

Review

# Analysis of Prohibited and Restricted Ingredients in Cosmetics

Rimadani Pratiwi , Nisa Nurul Auliya As, Rani Fitrilia Yusar and Adnan Aly Al Shofwan

Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Bandung 45363, Indonesia

\* Correspondence: rimadani.pratiwi@unpad.ac.id

**Abstract:** The general public uses cosmetics daily. Cosmetic products contain substances (ingredients) with various functions, from skincare to enhancing appearance, as well as ingredients that preserve the cosmetic products. Some cosmetic ingredients are prohibited or restricted in certain geographical regions, such as the European Union and the United States of America, due to their potential to cause adverse effects such as cancer, birth defects, and/or developmental and reproductive disorders. However, the ingredients may be used in other regions, and, hence, the monitoring of the cosmetic ingredients actually used is important to ensure the safety of cosmetic products. This review provides an overview of recent analytical methods that have been developed for detecting certain ingredients that are restricted or prohibited by the U.S. Food and Drug Administration (FDA) and/or EU legislation on cosmetic products.

**Keywords:** cosmetics; prohibited ingredients; restricted ingredients; analysis; analytical methods



**Citation:** Pratiwi, R.; Auliya As, N.N.; Yusar, R.F.; Shofwan, A.A.A. Analysis of Prohibited and Restricted Ingredients in Cosmetics. *Cosmetics* **2022**, *9*, 87. <https://doi.org/10.3390/cosmetics9040087>

Academic Editor: Enzo Berardesca

Received: 12 July 2022

Accepted: 17 August 2022

Published: 18 August 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

According to the FDA, cosmetics are defined as products intended to cleanse, beautify, enhance attractiveness, or change appearance [1]. The word cosmetic comes from the Greek “kosmetikos,” which means having the power to organize, or skilled in decoration; “kosmein” means to decorate and “kosmos” means harmony [2]. Furthermore, the European Union (EU) defines a cosmetic product as a substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips, or external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition, or correcting body odors [3].

Cosmetics can be classified according to the user's age, area of application, gender, etc., as well as by the function, dosage, and form [4]. Based on their application, cosmetics can be classified into seven categories: cosmetics for personal cleansing (e.g., soaps, deodorants, and shampoos); skin and hair cosmetics (e.g., toothpaste, external intimate care products); cosmetics for beauty (e.g., perfumes, lipsticks); protective cosmetics (e.g., sunscreen products, anti-wrinkle products); corrective cosmetics (e.g., beauty masks, hair dyes); maintenance cosmetics (e.g., shaving creams, moisturizers); and active cosmetics (e.g., fluoride toothpaste, antiseptics) [2].

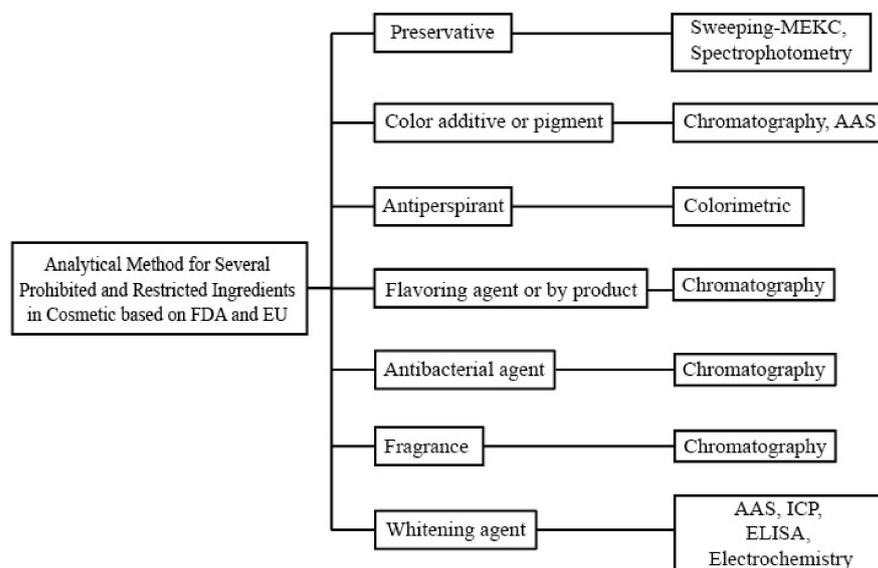
These cosmetic preparations are specially formulated depending on their function and application. For example, cosmetics for cleaning purposes usually contain surfactants to remove sebum and dirt from the hair and skin [5]. Like other products containing water and organic compounds, cosmetics need to be protected from microbial contamination to ensure consumer safety and extend shelf life. Therefore, in cosmetic formulations, preservatives are often added—either synthetic or natural compounds such as essential oils and nisin [2,6,7].

However, some cosmetics contain restricted and prohibited ingredients to increase sales and convince consumers to buy their products, even if that substance is known to cause diseases such as cancer, birth defects, and/or developmental and reproductive

disorders [8]. There are many cases around the world illustrating the effects of harmful substances in cosmetics. For example, in 2019, a Californian woman fell into a coma after using a mercury-contaminated skin lightener. Beforehand, the patient felt numbness in her hands and face, had slurred speech, and experienced trouble walking. Laboratory results showed that there was 500 times more mercury than the acceptable amount in her blood sample [9].

Skin-lightening cosmetic products have been reported to contain harmful chemical compounds such as mercury [10]. These substances can adversely affect circulatory, urinary, and neurological function [11]. Mercury is used in skin-lightening products as a skin-bleaching agent, inhibiting melanin production, and as a preservative in other cosmetics [12]. Other illegal cosmetics still use prohibited substances such as the preservatives parabens and formaldehyde. These substances offer high antimicrobial efficacy and prolong the product's shelf life, but may cause adverse skin reactions such as irritation or allergic reactions [6].

This review provides an overview of the analytical techniques used for the detection of prohibited and restricted ingredients in cosmetics based on the lists in FDA and EU regulations, as shown in Figure 1. To date, there is no comprehensive review available on this topic. The papers for the analysis were selected based on the topic, regardless of the year of publication, to provide a broad overview of the methods applicable to detecting prohibited and restricted ingredients in cosmetics, with examples (if available) provided from more recent publications (i.e., the last 10 years). The results show that many analytical techniques can be used to determine the concentration of prohibited and restricted substances in cosmetics. We found that the chromatographic method is widely used for the determination of hexachlorophene and halogenated salicylanilides as antibacterial agents, coumarin and furocoumarin as fragrances, and color additives. In general, metal compounds in cosmetics such as cadmium and mercury were analyzed using atomic absorption spectroscopy (AAS). A recent method for detecting bithionol and formaldehyde, used as preservatives, is also reviewed. The detailed and specific method for detecting each restricted compound is described in this review.



**Figure 1.** Analytical techniques used for the detection of prohibited and restricted ingredients in cosmetics based on FDA and EU regulations.

## 2. Regulatory Overview

Cosmetics available on the open market should not be harmful when applied to human skin. Cosmetic ingredients are primarily chemicals, often synthetically derived ones or mixtures of natural extracts. Careful selection of ingredients is an important factor in the safety of the final product. Safe cosmetic products must avoid reactions that can cause skin

irritation and skin sensitization. The selection of cosmetic ingredients needs to take into account the effects of systemic toxicity, especially those that may be caused by percutaneous absorption [13].

Halal pharmaceuticals and cosmetic products are of increasing demand among the 2.4 billion Muslim consumers worldwide. For Muslim consumers, knowing the origin of the raw materials and the production process of cosmetic ingredients is vital, due to the Islamic law stating that every Muslim must consume only halal and wholesome products. Some compounds in cosmetics are non-halal (prohibited) if they contain derivatives of body parts, blood, forbidden animal parts, insects, or other substances that are harmful or injurious. Materials that are recognized as non-halal, such as placenta, gelatin, and carmine dye, are included on the list of ingredients prohibited and restricted by the FDA [14–16].

Cosmetic products are regulated differently in different regions of the world. This makes it difficult to ensure compliance in all countries. To address this problem, the harmonization of regulatory frameworks was carried out. For example, in the EU, the cosmetic regulatory framework is provided by Regulation (EC) No. 1223/2009 of the European Commission, which has overall responsibility for cosmetic legislation [3]. In other regions such as the USA, laws related to cosmetic products are regulated by the FDA and the Fair Packaging and Labeling Act (FPLA) [17].

The U.S. Food and Drug Administration (FDA) has issued a list of substances that are restricted or prohibited in cosmetics, such as bithionol, chloroform, and mercury [16]. In addition, in the European Union, Annex II of the Cosmetic Products Regulation lists substances prohibited in cosmetic products. There are over 1600 substances on the list, such as formaldehyde, chloroform, a mercury compound, cadmium, and furocoumarin [3]. Prohibited means that a cosmetic product should not contain any of the prohibited substance. Meanwhile, restricted substances refer to substances that are not used in accordance with the restrictions laid down [3]. A list of some of the ingredients restricted or prohibited by the FDA and EU is given in Table 1.

**Table 1.** A list of some of the ingredients restricted or prohibited by the U.S. FDA and EU.

No.	Substance	Status by FDA Regulation	Status by EU Regulation
1.	Bithionol	Prohibited	Prohibited
2.	Formaldehyde	-	Prohibited
3.	Cadmium	-	Prohibited
4.	Azo dyes, rhodamine, yellow quinoline	Color additives are permitted in cosmetics only if the FDA has approved them for the intended use	-
5.	Zirconium-containing complexes	Prohibited	Prohibited
6.	Chloroform	Prohibited except as residual solvent or byproduct	Prohibited
7.	Halogenated salicylanilides	Prohibited	Prohibited
8.	Hexachlorophene	May be used only when no other preservative has been shown to be as effective and must not exceed 0.1%	Prohibited
9.	Coumarin	-	Prohibited
10.	Furocoumarin	-	Prohibited
11.	Mercury compounds	Limited to eye area products. No more than 0.0065% In a trace amount of less than 0.0001% Permitted only if no other effective and safe preservative is available	Prohibited, except in special cases

Given the frequent and close contact of these products with the skin and mucous membranes, they must be free of potentially dangerous substances. All ingredients used in cosmetic products are required to meet certain regulatory requirements, such as the guidance issued by the Scientific Committee on Consumer Products for consumer safety [18].

However, due to their toxicity, the use of many substances is restricted—they must be below a stated concentration or limit. Other important aspects need to be considered,

such as the potential long-term effects. On the other hand, some substances, e.g., mercury compounds, can cause acute side effects, such as contact dermatitis and allergic reactions. In addition, routine use and continued human exposure to chemicals from different personal care products may cause a “cocktail effect” due to the interaction of different substances or an “additive effect” because of the presence of the same ingredient in many products [1,19].

Therefore, providing analytical techniques for the detection of prohibited and restricted ingredients is important for ensuring cosmetic and consumer safety. Table 2 gives a summary of the analytical methods that are used for detecting several restricted and prohibited ingredients in cosmetics.

**Table 2.** Analytical methods for detecting several restricted and prohibited ingredients in cosmetics based on FDA and EU standards.

No.	Substance	Role in Cosmetic	Effect on the Body	Analytical Method	References for Analytical Method
1.	Bithionol	Preservative [20]	The substance may cause photocontact sensitization [21]	Sweeping-MEKC	[22]
2.	Formaldehyde	Preservative	Dermal allergies, characterized by red spots, swelling, irritation, pain, and burning sensation [23]	Spectrophotometry, Smartphone reader	[24]
3.	Cadmium	Pigments	Causes the kidneys to experience cadmium dysfunction [25]	GFAAS, AAS, LIBS	[25,26]
4.	Color additives (certain dyes or pigment)	Color additives can be used to color the cosmetic product itself or used to give color to a part of the body such as the hair, skin, eyelashes, or nails [27]	Azo dyes can have mutagenic, genotoxic, and carcinogenic effects [28]. Yellow quinoline dye can be absorbed through the skin and cause genotoxic effects [29].	MEKC, LC-PDA, LC-MS, LC-MS/MS, UHPLC-Q-Orbitrap HRMS, RP-HPLC-PDA	[30–35]
5.	Zirconium-containing complexes	Aerosol product [1]	Toxic effects on the lungs of animals, as well as the formation of granulomas in humans [36]	Colorimetric, with direct and fusion procedures	[37]
6.	Chloroform	Ingredient and flavoring agent	Tests on laboratory animals show the carcinogenic potential of using chloroform as a cosmetic [38].	GC	[39]
7.	Halogenated salicylanilides	Antibacterial agent	May cause serious skin disorders [40]	HPLC-FLD, SPE-UPLC-MS/MS	[41,42]
8.	Hexachlorophene	Antibacterial agent	Due to its toxic effect and ability to penetrate human skin, it cannot be used in cosmetics applied to the mucous membranes, such as the lips [43].	HPLC-PDA, CE-UV	[44,45]
9.	Coumarin	Fragrance [46]	Skin sensitization and eczema through dermal administration [46]	1D/2D GC-MS, UPLC-MS/MS, HPTLC, LC-MS/MS LRI	[46–49]
10.	Furocoumarin	Fragrance [50]	Phototoxicity, hyperpigmentation, erythematous rash, blisters, and sunburn if the user is exposed to UV-A radiation from the sun [51]	RP-HPLC-coupled HR/AM, LC-MS, LC-MS/MS LRI	[49,52,53]
11.	Mercury compound	Whitening agent, preservative	Allergic reactions, skin irritation, or neurotoxic problems [54]	ELISA, AAS, AFS, CE, CV-AAS, FAAS, FIA, ICP AES, ICP-MS, PVG ICP-MS, HPLC-ICP MS, MP AES, Electrochemical sensors	[55–74]

Abbreviation: Sweeping-MEKC—sweeping-micellar electrokinetic chromatography; GFAAS—Graphite Furnace Absorption Spectrometry; AAS—Atomic Absorption Spectrometry; LIBS—Laser-Induced Breakdown Spectroscopy; GC—Gas chromatography; HPLC-FLD—High-Performance Liquid Chromatography–Fluorescence Detector; SPE-UPLC-MS/MS—Solid Phase Extraction coupled with Ultra-Performance Liquid Chromatography Tandem Mass Spectrometry; HPLC-PDA—Reverse-phase High-Performance Liquid Chromatography with Photodiode Array Detector; CE—Capillary Electrophoresis; ELISA—Enzyme-Linked Immunosorbent Assay; AFS—Atomic Fluorescence Spectrometry; CV-AAS—Cold Vapor Atomic Absorption Spectrometry; FAAS—Flame Atomic Absorption Spectrometry; FIA—Flow Injection Analysis; ICP-AES—Inductively Coupled Plasma–Atomic Emission Spectrometry; ICP-MS—Inductively Coupled Mass Spectrometry; PVG ICP-MS—Photochemical Vapor Generation–Inductively Coupled Plasma Mass Spectrometry; MP AES—Microwave Plasma Atomic Emission Spectroscopy; LC-PDA—Liquid Chromatography with Photodiode Array; LC-MS—Liquid Chromatography–Mass Spectrometry; LC-MS/MS—Liquid Chromatography tandem Mass Spectrometry; UHPLC-Q-Orbitrap HRMS—Ultra-High-Performance Liquid Chromatography coupled with Quadrupole–Orbitrap High-Resolution Mass Spectrometry; 1D/2D GC-MS—One-dimensional/Two-dimensional Gas Chromatography–Mass Spectrometry; HPTLC—High-Performance Thin-Layer Chromatography; LC-MS/MS LRI—Linear Retention Index–Liquid Chromatography–Mass Spectrometry.

### 3. Bithionol

Bithionol is an aromatic organic compound that plays a role as an antibacterial in cosmetics [75]. Bithionol is widely used as a preservative in soaps and other cosmetics [20]. Bithionol belongs to the group of halogenated phenols, which have activity against Gram-positive bacteria. Bithionol is also used as a preservative in many cosmetics with a semisolid form such as toothpaste, lotions, and creams [22].

In the 1960s, bithionol was used as an antimicrobial in antiseptic creams in the USA. However, the compound caused many cases of photosensitization and is now prohibited from being used as an excipient in topical preparations. Currently, bithionol is no longer used because it has been banned by the FDA and EU [21]. From 2001 to 2010, patch testing of bithionol was performed in selected groups, specifically a group of patients suspected of having photosensitivity and patients experiencing pruritus after applying sunscreen. In addition, it has been reported that a man developed dermatitis on his forehead, scalp, and eyelids after applying a hair dressing containing bithionol [76].

The development of an analytical method for bithionol compounds in cosmetics was carried out by Zheng et al. in 2021 [22]; no one else has published a different analysis method yet. They used the electrophoresis method combined with sweeping-MEKC to improve the detection sensitivity. Sweeping-MEKC technique has good reproducibility and high recovery. The samples used were loose powder and body lotion, which were extracted by ultrasonication for 20 min and centrifuged for 10 min at 6000 r/min. The correlation coefficient value, linearity range, LOD, and LOQ were 0.9975, 0.20–4.00 g/mL, 0.024 g/mL, and 0.080 g/mL, respectively. The percent recovery for loose powder samples was 79.7–110.2%, while for body lotion samples it was 92.2–121.3%. This method has high sensitivity, a high enrichment factor, a simple operating system, good repeatability, and a low cost for detecting bithionol in cosmetic samples [22].

### 4. Formaldehyde

Formaldehyde is a naturally occurring compound that is endogenously produced by various organisms. It also occurs widely in the environment due to anthropogenic (e.g., use as a chemical intermediate) and natural sources (e.g., as part of a mixture of volatile organic compounds released by plants) [77].

Currently, it is rare to add pure formaldehyde to final cosmetics. Instead, compounds called formaldehyde donors or formaldehyde releasers are added. These compounds are designed to release small amounts of formaldehyde over time during multiple hydrolysis reactions in the presence of water. This release is probably the principal reason for the antimicrobial activity of the formaldehyde releasers. Some examples of compounds classified as formaldehyde releasers are Quaternium 15, 5-bromo-5-nitro-1,3-dioxane (Bronidox), Dimethylol dimethyl hydantoin (DMDM hydantoin), 2-bromo-2-nitropropane-1,3-diol (Bronopol), imidazolidinyl urea, and diazolidinyl urea. These ingredients are commonly used in cleansing and skin care cosmetics, but might also potentially cause allergies when used in excess. However, there has been some disagreement over the correct classification of imidazolidinyl urea and diazolidinyl urea as formaldehyde releasers [78].

In the European Union, concentrations of formaldehyde up to 0.1% are allowed in cosmetics [79], but if the concentration exceeds 0.05% (500 mg/kg), then the statement “contains formaldehyde” must be clearly displayed on the label [80].

Formaldehyde can affect cell proliferation and DNA protein crosslinking and has the potential to cause nasal cancer in humans and rodents due to its cytotoxicity and secondary genotoxicity [77]. Excessive contact with formaldehyde on the skin can cause dermal allergies, which are characterized by red spots, swelling, irritation, pain, and a burning sensation [23].

The formaldehyde content in a sample can be analyzed using a variety of methods. However, due to the low absorption of formaldehyde, it is necessary to convert it to its derivative form. Derivatization with 2,4-dinitrophenylhydrazine (DNPH) is the most commonly used method for measuring formaldehyde [81]. A method listed in the EU for

the determination of free formaldehyde in cosmetic products is 2,4-DNPH for derivatization and continued analysis by HPLC [79]. The methods for the analysis of formaldehyde in cosmetics are summarized in Table 3.

Formaldehyde derivatization can also be performed by reacting it with other substances. For example, reacting it with *p*-toluenesulfonic acid in ethanol forms diethoxymethane. According to the Hantzsch reaction, formaldehyde derivatization can also be accomplished by reacting formaldehyde with pentane-2,4-dione in ammonium acetate to form 3,5-diacetyl-1,4-dihydropyridine [81,82]. This derivatization modifies the functional groups of the compound, improving the stability and enabling detection.

It has been reported that spectrophotometry can be used as a method for measuring the formaldehyde concentration in cosmetics. For example, Temel et al. [83] used spectrophotometry to measure this compound in a cosmetic product. The sample was first extracted using the ultrasound method. A set of samples was placed in a centrifuge tube and centrifuged for 2 min at 1200 rpm, with 2-propanol containing 0.1% (*w/v*) SDS used as an extractant. Extractant was added to the tube and homogenized using an ultrasonic bath for 20 min at 40 °C. When clear homogenous solutions were obtained, they were centrifuged again at 3500 rpm for 5 min. The supernatant was withdrawn after filtration using a 0.22 µm membrane filter. Absorbance measurements were performed at a wavelength of 603 nm. The LOD and LOQ values were 0.38 µg/L and 1.26 µg/L, respectively. The results show that this method has good linearity, with a correlation coefficient of 0.9954 [83].

There is a newly developed method using smartphone readers for the determination of formaldehyde compounds in cosmetics, elaborated by Lamarca et al. in 2019 [24]. Digital images are created by the interaction of radiation and samples, with some of the radiation absorbed and some reflected. Colorimetric reactions are particularly attractive for use in digital image-based methods because, when exposed to visible light, the colored reaction products reflect radiation. The concentration of the colored product is measured using a digital sensor. The reflected radiation can be correlated with the concentration of the reaction between the analyte and the reagent. Images taken with a smartphone can be converted to red (R), green (G), and blue (B) model color patterns according to a proposal of the International Color Consortium (ICC). Each color variation, restricted to this range, is defined on a scale in the range 0–255 (8-bit format) or 0–1 (fractional format). The R, G, and B channel strength of captured digital images are measured using image processing programs such as Adobe Photoshop, Image Color Picker, and ImageJ, and smartphone apps such as Photometric. Therefore, the color intensity obtained from the image is as follows, and related to the concentration of colored products formed between the analyte and the reagent. The results show that this method has good linearity, with a correlation coefficient value of 0.9985. The LOD and LOQ values were 0.2 mg/kg and 0.5 mg/kg, respectively. The analytical methods for detecting formaldehyde in cosmetics are summarized in Table 3.

**Table 3.** Analytical method for determining formaldehyde in cosmetics.

No.	Sample	Derivatization Agents	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
1.	Cosmetic product (fixative gels, body moisturizer, hand cream, hair conditioner, shampoo, and shower gel)	0.100% acetylacetone	GDME (gas-diffusion microextraction)	Spectrophotometry	0.150 mg/kg	0.500 mg/kg	0.9999	-	[24]
		0.100% acetylacetone	GDME (gas-diffusion microextraction)	Smartphone reader	0.200	0.500	0.9985	-	
2.	Semi-solid and liquid hair cosmetics	Sulfite	Ultrasound-assisted cloud-point extraction	Spectrophotometry	0.38 µg/L	1.26 µg/L	0.9965	-	[83]

## 5. Cadmium

Cadmium is a natural element in the Earth's crust. It is usually seen as a mineral in combination with other elements such as oxygen (cadmium oxide), chlorine (cadmium chloride), or sulfur (cadmium sulfate, cadmium sulfide) [84]. Certain metals are naturally present in the raw materials used in the manufacturing of cosmetics, such as pigments [85]. Cadmium is a deep yellow to orange pigment. It is mainly added to cosmetics as a color pigment. Although the absorption of metals from cosmetics through the skin is quite low,

these elements can accumulate in the skin and internal organs, where they can exert toxic effects [86,87]. Cadmium (Cd) is also one of the most toxic elements and can cause bone decalcification, kidney dysfunction, brain damage, reproductive failure, and poisoning. Excessive exposure to Cd impairs lung function and increases the risk of lung cancer [88].

According to the guidelines on prohibited substances in cosmetics released by the European Union in Annex II of the Cosmetic Products Regulation, cadmium is prohibited [3]. Analysis of the cadmium in cosmetic samples is reported as shown in Table 4. Saadatzadeh et al. [26] used graphite furnace atomic absorption spectrometry (GFAAS; Varian 240FS AA) with an autosampler and deuterium light to determine cadmium levels in cosmetics. The cosmetic samples used included lipstick, mascara, eyeshadow, and eyebrow pencils. Each sample consisted of 18 pieces. The analysis was repeated three times and the concentration was given in  $\mu\text{g/g}$ . The operating conditions of the heating program and GFAAS analysis were carried out in several variations. The LOD value obtained by this method was  $0.14 \mu\text{g/L}$ . This method shows good linearity with a correlation coefficient of  $0.994 \pm 0.002$ . In this study, the average Cd concentration was  $0.011 \mu\text{g/g}$  in the lipstick sample,  $0.013 \mu\text{g/g}$  in the mascara sample,  $0.011 \mu\text{g/g}$  in the eyeshadow sample, and  $0.009 \mu\text{g/g}$  in the eyebrow pencil sample.

**Table 4.** Analytical method for determining cadmium in cosmetics.

No.	Sample	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
1.	Lipstick, mascara, eyeshadow, eyebrow pencil	-	GFAAS	$0.14 \mu\text{g/L}$	-	$0.994 \pm 0.002$	-	[26]
2.	Traditional scrub	Wet digestion	AAS	0.63 ppm	2.11 ppm	0.9982	Average recovery = 102.89%	[25]
3.	Low-quality pomade	ultrasound-assisted extraction (UAE)	LIBS	$0.016 \text{ mg/kg}$	-	0.9916	-	[88]

The AAS method was also used by Suhardiana and Srie in 2020 to determine the cadmium concentration in a traditional scrub. Before measuring the cadmium in a sample, it is necessary to extract the sample. The extraction method used was wet digestion, using  $\text{HNO}_3$  or  $\text{HClO}_4$  as a solvent at a ratio of 3: 1. The LOD and LOQ values with the AAS method were 0.63 ppm and 2.11 ppm, respectively. This method has good linearity, with a correlation coefficient value of 0.9982 [25,89].

Another analytical method was carried out by Liu et al. in 2020 [88]. The analytical technique used in their study was LIBS. LIBS is a new spectroscopic analysis technique used for multi-element detection [90]. Before analysis, samples of low-quality pomade were extracted. Extraction was performed by ultrasonic-assisted extraction (UAE). A total of 10 milliliters of hydrochloric acid solution ( $\text{HCl}$ ,  $\text{pH} = 1$ ) and 1 g of ointment were mixed by ultrasonic vibration in an ultrasonic cleaner. The mixed solution was transported in six centrifuges and centrifuged in a 4000 rpm centrifuge for 5 min. Afterwards,  $10 \mu\text{L}$  of supernatant were extracted with a micropipette and dropped onto a glass slide. The slide glass was placed in a heater at  $60 \text{ }^\circ\text{C}$  for about 5 min until the droplet solution dried. In this study, laser-induced breakdown spectroscopy was used as a method for analyzing cadmium content. The wavelength chosen to determine the cadmium content was 508.58 nm. The LOD value obtained by the UAE method was  $0.016 \text{ mg/kg}$ . This method also shows good linearity, with a correlation coefficient of 0.9916. The concentration of low-quality pomade obtained by the LIBS method was  $2.38 \pm 0.12 \text{ mg/kg}$ .

Flame atomic absorption spectrophotometer (FAAS) is typically used to determine the concentration of a metal in a solution in the range of parts per million (ppm) or parts per billion (ppb). To improve the detection limit, a graphite furnace atomic absorption spectrophotometer (GFAAS) is a more sensitive tool since it can detect very low metal con-

centrations in small samples [91]. In addition, the laser-induced breakdown spectroscopy (LIBS) method is useful for analyzing solid samples with little or no sample preparation [92]. This technique has many advantages such as rapid analysis with no or little sample preparation, small sample requirements, and low-cost instrumentation [93–95].

## 6. Color Additives

Color additives are dyes or pigments used to make a product more attractive. Dyes are synthetic organic compounds that are soluble in water or oil and are present in skincare products. Meanwhile, a pigment is an insoluble substance contained in products such as decorative make-up. In cosmetics, color additives are added to solid and semisolid products to improve the attractiveness of a cosmetic product by giving some color to the cosmetic product itself or being used to give color to a part of the body such as the hair, skin, eyelashes, or nails [27].

In this review, color additives refer to certain colorants that are known to have harmful effects on the body, such as azo dyes and rhodamine. In [28], it was stated that the azo dyes that are currently often used can cause mutagenic, genotoxic, and carcinogenic effects [28]. Skin bacteria can cause the biotransformation of azo dyes. After biotransformation, azo dyes release compounds called aromatic amines that can be dermally absorbed and have carcinogenic properties [96]. Another study proved that yellow quinoline dye can be absorbed through the skin and cause genotoxic effects [29]. Table 5 provides a list of analytical methods that have been developed over the years for determining restricted and prohibited color additives in cosmetics.

Quantitative analysis of synthetic dyes by MEKC was first developed in 1998 by Desiderio et al. [30]. This method was developed due to capillary electrophoresis, being a technique with high efficiency and resolution. In addition, this technique only requires a small number of reagents and samples with a short analysis time [30]. In previous studies, MEKC was proven to be useful for the analysis of charged and uncharged compounds. In this study, a micellar phase was added to the buffer and served as a solubilizing agent, so that the analyte could be separated into micellar and buffer phases. This method has a disadvantage in that the extraction is limited to xanthine and sulfonic dye compounds. The extraction method used is magnetic stirring-assisted extraction (MS-AE) with a methanol: ammonia solution (95: 5) and n-hexane [97,98].

In 2014, Bermudez et al. [31] developed a different method for identifying permitted and prohibited color additives in cosmetics. They used LC-with a PDA Detector. Most laboratories use TLC and LC methods for determining color additives in cosmetics, but these methods cannot be widely used in cosmetic samples because they require large amounts of solvent for extraction and are not very accurate depending on how many color additives are in the sample. Therefore, a new method was developed, LC with a PDA detector, which can be more widely applied to the analysis of color additives in cosmetics because the extraction is simple and efficient, as well as having a higher sensitivity than existing methods [31].

The extraction method used is liquid–liquid extraction (LLE) using a small amount of solvent—a combination of methylene chloride, methanol, acetic acid, and water. The effect of the matrix contained in the sample can be minimized by this extraction method. The samples used in this analysis were lip products, nail polishes, eye products, blushes, bath products, toothpaste, body glitter, creams, and face paints. In total, 14 color additive compounds were found, including 1 color additive that is prohibited from being used in cosmetics, rhodamine B. Rhodamine B was found in brow pencil and body glitter products with an LOD value of 0.34 mg/L. The LOD range for the 14 color additives was 0.1–1.5 mg/L [31].

**Table 5.** Analytical methods for determining restricted and prohibited color additives in cosmetics.

No.	Sample	Analyte	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
1.	Lipstick	Rhodamine B	MS-AE	MEKC	$6.25 \times 10^{-7}$ M	-	-	-	[30]
2.	Brow pencil and body glitter	Rhodamine B	LLE	LC with PDA detector	0.34 mg/L	-	-	-	[31]
3.	Shampoo, face paints, toothpaste, hairspray, nail polishes, soap, and eyeshadow	Acid orange 7, ponceau 4R, rhodamine, amaranth, and acid yellow 36	Miniaturized MSPD	LC-MS	0.0142–0.476 µg/g	1–50 ng/mL	≥0.9928	% recovery = 69.5–121%	[32]
4.	Lip product, body lotion, body butter, hand cream, age spot corrector mask, shampoos, shower gels, soap, rough skin remover, moisturizing mask, toothpaste, smoothing masks, and facial gel	Ponceau SX, amaranth, carmoisine, and ponceau 4R	Single-Step VE	LC-MS/MS	-	0.07–3.437 mg/kg	≥0.9918	RSD < 16% % recovery = 70.3–117%	[33]
5.	Lipstick, eyeshadow, toothpaste, nail polishes, blusher, and eyeliner	Color Additive	MSPD	UHPLC-Q-Orbitrap HRMS	0.0005–0.1 mg/kg	0.002–0.2 mg/kg	≥0.99	intraday precision = 1.0–10.7% interday precision = 0.5–11.7%	[34]
6.	Lipstick	Rhodamine B	-	RP-HPLC with PDA detector	3.85 ng/mL	12.82 ng/mL	≥0.999	Precision = 1.22% % recovery at concentration <100 ppm = 80–110%	[35]

Another method developed in 2017 is miniaturized matrix solid-phased dispersion (MSPD), combined with LC-MS/MS for the analysis of a color additive in cosmetics used by children. The samples used in this study were shampoo, face paint, toothpaste, hairspray, nail polish, soap, and eyeshadow [32]. The results showed that acid orange 7, ponceau 4R, rhodamine B, amaranth, and acid yellow 36 were present in these cosmetics samples. This method had a limit detection value of 0.0142–0.476 g/g with an LLOQ value of 1–50 ng/mL for all analytes. This method has advantages over the previous method with a lower limit of quantification. This method offers high selectivity and sensitivity, as does the MSPD extraction method, which can reduce the need for reagents used, the time required for analysis, and the number of samples [32].

The use of LC-MS offers advantages of the identification and quantification of color additive compounds with high selectivity. Guerra et al. [32] employed this method, using single-step vortex extraction (VE), for analyzing lip product, body lotion, body butter, hand cream, age spot corrector mask, shampoos, shower gels, soap, rough skin remover, moisturizing mask, toothpaste, smoothing masks, and facial gel. Vortexing is an extraction method that can be used for complex samples and offers extraction and clean-up in a single step. Sample preparation was carried out with an Eppendorf tube to minimize the amount of reagent used. To produce a good retention time, salt is also used, which can increase the ionic strength of the mobile phase. The result shows the limit of quantification is in the range of 0.07–3.437 g/g, with the RSD value being less than 16% and the recovery value 70.3–117% [33].

Chen et al. [34] also used matrix solid-phase dispersion (MSPD), as well as the method developed by Guerra et al. in 2017 [33] and LC-MS/MS UHPLC-Q-Orbitrap HRMS, for determining the color additives in 69 samples. The extraction method offers extraction and clean-up in a single step. Samples included lipstick, eyeshadow, toothpaste, nail polish, blusher, and eyeliner. This method has been validated with LOD and LOQ values of 0.005–0.1 mg/kg and 0.002–0.2 mg/kg, respectively [34].

A general analytical method is still used for the analysis of color additives in the cosmetic sample. Nevitasari et al. [35] used RP-HPLC with a PDA detector for determining rhodamine B in lipstick samples. The sample was prepared by dissolving in the mobile phase up to 10.0 mL and then filtering using 0.45 µm PTFE. The results showed LOD and LOQ values of 3.85 ng/mL and 12.82 ng/mL, respectively. This method is widely used due to its high accuracy, sensitivity, and precision and requiring only a short analysis time [35].

## 7. Zirconium-Containing Complexes

Zirconium is a very reactive heavy metal and is present in the form of complexes of zirconates, zirconium dioxide, and zircons. Zirconium is also found in the form of water-soluble salts due to the formation of complexes with water, such as zirconyl chloride. Zirconium has a high density and is resistant to heat and corrosion [99]. In cosmetics, zirconium can be used as an antiperspirant in aerosol preparations, lotions, creams, or ointments [37]. The use of zirconium is prohibited by the EU because it can cause some adverse effects. Water-insoluble zirconium compounds can cause mild asthma, granulomas, and fibrosis in the lungs if inhaled. Meanwhile, air-soluble zirconium can form aerosols and cause tissue damage at exposed sites, and systemic reactions can also occur. Allergic reactions have also been demonstrated in experimental animals such as rats, guinea pigs, and rabbits [36].

The analysis of zirconium in cosmetic samples was published in 1976. The method used is colorimetry with direct procedures and fusion procedures. The analyzed zirconium is soluble and insoluble zirconium in aerosol antiperspirants. In the direct procedure, zirconium was extracted using HCl with a ratio of 55:45 to obtain as much as 40–100 g/mL zirconium. In the fusion method, aerosol ashing is carried out and the ash is combined with potassium pyrosulfate to form an acid-soluble melt, then HCl is added in the same ratio as the direct procedure. After the addition of HCl, alizarin red S was added and the solution was stable for 2 h [37].

Percent recovery for the fusion procedure with the addition of 32.26, 29.18, 28.67, 28.65, or 28.39 mg of zirconyl chloride octahydrate was 100.9%, 100.9%, 101.0%, 101.1%,

and 101.4%, respectively. Fusion procedures take longer than direct procedures. However, the fusion procedure can be used for water-insoluble zirconium, so its application is more general [37].

## 8. Chloroform

Chloroform is a liquid compound that appears clear and colorless and is also known for its particular nonirritating odor. Chloroform is not flammable except at high temperatures. Chloroform is slightly soluble in water and is miscible with oils, ethanol, ether, and other organic solvents [100]. In the past, chloroform has been used as an inhaled anesthetic for surgery preparations, but today chloroform is mainly used as a solvent for the production of chemicals [100,101] and as an ingredient in the manufacture of cosmetics. In toothpaste preparations, chloroform is used as a flavoring agent. Based on previous studies, it has been found that chloroform has a carcinogenic effect in mice. Even though there is a lack of evidence of the carcinogenic effects of chloroform in humans, it is concluded that, based on these findings, chloroform is a detrimental substance to humans [38].

There have not been many analytical methods developed to analyze chloroform in cosmetic preparations. In 1974, Stutsman [39] reported an analytical method for determining chloroform levels in toothpaste samples using gas–liquid chromatography. This method uses internal standards and headspace analytical techniques. The extraction method is not reported, but the toothpaste sample was prepared by dissolving it in 3 mL of water, adding 20 mL of ethylene glycol monomethyl ether, and then adding the internal standard of 1,1,1-trichloroethane. The headspace gas was then withdrawn by injection into the instrument. The column used was stainless steel, packed with 20% (*w/w*) carbowax 20M on 80–100 mesh acid-washed gas chrom R. The LOD, LOQ, and linearity values were not reported. The percent recovery results were in the range of 95.1–101.6% for samples with 0.5% chloroform added, 95.9–103.8% for samples with 2.0% chloroform added, and 96.9–99.7% for samples with 4.0% chloroform added [39].

## 9. Halogenated Salicylanilides

Halogenated salicylanilides are a derivative of the salicylamide group known to have antiparasitic and antifungal properties [102,103]. In a study conducted by Garcia et al. in 2018, it was stated that the halogenated salicylanilides compound works by interfering with the mechanism of mitochondrial protein import in yeast [103].

Due to its antifungal and antiparasitic properties, halogenated salicylanilides are widely used as antibacterial agents in cosmetic preparations. Despite that beneficial function, halogenated salicylanilides are not allowed in cosmetics because they are photosensitizers and cross-sensitizers that can cause health problems, especially for the skin [42]. In certain cases, the photosensitization might last for a long time as a severe reaction [40]. Safer alternative antibacterial agents are available, such as phenoxyethanol, triclosan, and other preservatives listed in the EU and FDA regulations [104,105].

Various analytical methods used to determine halogenated salicylanilides in the cosmetic samples are given in Table 6. An analytical method for determining halogenated salicylanilides using the HPLC method with a fluorescence detector was reported by Li et al. in 2016 [41]. They analyzed the levels of seven halogenated salicylanilide derivatives, namely 5-chlorosalicylanilide (CSA), 4'-bromosalicylanilide (BSA), 5-bromo-4'-chlorosalicylanilide (BCSA), Dibromsalan (DBS), Metabromsalan (MBS), Tribromsalan (TBS), and 3,3',4',5-tetrachlorosalicylanilide (TCSA) in samples of eye shadow, lipstick, shampoo, and toner. The samples were extracted using the liquid extraction method, with an appropriate solvent for each sample. The eye shadow and toner samples were extracted using acetonitrile. Lipstick samples were extracted using hexane-saturated acetonitrile and the shampoo sample was extracted using 4% formic acetonitrile. The column used was a HSS T3 column with acetonitrile, and 0.1% formic acid (*v/v*) was used as the mobile phase. The LOD and LOQ values were 13.8–42.9  $\mu\text{g kg}^{-1}$  and 46.0–143  $\mu\text{g kg}^{-1}$ , respectively. This method also shows good linearity, with a correlation coefficient of 0.9996 to 0.9999. The accuracy of this method was in the range of 70–110%, with RSD below 13%.

**Table 6.** Analytical method for determining halogenated salicylanilides in cosmetics.

No.	Sample	Analyte	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
1.	Eye shadow, lipstick, shampoo, and toner	5-chlorosalicylanilide (CSA)	Eye shadow and toner = Liquid–liquid extraction with acetonitrile Lipstick = Liquid–liquid extraction with hexane saturated acetonitrile Shampoo = Liquid–liquid extraction with 4% formic acetonitrile	HPLC-FLD	33.0 µg/kg	110 µg/kg	0.9999	Recovery = 70–110% RSD < 13%	[41]
		4'-bromosalicylanilide (BSA)			42.9 µg/kg	143 µg/kg	0.9996		
		5-bromo-4'-chlorosalicylanilide (BCSA)			29.1 µg/kg	97.0 µg/kg	0.9998		
		Dibromsalan (DBS)			35.2 µg/kg	117 µg/kg	0.9998		
		Metabromsalon (MBS)			25.1 µg/kg	83.7 µg/kg	0.9999		
		Tribromsalan (TBS)			13.8 µg/kg	46.0 µg/kg	0.9999		
3,3',4',5-tetrachlorosalicylanilide (TCSA)	14.0 µg/kg	46.7 µg/kg	0.9996						
2.	Aftershave, acne-treating face wash, toner, moisturizer, shaving cream, facial cleanser, skincare cream, body wash, shampoo	Tribromsalan (TBS)	SPE	UPLC-MS/MS	0.8 µg/kg	2.5 µg/kg	0.9978	Recovery = 83.9–107% RSD intra-day = 2.9–6.5% RSD inter-day = 4.9–7.0%	[42]
		Dibromsalan (DBS)			0.5 µg/kg	1.5 µg/kg	0.9988		
		Metabromsalon (MBS)			0.5 µg/kg	1.5 µg/kg	0.9988		
		3,3',4',5-tetrachlorosalicylanilide (TCSA)			0.5 µg/kg	1.5 µg/kg	0.9992		
		5-bromo-4'-chlorosalicylanilide (BCSA)			0.8 µg/kg	2.5 µg/kg	0.9986		
		4'-bromosalicylanilide (BSA)			0.8 µg/kg	2.5 µg/kg	0.9992		
5-chlorosalicylanilide (CSA)	0.8 µg/kg	2.5 µg/kg	0.9974						

To increase the sensitivity and selectivity of the measurement of halogenated salicylanilides, Lin et al. [42] used Solid-Phase Extraction (SPE) coupled with Ultra-Performance Liquid Chromatography tandem mass spectrometry (UPLC-MS) for the analysis of halogenated salicylanilides in cosmetic samples [42]. The column used for analysis was a HSS T3 column (2.1 mm × 100 mm, 1.8 μm). The system was run on gradient elution with formic acid-water as mobile phase A and methanol as mobile phase B. The extraction method used for cream samples was vortexing and demulsification, while water and emulsion samples were extracted by vortexing and dispersion with ultrasonic-assisted extraction. Dichloromethane was used as the extraction solvent due to its favorable sample dispersion, good recovery, and less flocculent precipitate formation than other extraction solvents. Purification of the sample was carried out by the solid-phase extraction technique because the components of cosmetic preparations are complex and contain a lot of lipids. The cartridge used for SPE, the amine SPE cartridge (3 mL/200 mg), was chosen based on tests carried out on four different cartridges. Elution was carried out using acetone containing 5% formic acid (*v/v*). This method produced LOD and LOQ values of 0.5–0.8 μg/kg and 1.5–2.5 μg kg<sup>-1</sup>, respectively. This method also shows good linearity, with a correlation coefficient value of 0.9978 for the TBS sample, 0.9988 for the DBS and MBS samples, 0.9992 for the TCSA and BSA samples, 0.9986 for the BCSA samples, and 0.9974 for the CSA samples. The accuracy and precision were in the range of 83.9–107%, with an intraday RSD of 2.9–6.5% and an interday RSD of 4.9–7.0%.

## 10. Hexachlorophene

Hexachlorophene is a white, odorless powder. In the medical field, hexachlorophene is used as a surgical scrub [106]. Hexachlorophene is widely used in cosmetic preparations as a preservative because it can inhibit the growth of Gram-positive bacteria [43]. Hexachlorophene is widely used as an antiseptic in preparations such as deodorant soap, toothpaste, mouthwash, shampoo, aftershave lotion, etc. [107]. Its use has since expanded to acne-fighting skincare in the form of cleansers, creams, and lotions, as well as to liquid makeup, cake makeup, blush, and lipstick in the 1950s to 1960s. Based on FDA regulations (21CFR250.250), the use of hexachlorophene is allowed in cosmetic preparations only if it is required and the level is not more than 0.1%. Hexachlorophene should only be used if no other preservative compounds are found that have the same effectiveness, and the stability of the product formulation made is not yet published. In the same document, it is stated that hexachlorophene has a toxic effect on users. It was found that the absorption of hexachlorophene can occur in the skin, especially in infants, and can be lethal. Therefore, the use of hexachlorophene is only allowed if its safety has been tested [43]. Furthermore, under EU regulations, hexachlorophene is a prohibited ingredient in cosmetics product [3].

Analytical methods for hexachlorophene measurement in cosmetics are summarized in Table 7. In 2017, Liu et al. [44] carried out an analysis of hexachlorophene in cosmetics using the High-Performance Liquid Chromatography (HPLC) method, assisted by Magnetic-Solid Phase Extraction (MSPE) and Ionic Liquid Dispersive Liquid-Liquid Microextraction (IL-DLLME) [44]. The samples were of moisturizers, toners, and body lotions. The proposed extraction and purification procedure was developed due to the complex nature of the cosmetic matrix. MSPE has the advantage that it does not require much time for extraction because it contains magnetic nanoparticles that can be dispersed in a solution homogeneously through a vortex or shaking [44]. Meanwhile, IL-DLLME works by injecting a disperser and extraction solvent into the sample so that the contact between the analyte and the solvent solution increases and the efficiency of extraction increases [44].

**Table 7.** Analytical method for determining hexachlorophene in cosmetics.

No.	Sample	Analyte	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
1.	Moisturizer, toner, body lotion	Hexachlorophene	IL-DLLME and MSPE	HPLC-PDA	0.14 µg/mL	-	0.9976	Recovery = 74.5–97.7% RSD = 3.8–6.7%	[44]
2.	Loose powder, emulsion, and toner samples	Hexachlorophene	Centrifugation and filtration	CE-UV	0.06 µg/mL	0.19 µg/mL	0.9999	Recovery = 90.0–96.4% RSD = 0.52–3.02%	[45]
				HPLC-PDA	0.05 µg/mL	0.15 µg/mL	0.9999	Recovery = 96.8–109.0% RSD = 0.15–0.5%	

Magnetic nanoparticles were made using  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ , which were dissolved in deionized water in a water bath; then ammonium solution was added, and the supernatant was taken using a magnet. The precipitate was then rinsed thoroughly with magnetic decantation and redispersed using deionized water. Extraction using the MSPE method is done by adding magnetic nanoparticles to cosmetic samples that have been dissolved and subjected to ultrasound. The mixture was then vortexed and magnetic nanoparticles containing hydrophobic substances were attracted with Nd-Fe-B magnets. The resulting supernatant was then purified using IL-DLLME. In this process, the sample will move from the aqueous phase to [C6MM] [PF6] while being centrifuged. The optimal time for centrifugation is 10 min. The LOD of the developed method was  $0.14 \mu\text{g mL}^{-1}$ . Meanwhile, the recovery value of the analyte was 97.7% and 86.4% with an RSD of 6.2% and 5.1% for the moisturizer sample with the addition of spikes of  $4 \mu\text{g/mL}$  and  $8 \mu\text{g/mL}$ , respectively. For the toner sample with the addition of a spike of  $4 \mu\text{g/mL}$  and  $8 \mu\text{g/mL}$ , the recovery was 88.7% and 95.4% with RSDs of 4.7% and 3.8%, respectively. Meanwhile, the body lotion sample recovered 74.5% with an RSD of 5.2% in the sample with the addition of a spike of  $4 \mu\text{g/mL}$  and 92.4% with an RSD of 6.5% in the sample with the addition of a spike of  $8 \mu\text{g/mL}$ .

In 2021, Li et al. [45] developed an analytical method for hexachlorophene analysis using the capillary zone electrophoresis (CZE) method with a UV detector [45]. They compared their method with the standard HPLC method made by the National Standard of the People's Republic of China [45]. CZE was performed by preparing the capillaries by rinsing them with the following solutions in order: methanol, water, NaOH, water, and a buffer. The rinse solution used must be filtered using a  $0.45 \mu\text{m}$ -diameter microporous nylon filter. The duration of rinsing is: methanol—5 min, water—5 min, NaOH—20 min, water—10 min, and running buffer—30 min. After analysis, the capillary tube should be rinsed with a running buffer for 3 min. The analytical wavelength was set to 208 nm and the capillary was maintained at  $25^\circ\text{C}$ . The voltage used was +25 kV with an injection pressure of 0.5 psi for 7 s. Factors that influence the analysis include the concentration of running buffer solution, pH buffer solution, injection time, and voltage separation. In this research, the analyte cannot be separated in the presence of other components in the sample; therefore, an organic modifier in the form of 10% methanol was used in the buffer. The results obtained for the CZE method of analyte recovery in loose powder samples were 91.5% with an RSD of 1.80% (spiked  $2 \mu\text{g/mL}$ ), and 90.0% with an RSD of 1.42% (spiked  $5 \mu\text{g/mL}$ ). The emulsion sample required a recovery value of 92% with RSD 3.02% (spiked  $2 \mu\text{g/mL}$ ) and 90.6% with RSD 0.52%, and the toner sample required a recovery value of 93.5% with RSD 1.51% (spiked  $2 \mu\text{g/mL}$ ) and 96.4% with an RSD of 1.68% ( $5 \mu\text{g mL}^{-1}$ ). The LOD obtained from the CZE method was  $0.06 \mu\text{g mL}^{-1}$ , while the LOQ was  $0.19 \mu\text{g mL}^{-1}$ . Compared to the HPLC method, CE produces lower method validation parameters but, based on the system test parameters listed in the USP, the CE method is better than the HPLC method, as seen from the tailings parameter at a CE of 1.2—smaller than that of HPLC, 1.87. The theoretical plate value of CE is 25,116 and HPLC 4420, which reflects that CE has better column efficiency. In terms of analysis time, CE only takes 3.962 min, while HPLC takes 11.736 min. Capillary Electrophoresis (CE) offers high resolution, is faster, does not require a lot of samples and reagents, and can also be combined with various extraction methods [45].

## 11. Coumarin

Coumarin is a white to colorless powder or crystals. Coumarin and its derivatives belong to the benzo- $\alpha$ -pyrone class and have a vanilla aroma and a bitter taste. Because of its fragrant aroma, coumarin is widely used as a fragrance agent in cosmetics and can also be added to sunscreen products to increase tanning induced by UV radiation [46].

In EU regulations, coumarin derivatives that are prohibited from being in cosmetics are dicoumarol, 7-ethoxy-4-methylcoumarin, acenocoumarol, 7-methoxycoumarin, dihydrocoumarin, 7-methylcoumarin, and pyranocoumarin. Coumarins can cause skin

sensitization and eczema through dermal administration. Coumarin can be used at a concentration of 0.01% for rinse-off cosmetic products and 0.001% for leave-on cosmetic products. Apart from dermal administration, coumarins can also cause nausea, diarrhea, and hepatotoxicity if ingested orally [46]. The analytical methods for detecting coumarin in cosmetics are summarized in Table 8.

The method of coumarin analysis by GC-MS was developed by Devos et al. in 2012 [47]. Evaporation dynamic headspace (EDH) was chosen as the extraction method because it can extract both polar and nonpolar fragrance compounds, and can be used for all cosmetic samples, including water-matrix cosmetics. GC-MS can be used in one-dimensional or two-dimensional modes depending on the complexity of the perfume sample to be tested. The advantage of this analysis method is that there is no need to change the system configuration if you want to change modes or have high flexibility. LOD and LOQ are not mentioned, while the correlation coefficient obtained was 0.9999, indicating that the analytical method has good linearity; the RSD values for the standard and sample were 1.3% and 2.3%, respectively [47].

The next method developed was UPLC-MS/MS. UPLC-MS/MS is a rapid analytical method with high sensitivity and specificity. In addition, efficient ultrasound-assisted extraction and solid-phase extraction (UAE and SPE) methods were used for lotion, cream, lipstick, and shampoo samples [48]. UAE was optimized and the use of 90% dilute methanol as a solvent gave high extraction yields with a recovery of around 84.2–96.5%. If the sample is too complex, it can be further extracted by solid-phase extraction. Coumarin derivatives found in the sample were acenocoumarol, dicoumarol, coumarin, 7-methoxycoumarin, dihydrocoumarin, 7-methylcoumarin, and 4-methyl-7-ethoxycoumarin [46].

Simple sample preparation is preferred for analyzing an analyte in a complex matrix. Stiefel et al. [48] developed a method for analyzing coumarins in cosmetic samples using HPTLC. The extraction method used is UAE with oxolane as a solvent. Oxolane has been proven to be an effective solvent for extraction because its recovery is more than 98% and it can extract cosmetics based on alcohol, water, and oil [48].

Method validation was carried out by measuring LOD, LOQ, correlation coefficient, and RSD. The LOQ obtained was 200 ng/band for the standard solution, and 1.3 mg/kg for all samples; the correlation coefficient was 0.9998, and the RSD was in the range 0.7–5.8%. The LOQ value was 10 times lower than the permissible coumarin levels in cosmetics, so this method is sensitive for quantifying coumarins in cosmetics [48].

In 2021, Arigo et al. [49] developed an analysis of coumarin in a cosmetic sample using the linear retention index approach applied to LC-coupled triple quadrupole MS. The Linear Retention Index (LRI) allowed for similarity filtration for selective identification. LRI was calculated before and after the injection of standard and sample compounds. The calculation is saved in MS/MS libraries and can be transferred to another laboratory. Other laboratories can apply this method because the reproducibility is guaranteed, although there is a shift in retention time. The extraction process was carried out using liquid–liquid extraction, with ethyl acetate as a solvent. The LOD and LOQ for coumarin were 0.003–0.0087 mg/L and 0.0009–0.0291 mg/L, respectively. The combination of the LRI approach and MS/MS detection allows for highly reliable identification of each analyte.

**Table 8.** Analytical methods for determining coumarin in cosmetics.

No.	Sample	Analyte	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
1.	Perfume	Coumarin	EDH	1D/2D GC-MS	-	-	0.9999	RSD = 1.3% for standards and 2.3% for sample	[47]
2.	Cream, Lipstick, Shampoo, and lotion	Acenocoumarol	UAE and SPE	UPLC-MS/MS	-	10 µg/kg	0.9954	With 50 µg/kg spike: % recovery = 86.8% Intra/interday precision = 5.2/8.9%	[46]
		Dicumarol				20 µg/kg	0.9950	With 50 µg/kg spike: % recovery = 88.9% Intra/inter-day precision = 7.4/10.1%	
		Coumarin				15 µg/kg	0.9911	With 50 µg/kg spike: % recovery = 84.8% Intra/interday precision = 6.2/12.9%	
		7-Methoxycoumarin				15 µg/kg	0.9947	With 50 µg/kg spike: % recovery = 91.6% Intra/interday precision = 7.1/9%	
		Dihydrocoumarin				15 µg/kg	0.9950	With 50 µg/kg spike: % recovery = 83.1% Intra/interday precision = 6.5/9.9%	
		7-Methylcoumarin				5 µg/kg	0.9931	With 50 µg/kg spike: % recovery = 86.9% Intra/interday precision = 5.4/8.3%	
		4-Methyl-7-Ethoxycoumarin			5 µg/kg	0.9978	With 50 µg/kg spike: % recovery = 86.6% Intra/interday precision = 5.6/9.9%		
3.	Deodorant, body oil, body milk, body lotion, face cream, sunscreen, bath additive, conditioner, body butter, hand cream, and lip products	Coumarin	UAE	HPTLC	200 pg/band for standard	1.3 mg/kg for samples	0.9998	RSD = 0.7–3.7% (deodorant, body oil, lip care, body milk) RSD = 1.7–5.8% (deodorant, body butter, cleaning milk, face cream, body lotion, bath essence, and conditioner)	[48]
4.	Perfume and body wash	Coumarin	LLE	LC-MS/MS with LRI	0.0003–0.0087 mg/L	0.0009–0.0291 mg/L	-	Intraday precision = 2.3–8.6% Interday precision = 2.8–9.6%	[49]

## 12. Furocoumarin

Furocoumarins, also known as furanocoumarins or psoralens, are metabolites produced by the Rutaceae, Moraceae, Apiaceae, and Fabaceae families. Furocoumarins have a basic structure, similar to coumarins, being fused with the furan ring at the C6/C7 or C7/C8 positions, so that furocoumarins are included in the coumarin subfamily. Furocoumarin is contained in citrus essential oil, which is often used as a fragrance in cosmetics with a liquid form such as perfume [50].

Due to its adverse effects, such as phototoxicity, hyperpigmentation, erythematous rash, blisters, and sunburn if a user is exposed to UV-A radiation from the sun, the use of furocoumarin has been banned by the EU. The photosensitivity caused by furocoumarin can occur after dermal, parenteral, or enteral administration [108]. With long-term use, furocoumarin can also increase the risk of skin cancer [51]. The analytical methods for detecting furocoumarins in cosmetics are summarized in Table 9.

Corbi et al., in 2014 [52], developed a quantitative analysis method for furocoumarin compounds involving HPLC coupled with HR/AM. The liquid chromatography technique used is reverse-phase liquid chromatography combined with high-resolution spectrometry or accurate mass spectrometry. The sample used was perfume and the furocoumarin compounds detected were xanthotoxin, bergapten, isopimpinellin, oxypeucedanin, byakangelico, epoxybergamottin, and bergamottin. One of the advantages of this method is that no sample preparation is required for a simple matrix so the sample can be directly injected into the system. Mass detection also offers high selectivity and lower LOD when compared to UV detection [52].

In a complex matrix, ultrasonication and solid-phase extraction techniques can be used as extraction procedures, such as the method developed by Kreidl et al. in 2020 [53]. They mixed 1 g cosmetic product and 5 mL of methanol in a vortex for 2 min. Afterwards, ultrasonication was performed for 20 min at room temperature. The suspension was centrifugated and 0.5 mL of supernatant was diluted with 35% methanol to create 10 mL of solution. The LC-MS method developed by Kreidl et al. [53] has fairly good sensitivity, as indicated by LOD values in the range of 0.1–0.5 ng/mL for standard solutions and 1–5 µg/kg for samples, and an LOQ value of 10 µg/kg for samples [53]. The linearity of this method is also proven by the correlation coefficient value being above 0.99. Under the autosampler conditions, all analytes were tested and it was found that the analytes were stable. It is recommended to use internal standards to obtain unbiased analysis results [53].

In 2021, a more sensitive and selective method was developed, with the linear retention index approach applied to LC-coupled triple quadrupole MS, the same as the method previously described for coumarin analysis. For perfume samples, it can be injected directly, while for body wash samples, liquid–liquid extraction must be carried out first. The LOD and LOQ values for furocoumarin were 0.001–0.0156 mg/L and 0.003–0.0091 mg/L, respectively. Intraday precision was 0.9–16.5% and interday precision was 1.7–18.4%. Additional LRI systems allow for a more robust analysis [49].

**Table 9.** Analytical method for determining furocoumarin in cosmetics.

No.	Sample	Analyte	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
1.	Hydroalcoholic fragrance	Xanthotoxin Bergapten Isopimpinellin Oxypeucedanin Byacangelicol Epoxybergamottin Bergamottin	-	RP-HPLC-coupled HR/AM	-	0.03 mg/L 0.07 mg/L 0.1 mg/L 0.05 mg/L 0.01 mg/L 0.02 mg/L 0.1 mg/L	>0.995	SD on 5 replications < 15% RSD on 30 replications < 10% Recovery for each furocoumarin was close to 100%, except for epoxy bergamottin, which was around 70%	[52]
2.	Creams, pomade, shampoo, perfume, shower gel, and deodorant	Oxypeucedanin hydrate Byacangelicin Bergapten Isopimpinellin Oxypeucedanin Byacangelicol Epoxybergamottin Bergamottin	Ultra-sonification and SPE	LC-MS	Standard solution = 0.1–0.5 ng/mL Sample = 1–5 µg/kg	Sample = 10 µg/kg	0.9984 0.9993 0.9991 0.9991 0.9989 0.9994 0.9993 0.9990	RSD = 17.9% % recovery = 96% RSD = 4.9% % recovery = 100% RSD = 8.2% % recovery = 94% RSD = 2.8% % recovery = 96% RSD = 7.1% % recovery = 94% RSD = 3.5% % recovery = 98% RSD = 4.1% % recovery = 94% RSD = 2.7% % recovery = 68%	[53]
3.	Perfume and body wash	Furocoumarin	LLE	LC-MS/MS with LRI	0.00003–0.0008 mg/L	0.00008–0.0028 mg/L	-	Intraday precision = 0.9–16.5% Interday precision = 1.7–18.4%	[49]

### 13. Mercury Compound

Mercury is a heavy metal compound with a gray-white color and a liquid form at room temperature. It is used for the manufacture of thermometers, barometers, and other tools and also plays a role in gold extraction [109]. In keeping with regulation 21 CFR 700.13 of the U.S. FDA, mercury may only be used as a preservative in cosmetic preparations for use in the eye area and can have a maximum value of 65 ppm (0.0065%). In other cosmetic preparations, mercury may only exist as a trace element, with a concentration of <1 ppm [54]. In addition, under EU regulations, mercury is prohibited except in special cases, e.g., as a preservative, subject to concentration limits [3]. However, in many cases, mercury is used as a whitening agent because of its ability to inhibit the enzyme tyrosinase, which plays a role in melanin production [110].

Mercury can easily enter the body through inhalation, ingestion, and absorption through the skin. The presence of mercury is frequently found in topical face-lightening creams, whose long-term use can result in a variety of complaints [111,112]. Continuous exposure to mercury can cause various health problems such as irritation, allergies, and the appearance of dark spots on the skin. Mercury that is absorbed into the body can cause brain and kidney damage; in pregnant women, it can interfere with fetal development. Mercury has also been known to have a carcinogenic effect on users [113,114].

In recent years, many analytical methods have been developed for detecting mercury components in cosmetic preparations. Methods used to determine mercury levels include enzyme-linked immunosorbent assay (ELISA) [55], atomic absorption spectrophotometry [57,60–64], atomic emission spectroscopy [67,71,74], capillary electrophoresis [60], electrochemical sensors [72,73], and mass spectroscopy [68–70]. These methods are summarized in Table 10.

Determining mercury in a cosmetic sample using enzyme-linked immunosorbent assay (ELISA) was reported 10 years ago by Wang et al. [55]. The samples analyzed were facial cleansers and night creams. Antibodies detect heavy metals that have been complexed with chelators and carrier proteins. In this research, they used  $\text{CH}_3\text{Hg-MNA-BSA}$  as an immunogen and  $\text{CH}_3\text{Hg-MNA-OVA}$  as a coating antigen. This method had high sensitivity with an LOD value of 0.08 ng/mL, as well as good accuracy and precision, with a relatively high recovery value (80–113%) and a coefficient of variation in the range of 1.9–18.6% [55].

Nevertheless, Atomic Absorption Spectrometry (AAS) was a better general method for the determination of mercury in cosmetic samples. The AAS method is widely used because it is highly sensitive, specific, and can detect mercury even at very low levels [56,57,60–64].

Research by Ahmed et al. from 2017 [64] used the flame atomic absorption spectrometry (FAAS) method to measure heavy metal levels in eye shadow samples. FAAS was done using air-acetylene and microwave digestion. Solvents used for digestion were  $\text{HNO}_3$  69%,  $\text{H}_2\text{O}_2$  35%, HF 48%, and HCl 36%. This method showed good performance, with a correlation coefficient of 0.9993. The sensitivity of the method was well reflected in the LOD and LOQ values of 1.87 and 5.68 mg/kg, respectively.

In 2018, Dwijayanti and Susanti [57] analyzed mercury levels in whitening cream, also using the AAS method. Cosmetic samples were prepared by wet destruction by adding the sample to 10 mL of concentrated  $\text{HNO}_3$ , which was then heated until dissolved. Wet destruction was chosen because of the volatile nature of mercury. They also conducted a qualitative analysis by adding HCl, KI, and NaOH separately. With the addition of HCl, the sample was positive for mercury if there was a white precipitate; in the test with KI, the sample was positive if green (Hg(I)) and red (Hg(II)) precipitates formed. In the test with NaOH, the sample was positive if black (Hg(I)) and yellow (Hg(II)) precipitates formed. This research shows that the AAS procedure used is linear, which can be seen from the correlation coefficient value of 0.9985.

**Table 10.** Analytical method for determining mercury compounds in cosmetics.

No.	Sample	Analyte	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
1	Facial cleanser, night cream	Mercury	Extracted with 30% HNO <sub>3</sub> and centrifugation	ELISA	0.08 ng/mL	-	0.98	Recovery = night cream: 80.0–92.0% facial cleanser: 84.0–102.0% RSD = night cream: 7.5–12.0% facial cleanser: 5.8–18.6%	[55]
2	Body butter, body lotion, body milk, body oil, peeling, body serum, cream, eye cream, foam, gel, hydrolate, mask, micellar liquid, face serum, SPF cream, tonic	Mercury	-	AAS	-	0.003 ng	-	RSD < 1.5%	[56]
3	Whitening cream	Mercury	Wet destruction	AAS	-	-	0.9985	-	[57]
4	Cosmetics sample (not stated)	Mercury	Microwave digestion	AFS	2.4 ng/L	-	0.9992	Recovery = 94–106% RSD 2.8–4.2%	[58]
5	Loofah moisturizer (A), homemade moisturizing lotion emulsion (B)	Mercury	Sweeping via dynamic complexation	CE	50 ng/L	-	sample A: 0.998 sample B: 0.994	Recovery = sample A: 100–107% sample B: 76% RSD < 8.7%	[59]
6	Skin-lightening cream	Mercury	Microwave digestion	CV-AAS	0.0005 mg/kg	0.001 mg/kg	0.999	Recovery = 94% RSD = 4%	[61]
7	Shampoo, hairdressing gel, hair dye, body wash, hair conditioner, hand lotion, hand wash, facial cleanser, moisturizer/cream, whitening, eye gel, lip care, toner, nail saver, others	Mercury	-	CV AAS	0.04 µg/kg	-	>0.999	Recovery = 96.2%, 99.1% 103.1% RSD = 6.4%, 5.1%, 3.9% (shampoo I, shampoo II, cleanser)	[60]
8	Body lotion	Mercury	Wet destruction	CV AAS	0.004854 ppb	0.01681 ppb	0.9726	Recovery = 99.33% RSD = 1.829%	[62]
9	Skin-lightening cream,	Low-concentration mercury High-concentration mercury	Microwave-assisted digestion	CV AAS FAAS	0.005 ppm -	- -	0.9984 0.9998	Recovery = 98–102% RSD = 2.8% RSD = 0.94%	[63]
10	Eye shadow	Mercury	Microwave digestion	FAAS	1.87 mg/kg	5.68	0.9993	Recovery = 99.07%, RSD = 2.50674	[64]
11	Facial blemish balm creams, facial whitening creams	Mercury	-	FIA	0.03 µg/mL	0.14 µg/mL	0.9961	RSD = 1.32% (0.05 µg/mL) 0.78% (0.20 µg/mL)	[65]
12	Cosmetic sample	Mercury (Hg(II))	Digestion	Spectrophotometric determination based on peroxidase activity	0.5 µM	-	0.994	Recovery = 95.6–108.5% RSD = 4.5–8.2%	[66]
13	Skin-whitening cream	Mercury	Microwave digestion	ICP AES	3.3 ppb	-	>0.999	Recovery = 87.6–91.0% RSD < 3%	[67]

Table 10. Cont.

No.	Sample	Analyte	Extraction Method	Analytical Method	LOD	LOQ	Linearity (Correlation Coefficient)	Accuracy/Precision	Ref.
14.	Skin-whitening cream	Mercury	SPE	ICP AES	1.8 ng/mL	-	-	Recovery = 89.6–90.4% RSD = 1.1%	[74]
15.	Hair cream, beauty cream, hair gel, scrub, shampoo, shower gel, body lotion, hand wash, shaving cream, toothpaste, soap	Mercury	Dry-ashing digestion	ICP-MS	-	-	0.998–0.999	-	[68]
16.	Lotion, facial lightening mask, facial lightening cream, lightening serum	Mercury	Dissolution in formic acid	PVG-ICP MS	0.6 pg/mL	-	0.997	Recovery = 90–105% RSD intraday = 2.3% (0.5 ng/mL) 4.8% (0.02 ng/mL) RSD interday = 5.1% (0.5 ng/mL) 9.2% (0.02 ng/mL)	[69]
17.	Skin refreshers and hand moisturizing lotion	Hg <sup>2+</sup>	IL-DLLME	HPLC-ICP-MS	1.3 ng/L	-	0.9986	Recovery = 96.6–101.2% RSD = 7.4%	[70]
		MeHg <sup>+</sup>			7.2 ng/L	-	0.9987	Recovery = 86.7–89.7% RSD = 5.2%	
		EtHg <sup>+</sup>			5.4 ng/L	-	0.9999	Recovery = 88.2–93.5% RSD = 2.3%	
18.	Skin-lightening cream,	Mercury	Microwave digestion	MP-AES	0.59 µg/L	1.98 µg/L	0.993	Recovery = 92.78% RSD = 2.67%	[71]
19.	Talcum powder, skin lotion, eye shadow	Mercury (Hg(II))	Microwave digestion	Electrochemical sensor	0.5 µg/L	0.25 mg/kg	0.998	Recovery = 77.0–93.0%	[72]
20.	Lotion, serum, moisturizer, cream, lotion, gel, hair straightener, shampoo, dye, soap, oil, shower gel, face powder, foundation, lipstick, scented oil, deodorant, salve	Mercury	Centrifugation and ultrasonication	Electrochemical cyclic voltammetry (CV) and differential pulse voltammetry (DPV)	0.03 ppm	-	0.9969	Recovery = 96.6–97.5% RSD < 1%	[73]

Podgorska et al. [56] recently conducted testing of mercury levels using AAS in conventional and natural cosmetic preparations, which include preparations for the face and body. The authors conducted research on natural samples due to the growing popularity of natural cosmetics but lack of regulations governing their use. The use of AAS is based on the amalgamation technique, where the analyzer measures the release of Hg from organic and inorganic forms into their atomic forms. The difference between the mercury analysis by Podgorska et al. [32] and that by Dwijayanti and Susanti is that the sample preparation did not use wet destruction. The preparation involved drying and burning the sample in oxygen flow; the Hg vapor then continued into the catalytic column and the amalgamator. Hg was then measured at a wavelength of 254 nm. Through this study, an LOQ value of 0.003 ng and an RSD value of <1.5% were achieved [56].

An example of the development of the AAS analysis method for detecting mercury in cosmetic samples is the use of Cold Vapor AAS (CV AAS). The application of CV AAS itself can be developed with variations in pretreatment and sample extraction that are expected to increase the mercury content extracted from the sample matrix. In 2011, Peregrino et al. [63] conducted a study on the determination of mercury levels in cosmetic samples found in Mexico. They used two analytical methods: CV AAS to determine mercury levels in low concentrations, and FAAS for samples with higher mercury levels. For the CV AAS method, the microwave-assisted digestion method was used for sample preparation, using HNO<sub>3</sub> and H<sub>2</sub>O<sub>2</sub> as a solvent combination. The linear results are reflected in the recovery value of 98–102% with an RSD of 2.8%. The sensitivity of the method can also be seen from the detection limit value, 0.005 ppm. For the FAAS method, good results were obtained, with a correlation coefficient value of 0.9998 and an RSD of 0.94% [64]. Wang and Zhang [61] used CV AAS as it was more accurate and convenient compared to other methods. They used the MDA-80 Direct Mercury Analyzer, which combines the techniques of thermal decomposition, catalytic conversion, and absorption spectrometry. In their study, all samples contained mercury but below the specified limit, which indicated that the cosmetic samples were safe. Accuracy and precision testing of the method was carried out on three samples, two shampoos and one cleanser, and the results obtained met the criteria, namely a recovery value of 95–105% and RSD of 3.9–6.4%. The analytical method was linear and sensitive, with a correlation coefficient value >0.999 and an LOD of 0.04 µg/kg [60].

Ho et al. [61] analyzed mercury levels using the CV AAS method on samples of skin-whitening cream, classified by price category, with the microwave digestion extraction technique. Microwave digestion was carried out using 65% HNO<sub>3</sub> and 30% H<sub>2</sub>O<sub>2</sub>; then the sample was digested at a pressure of 50 bar, a limit of internal temperature of 200 °C, and a cooling temperature of 500 °C. It was found that this method is linear, accurate, and precise for analyzing mercury in cosmetic samples. The correlation coefficient value was 0.999 and recovery was 94%, with an RSD of 4%. The sensitivity of this method is also reflected in the LOD and LOQ values of 0.0005 mg/kg and 0.001 mg/kg, respectively [61].

Research by Safitri et al. [62] also produced a good profile of analytical methods, which was reflected in the validation parameters of the method. In their research, they used the CV AAS method but sample preparation was carried out by wet destruction. The wet destruction process is used to minimize evaporation from the analyte because of the volatile nature of Hg. Wet destruction is carried out using a mixture of strong acids such as chloric acid, sulfuric acid, and nitric acid. The wet destruction process is run at a temperature of 100 °C to accelerate the oxidation process and the decay of organic compounds in the sample. The results of this study produce good results, with a detection limit of 0.004854 ppb. This analytical method is proven to be sensitive and can detect analytes at very low levels [62].

Flow injection (FI) spectrophotometry was also developed for the determination of mercury in the cosmetic sample due to its simple, fast, and inexpensive nature compared to other methods such as ICP-MS and UPLC [65,115,116]. Prasertboonyai et al. [65] analyzed acne and face-whitening creams using FI spectrophotometry. A sample containing standard Hg(II) was injected into the instrument to a stream of H<sub>2</sub>SO<sub>4</sub>-SDS solution and mixed with

1,5-diphenylthiocarbazone/ascorbic acid. After the solutions were mixed and flowed through a reaction coil, complexation occurred. The absorbance of the colored complex was then measured at 490 nm when it reached the flowthrough cell in the spectrophotometer. The results showed that the FI spectrophotometry method is in good agreement with ICP-MS, with a LOD value of  $0.03 \text{ g mL}^{-1}$  and a good correlation coefficient ( $R^2 = 0.9961$ ) [65].

Another spectrophotometric analytical method was developed by Lu et al. [66]. They used spectrophotometric measurement of Hg(II) based on its stimulatory effect on the peroxidase-like activity of Molybdenum Disulfide Nanosheets. Cosmetic samples were first digested using concentrated nitric acid and peroxide acid, which were reacted and heated in a water bath. The mixture was adjusted to a pH of 4, and the total Hg in the sample was converted to  $\text{Hg}^{2+}$ . This analytical method is a reliable and accurate method for measuring  $\text{Hg}^{2+}$  in cosmetic samples, as seen from the recovery value in the range of 95.6–108.5%, with an RSD of 4.5–8.2% [66].

Atomic emission spectroscopy is also used for determining the quantity of mercury in cosmetic samples. Inductively coupled plasma atomic emission spectrometry (ICP-AES) is a fairly common analytical method used to determine mercury levels in cosmetic samples. In two publications by Alqadami et al. [67,74], the same determination of mercury levels was carried out using ICP-AES. The difference lies in the sample preparation. In their 2013 study, sample preparation was carried out using the solid-phase extraction method and multiwalled carbon nanotubes. In 2017, however, their sample preparation involved microwave acid digestion. In both studies, ICP-AES was proven to be a sensitive and selective analytical method for the determination of heavy metals (including mercury), with acceptable recovery, RSD, and LOQ values [67,74].

Another approach using the AES analysis method is to use microwave plasma (MP). MP-AES was conducted by Qudus et al. [71] to analyze mercury levels in 16 skin-lightening creams. MP-AES itself is a fairly new analytical method for metal analysis. Compared to other analytical methods, MP-AES has advantages in terms of cost and security. The validation parameters of the MP-AES method are an RSD value of 2.67%, a recovery value of 92.78%, and a correlation coefficient of 0.993. This method is also quite sensitive, with a detection limit value of  $15.01 \text{ ng/g}$ . In this publication, the authors recommend the use of other solvents and a comparison with other equivalent techniques [71].

The next method of analysis is ICP Mass Spectrometry (ICP-MS). ICP-MS has been widely used for determining mercury levels in cosmetic samples, with mass spectrometry coupled with various other methods [68–70]. Jia et al. [70] carried out an analysis using ICP MS, developed in tandem with HPLC. Sample preparation was carried out by ionic liquid-dispersive liquid–liquid microextraction (IL-DLLME). The research also describes factors that influence the analysis, such as the amount and type of ionic liquid used, solvent disperser, chelating reagent, pH, extraction time, centrifugation time, salt, and coexisting ions. This method produces accurate results, as seen from the recovery values, which are in the range of 86.7–101.2% in samples with a spike of  $20 \text{ ng/mL}$  [70].

In 2014, Gao et al. [69] developed an ICP-MS analysis method with photochemical vapor generation. In their study, the sample was prepared by dissolving it in formic acid. The result is that PVG-ICP MS is a simple analytical method, and has good reliability, repeatability, and LOD value, making it suitable to detect mercury in cosmetic samples. A study conducted by Salama [68] used the dry ashing method. This method was successful for detecting mercury in cosmetic samples, with good linearity, namely 0.998–0.999.

Wang et al. used electrochemical sensors to determine the levels of heavy metals in cosmetic samples [72]. This analytical method has the advantages of being inexpensive and having high sensitivity. In this publication, the authors used polyethylene terephthalate (PET) coated with gold as an electrode. Sample preparation was carried out by microwave-assisted digestion with  $\text{HNO}_3$ . Measurements were carried out using the spike method. It was found that this analytical method can be used for the analysis of heavy metals (including mercury), with good results, as seen from the recovery value in the range of 77–112% [72].

Another analytical method using an electrochemical sensor was developed by Bohari et al. [73]. The authors developed the method by modifying an indium tin oxide (ITO) electrode with a combination of polymers and nanoparticles. The polymer used was polyaniline (PANI) and the nanoparticles consisted of multiwalled carbon nanotubes (MWCNTs) and gold nanoparticles (AuNPs). This combination was chosen because of the advantages in terms of conductivity, mechanical strength, and electrocatalytic behavior, which are preferred over PANI, MWCNTs, and AuNPs, respectively. Cosmetic samples were prepared by centrifugation and filtration, then analyzed by cyclic voltammetry (CV) and differential pulse voltammetry (DPV). This method showed acceptable reproducibility (RSD 2.82%) and repeatability (1.24%). It also showed good sensitivity, as seen from the detection limit value of 0.03 ppm, and good linearity, as seen from the good correlation coefficient,  $R^2 = 0.9969$  [73].

Another method is capillary electrophoresis (CE), used by Chen et al. in 2017 [59]. In their research, they used simple extraction methods such as filtration, dilution, vortex, sonication, and centrifugation due to the CE method not requiring a complicated sample pretreatment process. They also used the online preconcentration technique due to the process being more efficient because it does not require additional instruments for the separation and preconcentration process. They also developed the analytical method using dynamic complexation via sweeping to produce an online preconcentration technique that is faster and more sensitive. The results obtained showed good results, as indicated by good linearity ( $R^2 > 0.998$ ), RSD  $< 8.7\%$ , and recovery in the range of 93–104% [59].

#### 14. Conclusions

Cosmetics are products widely used by the public. The safety of some cosmetic products is a concern, as they have been found to contain ingredients that are prohibited or restricted according to legislation in the USA and the EU. Many regulations state that cosmetic products are prohibited from containing certain substances. This is because they can have bad effects, especially on the skin. Even worse, the adverse effects of certain harmful substances in cosmetics can lead to comas. Reliable analytical techniques are important for detecting prohibited substances in cosmetics to ensure the quality of the products and protect human health. The methods used for the analysis of hazardous compounds in cosmetics vary widely. The analysis method can be selected based on the physicochemical compounds and required analytical data. For example, to analyze bithionol, a renewable method that can be used is sweeping-micellar electrokinetic chromatography (sweeping-MEKC). For metal compounds such as cadmium and mercury, AAS and ICP-MS or ICP-AES is a general method for routine analysis in the laboratory. Chloroform is usually analyzed using gas chromatography. Chromatographic methods such as HPLC-FLD and UPLC-MS were used to analyze halogenated salicylanilides compounds. Besides HPLC, there are methods that have been developed to analyze hexachlorophene, such as capillary zone electrophoresis (CZE). Formaldehyde analysis usually uses the spectrophotometric method; however, the method was developed using a smartphone reader to analyze the compound. Colorimetric methods have also been used to analyze zirconium compounds in cosmetic samples. There are many kinds of color additives in cosmetics, with chromatographic techniques such as HPLC widely used for their analysis. The improvement of analytical methods is still needed to provide alternatives that can be adapted as required.

**Author Contributions:** Conceptualization, R.P.; writing—original draft preparation, R.P., N.N.A.A., R.F.Y. and A.A.A.S.; writing—review and editing, R.P. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Directorate of Research and Community Service of Universitas Padjadjaran, through Article Review Grant 2022.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data is contained within the article.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. FDA Cosmetics. Available online: <https://www.fda.gov/industry/regulated-products/cosmetics-overview#:~:text=The%20FDA%20defines%20a%20cosmetic,attractiveness%2C%20or%20altering%20the%20appearance> (accessed on 6 May 2022).
2. Halla, N.; Fernandes, I.P.; Heleno, S.A.; Costa, P.; Boucherit-Otmani, Z.; Boucherit, K.; Rodrigues, A.E.; Ferreira, I.C.F.R.; Barreiro, M.F. Cosmetics Preservation: A Review on Present Strategies. *Molecules* **2018**, *23*, 1571. [[CrossRef](#)] [[PubMed](#)]
3. European Parliament. Council of the European Union Regulation (EC) No 1223/2009 of the European Parliament and of the Council on Cosmetic Products. Available online: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02009R1223-20220301&from=EN> (accessed on 7 August 2022).
4. Mitsui, T. *New Cosmetic Science*; Elsevier: Amsterdam, The Netherlands, 1997.
5. Bezerra, K.G.O.; Rufino, R.D.; Luna, J.M.; Sarubbo, L.A. Saponins and microbial biosurfactants: Potential raw materials for the formulation of cosmetics. *Biotechnol. Prog.* **2018**, *34*, 1482–1493. [[CrossRef](#)] [[PubMed](#)]
6. Dreger, M.; Wielgus, K. Application of essential oils as natural cosmetic preservatives. *Herba Pol.* **2013**, *59*, 142–156. [[CrossRef](#)]
7. Maurício, E.; Rosado, C.; Duarte, M.P.; Verissimo, J.; Bom, S.; Vasconcelos, L. Efficiency of Nisin as Preservative in Cosmetics and Topical Products. *Cosmetics* **2017**, *4*, 41. [[CrossRef](#)]
8. Kaličanin, B.; Velimirović, D. A Study of the Possible Harmful Effects of Cosmetic Beauty Products on Human Health. *Biol. Trace Element Res.* **2016**, *170*, 476–484. [[CrossRef](#)]
9. Kessler, B. California Woman in Semi-Comatose State Due to Mercury Poisoning from Mexican Skin Cream. Available online: <https://www.nbcnews.com/news/us-news/california-woman-semi-comatose-state-due-mercury-poisoning-mexican-skin-n1052961> (accessed on 18 June 2022).
10. Gbetoh, M.H.; Amyot, M. Mercury, hydroquinone and clobetasol propionate in skin lightening products in West Africa and Canada. *Environ. Res.* **2016**, *150*, 403–410. [[CrossRef](#)]
11. Michalek, I.M.; Benn, E.K.; dos Santos, F.L.C.; Gordon, S.; Wen, C.; Liu, B. A systematic review of global legal regulations on the permissible level of heavy metals in cosmetics with particular emphasis on skin lightening products. *Environ. Res.* **2019**, *170*, 187–193. [[CrossRef](#)]
12. Pramanik, S.; Kumar, M.; Qureshi, A. Mercury in skin-care products in India and consumer exposure risks. *Regul. Toxicol. Pharmacol.* **2021**, *121*, 104870. [[CrossRef](#)]
13. Health Sciences Authority Guidelines for Safety Evaluation of Cosmetic Products. Available online: <https://www.hsa.gov.sg/cosmetic-products/asean-cosmetic-directive> (accessed on 5 July 2022).
14. Briliana, V.; Mursito, N. Exploring antecedents and consequences of Indonesian Muslim youths' attitude towards halal cosmetic products: A case study in Jakarta. *Asia Pac. Manag. Rev.* **2017**, *22*, 176–184. [[CrossRef](#)]
15. Sugibayashi, K.; Yusuf, E.; Todo, H.; Dahlizar, S.; Sakdiset, P.; Arce, F.J.; See, G.L. Halal Cosmetics: A Review on Ingredients, Production, and Testing Methods. *Cosmetics* **2019**, *6*, 37. [[CrossRef](#)]
16. FDA Prohibited & Restricted Ingredients in Cosmetics. Available online: <https://www.fda.gov/cosmetics/cosmetics-laws-regulations/prohibited-restricted-ingredients-cosmetics> (accessed on 7 August 2022).
17. FDA Authority Over Cosmetics: How Cosmetics Are Not FDA-Approved, but Are FDA-Regulated. Available online: <https://www.fda.gov/cosmetics/cosmetics-laws-regulations/fda-authority-over-cosmetics-how-cosmetics-are-not-fda-approved-are-fda-regulated> (accessed on 7 August 2022).
18. Scientific Committee on Consumer Safety. The Scs Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation 11th Revision. *Regul. Toxicol. Pharmacol.* **2021**, *127*, 105052.
19. Park, J.-D.; Zheng, W. Human Exposure and Health Effects of Inorganic and Elemental Mercury. *J. Prev. Med. Public Health* **2012**, *45*, 344–352. [[CrossRef](#)] [[PubMed](#)]
20. Aronson, J.K. *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions*, 16th ed.; Elsevier: Amsterdam, The Netherlands, 2015.
21. Groot, A.C.D. *Monographs in Contact Allergy, Volume 1: Non-Fragrance Allergens in Cosmetics*; CRC Press: London, UK, 2018.
22. Zheng, Z.; Li, X.; Gao, F.; Liu, H.; Gao, Y. A sweeping-micellar electrokinetic chromatography method for the detection of three chlorophenols in cosmetic samples. *Acta Chromatogr.* **2021**, *33*, 387–393. [[CrossRef](#)]
23. Kim, K.-H.; Jahan, S.A.; Lee, J.-T. Exposure to Formaldehyde and Its Potential Human Health Hazards. *J. Environ. Sci. Health Part C* **2011**, *29*, 277–299. [[CrossRef](#)]
24. Lamarca, R.S.; Luchiani, N.D.C.; Bonjorno, A.F.; Filho, J.P.; Cardoso, A.A.; Gomes, P.C.F.D.L. Determination of formaldehyde in cosmetic products using gas-diffusion microextraction coupled with a smartphone reader. *Anal. Methods* **2019**, *11*, 3697–3705. [[CrossRef](#)]
25. Suhardiana, E.; Endah, S.R.N. Validation of The Cadmium Analysis Method (Cd) by Atomic Absorption Spectrophotometry in Traditional Scrub. *J. Midpro* **2021**, *12*, 311–318. [[CrossRef](#)]

26. Saadat zadeh, A.; Afzalan, S.; Zadehdabagh, R.; Tishezan, L.; Najafi, N.; Seyed Tabib, M.; Noori, S.M.A. Determination of heavy metals (lead, cadmium, arsenic, and mercury) in authorized and unauthorized cosmetics. *Cutan. Ocul. Toxicol.* **2019**, *38*, 207–211. [[CrossRef](#)]
27. Chisvert, A. Salvador Colouring Agents in Decorative and Other Cosmetics. Analytical Methods. In *Analysis of Cosmetic Products*, 1st ed.; Elsevier: Amsterdam, The Netherlands, 2007.
28. Platzek, T. Overview on toxicity and exposure to azo dyes and aromatic amines. *Toxicol. Lett.* **2013**, *221*, S53. [[CrossRef](#)]
29. Chequer, F.M.D.; Venâncio, V.D.P.; Prado, M.R.D.S.; Junior, L.R.C.D.S.E.C.; Lizier, T.M.; Zanoni, M.V.B.; Burbano, R.R.; Bianchi, M.L.P.; Antunes, L.M.G. The cosmetic dye quinoline yellow causes DNA damage in vitro. *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* **2015**, *777*, 54–61. [[CrossRef](#)]
30. Desiderio, C.; Marra, C.; Fanali, S. Quantitative analysis of synthetic dyes in lipstick by micellar electrokinetic capillary chromatography. *Electrophoresis* **1998**, *19*, 1478–1483. [[CrossRef](#)]
31. Miranda-Bermudez, E.; Harp, B.P.; Barrows, J.N. Qualitative Identification of Permitted and Non-permitted Color Additives in Cosmetics. *J. AOAC Int.* **2014**, *97*, 1039–1047. [[CrossRef](#)] [[PubMed](#)]
32. Guerra, E.; Llompарт, M.; Garcia-Jares, C. Miniaturized matrix solid-phase dispersion followed by liquid chromatography-tandem mass spectrometry for the quantification of synthetic dyes in cosmetics and foodstuffs used or consumed by children. *J. Chromatogr. A* **2017**, *1529*, 29–38. [[CrossRef](#)] [[PubMed](#)]
33. Guerra, E.; Alvarez-Rivera, G.; Llompарт, M.; Garcia-Jares, C. Simultaneous determination of preservatives and synthetic dyes in cosmetics by single-step vortex extraction and clean-up followed by liquid chromatography coupled to tandem mass spectrometry. *Talanta* **2018**, *188*, 251–258. [[CrossRef](#)]
34. Chen, M.; Bai, H.; Zhai, J.; Meng, X.; Guo, X.; Wang, C.; Wang, P.; Lei, H.; Niu, Z.; Ma, Q. Comprehensive screening of 63 coloring agents in cosmetics using matrix solid-phase dispersion and ultra-high-performance liquid chromatography coupled with quadrupole-Orbitrap high-resolution mass spectrometry. *J. Chromatogr. A* **2019**, *1590*, 27–38. [[CrossRef](#)]
35. Nevitasari, R.; Rohman, A.; Martono, S. Validation and Quantitative Analysis of Carmine and Rhodamine B in Lipstick Formulation. *Int. J. Appl. Pharm.* **2019**, *11*, 176–180. [[CrossRef](#)]
36. MAK Value Documentation Zirconium and Its Compounds [MAK Value Documentation, 1999]. *MAK-Collect. Occup. Health Saf.* **2012**, *12*, 224–236. [[CrossRef](#)]
37. Beavin, P. Colorimetric Determination of Zirconium in Antiperspirant Aerosols. *J. AOAC Int.* **1976**, *59*, 830–834. [[CrossRef](#)]
38. U.S. Government Information 21 CFR 700.18-Use of Chloroform as an Ingredient in Cosmetic Products. Available online: <https://www.govinfo.gov/app/details/CFR-2013-title21-vol7/CFR-2013-title21-vol7-sec700-18/context> (accessed on 29 April 2022).
39. Stutsman, M.J. Gas-Liquid Chromatographic Determination of Chloroform in Toothpastes, Using the Headspace Analytical Technique. *J. AOAC Int.* **1974**, *57*, 560–562. [[CrossRef](#)]
40. U.S. Government Information 21 CFR 700.15-Use of Certain Halogenated Salicylanilides as Ingredients in Cosmetic Products. Available online: <https://www.govinfo.gov/app/details/CFR-2013-title21-vol7/CFR-2013-title21-vol7-sec700-15> (accessed on 11 May 2022).
41. Li, S.; Liu, X.; Zhang, Y.; Lin, S.; Huang, J.; Li, X.; Guo, X.; Xian, Y.; Dong, H. Determination of seven restricted halogenated salicylanilides in cosmetics by high performance liquid chromatography. *Anal. Methods* **2016**, *8*, 5129–5135. [[CrossRef](#)]
42. Lin, S.; Xian, Y.; Xun, Z.; Li, S.; Liu, X.; Du, W.; Huang, J.; Guo, X.; Dong, H. Solid-phase extraction coupled with ultra performance liquid chromatography tandem mass spectrometry to determine seven halogenated salicylanilides in cosmetics. *RSC Adv.* **2016**, *6*, 49011–49018. [[CrossRef](#)]
43. U.S. Government Information 21 CFR § 250.250-Hexachlorophene, as a Component of Drug and Cosmetic Products. Available online: <https://www.govinfo.gov/app/details/CFR-2021-title21-vol4/CFR-2021-title21-vol4-sec250-250> (accessed on 11 May 2022).
44. Liu, R.; Liu, Y.; Cheng, C.; Yang, Y. Magnetic Solid-Phase Extraction and Ionic Liquid Dispersive Liquid-Liquid Microextraction Coupled with High-Performance Liquid Chromatography for the Determination of Hexachlorophene in Cosmetics. *Chromatographia* **2017**, *80*, 783–791. [[CrossRef](#)]
45. Li, X.; Gao, F.; Liu, H.; Gao, Y. Determination of hexachlorophene in cosmetics by capillary electrophoresis compared with high performance liquid chromatography. *Acta Chromatogr.* **2020**, *33*, 44–50. [[CrossRef](#)]
46. Ma, Q.; Xi, H.; Ma, H.; Meng, X.; Wang, Z.; Bai, H.; Li, W.; Wang, C. Simultaneous Separation and Determination of 22 Coumarin Derivatives in Cosmetics by UPLC-MS/MS. *Chromatographia* **2015**, *78*, 241–249. [[CrossRef](#)]
47. Devos, C.; Ochiai, N.; Sasamoto, K.; Sandra, P.; David, F. Full evaporation dynamic headspace in combination with selectable one-dimensional/two-dimensional gas chromatography-mass spectrometry for the determination of suspected fragrance allergens in cosmetic products. *J. Chromatogr. A* **2012**, *1255*, 207–215. [[CrossRef](#)]
48. Stiefel, C.; Schubert, T.; Morlock, G.E. Bioprofiling of Cosmetics with Focus on Streamlined Coumarin Analysis. *ACS Omega* **2017**, *2*, 5242–5250. [[CrossRef](#)]
49. Arigò, A.; Dugo, P.; Rigano, F.; Mondello, L. Linear retention index approach applied to liquid chromatography coupled to triple quadrupole mass spectrometry to determine oxygen heterocyclic compounds at trace level in finished cosmetics. *J. Chromatogr. A* **2021**, *1649*, 462183. [[CrossRef](#)]
50. Melough, M.M.; Cho, E.; Chun, O.K. Furocoumarins: A review of biochemical activities, dietary sources and intake, and potential health risks. *Food Chem. Toxicol.* **2018**, *113*, 99–107. [[CrossRef](#)]

51. International Fragrance Association (IFRA). *Information Letter 799*; International Fragrance Association (IFRA): Geneva, Switzerland, 2008; pp. 1–2.
52. Corbi, E.; Pérès, C.; David, N. Quantification of furocoumarins in hydroalcoholic fragrances by a liquid chromatography-high resolution/accurate mass method. *Flavour Fragr. J.* **2014**, *29*, 173–183. [[CrossRef](#)]
53. Kreidl, M.; Rainer, M.; Jakschitz, T.; Bonn, G.K. Determination of phototoxic furanocoumarins in natural cosmetics using SPE with LC-MS. *Anal. Chim. Acta* **2019**, *1101*, 211–221. [[CrossRef](#)]
54. U.S. Government Information 21 CFR 700.13-Use of Mercury Compounds in Cosmetics Including Use as Skinbleaching Agents in Cosmetic Preparations Also Regarded as Drugs. Available online: <https://www.govinfo.gov/app/details/CFR-2021-title21-vol7/CFR-2021-title21-vol7-sec700-13> (accessed on 11 May 2022).
55. Wang, Y.; Yang, H.; Pschenitzka, M.; Niessner, R.; Li, Y.; Knopp, D.; Deng, A. Highly sensitive and specific determination of mercury(II) ion in water, food and cosmetic samples with an ELISA based on a novel monoclonal antibody. *Anal. Bioanal. Chem.* **2012**, *403*, 2519–2528. [[CrossRef](#)]
56. Podgórska, A.; Puścion-Jakubik, A.; Grodzka, A.; Naliwajko, S.; Markiewicz-Żukowska, R.; Socha, K. Natural and Conventional Cosmetics—Mercury Exposure Assessment. *Molecules* **2021**, *26*, 4088. [[CrossRef](#)]
57. Dwijayanti, E. Susanti Analysis of Mercury (Hg) in Whitening Cream Distributed in Palu City by Atomic Absorption Spectroscopy. *J. Appl. Chem. Sci.* **2018**, *2018*, 430–433. [[CrossRef](#)]
58. Liu, S.; Zhang, P.; Liu, H.; Wang, W.; Lian, K. Determination of Trace Mercury in Cosmetics by Suspension- Sampling Hydride Generation Atomic Fluorescence Spectrometry. *Asian J. Chem.* **2013**, *25*, 7315–7318. [[CrossRef](#)]
59. Chen, K.-L.; Jiang, S.-J.; Chen, Y.-L. Determining lead, cadmium and mercury in cosmetics using sweeping via dynamic chelation by capillary electrophoresis. *Anal. Bioanal. Chem.* **2017**, *409*, 2461–2469. [[CrossRef](#)]
60. Wang, L.; Zhang, H. Mercury content in marketed cosmetics: Analytical survey in Shijiazhuang, China. *Cutan. Ocul. Toxicol.* **2014**, *34*, 322–326. [[CrossRef](#)]
61. Bin Ho, Y.; Abdullah, N.H.; Hamsan, H.; Tan, E.S.S. Mercury contamination in facial skin lightening creams and its health risks to user. *Regul. Toxicol. Pharmacol.* **2017**, *88*, 72–76. [[CrossRef](#)]
62. Safitri, E.; Irmawati, I.; Suhud, K.; Islami, N. Mercury Analysis of Body Lotion Cosmetic Using CVAAS Method: Case Study of Distributed Product in Banda Aceh. *Indones. J. Fundam. Appl. Chem.* **2020**, *5*, 35–41. [[CrossRef](#)]
63. Peregrino, C.P.; Moreno, M.V.; Miranda, S.V.; Rubio, A.D.; Leal, L.O. Mercury Levels in Locally Manufactured Mexican Skin-Lightening Creams. *Int. J. Environ. Res. Public Health* **2011**, *8*, 2516–2523. [[CrossRef](#)]
64. Ahmed, H.A.M.; Al-Qahtani, K.M.A.; Emara, H.; Janjua, M.N.; Alhafez, N.; Al-Otaibi, M.B. Determination of Some Heavy Metals in Eye Shadows Cosmetics. *Asian J. Chem.* **2017**, *29*, 1441–1446. [[CrossRef](#)]
65. Prasertboonyai, K.; Liawraungrath, B.; Pojanakaroon, T.; Liawraungrath, S. Mercury(II) determination in commercial cosmetics and local Thai traditional medicines by flow injection spectrophotometry. *Int. J. Cosmet. Sci.* **2015**, *38*, 68–76. [[CrossRef](#)]
66. Lu, Y.; Yu, J.; Ye, W.; Yao, X.; Zhou, P.; Zhang, H.; Zhao, S.; Jia, L. Spectrophotometric determination of mercury(II) ions based on their stimulation effect on the peroxidase-like activity of molybdenum disulfide nanosheets. *Mikrochim. Acta* **2016**, *183*, 2481–2489. [[CrossRef](#)]
67. Alqadami, A.A.; Naushad, M.; Abdalla, M.A.; Khan, M.R.; Alothman, Z.A.; Wabaidur, S.M.; Ghfar, A.A. Determination of heavy metals in skin-whitening cosmetics using microwave digestion and inductively coupled plasma atomic emission spectrometry. *IET Nanobiotechnol.* **2017**, *11*, 597–603. [[CrossRef](#)] [[PubMed](#)]
68. Salama, A.K. Assessment of metals in cosmetics commonly used in Saudi Arabia. *Environ. Monit. Assess.* **2016**, *188*, 1441–1446. [[CrossRef](#)]
69. Gao, Y.; Shi, Z.; Zong, Q.; Wu, P.; Su, J.; Liu, R. Direct determination of mercury in cosmetic samples by isotope dilution inductively coupled plasma mass spectrometry after dissolution with formic acid. *Anal. Chim. Acta* **2014**, *812*, 6–11. [[CrossRef](#)]
70. Jia, X.; Han, Y.; Wei, C.; Duan, T.; Chen, H. Speciation of mercury in liquid cosmetic samples by ionic liquid based dispersive liquid-liquid microextraction combined with high-performance liquid chromatography-inductively coupled plasma mass spectrometry. *J. Anal. At. Spectrom.* **2011**, *26*, 1380–1386. [[CrossRef](#)]
71. Qudus, H.; Purwadi, P.; Holilah, I.; Hadi, S. Analysis of Mercury in Skin Lightening Cream by Microwave Plasma Atomic Emission Spectroscopy (MP-AES). *Molecules* **2021**, *26*, 3130. [[CrossRef](#)]
72. Wang, W.; Bao, N.; Yuan, W.; Si, N.; Bai, H.; Li, H.; Zhang, Q. Simultaneous determination of lead, arsenic, and mercury in cosmetics using a plastic based disposable electrochemical sensor. *Microchem. J.* **2019**, *148*, 240–247. [[CrossRef](#)]
73. Bohari, N.A.; Siddiquee, S.; Saallah, S.; Misson, M.; Arshad, S.E. Optimization and Analytical Behavior of Electrochemical Sensors Based on the Modification of Indium Tin Oxide (ITO) Using PANI/MWCNTs/AuNPs for Mercury Detection. *Sensors* **2020**, *20*, 6502. [[CrossRef](#)]
74. Alqadami, A.A.; Abdalla, M.A.; Alothman, Z.A.; Omer, K. Application of Solid Phase Extraction on Multiwalled Carbon Nanotubes of Some Heavy Metal Ions to Analysis of Skin Whitening Cosmetics Using ICP-AES. *Int. J. Environ. Res. Public Health* **2013**, *10*, 361–374. [[CrossRef](#)]
75. NCBI Bithionol. Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/Bithionol> (accessed on 3 May 2022).
76. Greenspoon, J.; Ahluwalia, R.; Juma, N.; Rosen, C.F. Allergic and Photoallergic Contact Dermatitis. *Dermatitis* **2013**, *24*, 29–32. [[CrossRef](#)]

77. Agathokleous, E.; Calabrese, E.J. Formaldehyde: Another hormesis-inducing chemical. *Environ. Res.* **2021**, *199*, 111395. [CrossRef] [PubMed]
78. Jackson, E. Formaldehyde in Personal Care Products. *Ski. Pharmacol. Physiol.* **2012**, *25*, 236–240. [CrossRef] [PubMed]
79. Cekhov, A. *Determination of Free Formaldehyde in Cosmetic Products*; Council of Europe: Strasbourg, France, 2016.
80. Malinauskienė, L.; Blaziene, A.; Chomiciene, A.; Isaksson, M. Formaldehyde may be found in cosmetic products even when unlabelled. *Open Med.* **2015**, *10*, 323–328. [CrossRef]
81. Yuniati, W.; Amelia, T.; Ibrahim, S.; Damayanti, S. Analytical Method Development for Determining Formaldehyde in Cream Cosmetics Using Hypenated Gas Chromatography. *ACS Omega* **2021**, *6*, 28403–28409. [CrossRef]
82. Miralles, P.; Chisvert, A.; Alonso, M.J.; Hernandez, S.; Salvador, A. Determination of free formaldehyde in cosmetics containing formaldehyde-releasing preservatives by reversed-phase dispersive liquid–liquid microextraction and liquid chromatography with post-column derivatization. *J. Chromatogr. A* **2018**, *1543*, 34–39. [CrossRef] [PubMed]
83. Temel, N.K.; Gürkan, R. Combination of Ultrasound-Assisted Cloud-Point Extraction with Spectrophotometry for Extraction, Preconcentration, and Determination of Low Levels of Free Formaldehyde from Cosmetic Products. *J. AOAC Int.* **2018**, *101*, 1763–1772. [CrossRef] [PubMed]
84. NCBI Cadmium. Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/Cadmium> (accessed on 29 April 2022).
85. Bruzzoniti, M.C.; Abollino, O.; Pazzi, M.; Rivoira, L.; Giacomino, A.; Vincenti, M. Chromium, nickel, and cobalt in cosmetic matrices: An integrated bioanalytical characterization through total content, bioaccessibility, and Cr(III)/Cr(VI) speciation. *Anal. Bioanal. Chem.* **2017**, *409*, 6831–6841. [CrossRef] [PubMed]
86. Borowska, S.; Brzóska, M.M. Metals in cosmetics: Implications for human health. *J. Appl. Toxicol.* **2015**, *35*, 551–572. [CrossRef]
87. Godt, J.; Scheidig, F.; Grosse-Siestrup, C.; Esche, V.; Brandenburg, P.; Reich, A.; Groneberg, D.A. The toxicity of cadmium and resulting hazards for human health. *J. Occup. Med. Toxicol.* **2006**, *1*, 22. [CrossRef]
88. Liu, Y.; Chu, Y.; Hu, Z.; Zhang, S.; Ma, S.; Khan, M.S.; Chen, F.; Zhang, D.; Guo, L.; Lau, C. High-sensitivity determination of trace lead and cadmium in cosmetics using laser-induced breakdown spectroscopy with ultrasound-assisted extraction. *Microchem. J.* **2020**, *158*, 105322. [CrossRef]
89. Asra, R.; Rusdi; Yandra, R.B.; Nessa. Determination of Lead and Cadmium Added in Selected Lipstick Products Sold in Padang City Using Atomic Absorption Spectrophotometry. *Indones. J. Pharm. Clin. Res. (IDJPCR)* **2019**, *2*, 13–18. [CrossRef]
90. Hahn, D.W.; Omenetto, N. Laser-Induced Breakdown Spectroscopy (LIBS), Part I: Review of Basic Diagnostics and Plasma—Particle Interactions: Still-Challenging Issues within the Analytical Plasma Community. *Appl. Spectrosc.* **2010**, *64*, 335A–336A. [CrossRef] [PubMed]
91. Paudel, S.; Kumar, S.; Mallik, A. Atomic Absorption Spectroscopy: A Short Review. *EPRA Int. J. Res. Dev. (IJRD)* **2021**, *6*, 322–327. [CrossRef]
92. Lewen, N. The use of atomic spectroscopy in the pharmaceutical industry for the determination of trace elements in pharmaceuticals. *J. Pharm. Biomed. Anal.* **2011**, *55*, 653–661. [CrossRef] [PubMed]
93. Ma, S.; Tang, Y.; Ma, Y.; Dong, D.; Guo, L.; Zhu, H.; Liu, J.; Lu, Y. The pH effect on the detection of heavy metals in wastewater by laser-induced breakdown spectroscopy coupled with a phase transformation method. *J. Anal. At. Spectrom.* **2019**, *35*, 198–203. [CrossRef]
94. Ma, S.; Tang, Y.; Ma, Y.; Chu, Y.; Chen, F.; Hu, Z.; Zhu, Z.; Guo, L.; Zeng, X.; Lu, Y. Determination of trace heavy metal elements in aqueous solution using surface-enhanced laser-induced breakdown spectroscopy. *Opt. Express* **2019**, *27*, 15091–15099. [CrossRef]
95. Hahn, D.; Omenetto, N. Laser-Induced Breakdown Spectroscopy (LIBS), Part II: Review of Instrumental and Methodological Approaches to Material Analysis and Applications to Different Fields. *Appl. Spectrosc.* **2012**, *66*, 347–419. [CrossRef]
96. Brüsweiler, B.J.; Merlot, C. Azo dyes in clothing textiles can be cleaved into a series of mutagenic aromatic amines which are not regulated yet. *Regul. Toxicol. Pharmacol.* **2017**, *88*, 214–226. [CrossRef]
97. Brumley, W.C.; Jones, W.J. Comparison of micellar electrokinetic chromatography (MEKC) with capillary gas chromatography in the separation of phenols, anilines and polynuclear aromatics Potential field-screening applications of MEKC. *J. Chromatogr. A* **1994**, *680*, 163–173. [CrossRef]
98. Thompson, C.O.; Trenerry, V. Determination of synthetic colours in confectionery and cordials by micellar electrokinetic capillary chromatography. *J. Chromatogr. A* **1995**, *704*, 195–201. [CrossRef]
99. Bartter, T.; Irwin, R.S.; Abraham, J.L.; Dascal, A.; Nash, G.; Himmelstein, J.S.; Jederlinic, P.J. Zirconium Compound-Induced Pulmonary Fibrosis. *Arch. Intern. Med.* **1991**, *151*, 1197–1201. [CrossRef]
100. NCBI Chloroform. Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/Chloroform> (accessed on 29 April 2022).
101. National Toxicology Program. Substance Profile: Chloroform. In *NTP 11th Report on Carcinogens*; U.S. Department of Health and Human Services, Public Health Service: Durham, NC, USA, 2004.
102. Tripathy, H.; Pradhan, D.G.; Dash, B.C.; Mahapatra, G.N. Synthesis of Some New Halogenated N-Thiazolyl Substituted Hydroxy Acid Amides and Their Use as Possible Fungicides. *Agric. Biol. Chem.* **1973**, *37*, 1375–1383. [CrossRef]
103. Garcia, C.; Burgain, A.; Chaillot, J.; Pic, É.; Khemiri, I.; Sellam, A. A phenotypic small-molecule screen identifies halogenated salicylanilides as inhibitors of fungal morphogenesis, biofilm formation and host cell invasion. *Sci. Rep.* **2018**, *8*, 11559. [CrossRef] [PubMed]
104. Dréno, B.; Zuberbier, T.; Gelmetti, C.; Gontijo, G.; Marinovich, M. Safety review of phenoxyethanol when used as a preservative in cosmetics. *J. Eur. Acad. Dermatol. Venereol.* **2019**, *33*, 15–24. [CrossRef] [PubMed]

105. Alvarez-Rivera, G.; Llompart, M.; Lores, M.; Garcia-Jares, C. Chapter 9-Preservatives in Cosmetics: Regulatory Aspects and Analytical Methods. In *Analysis of Cosmetic Products*, 2nd ed.; Salvador, A., Chisvert, A., Eds.; Elsevier: Boston, MA, USA, 2018; pp. 175–224, ISBN 978-0-444-63508-2.
106. NCBI Hexachlorophene. Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/Hexachlorophene> (accessed on 11 May 2022).
107. Wade, N. Hexachlorophene: FDA Temporizes on Brain-Damaging Chemical on JSTOR. *Science* **1971**, *174*, 805–807. [[CrossRef](#)]
108. Kliegman, R.M.; Geme, J.S. *Textbook of Pediatrics*, 21st ed.; Elsevier: Amsterdam, The Netherlands, 2020.
109. NCBI Mercury. Available online: <https://pubchem.ncbi.nlm.nih.gov/element/Mercury> (accessed on 6 May 2022).
110. Denton, C.R.; Lerner, A.B.; Fitzpatrick, T.B. Inhibition of Melanin Formation by Chemical Agents. *J. Investig. Dermatol.* **1952**, *18*, 119–135. [[CrossRef](#)] [[PubMed](#)]
111. Ori, M.R.; Larsen, J.B.; Shirazi, F. Mercury Poisoning in a Toddler from Home Contamination due to Skin-Lightening Cream. *J. Pediatr.* **2018**, *196*, 314–317.e1. [[CrossRef](#)] [[PubMed](#)]
112. Wang, Z.; Fang, X. Chronic Mercury Poisoning from Daily Cosmetics: Case Report and Brief Literature Review. *Cureus* **2021**, *13*, e19916. [[CrossRef](#)]
113. Parengkuan, K.; Citraningtyas, G. *Analisis Kandungan Merkuri Pada Krim Pemutih Yang Beredar Di Kota Manado*; Sam Ratulangi University: Manado, Indonesia, 2013; Volume 2.
114. Omolaoye, J.A.; Uzairu, A.; Gimba, C.E. Heavy Metal Assessment of Some Eye Shadow Products Imported into Nigeria from China. *Arch. Appl. Sci. Res.* **2010**, *2*, 76–84.
115. Stockwell, P.B. The role of flow injection analysis within the framework of an automated laboratory. *J. Autom. Chem.* **1990**, *12*, 95–103. [[CrossRef](#)]
116. Mičová, K.; Friedecký, D.; Faber, E.; Polýnková, A.; Adam, T. Flow injection analysis vs. ultra high performance liquid chromatography coupled with tandem mass spectrometry for determination of imatinib in human plasma. *Clin. Chim. Acta* **2010**, *411*, 1957–1962. [[CrossRef](#)] [[PubMed](#)]