 compounds			UPLC–MS/MS	Milk	LOD: 0.1 – 0.5 µg/L LOQ: 0.5 – 2.0 µg/L		China	[118]

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	Macrolides Antibiotics	QuEChERS			LR: 1 - 200 µg/L R^2: > 0.990 R: 81.07 – 110.1% RSD: <5.1%	LOD<C<LOQ		
Azithromycin (AZI), clarithromycin (CLA), erythromycin (ERY), lincomycin (LIN), roxithromycin (ROX)	Macrolide antibiotics	mini-SPE	UHPLC-Q-TOF/MS	bovine milk	LOD: 0.017–0.76 µg/kg LOQ: 0.054–2.52 µg/kg MDL: 0.027–1.01 µg/kg MQL: 0.026–0.96 µg/kg R^2: > 0.99 R: 77.91 – 105.34 %	LIN: 2.16 µg/kg AZI:174.94 µg/kg ERY: 7.91 µg/kg CLA: 24.04 µg/kg ROX: 13.87 µg/kg	China	[119]
Gamithromycin	Semisynthetic macrolide Antibiotics	SPE	UHPLC-MS/MS	Milk	LOD: 0.30 – 0.40 µg/kg LOQ: 0.80 – 1.0 µg/kg LR: 1.0 – 200 µg/kg R^2: > 0.99 R: 109.8 - 114.8% RSD: 1.4 - 6.8%	ND	China	[120]
Lincomycin (LIN)	Lincosamide Antibiotics	CSMISPE	HPLC-UV	Pasteurized milk	LOD: 0.02 µg/mL LOQ: 0.08 µg/mL LR: 0.08-2 µg/mL R^2: 0.999 R: 80-89% RSD: ≤ 4.03%	0.10-0.61 µg/mL	Iran	[66]
Vancomycin, Teicoplanin, Telavancin, Oritavancin, Dalbavancin	Glycopeptide Antibiotics	SPE	UHPLC–MS/MS	Milk	LOD: 0.33 µg/kg LOQ: 1.00 µg/kg R^2: 0.9987 - 0.9999 R: 83 - 102% RSD: 1-6.8%	Spiked	China	[121]
Vancomycin and Norvancomycin	Glycopeptide antibiotics	Online SPE	LC-HRMS	Milk	LOD: 0.15 µg/kg LOQ: 0.5 µg/kg LR: 0-200 ng/mL R^2: > 0.9983 R: 80.00–92.96%, 80.68–91.31% RSD: 4.90– 9.35%	Spiked	China	[44]
Vancomycin and norvancomycin	Glycopeptide antibiotics	SMISPE	LC–MS/MS	Milk	LOD: 0.5 µg/kg LOQ: 1.0 µg/kg LR: 0.5 -50 µg/kg R: 83.3% - 92.1% RSD: < 16.8%	ND	China	[122]
Chloramphenicol (CAP)	Amphenicol antibiotics	MSPE	HPLC-UV	Milk	LOD: 0.24 µg/L LOQ: 0.79 µg/L LR: 7- 1.0 × 10^3 µg/L R^2: 0.9994 R: 80.5 - 105.0% RSD: 5.3-8.9%	ND	China	[123]
Chloramphenicol (CAP)	Amphenicol antibiotics	SS-DMNF-ME	HPLC-UV	Milk	LOD: 0.22–0.25 ng/mL LOQ: 0.73–0.85 ng/mL LR: 0.9–250 ng/mL R^2: ≥ 0.982 R: 91.4% – 95.1% RSD: ≤4.16	ND	Iran	[124]
Closantel, Nitroxynil, Niclosamide, Rafoxanide, Eprinomectin, Emamectin, Levamisole, Cymiazole, Praziquantel, Tetramisole, Thiophanate, Morantel, Pyrantel, Fluazuron,	Anthelmintics	LLE	LC-MS/MS	Milk	LOD: 0.1-5 µg/kg LOQ: 0.4-10 µg/kg R^2: ≥0.9752 R: 64.6 -112.6% RSD: ≤13.4	ND	Korea	[125]

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Guaifenesin, Carbendazim, Cambendazole,Trichlorfon								
Albendazole (ABZ), albendazole sulfoxide (ABZ-SO), benomyl (BEN), carbendazim (CBZ), fenbendazole (FBZ), fenbendazole sulfone (FBZ-SO_2), fenbendazole sulfoxide (FBZ-SO), mebendazole (MBZ), mebendazole-amine (MBZ-NH_2), thiabendazole (TBZ), 5-hydroxy-thiabendazole (5-OH-TBZ), triclabenda- zole (TCB), triclabendazole sulfone (TCB-SO_2), triclabendazole sulfoxide (TCB-SO), Albendazole-2-aminosulfone (ABZ-NH_2- SO_2)	Anthelmintics	SALLE	CLC-UV	Cow, sheep and goat milk	LOD: 1.0 - 2.8 µg/kg LOQ: 3.2 - 9.5 µg/kg LR:3.2–200 µg/kg R^2: > 0.9985 R:79.1- 99.6% RSD: 1.6 -14.2%	ND	Spain	[55]
Mebendazole	Anthelmintics	BSASLE + BUASLE	MLC-DAD	Milk	LOD: 0.2 ppm LOQ: 0.6 ppm r^2 = 0.9996 R: 98.5-99.8% RSD: <5%	1-7.4 ppm	India	[54]
Salicylic acid (SA), oxaprozin (OXP), diclofenac (DCF) and ibuprofen (IBF).	NSAIDs	UA-HDES-DLLME	HPLC-UV	Milk	LOD: 0.5-1 µg/L LOQ: 1-5 µg/L LR: 5–2000 µg/L R^2: 0.994-0.999 R: 65.88 - 110.80% RSD: 1.11 - 16.9%	ND	China	[126]
Ketoprofen (Ket), flurbiprofen (Flu), ibuprofen (Ibu), naproxen (Nap), and diclofenac sodium (DS)	NSAIDs	BSE	UPLC-DAD	Milk	LOD:1.14-4.50 ng/mL LOQ: 3.76-14.85 ng/mL LR: 10–1000 ng/mL R^2: 0.9988 - 0.9998 R: 80.8% to 110.2% RSD: 2.3-3.5%	ND	China	[127]
Diclofenac sodium (DS)	NSAIDs	MSPE	HPLC-MS/UV	Milk	LOD: 10 ng/kg LOQ: 25 ng/kg LR: 50–2000 ng/kg R^2: 0.9996 R: 87–103% RSD: 2.4–11.3%	28–68 ng/kg	China	[128]
Spironolactone (SPRL), canrenone (CR), chlorothiazide (CTZ), hydrochlorothiazide (HCTZ), acetazolamide (AZ), furosemide (FSM), 4-amino-6-chlorobenzene-1,3-disulfonamide (ACB)	Diuretics	modified QuEChERS	HPLC–MS/MS	Milk	LOQ: 0.5-1.0 µg/kg R^2: 0.9954 - 0.9999 R: 73-113.9% RSD: 2.45 -10%	ND	China[129]	[130]
Chloramphenicol (CAP) **Tetracycline (TC)**	Multiclass Antibiotics	MSPE	HPLC-DAD	Milk	LOD: 3.02, 3.52 ng/mL LOQ: 9.63, 9.83 ng/mL LR: 10.0–600.0 ng/mL R^2: 0.9954, 0.9973 R: 94.6 –105.4% RSD: <4.0%	CAP: (one sample): 53.3 ng/mL TC: (one sample): 75.8 ng/mL	Turkey	[52]

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SMM, OTC, CEF, MAR	Multiclass Antibiotics	SPE	HPLC-DAD	Milk	LOD: 0.02 µg/mL LOQ: 0.02 µg/mL LR: 0.02–2.00 µg/mL R^2: 0.993–0.998 R: 61.4% - 99.3%	NS	Italy	[129]
62 analytes	Multiclass Antibiotics	SPE	UPLC-quadrupole/electrostatic field orbitrap-HRMS	Goat milk	LOD: 0.5 - 1.0 µg/kg LOQ: 5.0 -10.0 µg/kg LR: 0.5 –100 µg/L R^2: 0.9901–0.9998 R: 60.1 - 110.0% RSD: <15%	Metronidazole: 2.45 & 5.02 µg/kg Enrofloxacin: 112.4 µg/kg	China	[131]
DC, TC, OTC, PNG, CAP, CIP, ENR	Multiclass antibiotics	MIL–based AALLME	HPLC–DAD	Milk	LOD: 0.09–0.21 ng/mL LOQ: 0.29–0.71 ng/mL LR: 0.71–500 ng/mL R^2: ≥ 0.994 R: 79–91% RSD: 3.6–5.2%	TC:56–112 ng/mL OTC: 89–149 ng/mL CAP: 41 ng/mL (one sample)	Iran	[132]
22 compounds	Multiclass Antibiotics	MSPE	UPLC-MS/MS	Bovine milk	LOD: 0.04–0.19 µg/kg LOQ: 0.13-0.64 µg/kg LR: 0.2–800 µg/kg R^2: 0.9958 - 0.9992 R: 85.9 - 107.5% RSD: < 9.2% CCα: 0.10 - 111.3 µg/kg CCβ: 0.13 - 125.8 µg/kg	0.54–97.18 µg/kg	Iran	[40]
103 analytes	veterinary drugs	Modified QuEChERS	UPLC-MS/MS	Cow milk and milk powder	LOD: 0.1-25 µg/kg LOQ:0.5-50 µg/kg R^2: 0.9902 - 0.9998 R: 31.1 - 120.7% RSD: 2.34 to 19.2%	LIN: 10.2 ± 1.5 µg/kg (one sample)	China	[133]
25 analytes	Multiclass veterinary drugs	LLE	UHPLC–MS/MS	commercial milk samples	LOQ : 0.1 – 4 ng/g CCα: 0.008 - 113.68 ng/g CCβ: 0.01 - 125.75 ng/g LR: 0.1- 384 ng/mL R^2: 0.9901- 0.9990 R: 65.9% - 123.5% RSD: ≤11.1%	Clorprenaline: 0.5 ng/g and 0.47 ng/g hydrocortisone 0.78 ng/g (one sample)	China	[134]
132 analytes	Multiclass veterinary drugs	MSPE	HPLC-MS/MS	Milk	LOD: 0.015- 0.3 µg/kg LOQ: 0.05 -1 µg/kg R^2: <0.990 R: 72 – 120% RSD: <20%	OCT: 1.5 µg/kg, CAP: 4.1 µg/kg, SMZ, LIN: 5.6 µg/kg CIP: 12.2 µg/kg	Russia	[135]
66 analytes	Multiclass Veterinary drugs	d-SPE and SPE	UHPLC-MS/MS	Cow milk	LOQ: 0.02 - 18.25 µg/kg CCα: 0.01 -150.07 µg/kg CCβ: 0.04 -150.14 µg/kg R^2: > 0.998 R: 70-120% RSD: ≤ 19.4%	Danofloxacin 0.7– 1.5 µg/kg	Spain	[136]
57 analytes	Multiclass veterinary drugs	modified QuEChERS	UPLC-MS/MS	Milk	LOD: 0.1~3.8 µg/kg LOQ: 0.2~6.3 µg/kg LR: 2~500 µg/kg R^2: ≥ 0.999 R: 60.7% - 116.0%	flumequine and pipemidic	China	[137]
16 analytes	Multiclass veterinary drugs	d-SPE & LLE	LC–MS/MS	Bovine and caprine milk	CCα: 0.023 - <5.0 µg/kg CCβ: 0.045 – 5.0 µg/kg LR: 5–250 µg/L R^2: ≥0.990	Blank samples are spiked	Netherlands	[26]
18 analytes	Multiclass veterinary drugs	modified QuEChERS	UHPLC-HR-Orbitrap-MS	Milk	LOD: 0.09 -15.1 µg/kg LOQ: 0.28–10 µg/kg R^2: > 0.9903 R: 65.1–120.1%	Imidocarb: 18 µg/kg (one sample)	Greece	[85]

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LOD, Limit of detection; LOQ, Limit of quantification; LR, linear range; R^2, determination coefficient; R, recovery; RSD%, Relative standard deviation; CCα, decision limit; CCβ, detection capability; CV, coefficient of variation; ND, not detected; NS, not specified; MDL, method detection limit; MQL, method quantification limit; SPE, solid phase extraction; MSPE, magnetic solid phase extraction; FPSE, fabric phase sorptive extraction; LLE, liquid-liquid extraction; dSPE, dispersive solid phase extraction; D-m-SPE, dispersive micro solid phase extraction; EME, electromembrane microextraction; CPME, Capsule phase microextraction; DLLME, dispersive liquid-liquid microextraction; SPME, solid phase microextraction; SALLE, salting out assisted liquid-liquid extraction; CSMISPE, core–shell molecularly imprinted solid phase extraction, SMISPE, Surface molecularly imprinted solid-phase extraction; SS-DMNF-ME, Syringe-to-syringe dispersive magnetic nanofluid microextraction, BSASLE + BUASLE, batch stirring-assisted solid-to-liquid extraction and batch ultrasound-assisted solid-to-liquid extraction, UA-HDES-DLLME, ultrasound-assisted hydrophobic deep eutectic solvents- dispersive liquid–liquid microextraction; BSE, bar sorptive extraction; MIL–based AALLME, Magnetic ionic liquid–based air–assisted dispersive liquid–liquid microextraction; TCs, tetracyclines; SAs, sulfonamides; Qs, quinolones; NASIDs, non- steroidal anti-inflammatory drugs; CLC, capillary liquid chromatography; MLC, micellar liquid chromatography.

Other classes of antibiotics that were observed to be of major concern that was reflected in the number of studies depicting them in milk, include Quinolones (Qs). Qs are non-steroidal synthetic antibiotics, their affordability, low toxicity and broad antibacterial activity have made them of the most used in livestock industry for treatment of some diseases including respiratory diseases associated with the two bacterium species Mannheimia haemolytica and Pasteurella multocida [138,139]. However, their excessive use and the subsequent presence of residues in food of animal origins like milk, can pose substantial safety and health concerns owing to their carcinogenicity and antibiotic resistance [112,140]. Other classes of antibiotics including beta-lactams (β-lactams), macrolides, sulfonamides (SAs), glycopeptides and amphenicol antibiotics were also reported in relatively less numbers of studies within the time period covered in this review [106,119,121,141].

Besides antibiotics, number of studies have developed chromatographic based analytical methods for determination of residues of other types of pharmaceuticals and veterinary drugs in milk such as anthelmintics, diuretics and non-steroidal anti-inflammatory drugs (NASIDs) [125,130,131].

Although variety of analytical methods were employed for the determination of those classes of pharmaceuticals in milk, the combination of liquid chromatography and tandem mass spectrometry was the method of choice in the majority of them, as can be observed from Table 1 data.

5.2. Endocrine-Disrupting Compounds

Food packaging serves a crucial function in the food sector; it extends shelf life and protects food contents from biological and chemical alterations post-processing [56]. Packaging materials comprise various components, including polymers, plasticizer additives, and endocrine disrupting compounds (EDCs)[142]. EDCs are exogenous substances that can interfere with the endocrine system, either by inhibiting the primary hormone functions or mimicking their actions [1,143]. A primary concern with EDCs is their migration from the packaging or storage materials into the food [143]. Another route for EDCs to enter the food chain is via contaminated animal feed [144]. Toxic EDCs, such as phthalates and bisphenols, have the potential to bioaccumalate, posing threats to human health [142]. They are associated with various physiological disruptions and are linked to diseases like diabetes, obesity, reproductive disorders, cardiovascular disease, congenital disabilities, and breast cancer [143]. Both phthalates and bisphenols can enter the human body through dermal absorption from consumer products or ingestion due to migration from the packaging material to food [142,145]. It is worth noting that their migration rate can increase at high temperatures [142].

Bisphenols and phthalates have a lipophilic nature. If animal feed becomes contaminated with these chemicals, they can accumulate in the livestock's adipose tissue and may subsequently be excreted into the milk [33]. Given milk's crucial role in children's nutrition, a special attention should be given to it. Milk is often consumed in plastic bottles; thus, it is assumed that bisphenols and phthalates can easily migrate from packaging materials into the milk due to the lipophilic nature of both the chemicals and the milk itself [146].

In addition to phthalates and bisphenols, concerns regarding endocrine disrupting effects have been raised for other chemical substances, such as parabens. Parabens, including methyl paraben, ethyl paraben, propyl paraben, and butyl paraben, are esters of para-hydroxybenzoic acid. Parabens serve as preservatives of antimicrobial activity and high stability in a broad array of cosmetics, personal care products, food products and pharmaceuticals [147–149]. Exposure to high levels of

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parabens induces alterations in normal hormonal levels, negatively impacting reproductive system, thyroid functions and dermal system among others . Similar to other types of EDCs, parabens can find their way into milk through different sources including contaminated feed, food packaging and contaminated surrounding environment.

Therefore, determining the levels of EDCs in dairy milk is essential for consumer safety. Table 2 provides a summary of the most relevant publications on the determination of EDCs in dairy milk using LC and GC based analytical techniques.

Table 2. Overview of the analytical methods for extraction and determination of EDCs residues in dairy milk.

Target EDCs	Extraction method	Analysis technique	Matrix	Analytical parameters	Conc. In real samples	Country	Ref
Bisphenol A (BPA), bisphenol BP (BPBP), bisphenol C (BPC), bisphenol F (BPF), bisphenol FL (BPFL), bisphenol G (BPG), bisphenol M (BPM), bisphenol S (BPS), bisphenol Z (PBZ), bisphenol A diglycidyl ether (BADGE), bisohenol A (2,3-dihydrox-ypropyl) glycidyl ether (BADGE·H_2O), bisphenol A bis (2,3-dihydrox- ypropyl) ether (BADGE·2 H_2O), bisphenol A (3-chloro-2-hydroxypropyl) glycidyl ether (BADGE·HCl), bisphenol A (3-chloro-2hydroxypropyl) (2,3-dihydroxypropyl) ether (BADGE·H_2O·HCl), bisphenol A bis(3- chloro-2-hydroxypropyl) ether (BADGE·2HCl), bisphenol F diglycidyl ether (BFDGE), bisphenol F bis(2,3-dihydroxypropyl) ether (BFDGE·2 H_2O), bisphenol F bis (3-chloro-2-hydroxypropyl) ether (BFDGE·2HCl)	UA-solvent extraction of porous membran e-packed samples	HPLC–MS/MS	Infants and toddlers Ready-to-feed milk and powdered milk	LOD: 0.24–0.40 ng/g LOQ: 0.72–1.2 ng/g LR: 1-50 ng/ml R^2: > 0.9962 R: 31–120% RSD: 0.3 - 10%	0.53–18.5 ng/g	Poland	[36]
BPA, BPAF, BPC, BADGE, BFDGE	Online SPE	HPLC-FLD	Cow and goat milk	LOD: 1.5 - 2.25 µg/kg LOQ: 5 - 7.5 µg/kg LR: 2.5–100 µg/kg R: 93.0–139.2% RSD: <10%	NS	Czech Republic	[143]
BPA	SPE	HPLC-DAD	Bovine Milk	LOD: 1.3 ng/mL LR: 0.02–2 mg/mL R^2: 0.9998 R: 96.4 - 102.8 % RSD: 1.5 – 6.3 %	Spiked	China	[150]
BBA		LC-FLD		LOD: 3.75 ng/mL LOQ: 12.51 ng/mL LR: 40.0–120.0 ng/mL R^2: 0.9970 R: 83 -88% RSD%: 2.21%, 9.55%	BPA: <LOQ - 102.18 ng/mL		
	SPE		Cow milk filled in plastic baby bottles of different brands			Italy	[65]
BPS		LC-UV		LOD: 80.00 ng/L LOQ: 260.00 ng/mL LR: 1.0–3.0 µg/mL R^2: 0.9989 R: 95 -108% RSD: 1.81%, 5.03%	ND		
		HPLC–FLD		LOD: 0.2, 0.6 ng/g		Italy	[33]

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BPA, BADGE, BPAF, BPAP, BPB, BPBP, BPC, BPE, BPF, BFDGE, BPM, BPP, BPZ, 4-Octylphenol (4-OP) 4-tert-Octylphenol (4-t-OP) 4-Nonylphenol (4-NP)	dSPE + QuEChERS		Raw buffalo milk and retail bovine milk	LOQ: 1.0, 3.0 ng/g LOD: 0.03–1.5 ng/mL	Raw buffalo milk: 4-t-OP : 1.41 ng/g BFDGE: 1.10 and 1.33 ng/g BPF, BPC, and 4-NP: between LODs and LOQs Retail bovine milk: BPA: 1.11 - 3.05 ng/g BPP, BPM, 4-t-OP, 4-OP : >LOD detected but not quantified		
BPA, BADGE, BPAF, BPAP, BPB, BPBP, BPC, BPE, BPF, BFDGE, BPG, BPM, BPP, BPS, BPZ , Bisphenol PH (BPPH), Bisphenol TMC (BPTMC)	SPE	UHPLC–MS/MS	Raw Buffalo milk and retail bovine milk	LOQ: 0.1–5.0 ng/mL	Raw buffalo milk: BPA: 0.5–5.6 ng/mL BPF: 0.5–8.7 ng/mL BPAF: 3.0 ng/mL Retail bovine milk: BPA: ND - 2.8 ng/mL BPF: ND – 10.6 ng/mL	Italy	[33]
BPA, BPB, BPAF, BPC	MSPE	HPLC-UV	Milk	LOD: 0.011 – 0.36 ng/mL LOQ: 0.035 - 0.120 ng/mL LR: 0.05–100 ng/mL R^2: 0.9980–0.9998 R: 85.70–119.7% RSD: 0.12 - 5.02%	BPA: 0.79-4.56 ng/mL	China	[151]
BPA, BADGE, BPAF, BPAP, BPB, BPBP, BPC, BPE, BPF, BFDGE, BPG, BPM, BPP, BPPH, BPS, BPTMC and BPZ	SPE	UHPLC-MS/MS	Bovine and buffalo milk	LOD: 0.03 – 0.6 ng/mL LOQ: 0.1 – 5.0 ng/mL R^2: > 0.95	0.1–2.0 ng/mL	Italy	[33]
BPA	SPE	HPLC-FLD	Raw cow milk	LOD: 0.01 µg/kg LOQ: 0.03 µg/kg LR: 0.03 -100 µg/L R^2: 0.9969 R: 70 - 100% RSD: ≤ 10%	0.035 - 2.776 µg/L	Italy	[146]
BPA	DME	HPLC-FLD	Skim milk samples	LOD: 0.016 µg/L LOQ: 0.050 µg/L LR: 0.1–50 µg/L R^2: 0.9964 R: 80.7% - 102.4% RSD: <4.2%	ND	China	[152]
BPA, BPF, BPAF, 4-CP	UA-DLLME	HPLC-UV	commercial boxed milk	LOD: 0.25–1 µg/L LOQ: 0.5–1 µg/L	ND	China	[153]

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BPA	SPE	HPLC-FLD	Milk	LR: 0.5–400 µg/L R^2: 0 .9976 - 0.9988 R: 82.77– 118.92% RSD: < 14% LOD: 0.03 µg/L LOQ: 0.1 µg/L	<LOQ - 2.833 µg/L	Italy	[154]
Nonylphenol (NP), BPA, Hexestrol (HEX)	MSPE	HPLC-UV	Milk	LR: 0.1–100 µg/L R^2: 0.999 R: 78.4-107.2% RSD%: 1.9 – 11.3% LOD: 0.1 – 0.3 µg/L LR: 0.04~50 mg/L R^2: 0.9978 - 0.9992 R: 89.9 - 98.7 % RSD: <3%	ND	China	[35]
BPA, NP, octylphenol (OP), 4-n-nonylphenol (4NP)	QuEChERS	LC-LTQ/Orbitrap MS	Milk	LOD: 0.05–5 ng/g LOQ: 0.1–20 ng/g LR: 0.1–200 ng/g R^2: 0.9966- 0.9999 R: 91- 108% RSD: 0.9 - 11.7%	BPA: MDL-10.4 µg/Kg OP: <4.5 µg/Kg NP & 4NP: <428.7 µg/Kg	Greece	[155]
BPA, α-Estradiol (α-E2), genic EDCs; 17α-ethinyl estradiol (17α-EE2), estrone (E1), diethylstilboe- strol (DES), and hexestrol (HEX)	FPSE	HPLC-UV & LC-MS/MS for confirmation	Milk	LOD: 7.5 – 15 ng/mL LOQ: 25.0 - 50.0 ng/mL LR: 25-20000 ng/mL R: 13.7 - 69.2 % RSD: 3.6 – 13.9	All spiked	USA	[14]
BPA	SPE	HPLC-FLD	Raw cow milk	LOD: 0.01µg/kg LOQ: 0.03 µg/kg LR: 0.03-100 µg/L	ND- 2.340 µg/L	Italy	[156]
BPF	SPE	HPLC-FLD	Milk	LOD: 0.03 µg/L LOQ: 0.1 µg/L LR: 0.1 - 100 µg/L R^2: 0.999 R: 97.60 - 107.16% RSD: <15%	<LOQ - 2.956 µg/L	Italy	[157]
BFDGE·2H$_2$O, BADGE·2H$_2$O, BFGDGE·H$_2$O, BPE, BPA, BPB, BPC, para-para-BFDGE, BADGE	QuEChERS	HPLC–FLD	Milk	LOD: 1.0 – 3.1 µg/kg LOQ: 3.5 – 9.8 µg/kg LR: 5–100 µg/kg R^2: 0.9942 - 0.9997 R: 75.82 – 93.86% RSD: 2.6 - 11.1%	BPA: 13.74 µg/kg (one sample) BADGE·2H2O: 15.80 µg/kg (one sample) BFDGE·2H2O: 16.23 and 17.82 µg/kg	China	[86]
BPF	SPE	HPLC-FLD	Milk	LOD: 0.03 µg/L LOQ: 0.1 µg/L LR: 0.1-100 µg/L R^2: 0.999 R: 97.60 -107.16% RSD: <15%	< LOQ - 2.686 µg/L	Italy	[154]
Methylparaben (Me-P), ethylparaben (Et-P), propyl-paraben (Pr-P), butylparaben (BP), benzylparaben (BzP), BPA, BPS, BPF, BPB, BPE, BPAF	QuEChERS +d-SPE	HPLC-MS/MS	Raw and processed cow milk	LOD: 0.01 – 0.2 ng/mL LOQ: 0.03 – 0.73 ng/mL LR: 0.5 – 2000 ng/mL R^2: 0.9988 – 0.9997 R: 80.1% - 115.5% RSD: 1.8 – 9.4 %	Bisphenols: <LOD – 1.71 ng/mL Parabens: <LOD – 1.40 ng/mL	Poland	[147]

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Me-P, Et-P, Pr-P	SC-μSPE	HPLC-UV	Milk	LOD: 3.0 - 7.0 ng/mL LOQ: 10 -20 ng/mL LR: 10-1000 ng/mL R^2: 0.9960 - 0.9971 R: 81.7–97.8% RSD: 2.7-8.6%	< LOQ - 130.3 ng /mL	Iran	[149]
Estrone E1, 17β-Estradiol (E2) , Estriol E3 and BPA	MSPE	HPLC-MS/MS	Cow milk	LOD: 0.37 – 0.85 μg/L LOQ: 1.31 - 2.94 μg/L LR: 0.25 –100 μg/L R^2: ≥ 0.9983 R: 92.1 - 118.3 % RSD: ≤ 7.2 %	ND	China	[158]
BBP, benzyl butyl phthalate; DEHP, bis (2-ethylhexyl) phthalate; DIDP, diisodecyl phthalate; DIHP, diisoheptyl phthalate; DNOP, di-n-octyl phthalate; DPP, dipentyl phthalate.	MSPE	GC-MS/MS	Milk	LOD: 0.8–2.1 μg/L LOQ: 2.7– 7.0 μg/L LR: 3.0– 100 μg/L R: 76.8–99.2% RSD: ≤ 7.3%	ND	China	[60]
BBP, butyl benzyl phthalate; BPA, bisphenol A; DBP, dibutyl-o-phthalate, DEHP, di(2-ethylhexyl) phathalate; DEP, diethyl-o-phthalate; DNOP, di-n-octyl phthalate	PFSPE	GC-MS	Milk	LOD: 0.01 - 0.06 μg/L LOQ: 0.05 - 0.53 μg/L LR: 0.1 – 50 μg/L R^2: 0.9925–0.9987 R: 89.6 – 118.0% RSD: 0.6 - 10.9%	DEP: ND-2.18 μg/L DBP: ND-1.5 μg/L BPA: 0.28 – 2 μg/L BBP: 10.98 – 16.0 μg/L DEHP: ND-16.20 μg/L DNOP: 0.27 – 0.50 μg/L	China	[59]
Phenol, 2,5-Dimethylphenol, 4-Chlorophenol, 3,4-Dimethylphenol, 4-Chloro-3-methylphenol, 4-tert-Butylphenol, 2-tert-Butyl-4-methylphenol, 4-Pentylphenol, 2-Phenylphenol, 4-Hexylphenol, 4-tert-Octylphenol, 4-Heptylphenol, Nonylphenol, 4-Phenylphenol, Pentachlorophenol, Triclosan, Bisphenol F, Bisphenol A, Bisphenol B, Bisphenol Z, Bisphenol S	SPE	GC-MS	cow, goat, and sheep milk	LOD: 6 - 35 ng/kg LR: 20– 10 000 ng/kg R^2: 0.994-0.999 R: 86–106%	BPA: 30–940 ng/kg BPZ: 96–1100 ng/kg BPF: 270–950 ng/kg NP: 58–390 ng/kg 4-t-BP: 310–2100 ng/kg 3,4-DMP: 130–1800 ng/kg	Spain	[159]
2-chlorophenol, o-cresol m-cresol, 2,4-dichlorophenol, 4-tert-butylphenol, 4-chlorophenol, 4-tertoctylphenol, alpha-naphthol	EA–SPME	GC–FID	Milk	LOD: 0.001-0.1 μg/L LOQ: 0.1 μg/L LR: 0.005-50 μg/L R^2: > 0.99 R: 87.3-118.9% RSD: 1.9-12.3%	ND- 31.07 μg/L	China	[57]
metylparaben, ethyl- paraben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, benzyl-paraben, dichlovos, dimethoate, diazinon, bromophos methyl, chloropyrifos, fenthion, fenthion sulphoxide, parathion methyl, malathion, methidathion, nonylphenol, 4-tert-ocylphenol, 2-phenylphenol, 4-	SPE	GC-MS	cow, sheep and goat milk	LOD: 6-40 ng/kg LR: 20-10,000 ng/kg R: 80 -107% RSD: 2.6–7.1%	ethylparaben 120– 3100 ng/kg 2-phenylphenol: 130–2000 ng/kg BPA: 980–4600 ng/kg 4-Phenylphenol: 130 – 230 ng/kg	Spain	[160]

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phenylphenol, BPA and triclosan (TCS)					Butylparaben: 620 ng/kg		
Mep, EtP, *n*-Prp, propyl 4-hydroxybenzoate; *n*-Bup, butylparaben; i-Prp, isopropyl 4-hydroxybenzoate; i-BuP, isobutylparaben	MSPE	GC–MS	Milk	LOD: 0.1 ng/mL LOQ: 0.5 ng/mL LR: 0.1–600 ng/mL R^2: 0.9991 – 0.9997 R: 95-105 % RSD: 2.7-5.0 %	NS	China	[161]

LOD, Limit of detection; LOQ, Limit of quantification; LR, linear range; R^2, determination coefficient; R, recovery; RSD%, Relative standard deviation; CCα, decision limit; CCβ, detection capability; CV, coefficient of variation; ND, not detected; NS, not specified; UA, ultrasound assisted; SPE, solid phase extraction; dSPE, dispersive solid phase extraction; MSPE, magnetic solid phase extraction; DME, dispersive-membrane-solid-phase-extraction; UA-DLLME, ultrasound-assisted dispersive liquid-liquid microextraction ; FPSE, fabric phase sorptive extraction; SC-µSPE, spin-column micro solid phase extraction; PFSPE, Packed-nanofiber solid-phase extraction; EA-SPME, Electrochemical assistance solid-phase microextraction.

5.3. Pesticides

Pesticides play a pivotal role in agriculture. They are used not only to boost yield and ensure the quality of crops, but also to control diseases and deter pests [124]. These chemicals can be applied to the feed and fodder of livestock. Additionally, they might be applied directly to breeding animals or their habitats to protect against pests and pathogens or to treat diseases caused by them [31]. However, these chemicals don't solely affect their intended targets. Residues can make their way to non-targeted species, including livestock. Due to the persistent nature of pesticides, their residues may accumulate in animal tissues and subsequently find their way into the human food chain [31,162].

Owing to milk's rich fat content, it is particularly susceptible to contamination by pesticide residues due to their lipophilic nature [143,163]. Milk's nutritional benefits make it a primary dietary component, especially for children and infants [37] . While milk is a rich source of nutrients, its contamination with pesticide residues can have detrimental effects on consumer health. Consuming milk contaminated with these residues can lead to immediate health concerns such as lacrimation, seizures, headaches, and abdominal pain [163]. In the long term, exposure to these toxic chemicals can raise the risk of severe health problems, including genetic disorders, nervous system complications, cancer, and congenital disabilities [37]. In response to these risks, international regulatory authorities have set MRLs for pesticide residues in milk to ensure public health. Numerous studies have been conducted to investigate and quantify the levels of pesticide residues in dairy milk employing chromatographic techniques [31,81,92,164]. Table 3 offers a comprehensive summary of these key publications in the time period of 2018 – 2023.

Table 3. Overview of the analytical methods for extraction and determination of pesticides residues in dairy milk.

Target pesticides	Extraction method	Analysis technique	Matrix	Analytical parameters	Conc. In real samples	Country	Ref
Lindane, Alachlor, Aldrin, Bromophos methyl, Heptachlor epoxide, α-Endosulfan, Hexaconazole, Dieldrin, Endrin, β-Endosulfan, Diazinon, Endosulfan- sulfate, Bromopropylate, Fenpropathrin, Tetradifon, Fenvalerate	QuEChERS-TA-SFOD	GC-µECD	Pasteurized bovine milk	LOD: 0.01 -0.11 µg/kg LOQ: 0.03– 0.38 µg/kg LR: 0.03–250 µg/kg R: 61–119% RSD: 2.1–18.2%	1.24–4.68 µg/kg	Iran	[162]
Acetamiprid, Azinphos-methyl, Azoxystrobin, Benalaxyl, Boscalid, Bupirimate, Carbaryl, Carbendazim, Cymoxanil, Cyprodinil, Dichlorvos, Dimethoate, Fenthion sulfoxide, Imidacloprid,	Modified QuEChERS	UHPLC-LTQ/Orbitrap MS	Full fat Cow and goat milk	LOD: 0.2 -8.1 µg/kg LOQ: 0.61 – 24.8 µg/kg LR: 1–250 µg/kg R^2: ≥ 0.9918 R: 79.5–119.5% RSD: ≤ 11.7%	carbendazim <LOQ one sample	Greece	[165]

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Iprovalicarb, Metalaxyl, Myclobutanil, Tebuconazole, Thiacloprid, Thiamethoxam							
Imidacloprid, Acetamiprid, Nitenpyram, Thiacloprid	DSPE–SFOD–DLLME	HPLC–DAD	pasteurized semi-skimmed cow milk	LOD: 0.13–0.21 ng/mL LOQ: 0.43–0.70 ng/mL LR: 0.70–500 ng/mL R: 73%–85% RSD: 1.4–5.1	All samples are spiked	Iran	[163]
195 pesticides	modified QuEChERS	LC-Q-TOF/MS	raw milk	screening detection limits (SDL): 0.1–20 µg/kg LOQ: 0.1–50 µg/kg LR: 1–200 µg/kg R^2: >0.99 R: 70.0% - 120.0 RSD: < 20	ND	China	[31]
Dimethoate, Imidacloprid, Pirimicarb, Carbaryl, Fenitrothion, Hexythiazox, Phosalone	OPD-SPME-DES	HPLC-MS/MS	pasteurized cow milk	LOD: 0.09-0.27 ng/mL LOQ: 0.31-0.93 ng/mL LR: 0.93-500 ng/mL R: 81-94% RSD: < 9%	ND	Iran	[41]
Imidacloprid, Thiamethoxam, Thiacloprid, Clothianidin, Acetamiprid	SPE	LC–MS/MS	Sheep and Cow Milk	LOD: 0.5 µg/kg LOQ: 1 µg/kg LR: 1–100 µg/kg R^2: > 0.999 R: 75.1 - 88.3% RSD: 4.3 - 31.2%	ND	Jordan	[166]
Azinphos-methyl, Parathion- methyl, Phosalone, Diazinon, Chloropyrifos	DSPE–DLLME	HPLC–DAD	Milk	LOD: 0.17–0.36 ng/mL LOQ: 0.57–1.34 ng/mL LR: 1.34–1000 ng/mL R^2: 0.992 – 0.996 R: 79–92% RSD: ≤7.2%	Chloropyrifos in one sample: 19 ± 0.8 ng/mL	Iran	[167]
Metolcarb, Carbaryl, Isoprocarb, Bassa, Diethofencarb	SPE	HPLC-DAD	Milk	LOD: 0.12 -0.40 ng/mL LOQ: 0.36 -1.20 ng/mL LR: 1.0-320.0 ng/mL R: 86.0 to 110.0% RSD: 4.9 -6.3	ND	China	[168]
spinosyn A and D, temephos, piperonyl butoxide	LLE followed by QuEChERS	LC-MS/MS	Milk	LOD: 0.1–1.4 µg/kg LOQ: 0.3-4.1 µg/L LR: 1.5-50 µg/kg R^2: 0.983 - 0.996 R: 78-99% RSD: <8%	ND	Korea	[169]
tebufenozide (TEB) and indoxacarb (IND)	LLE	LC-MS/MS	Milk	LOD: 5, 1 µg/kg LOQ: 10, 3 µg/kg LR: 5–50 µg/kg R^2: 0.998 -0.9993 R: 87.79 -114.93 % RSD: < 6.4%	ND	Korea	[79]
α-HCH, HCB, β-HCH, lindane, δ-HCH, chlorthalonil, heptachlor, aldrin, chlorpyrifos, bromophos, α-endosulfan, dieldrin, p,p′-DDE, p,p′-DDD, p,p′-DDT	Modified QuEChERS	GC-ECD	Cow Milk	LOD: 0.00015 - 0.0009 mg/kg LOQ: 0.0005 - 0.003 mg/kg LR: 0.0005–0.5 mg/kg R^2: 0.9943 - 0.9995 R: 65 -118%	-	Iran	[37]

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Carbendazim, thiabendazole, dichlorvos, carbofuran, dimethoate, carboxin, pirimicarb, terbutryn, thiacloprid, imidacloprid, trichlorfon, fenitrothion, fenthion, cyproconazole, thiamethoxam, tridemorph, fenamiphos, diazinon, pirimiphos-methyl, tebuconazole, butachlor, fenamidone, kresoxim-methyl, sulfotep, diniconazole, malathion, bitertanol, propiconazole, thiophanate-methyl, clodinafop-propargyl, flamprop-isopropyl, phosalone, ethion, dimethomorph, nicosulfuron	Modified QuEChERS	UHPLC-MS/MS	Cow Milk	RSD: 1-15% LOD: 0.0003 – 0.03 mg/kg LOQ: 0.001 - 0.05 mg/kg LR: 0.001–0.5 mg/kg R^2: 0.9830 - 0.9993 R: 74- 121% RSD: 1-17%	dimethoate in raw milk: 0.045 mg/kg	Iran	[37]
156 pesticide residues	Modified QuEChERS	LC–MS/MS	Milk	LOD: 0.11–- 2.70 µg/kg LOQ: 0.38–8.10 µg/kg LR: 5 - 100 µg/kg R^2: ≥ 0.99 R: 70.38 - 116.40% RSD: < 19%	ND	Turkey	[170]
Sulfoxaflor	modified QuEChERS	LC-MS/MS	Milk	LOD: 1.8 µg/kg LOQ: 5.0 µg/kg R^2: 0.9990 R: 81.1 - 95.0% RSD: 2.3-11.2%	< LOQ	China	[171]
Coumaphos, Phosmet, Fonofos, Parathion, Pyridaphenthion, Phosalone, Temephos, Profenofos, Terbufos, Phenthoate, Ethion, Tetrachlorvinphos, Isazophos, Pirimiphos-ethyl, Fenthion, Phoxim, Methidathion, Triazophos, Pirimiphos-methyl, Dichlofenthion	MSPE	LC-MS/MS	Fatty whole milk	LOD: 0.001-0.01 µg/L LOQ: 0.2-0.5 µg/L LR: 0.2-250 µg/L R^2: 0 .9978 -0.9999 R: 0.0-105 % RSD: <12.3 %	Pirimiphos-methyl: 0.23 µg/L) (One sample)	China	[172]
Carbofuran, Carbaryl, Propoxur, Aminocarb, Phenmedipham, Ethiofencarb, Desmedipham, Fenoxycarb, Pirimicarb, Bendiocarb, Methiocarb	LLE	UHPLC-MS/MS	Camel milk	LOD: 0.01 µg/kg LOQ: 0.03 - 0.04 µg/kg LR: 0.00001 - 0.5 mg/kg R^2: 0.9982 -1.0000 R: 88 - 103% RSD: ≤5%	0.345- 9.509 µg/kg	UAE	[164]
Lindane, Diazinon, Fenitrothion, Malathion, Aldrin, α-Endosulfan, β-Endosulfan, Methoxychlor	DLLME	GC-MS	Bovine milk	LOD: 0.90-5.00 ng/mL LOQ: 2.5 -15 ng/mL LR: 2-1000 ng/mL R^2: 0.995-0.999 R: 86.15 - 112.45 % RSD: 1.06 – 2.20 %	ND	India	[81]
endrin and δ-keto endrin	modified QuEChERS	GC-µECD	Milk	LOD: 0.003 mg/kg LOQ: 0.01 mg/kg	ND	Korea	[61]

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41 multiclass pesticides	QuEChERS	GC-ECD followed by GC-MS	commercial liquid milk	R^2: 0.9979, 0.9966 R: 84.27 - 105.29% RSD: 2.12 - 7.59% LOD: 0.001–0.02 µg/mL LOQ: 0.002–0.05 µg/mL LR: 0.002 - 1 µg/mL	below the LOQ	India	[16]
Permethrin (Perm), deltamethrin (Del), and cypermethrin (Cyp)	USA-MNF-LPME	GC-MS	Cow milk	R^2: >0.98 R: 91.38 - 117.56% RSD: <2.79% LOD: 2.8, 2.7 and 2.0 ng/mL LOQ: 9.43, 8.95, and 6.47 ng/L LR: 0.01–250 µg/L	Per: 18.0 ng/L Del: 25.0 ng/L Cyp: 48.0 ng/L	Iran	[173]
chlorpyriphos, malathion, disulfoton, pirimiphos	d-SPE	GC-MS	commercial bovine milk	R^2: 0.9991, 0.9995 R: 91.0–105% RSD: 3.5, 3.2, 2.8 % LOD: 0.36-0.95 µg/L LOQ: 5.0 µg/L LR: 5.0- 40.0 µg/L	ND	Brazil	[58]
α-HCH; β-HCH; γ-HCH; δ-HCH; Heptachlor; Aldrin; Heptachlor Epoxide; Trans-Chlordane; α- Endosulfan; Cis-Chlordane; p.p′-DDE; Endrin; β-Endosulfan; Endosulfan Sulfate; p.p′-DDT; Endrin Ketone; Methoxychlor; Phthalic Acid and p,p′-DDD.	QuEChERS	GC-MS/MS	Cow milk	R^2: 0.9902 -0.9963 RSD: < 19.9% LOD: 0.011 - 0.034 µg/kg LOQ: 0.049 - 0.087 µg/kg LR: 5 - 200 ppb R^2: 0.92 - 0.99 R: 79.23% - 98.65%	p,p-DDE: 0.09 µg/kg p,p-DDT: 0.07 µg/kg	Bangladesh	[174]
α- and β-hexachlorocyclohexane, lindane, hexachlorobenzene, p,p′-DDE, aldrin, dieldrin, and α-endosulfan	GDME	GC-ECD & GC-MS	Milk	LOD: 3.7 to 4.8 µg/L LOQ: 12-16 µg/L R^2: 0.991 - 0.995 R: 71- 99% RSD: <10%	aldrin was found in one sample below the LOD	Brazil	[92]
Alpha-Cypermethrin,Beta-Cyfluthrin, Bifenthrin, Bromopropylate, Chlorothalonil, Chlorpropham, Deltamethrin, Dicofol, Endosulfan alpha, Endosulfan beta, Endosulfan sulfate, Fenitrothion, Fenthion, Fenvalerate, Formothion, Kresoxim methyl, Lambda Cyhalothrin, Oxyfluorfen, Permethrin, Procymidone, Prothiofos, Tau-fluvalinate, Tetradifon, Trifluralin, Vinclozolin	QuEChERS	GC–MS	Milk	LOD: 0.31 – 1.91 µg/kg LOQ: 1.05 - 6.62 µg/kg LR: 5 - 100 µg/kg R^2: > 0.99 R: 72.50–119.54% RSD: 1.17 - 14.62%	ND	Turkey	[175]
Linden, Heptachlor, Aldrin, Dieldrin, Endrin, Endosulfan, Dichlorodiphenyltrichloroethane (DDT)	QuECheRS	GC-ECD	organic and conventional goat milk	LOD: 0.3 ppb	ND	Indonesia	[176]
Dichlorvos, Carbaryl, Atrazine, Ametryne,	QuChERS-DLLME	GC-FID	Milk	LOD: 4.2–27.4 ng/mL	Dichlorvos, Atrazine,	Iran	[177]

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Diazinon, Pirimiphos-methyl, Carbofuran, Chlorpyrifos, Prothioconazole, Tebuconazole				LOQ: 11.89–82.23 ng/mL LR: 0.5–100 ng/mL R: 77.69–147.69% RSD: 1.6–9.7% LOD: 0.90–3.9 ng/mL	Diazinon, Chlorpyrifos and Tebuconazole 2.49– 10.48 ng/mL		
Carbaryl, Hexythiazox, Pretilachlor, Iprodione, Famoxadone, Sethoxydim, Fenazaquin	In matrix-DES-SFO-DLLME	GC-FID	Cow milk	LOQ: 3.1 -13 ng/mL LR: 4.5–5000 ng/mL R: 64 - 89% RSD: 3.8–5.3%	ND	Iran	[178]

LOD, Limit of detection; LOQ, Limit of quantification; LR, linear range; R^2, determination coefficient; R, recovery; RSD%, Relative standard deviation; CCα, decision limit; CCβ, detection capability; CV, coefficient of variation; ND, not detected; NS, not specified; SPE, solid phase extraction; MSPE, magnetic solid phase extraction; LLE, liquid-liquid extraction; dSPE, dispersive solid phase extraction; DLLME, dispersive liquid-liquid microextraction; QuEChERS-TA-SFOD, QuEChERS-temperature-assisted-Solidification of floating organic droplet; OPD-SPME-DES, Organic polymer based dispersive solid phase microextraction-deep eutectic solvent; USA-MNF-LPME, ultrasound assisted magnetic nanofluid-based liquid phase microextraction; GDME, Gas-diffusion microextraction.

5.4. Mycotoxins

Mycotoxins are secondary metabolites produced by specific types of fungi belonging mainly to Aspergillus, Penicillium, and Fusarium genera that infest and colonize many crops in fields, during storage or during processing and preparation [179,180].

When food producing animals consume contaminated feed, mycotoxins undergo metabolism and biotransformation, ultimately being transferred to eggs, milk and meat, posing potential health risks owing to their hepatotoxic, carcinogenic and genotoxic effects [181,182]. Among different types of mycotoxins such as Zearalenone, Ochratoxins, Sterigmatocystin and Fumonisins, aflatoxins have gained popularity and special attention [183,184]. Aflatoxins (AFs), that are mainly produced by Aspergillus flavus, Aspergillus nominus and Aspergillus parasiticus fungi, are of the most studied types of mycotoxins in literature, given their acutely toxic properties, in addition to their carcinogenicity, teratogenicity, mutagenicity and hepatotoxicity [181,184–186].

Aflatoxin B1 (AFB1) is the most prevalent form of aflatoxins that contaminates crops, AFB1 is known to be highly toxic and it is classified as a human carcinogen (group 1) by the International Agency for Research on Cancer (IARC)[187,188].

In milk, when milk producing animals are fed with AFB1-contaminated feed, it undergoes hydroxylation process by the action of cytochrome P450 enzyme producing the hydroxylated metabolite AFM1 which also demonstrates toxic effects on human [189,190]. Several regulatory organizations have set maximum residue limits (MRLs) for AFM1 and other mycotoxins in milk and food products, Flores-Flores et al. have summarized some of those regulations [191,192].

As milk is a very popular and a widely consumed nutritious meal, numerous research studies were devoted to analyzing and determining aflatoxins and other types of mycotoxins in milk using chromatographic based analytical techniques. Table 4 provides an overview of those methods and their analytical performance parameters.

Table 4. Overview of the analytical methods for extraction and determination of mycotoxins residues in dairy milk.

Target mycotoxins	Extraction method	Analysis technique	Matrix	Analytical parameters	Conc. in real samples	Country	Ref
Aflatoxin B_1 (AFB_1), Aflatoxin B_2 (AFB_2), Aflatoxin G_1 (AFG_1), Aflatoxin G_2 (AFG_2), Aflatoxin M_1 (AFM_1), Alternariol Methyl Ether (AME), Alternariol (AOH), Beauvericin (BEA), Cyclopiazonic Acid (CTA), Citrinin (CTN), Diacetoxyscirpenol (DAS), Deepoxy-deoxynivalenol (DOM-1), Deoxynivalenol	QuEChERS	UHPLC-MS/MS	Raw milk	LOD: 0.001 - 3.26 µg/L LOQ: 0.002 - 10.76 µg/L LR: 0.002 - 200 µg/L R: 61.22 - 120.63% RSD: <16%	T-2, RC, ENNA, $ENNA_1$, ENNB, $ENNB_1$ and BEA: <LOD - 4.76 µg/L	Portugal	[193]

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(DON), 15 Acetyl-Deoxynivalenol (15 AC-DON), 3 Acetyl-Deoxynivalenol (3 AC-DON), Enniatin A (ENNA), Enniatin A1 (ENNA1), Enniatin B (ENNB), Enniatin B1 (ENNB1), Fusaric acid (FA), Fumonisin B_1 (FB_1), Fumonisin B_2 (FB_2), HT-2 toxin (HT-2), Hydrolyzed fumonisin B_1 (Hydro-FB_1), Mycophenolic acid (MPA), Neosolaniol (NEO), Ochratoxin A (OTA), Roquefortine C (RC), Sterigmatocystin (STC), T-2 toxin (T-2), Zearalenone (ZEN), Zearalanone (ZOL), α-Zearalenol (α-ZEN), α-Zearalanol (α-ZOL), β-Zearalenol (β-ZEN), β-Zearalanol (β-ZOL), Deoxynivalenol-3-glucoside (DON-3-Gluc), Fusarenon X (FX), Patulin (PAT), T-2 triol							
AFB_1, AFB_2, AFG_1, AFG_2, AFM_1, AFM_2	IAC	HPLC-MS/MS	Milk	LOD: 0.005 – 0.010 µg/L LOQ: 0.010 - 0.026 µg/L LR: 0.010-10.0 µg/L R^2: 0.988 - 0.997 R: 85.5 - 106.2 % RSD: < 12.5%	AFM_1: 0.072 µg/L (One sample)	China	[194]
AFM_1	IAC	HPLC- FLD	Pasteurized cow milk gathered during different seasons	LOD: 0.0001 µg/L LOQ: 0.0005 µg/L R^2: > 0.999	0.002 - 0.09 µg/L	Iran	[195]
AFM_1	AALLME	HPLC–FLD	Unpasteurized milk	LOD: 0.9 ng/L LOQ: 3 ng/L LR: 3–3000 3 ng/L R^2: 0.9976 R: 87 ± 4% RSD: ≤ 9%	46 – 96 ng/L	Iran	[83]
OTA, AFM_1	DSPE - DLLME-SFO	HPLC-FLD	Raw cow's milk	LOD: 0.25, 0.37 ng/L LOQ: 0.83, 1.23 ng/L LR: 0.83–10^5, 1.23 – 10^5 R^2: 0.998, 0.997 R: 87, 75% RSD: ≤ 5.1	OCT A: 35 – 43 ng/L AFM_1: 15 - 182 ng/L	Iran	[45]
OTC, AFB_1, AFB_2 , AFG_1 , AFG_2 , AFM_1, AFM_2, HT-2 Toxin, T-2 Toxin, OTA, DON, OCT α, OCT B, ZEN, α-ZEN, α-ZOL, β-ZEN, β-ZOL, stachybotrylactam, and (S)-zearalanone	QuEChERS	HPLC-MS/MS	cow milk	LOD: 0.007– 1.300 µg/kg LOQ: 0.02–4.00 µg/kg LR: 0.01–10 µg/L R^2: ≥0.9933 R: 80.00 - 112.50% RSD: 2.67–14.97%	<LOD	China	[196]
AFB_1, AFB_2, AFM_1, AFM_2	ISDµSPE	HPLC-FLD	Cow milk	LOD: 0.003 - 0.005 ng/mL LOQ: 0.01 - 0.02 ng/mL LR: 0.01–1.0 ng/mL R^2: 0.992 - 0.999 R: 73.0 - 109.6% RSD: < 17.3%	AFM_1: 0.038 ng/mL (One sample)	Malaysia	[76]
AFB_1, AFM_1	QuEChERS		Milk	LOD: 0.001 µg/L LOQ: 0.002 µg/L	ND	Italy	[197]

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		UHPLC-Q-Orbitrap HRMS		LR: 0.002 - 20 µg/L R^2: >0.9990 R: 75–96% RSD: < 16			
AFM_1	IAC	LC-FLD	Milk	LOD: 0.01 ng/mL LOQ: 0.03 ng/mL R: 87–95% CV: <15%	10 - 77 ng/L	Morocco	[75]
AFM_1, AFB_1, AFB_2, AFG_1, AFG_2, OTA, OTB, FB_1, FB_2, FB_3, HT-2 and T-2 toxins, nivalenol (NIV), DON, DOM-1, 3 AC-DON, 15 AC-DON, DAS, FX, NEO, STC, and ZEN	LLE	LC–MS/MS	Cow Milk	LOD: 0.010 - 5.07 ng/mL LR: 0.04 - 101.4 ng/mL R^2: 0.9935 - 0.9997 R: 61.2 - 83.9% RSD: 3.8 – 11.8%	OCT A: <LOQ (0.2 ng/mL)	Peru	[187]
AFM_1	IAC	HPLC-FLD	Liquid and powder milk	LOD: 0.002 µg/L R^2: 0.99995 R: 102.94 - 108.31% RSD: < 10%	0.021 - 2.89 µg/L	Yemen	[46]
AFM_1	IAC	UPLC-MS/MS	Cow, goat and sheep milk	LOD: 0.0027 µg/kg LOQ: 0.0089 µg/kg LR: 0.75 - 22.5 µg/L R^2: 0.997 R: 77.9–81.0% RSD: 6.1- 12%	<LOD - 0.0370 µg/kg	Greece	[198]
AFB1, AFB2, AFG1, AFG2, AFM_1, AFM_2, OTA, ZEN, ZOL, α-ZEN, β- ZEN, α-ZOL, β-ZOL	MSPE	UHPLC-Q-Exactive HRMS	Commercial liquid milk	LOD: 0.005 - 0.050 µg/kg LOQ: 0.015 - 0.150 µg/kg LR: 0.15 – 100 ng/mL R^2: 0.9963 – 0.9999 R: 81.8–106.4% RSD: 2.1– 11.7%	0.026 - 0.039 µg/kg	China	[199]
AFB_1, AFB_2, AFG_1, AFG_2, OTA, ZEA	IAC	HPLC-FLD	Raw cow milk	LOD: 0.02 – 0.92 µg/kg LOQ: 0.06 – 2.8 µg/kg	AFM_1: <LOQ - 0.19 µg/kg	Egypt	[74]
AFB_1, AFB_2, AFG_1, AFG_2, AFM_1, BEA, CTN, DON, ENNA, ENNB, FB_1, FB_2; Moniliformin (MON); MPA, NIV, OTA, Penicillic Acid (PA), PAT, Tenuazonic acid (TEA),Tentoxin TTX, ZEN.	modified QuEChERS	UHPLC-MS/MS	Raw cow milk	LOD: 0.001 -9.88 ng/mL LOQ: 0.005 -13.54 ng/mL LR: 0.025 - 200 ng/mL R^2: 0.9519 – 0.9996 R: 67.5 - 119.8% RSD: < 25%	NS	Portugal	[200]
AFM_1	DLLME	HPLC-FLD	Cow and buffalo milk	LOD: 0.002 µg/L LOQ: 0.007 µg/L LR: 0.01 - 1.0 µg/L R^2: 0.999 R: 80.9 - 89.2 % RSD: < 14%	0.01–9.18 µg/L	India	[201]
AFM_1, AFM_2	IAC	HPLC-FLD	Cow, goat and sheep milk	LOD: 11.99, 16.95 ng /kg CCα: 56.52, 57.27 ng /kg CCβ: 63.97, 65.57 ng /kg R^2: 0.999, 0.996 R: 74 –120 % RSD: <17%	AFM_1: 47.1 - 73.4 ng /kg AFM_2: <LOQ	Greece	[202]
AFB1, AFM1, OTA, ZEN, α-ZEN, β-ZEN, ZOL, α-ZOL, β-ZOL	SPE	UHPLC-MS/MS	Milk	LOD: 0.01–0.07 ng/mL LOQ: 0.02–0.18 ng/mL	AFM_1: 0.03–0.30 ng/mL	China	[69]

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				LR: 0.02–200 ng/mL R^2: ≥0.992 R: 70.2–111.2% RSD: 2.0–14.9%	ZEA: 0.3, 1.46 and 2.99 ng/mL		
ENNA, ENNA1, ENNB, ENNB1, BEA.	LLE	LC-MS/MS	Cow milk	LOD: 0.088 - 0.099 µg/kg LOQ: 0.099 - 0.130 µg/kg LR: 0.15–50 µg/kg R: 72 – 99% RSD: 3.4 – 17.5 %	ENNB: 0.157 -0.587 µg/kg BEA: 0.101-6.17µg/kg	Poland	[203]
AFM1, AFB1	QuEChERS	HPLC-FLD	Milk powder	LOD: 0.038, 0.027 µg/kg LOQ: 0.125, 0.083 µg/kg R: 65 - 110% RSD: < 20%	AFM_1: 0.20–1.19 µg/kg	Colombia	[204]
AFM1	IAC	HPLC-FLD	Milk	LOD: 0.01 µg/L LOQ: 0.03 µg/L R^2: > 0.98 R: 90.6% (mean) RSD: 5.7%	0.016 - 0.030 µg/kg	Iran	[205]
AFB_1, AFB_2, AFG_1, AFG_2, AFM_1, AFM_2, FB1, FB2, STE, ZEN.	MSPE	HPLC–MS/MS	Milk	LOD: 0.003-0.442 µg/kg LOQ: 0.008 - 1.219 µg/kg LR: 0.02–200 µg/kg R: 88.3 - 103.5% RSD: 2.4 - 6.5%	NS	China	[70]

LOD, Limit of detection; LOQ, Limit of quantification; LR, linear range; R^2, determination coefficient; R, recovery; RSD%, Relative standard deviation; CCα, decision limit; CCβ, detection capability; CV, coefficient of variation; ND, not detected; NS, not specified; IAC, immunoaffinity column; SPE, solid phase extraction; LLE, liquid-liquid extraction; AALLME, air-assisted liquid-liquid microextraction; MSPE, magnetic solid phase extraction; DLLME, dispersive liquid-liquid microextraction; DSPE -DLLME-SFO, Dispersive solid phase extraction–dispersive liquid–liquid microextraction–solidification of organic drop; ISDµSPE, in-syringe dispersive micro-solid phase extraction.

5.6. Other Emerging Pollutants

Considerable attention has been dedicated to drugs, EDCs, mycotoxins and pesticides and their residual levels in milk. However, in this review, we expand our discussion to encompass other types of contaminants, including hormones, per- and polyfluoroalkyl substances (PFAS), Polyaromatic hydrocarbons (PAHs), Polychlorinated biphenyls (PCBs), melamine as a non-protein nitrogen supplement and formaldehyde.

The presence of hormones in edible matrices, such as milk, has raised concerns due to their significant impact on the endocrine system and cell signaling, leading to disruptions in the homeostasis of consumers [27]. Moreover, elevated levels of estrogen have been associated with breast, uterine, and ovarian cancers in women [206]. Natural and synthetic steroid hormones are extensively employed in cattle to treat certain diseases, promote growth, and address reproductive disorders [207]. However, exceeding acceptable dosages, improper injection, or the use of banned hormones can result in the presence of their residues in milk. Therefore, it is imperative to investigate the extent of hormonal contamination in milk to ensure food safety.

PFAS are highly stable compounds, leading to their extensive use in food packaging materials and flame retardants. However, their resistance to biodegradation results in their accumulation in the environment. Milk is considered one of the most contaminated food items with various PFAS[42]. The entry of PFAS into milk and dairy products can occur through processing and packaging or via contaminated animal feed. PFAS can pose serious threats to human health, including cancer, allergies, and infertility [42]. Hence, the determination of PFAS in milk and food matrices has garnered significant attention from researchers. However, a comprehensive knowledge and understanding regarding their occurrence, migration, associated risks and tolerable limits still limited.

Melamine, a nitrogen-rich organic compound, finds applications in different industries including plastics, adhesives, coatings, amino resins and laminates [208,209]. Beyond its typical commercial and industrial uses, melamine, as a cheap and available substance rich with nitrogen, is

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illegally introduced into milk and dairy products to artificially and falsely boost their apparent protein content. Various health effects have been reported to be induced by melamine, including nephrolithiasis, stones formation, bladder carcinoma and kidney inflammations [210,211]. In 2008, China experienced several human death cases arising from kidney failure in addition to other health complications as a result of melamine adulteration [212]. To protect public health, intensive guidelines and regulations were conducted by several organizations and authorities to control the use and the exposure to melamine [213]. Therefore, analytical methods are being continuously developed for melamine tracking in milk and milk products [48,49,214].

Various chemical substances are being added to food Under the category of food adulterants and preservatives, to elongate and extend their shelf life. Such chemicals include formaldehyde (FA), which is the most common and the most accessible. FA can reach food matrices including milk via several pathways, including its direct application as a preservative, or migrating from the packaging material or from the contaminated environment. Consequently, such contamination can lead to severe health impacts owing to the toxic and carcinogenic nature of FA [215,216]. Therefore, there is a need for special interest and monitoring efforts to track the presence of FA in food matrices, particularly in highly consumed products like milk.

Due to their physical and chemical stability, Polychlorinated biphenyls (PCBs) are widely used in different industrial applications such as paints, rubber and plastics industries [34]. However, due to their tendency to bioaccumulate in adipose tissue, they can be transferred to food of animal origin such as milk. PCBs are toxic chemicals that can lead to cancer, neurological, reproductive and immune system disorders [217]. Consequently, their monitoring in milk is of a significant importance. Similarly, polyaromatic hydrocarbons (PAHs), a type of organic pollutants, that can contaminate food through different ways, such as environmental contamination or during food processing and preparation, are a matter of concern for public health due to their mutagenicity, carcinogenicity, and immune system suppression effect [218–220]. This underscores the need for developing analytical methods for tracking and quantifying such pollutants in milk.

Table 5 provides data from previous studies regarding the presence of hormones, PFAS, PCBs, PAHs, melamine and other contaminants in dairy milk, in addition to multiclass residues that are simultaneously analyzed by the same analytical methods.

Table 5. Overview of the analytical methods for extraction and determination of residues of other EPs including hormones, mycotoxins and PFAs and multiclass residues in dairy milk.

Target EPs	Category	Extraction method	Analysis technique	Matrix	Analytical parameters	Conc. in real samples	Country	Ref
Perfluorobutanoic acid (PFBA), Perfluoropeptanoic acid (PFPeA), Perfluorohexanoic acid (PFHxA), Perfluoroheptanoic acid (PFHpA), Perfluorooctanoic acid (PFOA), Perfluorononanoic acid(PFNA), Perfluorodecanoic acid (PFDA), Perfluoroundecanoic acid (PFUnDA), Perfluorododecanoic acid (PFDoDA), Perfluorotridecanoic acid (PFTriDA), Perfluorotetradecanoic acid (PFTeDA), Perfluorobutane sulfonate (PFBS) Perfluoropentane sulfonate (PFPeS), Perfluorohexane sulfonate (PFHxS*), Perfluoroheptane sulfonate (PFHpS), Perfluorooctane sulfonate (PFOS*), Perfluoro-	PFAS	SLE	HPLC-MS/MS	Cow milk	LOD: 0.8 - 22ng/L (PFBA:144 ng/L) R: 70 - 141%	PFCA, PFSA, PASF: < MDL FTS <MDL–6.59 ng/L	USA	[221]

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4-ethylcyclohexanesulfonate (PFECHS), Perfluorononane sulfonate (PFNS), Perfluorodecane sulfonate (PFDS), Perfluorobutane sulfonamide (FBSA), Perfluorooctane sulfonamide (FOSA), N-methylperfluoro-1-octanesulfonamid (N-MeFOSA), N-ethylperfluoro-1-octanesulfonamide (N-EtFOSA), 4:2 fluorotelomer sulfonate (4:2 FtS), 6:2 fluorotelomer sulfonate (6:2 FtS), 8:2 fluorotelomer sulfonate (8:2 FtS)							
PFBA, PFPeA, PFBS, PFHxA, PFHpA, PFOA, PFHxS, PFNA, PFOS, PFDA, PFUdA, PFDS, PFDoA, PFTrDA, and PFTeDA	PFAS	QuEChERS	UHPLC-MS/MS	Dairy milk and infant formulas	LOD: 0.005-0.05 ng/mL LOQ: 0.005-0.05 ng/mL R^2: 0.987 -0.999 R: 93- 120% RSD: 3-18%	The Σ15 PFAS in dairy milk: 0.08–15.51 ng/mL The Σ15 PFAS in infant formula: 0.01–5.24 ng/mL	South Africa	[42]
PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUdA, PFDoA, PFTrDA PFTeDA, PFBS, PFHxS, PFOS, PFDS	PFAS	QuEChERS	UHPLC–MS/MS	Dairy milk and infant formula	CCα: 30–50 ng/kg CCβ: 40–100 ng/kg LOQ: 5–50 ng/kg LR: 5–1200 ng/kg R^2: 0.9843–0.9998 R: 60–121% RSD: 5–28%	Infant formulae: <LOQ–259 ng/ kg dairy milk: <LOQ–294 ng/kg	South Africa	[222]
PFPA, PFBS, PFHpA, PFOA, PFHpS, PFNA, PFOS, PFDA	PFAS	SPME	UHPLC-MS/MS	Milk and milk powder	LOD: 0.1–0.8 pg/g LOQ: 0.4 - 2.5 pg/g R^2: ≥ 0.992 R: 89.8–111% RSD: ≤ 10%	ND-4.12 pg/g	China	[223]
PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDoA, PFBS, PFHxS, PFOS,	PFAS	QuEChERS	LC-MS/MS	Cow milk	LOD: 7.78–16.35 ng/kg LOQ: ALL: 50 ng/kg GenX and C6O4 : 100 ng/kg R: 91.3 – 121.8% RSD: ≤ 10.9%	NS	Italy	[224]
PFOA, PFOS	PFAS	DFE	LC-MS/MS	Milk	LOD: 0.006–0.022 ng/mL LOQ: 0.020-0.072 ng/mL LR: 0.05–100 ng/mL R^2: ≥ 0.9998 R: 94.7–109 % RSD: ≤ 9.5 %	0.08 - 2.19 ng/mL	China	[225]
Melamine	Non-protein nitrogen supplement	DLLME	HPLC-UV	Milk	LOD: 63.64 µg/kg LOQ: 210.03 µg/kg LR: 210.03–1000 µg/kg R^2: 0.9898 R: 72.5-104.0 % RSD: <10.2	ND	Iran	[49]
Melamine	Non-protein nitrogen supplement	MSPE	UPLC-MS/MS	Milk powder	LOD: 0.00045 mg/kg R: 90.3-95.7%	0.023 mg/kg (One sample)	China	[226]

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Melamine	Non-protein nitrogen supplement	SPE	HPLC-DAD	Milk powder	RSD:0.3–4.7 % LOD: 0.006 mg/kg LOQ: 0.019 mg/kg R^2: > 0.999 R: ≥ 83.8%	0.017 -0.082 mg/kg	Uruguay	[227]
Melamine	Non-protein nitrogen supplement	LPME	HPLC-UV	Milk	RSD: 0.5 - 9.9% LOD: 0.03 mg/L LOQ: 0.1 mg/L LR: 0.1–30 mg/L R^2: 0.994 R: 95%	<LOD	Russia	[48]
Melamine	Non-protein nitrogen supplement	SPE	HPLC-FLD	milk and infant formula	RSD: < 7% LOD: 0.005 -0.042 µg/mL LOQ: 0.015 - 0.126 µg/mL R: 78-103%	0.18- 2.90 µg/mL	Turkey	[209]
Prednisone (PRD), Hydrocortisone (HCOR), Methylprednisolone (MPRD), Dexamethasone (DXM), Betamethasone (BEM), Prednisone acetate (PRDA), Beclomethasone (BCM), Fludrocortisone acetate (FCORA), Dexamethasone acetate (DXMA), Fluocinolone acetonide (FCA), Halcinonide (HAL), Triamcinolone acetonide acetate (TCAA), Fluocinonide (FLC), Nandrolone (NAN), Methyltestosterone (MTES), Testosterone propionate (TESPR), Chlormadinone acetate (CHMA), Megestrol acetate (MGA), Medroxyprogesterone acetate (MXPROA), Estrone (E1), 17 α -Oestradiol (17α-E2), Estriol (E3)	Hormones	SPE	HPLC-MS/MS	Bovine milk	RSD: ≤1.21 % LOD: 0.10 - 1.20 µg/kg LOQ: 0.33- 3.96 µg/kg LR: 2.5 – 500 µg/kg R^2: 0.9943- 0.9998 R: 82.6 - 95.3%	NAN, MTES, MXPROA TESPR, HCOR, E1, 17α-E2, E3: 0.11 - 5.79 µg/kg	China	[30]
Estrone (E1), 17β-Estradiol (β-E2), 17α-Ethynylestradiol (EE), Estriol (E3), Diethylstilbestrol (DES), Levonorgestrel (NOR), Norethisterone (NORET), Megestrol actetate (MGA), Progesterone (PRO), Testosterone (TES), Boldenone (BOL), Nandrolone (NAN), Cortisone (COR), Prednisone (PRD), Prednisolone (PRDNL)	Hormones	FPSE	UHPLC-MS/MS	Cow and goat milk	LOD: 0.012 - 1.242 ng/mL LOQ: 0.04-4.14 ng/mL R: 17.91- 59.01%	ND	Spain	[27]
β-E2, EE, E1, hexestrol (HEX)	Hormones	MSPE	HPLC-VWD-FLD	Milk powder	LOD: 0.5–0.9 µg/kg LOQ: 1.5–3 µg/kg R: 75.1–97.2 % RSD: ≤ 14.2	ND	China	[228]
E3, PRDA, HCOR, DES, E1	Hormones	Online-SPE	HPLC-UV	Cow Milk	LOD: 0.004 - 0.054 µg/mL LOQ: 0.015 - 0.180 µg/mL	ND	China	[229]

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E2, TES, PRO	Hormones	VALLME-MSPE	HPLC-DAD	Milk	R: 70.82–112.90% LOD: 1.0–1.3 ng/mL LOQ: 2.5–4.5 ng/mL	0.2 - 4.6 ng/mL	China	[230]
Progesterone (PRO), Trenbolone (TRB), Norethisterone (NORET), Gestodene (GSD), Altrenogest (ALT), Dienogestrel (DNG), Norgestrel (NOG), Demegestone (DMG), 17α-Hydoxy progesterone (17 α -HPRO), 21α-Hydoxy progesterone (21 α -HPRO), Megestrol (MEG), Medroxyprogesterone (MXPRO), Melengestrol (MLG), Chlormadinone (ChMD), Drospirenone (DROS), Cyproterone (CYP), Norethindrone acetate (NORA), Megestrol acetate (MGA), Medroxyprogesterone acetate (MXPROA), Melengestrol acetate (MLGA), Chlormadinone acetate (ChMDA) and Cyproterone acetate (CYPA)	Hormones	SPE	UHPLC-QE HF HRMS	Cow and ewe milk	R 80.1-116.4% RSD: ≤ 13.9% LOD: 0.05 – 0.3 µg /kg LOQ: 0.2-1 µg /kg R^2: > 0.99 R: 80.7- 108.3% RSD: <15%	PRO: 0.48-54.2 µg/kg NOG: 1.45 ± 0.21 µg/kg GSD: 3.1 µg/kg MXPROA: 8.05, 152 µg/kg MXPRO: 13.5 µg/kg CYP: 61.2 ± 2.7 µg/kg	China	[29]
PCB81, PCB153, PCB105, PCB126, PCB157	PCBs	DSPE	GC–MS/MS	Milk	LOD: 0.14 - 0.57 pg/g LOQ: 0.47 -1.90 pg/g LR: 0.002–1.000 ng/g R^2: 0.9995 - 0.9998 R: 82.8 - 106 % RSD: ≤ 6.6 %	<lOQ- 5.27 pg/g	China	[231]
PCB28, PCB52, PCB101, PCB138, PCB153, PCB180, PCB209, Napthalene (NA), 2-methylnapthalene (2-MNA), 1-methylnapthalene (1-MNA), Acenapthylene (AcNy), Acenapthalene (AcNA), Fluorene (FLN), Phenanthrene (PhN), Anthracene (ANT), Fluranthene (FLT), Pyrene (PY), Benzo (A) Anthacene (B-A-ANT), Chrysene (Chr), Benzo (B) Fluoranthene (B-B-FLT), Benzo (K) Fluranthene (B-K-FLT), Benzo (A) Pyrene (B-A-PY), Indeno (1, 2, 3-CD) Pyrene (IPY), Dibenz (A, H) Anthracene (DANT)	PCBs & PAHs	QuEChERS	GC-MS/MS	Cow milk	LOD: PCBs: 0.016 - 0.031 ng/g PAHs: 0.3, 1.0 ng/g LOQ: PCBs: 0.059 - 0.08 ng/g PAHs: 1.0, 4.0 ng/g R: PCBs: 77.53 - 92.49% PAHs: 67.90–99.76%	PCBs: ND-3.35 ± 0.87 ng/g B-A-ANT: 0.5497 ± 0.30 ng/g Chr: 1.077 ± 0.88 ng/g	Banglade sh	[34]
NA, AcNy, AcNA, FLN, PhN, ANT, FlT, PY, B-A-ANT, Chr, B-B-FLT, B-K-FLT, B-A-PY, IPY, DANT,	PAHs	MSPE	GC–MS	Milk and powder milk	LOD: 0.040 - 0.075 µg/kg LOQ: 0.121 - 0.227 µg/kg R: 86.1 – 100.3 %	0.48 – 1.98 µg/kg	Iran	[232]

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Benzo[g,h,i] perylene (BPer)					RSD: ≤10.1%			
Furan	Toxic heterocyclic compounds	Automated HS-SPME	GC-MS	Milk	LOD: 0.01 ng/g LOQ: 0.04 ng/g R^2: 0.9928 - 0.9990 R: 88.93 - 95.22% RSD%: 0.91-12.81% RSD: ≤4.9	ND	Korea	[72]
Formaldehyde	Adulterants and preservatives	Derivatization, protein precipitation and solvent extraction	MEKC-UV/DAD	bovine milk	LOD: 15.0 µg/L LOQ: 50.0 µg/L LR: 50.0–1000 µg/L R^2: > 0.99 R: 94.2 ± 0.7% RSD: <3.9%	< LOD- 0.13 ± 0.02 mg/kg	Brazil	[233]
Formaldehyde	Adulterants and preservatives	Defatting, protein precipitation and derivatization	UHPLC-MS/MS	cow, goat and buffalo milk	LOD: 1 ng/mL LOQ: 6.25 ng/mL LR: 3.12 - 200 ng/mL R^2: 0.997 - 0.999 R: >95% RSD: 2.84 - 8.02%	134-255 ng/mL	India	)[216]
54 analytes	Veterinary drugs and mycotoxins	QuEChERS	UHPLC-Q-Orbitrap HRMS	Milk	LOD: 0.001–0.010 ng/g LOQ: 0.005–0.030 ng/mL R: 60 - 97% RSD: <14%	0.007 – 4.530 ng/mL		[2 8]
316 analytes	Veterinary drugs and pesticides	LLE + dSPE	LC-MS/MS and GC–MS/MS	bovine milk	LOQ: 0.02–25 ng/g R^2: ≥ 0.99 R: 70 –120% for most of the compounds	Vet drugs: 1.2–18.2 ng/g	India	[39]
209 analytes	Veterinary drugs, mycotoxins and pesticides	QuEChERS	UHPLC-Qtrap-MS	Raw and commercial milk	LOD: 0.01- 1 µg/kg LOQ: 0.05–5 µg/kg R^2: ≥ 0.99 R: 51.20–129.76% RSD: 0.82- 19.76%	Sulfamethazine: 1.79 µg/kg Cloxacillin: 7.12–69.70 µg/kg aflatoxin M1: 0.17, 0.24 µg/kg fipronil sulfone: 0.08 µg/kg imidacloprid: 6.24 µg/kg acetamiprid: 2.36–12.24 µg/kg	China	[13]
69 analytes	Veterinary drugs, mycotoxins and pesticides	Solvent extraction and SPE	LC–MS/MS	Bovine milk	LOD: 0.0036 - 47.94 µg/L LOQ: 0 .053 - 59.43 µg/L CCα: 0.062 - 211.32 µg/L CCβ: 0.080 - 233.71 µg/L R^2: > 0.99 R: 70.83 - 109% CV: <24%	Sulfadimethoxine: 27.4, 18.2 µg/L Enrofloxacin: 25.7 µg/L Tetracycline: 30.1 µg/L Oxytetracycline: 41.3 µg/L	North Macedonia	[234]
Clanobutin, dichlorvos, and naftazone	Pharmaceuticals and pesticides	LPE	LC–MS/MS	Milk	LOD: 0.04, 0.4,0.1 ng/g LOQ: 0.1,1,0.4 ng/g LR: 5–50 ng/g	ND	Korea	[235]

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BPA, E2, DES, CAP	Hormones, EDCs & antibiotics	MSPE	HPLC-UV	Whole milk and skimmed milk	R^2: 0.9916, 0.9807, 0.9833 R: 77.5 -108.2% RSD: 0.9–12.9% LOD: 0.004–0.106 µg/mL LOQ: 0.008–0.209 µg/mL LR: 0.05–5.00 µg/mL R: 88.17–113.46% RSD: 0.002–1.951%	ND	China	[236]

LOD, Limit of detection; LOQ, Limit of quantification; LR, linear range; R^2, determination coefficient; R, recovery; RSD%, Relative standard deviation; CCα, decision limit; CCβ, detection capability; CV, coefficient of variation; ND, not detected; NS, not specified; PFAS, Perfluoroalkyl and polyfluoroalkyl substances; PCBs, Polychlorinated biphenyls; PAHs, Polyaromatic hydrocarbons; SLE, solid liquid extraction; SPE, solid phase extraction; MSPE, magnetic solid phase extraction; SPME, solid phase microextraction; FPSE, fabric phase sorptive extraction; LPE, liquid phase extraction; dSPE, dispersive solid phase extraction; LLE, liquid-liquid extraction; DFE, dispersive filter extraction; DLLME, dispersive liquid-liquid microextraction; LPME, liquid-phase microextraction; HS-SPME, headspace solid phase microextraction; VALLME, vortex-assisted liquid-liquid microextraction.

6. Concluding Remarks and Future Directions

Chromatographic-based analysis techniques are continuously evolving to precisely determine EPs in milk. Residues commonly analyzed include veterinary drugs, especially antibiotics, EDCs such as phthalates and bisphenols, pesticides, and mycotoxins. Several studies have also explored other categories of EPs, encompassing hormones, food adulterants, PCBs and PFAS.

Chromatography, due to its range of detector options, facilitates the application of various analytical methods tailored for selectively and sensitively determining different categories of EPs. While LC and GC coupled to MS remain the most prevalent combinations, other reported techniques include LC-UV, LC-FLD and GC-FID. Among the 155 studies included in this review, LC paired with MS emerged as the most frequently employed method for determining EPs in milk, accounting for more than 45% of all reported techniques.

In the analysis of veterinary drug residues, LC -MS/MS emerged as the most prominent method, followed by LC combined with UV. Notably, LC coupled to FLD was reported in only one study for analyzing residues of veterinary drugs. Interestingly, no studies within the reviewed period utilized GC-MS for analyzing veterinary drug residues in milk, suggesting an unexplored avenue for future research. On the other hand, in the examination of EDC residues, including phthalates, bisphenols and parabens, the most commonly employed analytical techniques were LC coupled to UV and FLD, surpassing both LC-MS and GC-MS. However, regarding pesticide residues, both LC and GC based techniques were used in comparable number of studies. Finally, in the determination of mycotoxins residues, LC coupled to FLD was the dominant method of choice for analysis.

Although the aforementioned chromatographic techniques, especially LC-MS and GC-MS, were heavily utilized and proven to be well-suited for analyzing the majority of EPs in food matrices like milk, there is a suggestion to explore other types of chromatographic techniques. These may include capillary liquid chromatography (CLC), micellar liquid chromatography (MLC), supercritical fluid chromatography (SFC), ion chromatography (IC), and capillary electrophoresis (CE). Moreover, advancements in chromatographic instrumentation and column technologies could further enhance the performance and efficiency of chromatographic-based methods for analyzing EPs in complex food samples like milk. These innovations encompass the integration of high-resolution mass spectrometry (HRMS), monolithic chromatographic columns, multidimensional chromatography, portable miniaturized LC systems, and microfluidic devices.

Milk, being a complex matrix due to its content of fat, proteins, and vitamins, requires a pretreatment step for purification and preconcentration. Various approaches have been developed and improved from the classical SPE and LLE to ensure the specific and efficient extraction of different EPs from milk samples before their assessment using chromatographic techniques.

Among all the reviewed papers, SPE and its variations were the most commonly applied extraction approaches, constituting approximately 45% of the total studies. Specifically, SPE and its different modes were the predominant approaches for extracting residues of both veterinary drugs and EDCs, while QuEChERS-based extraction was the most frequently applied method for pesticide

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residues. A diverse array of materials was reported to be used as SPE adsorbents, including traditional silica NPs, C8, C18, Urea, MOFs, COFs, and MIPs. MOFs, COFs, MIPs, and carbon nanomaterials, reported as solid-phase adsorbents in several studies covered in this review, are anticipated to undergo further development and widespread utilization for the purpose of EPs separation. These materials are expected to gain more attention due to their promising advantages, such as high surface areas, tailorable properties and structures, and exceptional chemical stability.

Regarding future research and the growing emphasis on green chemistry, it is noteworthy that biosorbents like cellulose, lignin, and chitin hold promise as candidates for exploration and incorporation as novel green adsorbents in extracting various EPs from milk. Their abundance and environmentally friendly nature contribute significantly to the overall greenness of the analysis method.

While the sample preparation process is crucial, particularly in complex matrices like milk, it inevitably adds time to the overall analysis duration. This time factor, especially during large-scale and routine analyses, can be considered a drawback. Consequently, trends towards automated extraction are expected to accelerate in the future, driving increased utilization of on-line and in-line extraction methods.

According to the Food and Agriculture Organization (FAO), cows contribute approximately 82% to the world's milk production, followed by buffaloes at 13%, goats at 2%, sheep at 1%, and camels at 0.4%. Consequently, the majority of the reviewed research studies focused on the analysis of EPs in cow milk, representing more than 80% of the studies. International organizations such as the Republic of China, the EU, and the CAC have established MRLs for various EPs in cow's milk. However, the MRLs of these compounds in other types of milk might not be available due to the limited research investigating and monitoring EPs in other types of milk. Therefore, it is imperative to develop analytical methods specifically tailored for analysis of EPs in these diverse milk types. Due to significant variations in fats, vitamins, and protein composition among different milk types, distinct extraction procedures should be further developed and validated before conducting chromatographic analysis. Camel milk, in particular, is one of the primary dietary components in many parts of the world, including Gulf countries, and the Middle East. Its increasing popularity is attributed to its unique nutritional values and reported therapeutic properties in numerous studies. Its distinct composition makes it a valuable yet challenging subject for study. Addressing these knowledge gaps in research data will not only enhance our understanding of this topic but also aid regulatory agencies in making informed decisions and establishing suitable MRLs.

Despite the extensive body of research dedicated to the analysis of various categories of EPs in milk, there are still unexplored areas in this field. Other categories of EPs, such as personal care products, dioxins, volatile organic compounds (VOCs), flame retardants, hormones, nitrates, and nitrites remain understudied. Knowledge gaps persist regarding their presence, contamination pathways in milk, and potential impacts.

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