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TFOS Lifestyle: Impact of cosmetics on the ocular surface

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ABSTRACT

In this report the use of eye cosmetic products and procedures and how this represents a lifestyle challenge that may exacerbate or promote the development of ocular surface and adnexal disease is discussed. Multiple aspects of eye cosmetics are addressed, including their history and market value, psychological and social impacts, possible problems associated with cosmetic ingredients, products, and procedures, and regulations for eye cosmetic use. In addition, a systematic review that critically appraises randomized controlled trial evidence concerning the ocular effects of eyelash growth products is included. The findings of this systematic review highlight the evidence gaps and indicate future directions for research to focus on ocular surface outcomes associated with eyelash growth products.

1. Introduction

Eye cosmetics, or makeup, comprise a diverse array of products (Fig. 1). They include concealers, conditioners, creams, extensions, eyeliners, foundations, glues, mascaras, primers, removers, serums, shadows, and toners. These products may be either leave-on or rinse-off. Leave-on products are those intended to stay in contact with the skin for a certain period of time; rinse-off products are applied and removed soon afterwards [1]. A number of the ingredients in these products may act as allergens, carcinogens, endocrine disruptors, immunosuppressants, irritants, mutagens, toxins and/or tumor promoters, and may damage the ocular surface and adnexa.

In addition, there are numerous cosmetic procedures for the eye, including eyelash curling, dyeing, tinting, and perming, botulinum toxin, filler and platelet-rich plasma injections, chemical peels, conjunctival tattooing, eyelid piercing and tattooing, micro-dermabrasion, microneedling, and skin resurfacing and tightening. A number of these procedures may also be associated with adverse ocular events.

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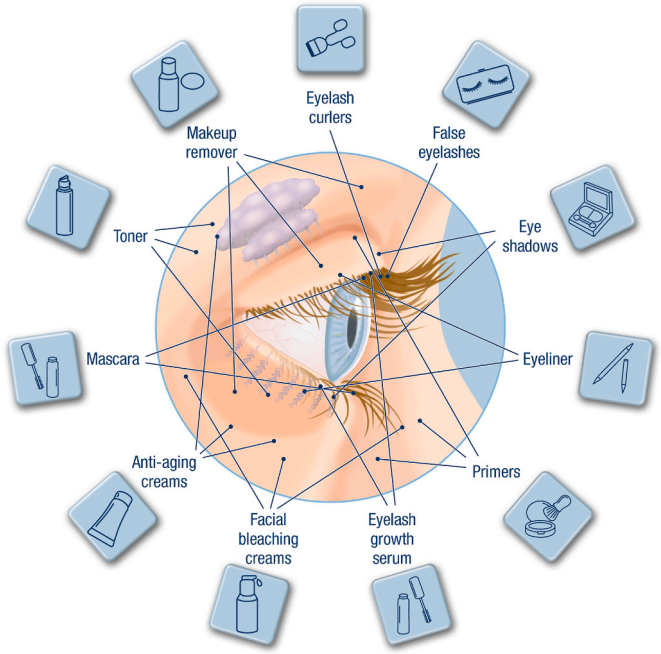

Fig. 1. Where to apply eye makeup and cosmetic products.

www.tearfilm.org) Workshop, entitled "A Lifestyle Epidemic: Ocular Surface Disease," which was undertaken to establish the direct and indirect impacts that everyday lifestyle choices and challenges have on ocular surface health. This article seeks to explain how the use of eye cosmetic products and procedures represents a lifestyle challenge, which may exacerbate or promote the development of ocular surface and adnexal disease. For the purpose of this Workshop, the 'Ocular Surface' is defined as the cornea, limbus, conjunctiva, eyelids and eyelashes, lacrimal apparatus and tear film, along with their associated glands and muscular, vascular, lymphatic and neural support. 'Ocular Surface Disease' includes established diseases affecting any of the listed structures, as well as etiologically related perturbations and responses associated with these diseases. Disease is considered from an etiological perspective, to include infection, inflammation, allergy, trauma, neoplasia, dysfunction, degeneration and inherited conditions. This article addresses multiple aspects of eye cosmetics, including their definition and history; market value and prevalence of use; psychological and social impacts; problems associated with cosmetic ingredients, products, and procedures; and regulations for use. This information was summarized in a narrative style review that, wherever possible, refers to outcomes from high-quality systematic review (Level I) evidence. In alignment with the other TFOS Lifestyle Workshop reports, the Evidence Quality Subcommittee provided a comprehensive database of appraised Level 1 evidence judged to be of potential relevance, which was considered in the writing of the report [2].

In addition, a systematic review that critically appraises randomized controlled trial evidence concerning the ocular effects of eyelash growth products is included. This systematic review focused on the question "Is the use of eyelash growth products associated with symptoms or signs of ocular surface disease?" The findings of this review, which are reported in Section 5.2.14, highlight the evidence gaps, and indicate future directions for research to focus on ocular surface outcomes associated with eyelash growth products.

1.1. Definitions

"Cosmetics." What are they? The answer depends upon where you live. As shown in Table 1, "cosmetics" are defined differently in various countries and regions around the world. Indeed, there is no global consensus on the definition of cosmetics.

The origin of the word "cosmetic" stems from the Greek language, and specifically from *kosmētikos,* skilled in adornment, *kosmein,* to arrange or adorn, and *kosmos,* order [3]. Of interest, classical Grecians considered an ordered arrangement as underlying beauty and morality [4]. As millennia passed, though, the cosmetic-induced enhancement of beauty has often been at odds with the concept of morality.

2. Eye cosmetics history

2.1. Cosmetic development and usage

2.1.1. Antiquity

Since before the age of antiquity (3000 BCE - 476 BCE), people have used eye makeup to "speak with the eyes" [5]. Whether it was the green pigment udju, applied heavily to the upper and lower eyelids in ancient Egypt beginning around 5500 BCE, or later in 3100 BCE the black kohl applied to eyelid skin and eyelashes, ocular cosmetics have been used for many millennia in Egyptian, Greek, Roman, Chinese, Japanese, Phoenician, Indian and Muslim civilizations. A primary goal was to darken the eyes, make them more expressive, attractive, and seductive, and present the appearance of youth and beauty [5-17].

However, the historic use of eye makeup was not limited to promoting allure. Rather, there were several additional reasons for the application of ocular cosmetics. For example, in ancient Egypt eye makeup was also used for health, protection, and resurrection after death. The objectives were to imitate the gods, seek divine assistance, shield the eyelid skin from the sun's glare, deter flies, protect against the Evil Eye, and serve as an essential funerary gift, to purify and permit entrance into the afterlife [5,6,10,14,16-18]. Of particular importance, ocular cosmetics were used with the intent of imparting medicinal benefits. In the Ebers papyrus from ~1550 BCE, green eyelid paint is mentioned in 39 out of 877 medical recipes, and was used for its perceived therapeutic properties as an eye salve (for example, to treat burns and inflammation) and an antibacterial agent [14,15]. Further, kohl eyeliner was applied for the prophylaxis and treatment of various eye conditions, including parasitic, bacterial, and viral infections [5,7,13,17,18]. As said by the Prophet Muhammed, "Treat your eyes with kohl, for it nourishes eyes and eyelashes" [19].

In the ancient world eye makeup was worn by both sexes in Egypt, but only by married women in Iran [5,8,11,12]. Grecian women used relatively little makeup, as they wanted to keep their skin pale [20,21]. They used kohl, as well as ground charcoal mixed with olive oil to create eyeshadow [20]. Roman women painted their eyes in many colors to produce the effect of longer eyelashes [22]. Roman women also used *Atropa belladonna* to induce pupillary mydriasis, which lasted for several days and was considered a sign of beauty [23]. Japanese women, in turn, whitened their face and eyelids with rice powder, and colored their eyelid edges and eyebrows orange-yellow with crushed safflower petals [5].

There were many ingredients in these ancient eye cosmetics. As noted by Juan Murube [5], ocular makeup in Pharaonic Egypt was often obtained from botanical sources (for example, henna, myrrh, incense, burnt almonds, olive oil), animals (for example, fat, honey, mammalian, lizard or bat blood, women's or animal milk, turtle brain), and/or minerals (for example, galena, stibnite, malachite). The most frequently used eye applications were the black mesdement, now known as kohl in modern Egypt, and composed mainly of galena (i.e., lead sulfide) or stibnite (i.e., antimony sulfide), as well as the green udju containing malachite (i.e., copper carbonate) [5,7,9,13,15,16,18,23]. Galena gradually became the chief constituent in kohl [6,15,18].

However, some of these ingredients may have been toxic [24-26]. Antimony and lead, for example, are prohibited from intentional inclusion in cosmetics in Canada and the European Union because of their toxic properties [26,27]. Application of lead sulfide-containing kohl to the eyelids of infants is associated with a significant increase in blood

Table 1
Cosmetics definitions in various countries or regions.

Country or region	Definition of a cosmetic product	Reference
USA	Product intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or function	[828, 844]
Canada	Any substance or mixture of substances, manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth and includes deodorants and perfumes	[845, 846]
Brazil, Argentina, Uruguay, Paraguay & Venezuela	Grade 1 products: personal hygiene products, cosmetics and perfumes which fall within the definition present in GMC Resolution n° 110/94 and which are characterized by having basic or elementary properties whose verification is not initially necessary and which do not require detailed information as to their mode and restrictions of use, due to the intrinsic characteristics of the product	[847]
European Union (EU) and Great Britain (post-Brexit; EU regulations may apply for Northern Ireland)	Any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and 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 odours	[848, 849]
South Africa	Any article, preparation or substance (except a medicine as defined in the Medicines and Related Substances Act (Act 101 of 1965) intended to be rubbed, poured, sprinkled or sprayed on or otherwise applied to the human body, including the epidermis, hair, teeth, mucous membranes of the oral cavity, lips and external genital organs, for purposes of cleansing, perfuming, correcting body odours, conditioning, beautifying, protecting, promoting attractiveness or improving or altering the appearance, and includes any part of the ingredient of any such article or substance	[850]
India	Any article intended to be rubbed, poured, sprinkled or sprayed on, or introduced into, or otherwise applied to, the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance	[851]
China	Products which can be spread on the outer surface of the human body (for example, skin, hairs, nails, lips etc.), the teeth and oral mucosa for the purpose of cleaning, protecting, beautifying, deodorizing and keeping in good condition, by way of smearing, spraying or other similar means	[852]
Japan	Articles with mild action on the human body, which are intended to be applied to the human body through rubbing, sprinkling or other methods, aiming to clean, beautify and increase the attractiveness, alter the appearance or to keep the skin or hair in good condition	[853]
Australia	A substance or preparation intended for placement in contact with any external part of the human body, including: the mucous membranes of the oral cavity; and the teeth with a view to altering the odours of the body; or changing its appearance; or cleansing it; or maintaining it in good condition: includes controlling through, for example, cleansing, moisturizing, exfoliating, and or drying: or perfuming it; or protecting it; or a substance or preparation prescribed by regulations made for the purposes of this paragraph; a substance or preparation that should not be intended to be systemically absorbed	[854]

levels [28], as well as asymptomatic [28] or symptomatic [29] lead poisoning. Yet even though lead is a cumulative toxin, there is no record of such symptoms occurring in the ancient Egyptians [13]. Another possible toxic compound was copper. Although it is recognized as an essential trace element [30], application around the eyes can produce acute local toxic effects, such as conjunctivitis, ulceration, and allergic contact dermatitis [14].

2.1.2. Medieval period

The medieval period, termed the Middle Ages in Europe, lasted from the 5th to late 15th centuries [31] and was a "dark time" for ocular cosmetics [10]. European society was dominated by strict Christian religions and makeup was considered immoral and sinful, because by changing appearance, one was thought to be altering the work of God [5, 10,32,33]. Indeed, for a period the church outlawed cosmetics, which were used only in brothels [32].

In European countries in the 1400's women equated beauty with a high forehead, egg-shaped face, small nose and lips, and no eyelashes and eyebrows. This look was thought to resemble the purity and innocence of a child [34]. Later in the 1500's, Venetian women resurrected the ancient Roman practice of dilating their pupils with "herba belladonna" extracts to create greater brilliance [35]. In the following centuries cosmetics continued to be used, but attitudes towards makeup varied and the use of cosmetics was openly frowned upon at many points in Western world history [8].

2.2. Modern times

2.2.1. 20th century

The beginning of the 20th century was revolutionary for eye cosmetics. A focus was "safety" and the use of substances that were not dangerous (such as lead, sulfur and mercury) [8]. Eyes were groomed using a variety of different devices including brushes, sticks and fingers [10]. As eyelash cosmetics were the most popular among all eye products, special brushes for eyelashes were in high demand [8].

Twentieth century society started to become more tolerant of eye makeup [7]. Women could choose their styles and many celebrities and high society women wore day and evening makeup [36]. Heavy makeup in Europe was also very popular in the theater [11]. Faces needed enhancement in the low light conditions of the stage.

One of the biggest makeup factories was situated in Berlin and belonged to Ludwig Leichner [37]. Leichner spent most of his career in Vienna as an opera singer. However, his basic and subsequently continued education was in chemistry. Leichner was very inventive not only in colors but also in the consistency and packaging of his products [38]. At the beginning of the 20th century, he was the most established cosmetic producer in Germany and one of the greatest exporters in Europe. The success of the Leichner factory was based on research and knowledge, close work with pharmacies, and with an emphasis on safety. Leichner spearheaded "the lead-free policy" for eye makeup [38]. This approach was based not only on common sense, but also on his own negative experience in the opera, as many singers at that time suffered lead poisoning because of heavy cosmetic use.

During the first decade of the 20th century, women typically used their own "in house" formulas for eye makeup [9]. The first individual to attempt commercialization of products for every woman was Mabel Williams, who was a drug manufacturer employee [39]. She created an item marketed as "lash-brow-ine," that was a mixture of petroleum jelly and oils, and led to the creation of Maybelline [39]. During the same time period, the film director David W. Griffith (1916) invented artificial eyelashes for the film industry [8].

On the USA West Coast another trend was developing. A Russian wig maker named Max Factor emigrated to that area and started production of custom made eye makeup for the movie industry [39,40]. Among his most notable clients were Gloria Swanson, Mary Pickford, Jean Harlow, Claudette Colbert, Bette Davis, Joan Crawford, Lucille Ball and Judy

Garland. He later launched a full range of cosmetics, calling it "make-up" [40].

The first commercial product branded as "eye shadow" was developed in 1910 in the USA [22]. Probably the most significant contributors to this development were Elizabeth Arden, Helena Rubinstein and Max Factor [37,41].

In the early 1920's suntans became an obsession of high-class society [42]. A bronze face was a most desired complexion, and many women and men spent hours exposing their face and body to acquire the desired tan. This is important not only because of the UV effect on the ocular surface, but also because of the fast-developing tanning cosmetics that were used on the eyelids as well.

The eagerness for more vivid and magnificent eyes continued with attempts to improve the attractiveness of the eyelashes. There is some controversy as to who invented the commercialized eyelash curler. The historical evidence leads us to William J Beldue [43], who called it the "Kurlash" in 1931. In the 30's, consumers were increasingly interested in ideas for eye beauty, and therefore the industry started to commercialize related products. The term mascara was coined in 1933 and the commercial product of Maybelline was sold to the mass market in drug stores [44]. This, with the affordable price of approximately 10 cents, was probably responsible for the first mass use of mascara. As interest in mascara increased in the early 40's a waterproof version gained popularity. The content of this mascara was mostly turpentine and a significant disadvantage was the strong smell. However, it was not until 1958 when the contemporary mascara tube with a spiral brush was introduced by Helena Rubinstein [37]. The so-called "automatic mascara" was named by the inventor "Mascara-matic". A similar product was commercialized later by Revlon. An analogous product was also released by Maybelline and called Ultra Lash Mascara [37].

It was following the introduction of the precursor commercial products for eyelash makeup, when serious complications were encountered. The most striking were those associated with Lash-lure – a mascara very popular in the early 30's [45]. This product, which contained a coal tar component, paraphenylenediamine (please see Section 7.1.3.), led to one death and the loss of sight of a number of people [45]. Given these adverse effects, the US Food and Drug Administration (FDA) began to regulate mascara products. Since then, the most described complication of mascara use is pigmentation of the bulbar and palpebral conjunctiva [46-48].

The second World War seriously interfered with cosmetic use and the fast developing cosmetic business [49]. The most inventive producers stopped their original products and started to produce camouflage wax, used by the soldiers.

In 1954 a brand of Max Factor called "Erace" was developed as a concealer and produced specially for the requirements of television (TV) stars [10]. This product addressed the special conditions in the TV studio and its use lasted until high-definition TV was introduced.

In the 60's the liquid eye liner in black and white colors was commercialized [50]. The trend was for all women to use such makeup in day-to-day life.

In the early 70's an automatic water-based mascara was introduced with the aim of being washable and easy to remove. About 10 years later Max Factor introduced the first colorless mascara, which was a base for future developments [40].

By the mid 90's newer technologies improved the application and wearability of eye makeup. Although, an emphasis on easy removal continued to be made, volume and eyelash elongation were in high demand [50]. To create thicker and longer eyelashes companies started to use acrylic co-polymers. Since then, the composition of mascara has been diverse and complex.

2.2.2. 21st century

The 21st century has ushered in a thriving makeup industry [51,52]. For example, market research in the UK showed that 80% of adult women had used face and eye cosmetics during the previous year, and that this percentage jumped to almost 90% for women under the age of 55. The most commonly applied products were mascara, eyeliner and eyeshadow [53].

Today, the glamour world and social media influence the way people apply makeup. This is not limited only to women as men too are seen sporting trending looks. Celebrities and icons have established numerous groundbreaking styles, such as frosted or smoky eye makeup, colorful eyeliner and eye shadow, and glossy or sparkly eyelids with pearlescent pigments. The use of mascaras, eyebrow pencils and eyebrow brushes for taming unruly brows, eyelash primers, eye cosmetic removers, eyelash conditioners, eyelash perming (lash-lift) and solutions (for example, hydrogen peroxide and thioglycolic acid), lash dyeing/tinting, among others, have gained popularity [51].

To maintain a naturally curled look of the eyelashes, eyelash curlers (electric or non-electric) are being extensively used [54]. Another indication for using hair curlers is for curling surgically transplanted scalp hair applied to the eyelash margin or brows [5]. False eyelashes, eyelash extensions with eyelash glue adhesives as well as the use of eyelash growth serum have become widespread [55-57]. Until the 2000's, over the counter makeup products like eyeliner, mascara and eye shadow were the only products to enhance defining the eyes. In 2008, there was another addition to the armamentarium with approval by the US FDA of Bimatoprost 0.03%, as an eyelash growth stimulator. This molecule was previously being used solely as an anti-glaucoma agent. However, this prostamide found new indications in the treatment of eyelash hypotrichosis by just a single daily application to the skin of the upper eyelid margin.

Eyelid tattooing using various chemicals for polychromatic figures has gained popularity too. Supplementary adornment like eyebrow and eyelid piercings is common across sexes in younger age groups. To minimize signs of aging around the eyes, people are also increasingly using periocular anti-aging and rejuvenating creams.

With the recognition of need for 'long-lasting' or 'ever-lasting' cosmetic products, formulations containing stronger preservatives, fragrances, emulsifiers and surfactants have emerged [53].

"Cosmeceuticals" is a term used for an ever-expanding category of cosmetic products that contain an active ingredient and claim drug-like benefits but have none of the oversight such as premarket approval or post-market surveillance mechanisms that the US FDA affords to medical devices or pharmaceuticals (for example, isopropyl cloprostenate, a prostaglandin analogue for eyelash growth) [58]. The current eye cosmetics manufacturing trend is the inclusion of preservatives to prolong shelf life and prevent growth of bacteria during storage to control infection. Benzalkonium chloride (BAK) is the most commonly used preservative in eye cosmetics [59,60], and is discussed in detail in Section 6.1.1.

Eye makeup products included in 'toy makeup sets' intended for children and teenagers are also in vogue and may include face paints, glitter, and eyeshadow. They have, however, been shown to contain high quantities of zinc, cobalt and chromium [61], as well as asbestos [62].

Eye cosmetic removal products are also used extensively, including oil- and alcohol-free formulations, oil-based microemulsions or hyaluronic acid-containing micelle solutions [63]. Dark circles under the eyes have a similar association across societal cultures with tiredness, sadness and aging. Dark circles are a main reason for people around the world to purchase eye concealer [64,65]. The desire for effective management of hyper-pigmentary skin disorders has led to the marketing of depigmenting products and chemical peels. Combinations of vitamin C have been used in combination with peels and α-hydroxy acids for melasma or patients with dark circles on the lower eyelids [66-70]. Retinol, a natural form of vitamin A, has also been used for the correction of under-eye dark circles [71,72]. Topical retinoids can cause dryness and irritant reactions, especially if used near the lower eyelid region where the skin is extremely thin (see Section 5.2.15). Vitamin E is considered an active ingredient and a potent antioxidant to protect

against ultraviolet rays and environmentally induced free radicals [73,74]. Topical vitamin K has a lightning effect on the skin and leads to the faster resolution of bruising after laser treatment [75,76]t.

3. Psychosocial aspects of eye cosmetics

3.1. Sex and gender variations

As described in Section 4, cosmetics are typically associated with use by females. However, since the 1980s, it has become socially acceptable and increasingly mainstream for men to pay greater attention to their physical appearance [77]. In 2020, the global men's personal care market was valued at $124.8 billion and is forecasted to reach over $275 billion by 2030 [78].

To counteract the perception that masculinity is reduced if men use cosmetic products, marketing campaigns regularly involve product endorsements by popular male or nonbinary celebrities. Combined with frequent exposure to these advertisements, social acceptance for men to use cosmetic products has increased [79,80]. The male cosmetics markets have been well established in China, South Korea and Japan where the influence of boy bands and pop culture has fueled interest [81]. Western print media, including news outlets such as the New York Times [80], The Guardian [82,83] and men's lifestyle magazines [84] have included pieces with advice specifically targeted at men. Men are commonly reported to be using concealer, foundation, tinted moisturizer and eyeliner, as means of minimizing blemishes and dark eye circles or enhancing their natural features. In 2018, global brand, Chanel launched a male-specific color cosmetics line, "Boy de Chanel" [85] that included such products.

MAC cosmetics were one of the first brands to position themselves as an all-inclusive, sex-neutral beauty brand when they launched in 1984 [86]. Data from 2021 suggest sex-neutral or unisex makeup brands will likely become mainstream with sex stereotypes softening and consumers being more aware of changing social norms including the importance of inclusivity [87].

3.2. Variations in cosmetic use in adults, teenagers and children

"Playtime" or "dress-up" is likely one of the earliest times children encounter cosmetic-like toy products. Toy makeup kits may include eyeshadows, lip products and nail products [61]. These products are usually water-based formulations and should be easy to wash off but may contain allergenic fragrances [88] and powder-based toy products may contain sensitizing contact allergens, such as nickel [61].

As children grow older, they may explore the use of cosmetic products that are used by adults. A 2016 report found 54% of 12- to 14-year old children in the USA use eye makeup (mascara or eyeliner) [89]. The report also found that teens tended to prefer a natural look and cosmetics use is higher among teen girls and those with a smartphone [89]. The popularity of online tutorials and the desire for teens to use makeup as a means of self-expression have been attributed to the popularity of makeup in this age group [89].

3.3. Geographic variations

In the USA, 62% of women report regular application of ocular cosmetics with mascara being most commonly used (i.e., 48% of women) [90]. Similarly, eye makeup was found to be used by 80% of women in the UK [91], 49.7–59.4% of Korean women [92] and 26.5–61.6% in women from the Netherlands [93].

3.4. Drivers for eye makeup use: anti-aging goals, professional needs, peer pressure, general media, social media, and influencers

What is beauty? This is a difficult question to answer [94]. Societal pressures, the influx of near constant information through social media, and the COVID-19 pandemic all play roles in the increasing demand for cosmetics to enhance beauty. The advent of filters on different social media platforms are certainly contributing to ideals and is thought to drive the population to seek out information and invest in aesthetic procedures [95]. During the COVID-pandemic the demand for facial plastic surgery rose to unprecedented numbers [96]. The combined effect of utilizing work-from-home video conferencing and being able to incur downtime to have procedures is thought to have increased the interest in aesthetic procedures and cosmetics. Video conferencing can prompt an increase in the attention paid to facial features, especially the eyes [96]. Social media platforms encourage the use of filters that portray unrealistic ideals of how skin and facial features should look [96]. One study also suggested that people could have been motivated by the overall psychological impact of the COVID-19 pandemic. Isolation, depression, and a feeling of uncertainty could be the reason why people chose to seek out aesthetic procedures [96].

There are many social networking sites for posting photography. Instagram and Facebook are two of the most popular [97]. Do these platforms drive behavior? These platforms allow for photos to be edited by the participants uploading personal photos. One of the most common reasons that cause people to edit photos is to hide skin lesions. The filters can "remove" fine lines and wrinkles. All these behaviors encourage unrealistic expectations and increase societal pressures to look a certain way. For some it's looking younger, for others it is looking good naturally, and still for others there is this need to look a certain way to be happy [98-100]. This can translate into seeking out cosmetic dermatological procedures and cosmetics that mimic the digital filters applied to the photographs [98-100].

There are many reasons why people are motivated to enhance or change their appearance. Whatever their motivation, it's rarely just about physical beauty and the ideals that go along with that; it is more about what that physical change has on how the person feels about themselves [101]. Age is one of the reasons for seeking a certain procedure. Someone in their 20's or 30's will likely have different motivations and expectations than someone in their 50's or 60's [102].

Interestingly, many motivations are not to please anyone but instead the patients' perception of themselves. Rarely are patients choosing to have cosmetic procedures because of a spouse preference or request; it tends to be a very personal decision that was not prompted by another person [102].

The use of cosmetics and cosmetic surgery has grown exponentially. As these two industries have expanded, so has the money spent to compete with the growing markets. Advertisers recognize the power of influencers, who are individuals with established credibility in a specific industry. The influencer market grew from $1.7 billion in 2016 to $9.7 billion in 2020. In 2021, it soared to $13.8 billion, indicating a steady growth. In 2022, the market is projected to expand to a $15 billion industry [103].

Social media influencers are paid by advertisers anywhere from $100-$1000/post depending on if they are a micro or macro influencer [104]. These social media influencers are simply utilizing the products in their everyday lives. Consumers may not be making decisions based on evidence-based medicine and are instead relying on influencers' personal anecdotal experiences to make choices.

A desire to alter skin appearance is why so many choose to edit their personal photos on social media [98]. Skin aging is a complex and dynamic process that has a strong social and psychological impact [105]. Bone loss, muscle atrophy, loss of collagen and elastin, as well as skin thinning all contribute and will manifest in various ways, such as wrinkles and decreased volume [106]. The eyes are centrally located on the face and are often the center of attention for cosmetic and cosmetic surgery discussions. Through the COVID-19 pandemic this has been even more amplified, as that is the only part of the face that is exposed while wearing a mask. Due to the anatomy and structures of the periorbital region this is the first area to be affected and noticed by the observer and patients alike [105]. The skin in the periorbital region is

thinner, measuring 0.5 mm vs 1 mm or thicker for the rest of the body [107]. The youthful face demonstrates full brows and skin with volume and elasticity. The midface is wider through the cheeks and represents an upside-down triangle. Aging causes the brow to droop, the upper and lower eyelids begin to sag either due to dermatochalasis or blepharoptosis when the levator tendon is stretched; the lower half of the face gets wider and now represents a triangle [108]. Tear film integrity is important to beauty too. The Purkinje images that are reflected in the healthy tear film create beautiful reflections. Those images that we see contribute to the perception of the eye sometimes described as "sparkle" [109]. When a patient's tear film is disrupted due to ocular surface disorders the "sparkle" is diminished. In chasing eye beauty, people make choices that can make their eye appearance less desirable, and then may seek more cosmetics and cosmetic procedures to offset those choices creating a vicious cycle that can compromise ocular health further [109].

The perception of beauty and how beauty is defined depends on many factors. The biological make up of the person, how they feel about themselves and others, where they live, whom they surround themselves by, what their family and friends believe, whom they choose to follow on social media, all influence beauty [110]. Symmetry, averages, ratios, and homogeneity allow for the perception that things are aligned with the primitive brain [111]. Perhaps this is the origin of beauty ideals. Marketers have been utilizing these and establishing beauty ideals since mass communication has been introduced. These ideals are perpetuated in the market and throughout cultures with billboards, print, television, magazines, and now with social media. Social media platforms have influenced and will further influence how society adapts and sets beauty principles. The onus on eye care professionals is to learn what their patient's aesthetic desires and how to ensure they do not jeopardize their ocular health in the name of beauty [112].

3.5. Perceptions regarding branded/premium products

Beauty brands can be subdivided into premium and mass-produced segments. For example, in 2020, L'Oréal dominated the global beauty industry with revenue of €27.99 billion (USD$33.93 billion), with 37% revenue attributed to the Luxe division which includes brands such as Lancôme and Yves Saint Laurent [113]. Consumers perceive premium branded products to be of better quality [114]. The inclusion of natural or organic ingredients, products that target specific skin complaints (for example, anti-aging), innovative packaging, eco-friendly business practices and exclusivity all contribute to the positioning of cosmetic products under the premium sector [115,116].

Premium products (and therefore price) do not correlate with higher effectiveness [115]. In addition, premium products may use packaging to influence consumer perception, application habits and compliance. This concept was shown in a randomized controlled study by Lodén et al. that compared the effect of a premium anti-wrinkle cream with a regular moisturizing cream in eighty women aged 35–64 years over six weeks [115]. Participants were randomly assigned to either: the premium product in its luxury jar (group A), a regular moisturizer filled in a luxury jar (group B), or the premium product in an unlabelled, neutral jar (group C). Participants assigned to products supplied in the luxury jar (group A and B) used significantly more cream than those assigned to the premium product in an unlabelled jar. However, after six weeks of use, there were no significant differences between the three groups relating to the effects on wrinkles and smoothness, or in the assessment of the skin of participants feeling younger or more beautiful.

Terminology associated with premium cosmetic products includes "medical grade" which is not a regulated term bound by definitions, rules or industry standards. Personal care products can either be a drug or a cosmetic; both terms are clearly defined by individual jurisdictions globally and are regulated in very different ways. While consumers may perceive "medical grade" products to be more efficacious, this is unlikely. Inclusion at a therapeutic dose would exceed the maximal allowable concentration and force regulatory approval as a medicine rather than as a cosmetic.

3.6. Religious/cultural practices

Application of Kajal, collyrium, surma or kohl to highlight the eyes is a common practice in Asia, Africa, and the Middle East. They are applied not only to the eyes of adult women and men, but to infants and children too for the intended purposes of protecting the eyes and for the treatment of various ailments. Kajal is a black-colored semisolid material which consists of carbon black and is either applied by a blunt applicator, as a stick or pencil or using the fingertip. The Siddha and Ayurveda systems of indigenous medicine use Kajal for its therapeutic benefits, for example as a coolant for the eyes and is believed that it provides protection from the harmful rays of the sun [117]. Traditionally, it is also thought that applying a little kajal dot on the forehead or behind the ear or a thicker lining over the lower eyelid margin of women and children, protects them from the 'Evil Eye' [117]. In many of the traditional dance forms in India, Kajal is applied to highlight the eye expressions and movements.

'Surma' is a fine powder produced by grinding certain mineral stones, along with the addition of some other herbs and can be applied directly on the eyelid margin using an applicator or fingertip, to enhance appearance. In Arab countries black and lustrous antimony trisulfide and the ore stibnite were used to formulate 'Kohl' (Arabic for eye makeup). But as this was expensive, galena (lead sulfide) with similar properties, became a more popular alternative [118]. It was believed to protect the eyes from the dust particles and harmful effects of ultraviolet radiation from the sun [119].

Kohl was extremely popular in Islam and was used by both sexes during festivals, weddings and even for offering prayers in the mosques. It is said that Prophet Muhammad used kohl and recommended others to use it because he believed that it was beneficial for the eyes [49,120]. According to the Prophet- "One of the best kinds of kohl that you use is Ithmid (antimony); it brightens the vision and makes the hair (eyelashes) grow" [120]. Amongst the Sunna community, applying kohl is advocated as a part of a behavioral guideline [49].

However, over time, kohl preparation practices have varied greatly and excessive use of lead has been reported to cause systemic adverse effects [121-123]. As a result of this, strict manufacturing regulations have come into force in various regions of the world.

In recent years, new entities like 'halal cosmetics' and 'halal makeup' have emerged among young Muslim population, wherein cosmetic products are free from forbidden ingredients (for example, pig-derived) and are also 'wudu-friendly' (permeable to water) and compliant to Islamic standards. These products are now in vogue globally, but especially in the Middle East [124].

Additional information concerning the influence of religious and cultural practices on the ocular surface may be found in the Societal Challenges Subcommittee report [125].

3.7. Community sharing practices

The repeated use of a single cosmetic product over time can introduce microbes into the container. After 3 months of use, microbial presence was found in over 35% of tested mascaras that were assigned to participants for their sole use [126]. A separate study reported 79% of used mascaras tested positive for *Staphylococcus aureus* and 13% were contaminated with *Pseudomonas aeruginosa* [127], a pathogen that can cause severe corneal infection [128]. The amount of product contamination is related to the amount of use, the age of the product and the number of users; for example, where cosmetics are shared between users, or perhaps if the product is a 'tester' at a cosmetic counter [129,130]. Testers at cosmetic counters and the sharing of cosmetics (such as those used by professional makeup artists) have been the subjects of concern since the COVID-19 pandemic. Sharing of eye makeup may also

serve as a conduit for the transfer of Demodex [131] and viruses [132]. As personal microbes accumulate on brushes, sponges, and other applicators, these tools should not be shared between individuals [133].

The practice of sharing cosmetics among people in a community can result in outbreaks of eye infections [134]. In a survey of 484 Malaysian adults, only 29% agreed with the statement "sharing cosmetic products with family members/friends can transmit bacterial infection". Variations in how eye cosmetics are applied may impact the likelihood of contaminating a cosmetic product and the chance of subsequent transmission to the next user. For example, eyeliner can be applied to the eyelid margin at the mucocutaneous junction (also referred to as "tightlining" or "waterlining") or along the periocular skin [135]. The tip of a pencil eyeliner or applicator brush that is in contact along the mucocutaneous region of the eyelid would be expected to be contaminated with any pathogens in or around the eye. The higher water content of a liquid eyeliner likely further increases the chances of contamination; a contaminated liquid eyeliner should be discarded. However a pencil eyeliner tip can be broken off and resharpened to remove exposed eyeliner, therefore reducing contamination [131,135,136].

4. Eye cosmetic market and prevalence of use

4.1. Current worth and estimated future net worth

The global eye makeup market was valued at $15.5 billion (USA) in 2020 [137]. It is projected to grow at a compound annual growth rate of approximately 6% during from 2021 to 2026 [137], which will duplicate the rate from 2014 to 2019 [138]. Analysts estimate that the worldwide eye makeup market will exceed $23 billion (USA) by 2028 [139]. The makeup products that will dominate the market share will most likely first be mascara [140], followed by eyeliner [141] and eyeshadow [142].

North America is the largest consumer of eye makeup products and Europe is second, whereas Asia Pacific is the fastest growing market [143-146].

Although the projected eye makeup sales are considerable, they pale in comparison to those of the global beauty industry. That market's value was estimated to be $603 billion in 2021 [147], with an annual total predicted to exceed $716 billion by 2025 [139,148].

4.2. Main trends

The predicted trend in the eye makeup market is towards products that are natural, clean and sustainable, and that are aligned with wellness and health [142,148,149]. "Natural" refers to products that are made completely from natural, not artificial, ingredients; "clean" reflects the desire for healthy, as compared to "bad" ingredients; and "sustainable" signifies materials that are produced with minimal impact on the Earth's natural resources [148]. This beauty trend is fueled, at least in part, by increased consumer awareness of the adverse effects of harmful chemical ingredients in eye makeup [139,150,151]. To help achieve this safety trend, we need standardized and universally accepted definitions of the words "natural" and "clean" [149]. To date, such definitions do not exist. Instead, the meaning of these words is typically subjective and brand-driven [149].

In terms of products, there is a trend towards creative eye makeup, with bolder mascaras, multi-chromatic eyeshadows, brighter eyeliners and embellishments (for example, appliqués) [152-154]. Also gaining popularity are waterproof products, that can survive hot and humid summer conditions [149]. The focus of this trend is the female, because women are the primary users of eye cosmetics [139]. However, cosmetic use is also increasing among men [137].

The specific trends in the global eye makeup market show country-specific variations. One example is in Saudi Arabia, where a recent law echoes the sentiments of the strict Christian religions of the medieval period (Section 2.1.2). This Saudi law seeks to ban "tempting eyes" of women, in particular those "uncovered eyes with a nice shape and makeup," or "even without makeup if they are beautiful" [155]. In effect, women with "alluring eyes" will be required to wear a full veil, as dictated by Saudi Arabian Committee for the Promotion of Virtue and the Prevention of Vice [155].

4.3. Commercialization

Because of the COVID-19 pandemic, governments of many countries imposed complete lockdowns, resulting in numerous supply chain disruptions [137,149]. These difficulties led to a decline in the production and distribution of eye makeup [139,142,149]. Pandemic-related travel restrictions have also contributed to a change in the way people obtain their ocular cosmetics. In the past, consumers purchased most beauty products in person in traditional stores, but they have now increasingly gravitated to e-commerce [149,156]. Indeed, online sales are projected to soon make up almost 50% of the total [148,156].

Social media platforms, such as Facebook, Instagram, Twitter and YouTube, have played a significant role in promoting the online sales of eye makeup [139,142]. These digital outlets have driven product demand and provided product-specific beauty education [6,19]. The decision of the consumer about what eye makeup to buy, though, is not influenced solely by immersive digital experiences; rather, it is also profoundly impacted by close friends and family members, as well as by celebrities [148,149,151].

In the future artificial intelligence may play a major role in commercialization strategies [149]. Artificial intelligence could serve as an eye makeup advisor by analyzing the self-image of a consumer and offering personalized recommendations based upon their ocular features [149]. It has been estimated that by the year 2025, approximately half of all supply chain organizations will be investing to support artificial intelligence and advanced analytics for their eye makeup market [149].

4.4. Marketing considerations

Cosmetics companies are aware of consumer purchasing habits. These are significantly influenced by personal emotions and experience, by the brand name, quality, price, accessibility, and packaging of the product, and by company advertising, promotions and service [157-161]. Companies are also aware that cosmetics are extremely important for consumer wellbeing. According to a survey, 88% of Europeans polled claimed that it is hard to live without cosmetics [162]. These understandings serve as a basis for marketing considerations used in the world of cosmetic goods [163].

5. Eye cosmetics: ingredients

Cosmetic ingredients serve a myriad of purposes and are often included in eye makeup to function as an abrasive, absorbent, antimicrobial, antioxidant, buffer, colorant, emollient, emulsifier, film-former, humectant, pH adjuster, preservative, ultraviolet light protector, skin conditioner, solvent or surfactant, as well as anticaking, antifoaming, antistatic, bulking, emulsifying, opacifying or viscosity decreasing agents (Tables 2 and 3). The ingredients provide these functions in products such as around-eye-creams, eyeliners, eyeshadows, eyelash glues, lotions, makeup primers, makeup removers, mascaras, moisturizers, serums or wet wipes (Tables 2 and 3).

However, there are significant concerns related to many cosmetic ingredients. The US FDA has estimated that 12,500 chemicals are used in cosmetics, but fewer than 20% of these compounds have been reviewed for safety by scientists in the Cosmetic Ingredient Review [164]. Eleven of these ingredients have been banned in the USA, whereas more than 1300 of these chemicals are restricted or banned in the European Union [165-170]. A number of these ingredients may act as allergens, carcinogens, endocrine disruptors, immunosuppressants, irritants, mutagens, toxins and/or tumor promoters, and may damage the ocular surface and

Table 2
Evidence-based concerns about various ingredients in ocular cosmetics. Preservatives to avoid are italicized.

Ingredient	Function	Products	Concerns/adverse effects
Acetyl hexapeptide	anti-wrinkle	around-eye cream, serum	mild neurotoxin and irritant [298]
Acrylates	suspending agent film-former, adhesive	around-eye cream, eyelash glue, eyeliner, eyeshadow, glitter, makeup remover, mascara, serum	carcinogenic [245], allergen [855]
2-Bromo-2-nitropropane-1, 3-diol)	*preservative*	*serum*	*formaldehyde-releasing preservative - toxic [188]*
Benzalkonium chloride	*antimicrobial, antistatic agent, cosmetic biocide, preservative, surfactant*	*eyeliner, makeup remover, mascara*	*toxic [188,205], allergen [216], irritant [177]*
Benzophenone	protect against ultraviolet light	Moisturizer	carcinogen [856,857], endocrine disruptor [858-861], toxic
Butylated hydroxyanisole	antioxidant	around-eye cream, eyeliner, eyeshadow, mascara, moisturizer, serum	possible carcinogen [862-864], endocrine disruptor [865], allergen [866], irritant [867]
Butylated hydroxytoluene	antioxidant	around-eye cream, eyeliner, eyeshadow, makeup primer, makeup remover, mascara, moisturizer, serum	carcinogen [868], tumor promoter [869,870], allergen [216, 866], toxic or harmful [871], endocrine disruptor [868]
Butylene glycol	humectant, skin-conditioning, viscosity decreasing agent	around-eye cream, eyeliner, eyeshadow, eyelash glue, makeup primer, makeup remover, mascara, moisturizer, serum	irritant [872]
Caffeine	antioxidant, protects against ultraviolet B radiation	eyeliner, eyeshadow, makeup primer, mascara, moisturizer, serum	may delay wound healing [873]
Carbon black (D&C Black No. 2)	colorant	eyelash glue, eyeliner, eyeshadow, mascara	carcinogen [874-877]
Carnauba wax	emulsifier	around-eye-cream, eyeliner, eyeshadow, glitter, makeup primer, makeup remover, mascara, moisturizer, serum	contact dermatitis [249,250]
Castor oil	eyelash conditioner	around-eye-cream, eyeliner, eyeshadow, glitter, makeup primer, makeup remover, mascara, serum	irritant [236]
Chlorhexidine digluconate	*antimicrobial, cosmetic biocide, preservative*	*around-eye cream, eyeliner, makeup remover, serum*	*allergen [216]*
Chlorphenesin	*antimicrobial, cosmetic biocide, preservative*	*around-eye cream, eyeliner, eyeshadow, eyelash glue, makeup primer, makeup remover, mascara, moisturizer, serum*	*toxic* [215], *allergen* [878], *irritant* [177,879], *immunosuppressant* [878]
Cocamide diethanolamine	emollient, thickener, dispersant	cleanser	irritant [257], carcinogenic [258]
Cocamidopropyl betaine	surfactant	eyeliner, glitter, makeup primer, makeup remover, moisturizer, serum	contact dermatitis [260]
Cyclopentasiloxane (cyclomethicone)	skin-conditioning agent	eyeshadow, eyeliner, makeup primer, mascara, serum, eye makeup remover, glitter	expected to be toxic or harmful [871], endocrine disruptor [880]
Cysteamine	skin lightning agent	cream	minimal to no side effects [881]
Dehydroacetic acid	*preservative*	*around-eye cream, eyeliner, eyeshadow, makeup primer, makeup remover, mascara, moisturizer, serum*	irritant [177,882]
Diamond dust/powder	optical diffusion	around-eye cream, eyeshadow, glitter, makeup primer, mascara, serum	corneal and conjunctival mechanical abrasion/trauma [386]
Diazolidinyl urea	*preservative*	*moisturizer, mascara, eye makeup remover, around-eye cream, eyeliner, serum, glitter*	formaldehyde-releasing preservative - toxic [188]
Diethanolamine	pH adjuster	serum	carcinogenic if converted to *n*-nitrosamines [863,883,884], toxic or harmful [871,885], prohibited for use in Europe [886]
DMDM-hydantoin [1,3-Bis (hydroxy-methyl)-5,5-dimethylimidazolidine-2,4-dione]	*preservative*	*moisturizer, eye makeup remover, around-eye cream, eyeliner, serum, glitter*	*formaldehyde-releasing preservative - toxic [188]*
Ethanolamine	pH adjuster, buffer	moisturizer	carcinogenic if converted to *n*-nitrosamines [887], prohibited for use in Europe [885]
Ethylhexylglycerin	*preservative, surfactant, emollient, skin-conditioner*	*around-eye-cream, eyelash glue, eyeliner, eyeshadow, glitter, makeup primer, makeup remover, mascara, moisturizer, serum*	*contact dermatitis [231], eye toxicity [232]*
Ferulic acid	anti-oxidant	around-eye-cream, moisturizer, serum	restricted use in Japan [888]
Formaldehyde-releasing compounds	*cosmetic biocide, preservative*	*serum, eyelash glue*	toxic [188], mutagen, carcinogen and allergen [184,210,214]
Gold	colorant	eyeshadow	allergy [265]
Glycolic acid	cleanser	serum, moisturizer, around-eye-cream, makeup primer, makeup remover	irritant [889]
Imidazolidinyl urea	*preservative*	*mascara, eye makeup remover, around-eye cream, eyeliner, serum, eyeshadow*	formaldehyde-releasing preservative - toxic [188]
Isopropyl alcohol	antifoaming, solvent, viscosity decreasing agent	eyeliner, makeup remover, mascara, moisturizer, serum	skin barrier disruptor [890], irritant [891], toxic [871,892,893]
Kohl (lead-containing)	colorant	eyeliner	toxic [28]
Kojic acid	antioxidant	serum	possible carcinogen [887]
Lanolin	emollient	eyeliner, makeup primer, makeup remover, mascara, moisturizer	allergen [272]
Methyldibromo glutaronitrile	*preservative*	*lotions, wet wipes*	*allergen, banned for use in cosmetics buy European Union [894]*

(*continued on next page*)

Table 2 (*continued*)

Ingredient	Function	Products	Concerns/adverse effects
Methylisothiazolinone	*preservative*	*eyeshadow, glitter, makeup remover, mascara, moisturizer, serum*	*toxic [236], neurotoxic [237], allergen [234,235], banned in Canada [239]*
Nylon	bulking and opacifying agent	around eye cream, eyeliner, eyeshadow, makeup primer, mascara, serum	inflammation [274]
Paraben (for example, ethylparaben & methylparaben)	*preservative*	*moisturizer, mascara, eyeshadow, eyeliner, around-eye cream, serum, glitter*	*toxic [215], endocrine disruptor [219,865], allergen [216,895], genotoxic [219]*
Para-phenylenediamine	colorant	eyeliner, eyeshadow, mascara	toxic [896]
Per- and poly-fluoroalkyl substances	skin-conditioning	eyeliner, eyeshadow, mascara	endocrine disruptor [897], carcinogenic [898]
Petrolatum	skin-conditioning agent	moisturizer, eyeshadow, eyeliner, around eye cream, makeup primer, glitter	expected to be potentially toxic or harmful [871], possible contamination with polycyclic aromatic hydrocarbons [899], which are toxic, mutagenic and carcinogenic [900]
Phenoxyethanol	*preservative*	*eyeshadow, moisturizer, mascara, serum, eyeliner, makeup primer, around-eye cream, makeup remover, glitter, eyelash glue*	*toxic [215,901], allergen [902], irritant [177]*
Phenylethyl resorcinol	skin-lightning	around-eye-cream, serum	contact dermatitis [282,283]
Phthalate	solvent	fragrances, makeup remover	cytotoxic [285], endocrine disruptor [286,287], neurotoxic [288], sleep problems [290]; dibutyl phthalate is banned in Europe [293]
Polyethylene glycol	humectant	cream	generally regulated as safe for use in cosmetics, with the conditions that impurities and by-products, such as ethylene oxides and 1,4-dioxane, which are known carcinogenic materials, should be removed before they are mixed in cosmetic formulations [903]
Polymethyl methacrylate	film former	eyeshadow, eyeliner, makeup primer, around-eye cream, glitter, serum, mascara	toxic or harmful [871]
Prostaglandin analogues (for example, isopropyl cloprostenate)		eyelash growth serum	periorbitopathy, periorbital discoloration, hyperemia, pruritis, eyelid ptosis, meibomian gland dysfunction, blepharophimosis, thinning of eyelid skin and orbital fat [298-307,904,905]
Quaternium-15	*preservative, antistatic agent*	*mascara, eye makeup remover, around-eye cream, serum, eyeshadow*	*formaldehyde-releasing preservative - toxic [188]*
Retinoids (Vitamin A metabolites, such as13-cis retinoic acid; isotretinoin)	skin-conditioning agent	serum, around-eye cream, moisturizer, makeup primer, makeup remover, mascara, eyeliner	toxic for meibomian glands [342,906]
Salicylic acid	skin-lightener	around-eye-cream, makeup primer, makeup remover, moisturizer, serum	restricted use in Canada [239], Europe [907] and Japan [888], irritant [908]
Shellac	viscosity controller, film-forming agent, emollient, protection from ultraviolet rays	mascara	contact dermatitis [349]
Sodium benzoate	*preservative*	*eyeshadow, eyeliner, mascara, around-eye cream, moisturizer, serum, glitter, eye makeup remover, eyelash glue*	*irritant [177]*
Sodium hydroxy-methylglycinate	*preservative*	*moisturizer, serum*	*formaldehyde-releasing preservative - toxic [188]*
Sodium laureth sulfate	surfactant-cleansing agent	mascara, eyeliner, eye makeup remover, makeup primer, serum	irritant [236], expected to be toxic or harmful [871]
Sorbic acid	*preservative*	*eyeshadow, moisturizer, mascara, serum, around-eye cream, eye makeup remover, makeup primer, glitter, eyeliner*	*toxicant or allergen [216,236]*
Talc	bulking agent	around-eye-cream, eyeliner, eyeshadow, glitter, makeup primer, mascara, moisturizer, serum	may contain asbestos [350,351,353]
Tea tree oil and terpinen-4-ol		eyelash cleanser, eye makeup remover, moisturizer, toner	toxic to human meibomian gland epithelial cells, endocrine disruptor, allergen, may contribute to antibiotic resistance [371-374,377,378]
Thimerosal	*preservative, mercury-derived*	*bleaching creams, eye moisturizer, makeup remover, mascaras*	*toxic or harmful [871,885], neurotoxic [241], endocrine disruptor [907], allergen [240], banned in Canada [239]*
Triclosan	*cosmetic biocide, preservative*	*eyeshadow*	*irritant [885], expected to be toxic or harmful [871], endocrine disruptor [909,910]*
Triethanol-amine	pH adjuster, surfactant-emulsifying agent, buffer	serum, moisturizer, mascara, around-eye cream, eyeshadow, eyeliner, glitter, makeup primer, makeup remover, eyelash glue	carcinogenic if converted to *n*-nitrosamines [884], allergen [236], toxic or harmful [871], irritant [885], prohibited for use in Europe [886]

A considerable amount of information about these ingredients may be found in Ref. [497].

adnexa (Table 2 [169-175]). Further, multiple adverse reactions may occur following the application of eye cosmetic products containing these ingredients and/or the performance of ocular cosmetic procedures (Table 4). These reactive effects are referenced in various sections of this report.

5.1. Preservatives

Many of the chemicals used in cosmetics are added as preservatives to prevent bacterial, fungal, yeast and/or mold contaminations [169, 176,177]. Some of the most common cosmetic preservatives are benzalkonium chloride (BAK), formaldehyde (FA)-releasing compounds, parabens, phenoxyethanol and chlorphenesin [165,178-184]. These preservatives are used in numerous eye care cosmetics (for example,

serums, mascaras, eyeliners, eyeshadow and mascara) that are leave-on, as compared to rinse-off.

5.1.1. Benzalkonium chloride

BAK is a bactericidal quaternary ammonium that is commonly used not only in cosmetics, but also in topical ophthalmic solutions [185,186]. It is a compound that has a long half-life retention and can be found in ocular tissues 168 h after a single topical drop of 0.01% BAK in rabbits [187]. In the European Union (EU), BAK is authorized for use in cosmetic products at maximum concentrations of 0.1% (1 mg/ml) [178]. However, BAK concentrations that are hundreds-fold below limits set for human commercial products kill all human corneal, conjunctival and meibomian gland epithelial cells *in vitro* within 18 h [188]. Indeed, BAK amounts that are 20,000-fold lower (0.005 μg/ml) than approved levels are still toxic to ocular surface and adnexal cells *in vitro* [188]. These findings are consistent with previous reports on BAK toxicity in both *in vitro* and *in vivo* models [189-195]. *In vivo*, BAK has been reported to induce tear film instability, goblet cell loss, conjunctival squamous metaplasia and apoptosis, corneal neurotoxicity, and disruption of the corneal epithelium barrier [196-203]. Application of BAK to the ocular surface may also lead to an increased prevalence of irritation, burning, itching, foreign body sensation, conjunctival hyperemia, blepharitis, meibomian gland loss, dry eye disease, glaucoma surgery failure, and even anaphylaxis [189,200,204-206].

5.1.2. Formaldehyde-releasing compounds

Formaldehyde-releasing compounds (for example, DMDM-hydantoin; quaternium-15; imidazolidinyl urea; diazolidinyl urea; and 2-bromo-2-nitropropane-1, 3-diol [169,181]) possess an easily detachable formaldehyde moiety, which permits the gradual release of small amounts of biocidal formaldehyde at room temperature. The maximum limit of formaldehyde allowed in EU cosmetics is 0.2% (2 mg/ml) [178], although a Cosmetic Ingredient Review (CIR) panel recommended a lower limit of 0.074% (0.74 mg/ml) [179]. However, at concentrations 740- to 2000-fold lower than the CIR and EU limits, respectively, formaldehyde is toxic to human corneal, conjunctival and meibomian gland epithelial cells *in vitro* [188]. Further, treatment of rabbit corneal epithelial cells *in vitro* with up to 0.1 mg formaldehyde/ml for 3 min attenuates cell survival and increases apoptosis/necrosis [207]. Similarly, exposure of Chang conjunctival epithelial cells *in vitro* to environmental formaldehyde may promote cell death [208]. For comparison, the cytotoxic action of formaldehyde has also been identified in human bronchial epithelial cells, human endothelial cells, natural killer cells, and lymphocytes *in vitro* [209-212]. Additional research has shown that formaldehyde levels between 0.5 and 1.0 ppm (0.5–1.0 μg/ml, or 0.00005–0.0001%) can elicit ocular irritation and conjunctival redness, and that concentrations above 1.0 ppm can irritate the nose and throat [213]. Of particular importance, the mutagenic, carcinogenic and pro-allergenic potential [210,214] of formaldehyde has prompted increased public health attention. The International Agency for Research on Cancer classified formaldehyde as carcinogenic to humans [184].

5.1.3. Parabens

Parabens are preservatives that are included in over 22,000 cosmetic products in the USA [182]. The most utilized parabens are methylparaben and ethylparaben [53]. These *p*-hydroxybenzoic acid esters are approved for cosmetic use at concentrations up to 0.8% for paraben mixtures and 0.4% for a single paraben [182]. However, methylparaben at a dosage 400-fold less than that approved for human use, and ethylparaben at a concentration 40-fold less, significantly reduces the survival of human meibomian gland epithelial cells *in vitro* [215]. These toxic effects are similar to those discovered after exposure of human corneal and conjunctival epithelial cells to methylparaben and ethylparaben [195]. Of note are the findings that parabens are allergens [216] and endocrine disruptors and possess estrogen potency [217-220]. In fact, chronic topical application of parabens may cause prolonged local estrogenic effects, due to the inhibition of estrogen sulfotransferase activity [221]. Estrogens are known to decrease the secretagogue-induced cyclic AMP accumulation in, and the proliferation of, human meibomian gland epithelial cells [222], and may also promote the development of meibomian gland dysfunction [223,224]. Parabens have also been shown to express antiandrogen activity [219], which could lead to meibomian gland dysfunction and dry eye disease [223,225]. Indeed, high urinary levels of methylparaben and ethylparaben are associated with the signs and symptoms of dry eye disease [226]. To add to these observations, parabens may also increase the risk of malignancies (for example, breast cancer) [227].

Table 3
Common nontoxic ingredients in ocular cosmetics.

Ingredient	Function	Products	Comment
Aluminum powder	cosmetic colorant	around-eye cream, eyeliner, eyeshadow, makeup primer, mascara, moisturizer	no adverse effects related to the eye [911]
Aluminum silicate	abrasive, absorbent, anticaking agent, bulking agent, opacifying agent	serum	no adverse effects related to the eye [912]
Azelaic acid	buffer, pH adjuster	makeup primer, moisturizer, serum	determined safe for use in cosmetics, subject to concentration or use limitations - distinction between safe concentrations in leave-on and rinse-off [236,869,913]
Azulene (chamomile extract)	skin-conditioning	around-eye cream, serum	not expected to be potentially toxic or harmful [871]
Biotin	skin-conditioning	around-eye cream, eyeliner, eyelash glue, makeup primer, makeup remover, mascara, serum	not expected to be potentially toxic or harmful [871]
Bismuth oxychloride	cosmetic colorant	around-eye cream, eyeliner, eyeshadow, makeup primer, mascara, moisturizer, serum	not expected to be potentially toxic or harmful [871]
Hyaluronic acid	hydration	serum, moisturizer, cleanser, around-eye-cream,eyeliner, makeup remover, makeup primer, eyelash glue, mascara	not expected to be potentially toxic or harmful [871]
Isoleucine	skin-conditioning agent	serum, around-eye cream, makeup primer, makeup remover, mascara	not expected to be potentially toxic or harmful [871]
Palmitoyl pentapeptide-4	skin conditioning	serum, around-eye cream, makeup primer, makeup remover, moisturizer	no adverse effects related to the eye
Pomegranate seed oil (plant-based source of punicic acid)	emollient	serum, eyeshadow, moisturizer, around-eye cream, makeup remover	no adverse effects related to the eye
Sodium glycerophosphate	moisturizing agent	makeup primer	not expected to be potentially toxic or harmful [871]
Undecylenoyl phenylalanine	skin-conditioning agent	moisturizer, serum	not expected to be potentially toxic or harmful [914]

Table 4
Spectrum of possible adverse effects of certain ocular cosmetic products and procedures.

Abscess	Globe perforation
Abrasion	Goblet cell dysfunction
Argyria	Granulomatous reactions
Arterial occlusion	Haematoma
Blepharitis	Hyperpigmentation
Blindness	Incomplete blink
Blisters	Inflammation
Bruising	Injection site bruising or swelling
Cancer	Keloid development
Canthal laxity	Keratitis
Cataract	Lacrimal drainage obstruction
Cellulitis	Lagophthalmos
Chemical burn	Lash base calcification
Chemosis	Lower eyelid retraction
Conjunctival epithelial cell toxicity	Madarosis
Conjunctival hyperemia	Mascaroma
Corneal epithelial cell toxicity	Meibomian gland dysfunction
Corneal ulceration	Meibomian gland epithelial cell toxicity
Cosmetic migration across eyelid margin	Meibomitis
Dacryolith formation	Neurotoxicity
Debris within conjunctiva	Nodules
Demodex infestation	Orbicularis oculi denervation
Dermatitis	Pain
Dry eye disease	Ptosis
Dysesthesia	Pruritus
Ecchymosis	Pustules
Ectropion	Scarring
Edema	Tear film instability
Embolism	Telangiectasia
Endocrine disruption	Trauma
Entropion	Trichiasis
Epiphora	Venous occlusion
Erosion	Xanthelasma
Fibrosis	

The adverse effects listed in this Table have been demonstrated following the use of certain cosmetic products and/or procedures. These effects are referenced in various sections of this Cosmetics Subcommittee report.

5.1.4. Phenoxyethanol

Phenoxyethanol is a broad-spectrum preservative that is active against a wide range of gram-negative and gram-positive bacteria, yeasts, and molds, and is permitted in consumer products up to a concentration of 1.0% [177,181,228]. However, one-tenth of this concentration significantly decreases the survival of human meibomian gland epithelial cells [215]. Further, exposure to phenoxyethanol fumes is associated with reduced tear film break up time [228]. These adverse effects of phenoxyethanol are not unique to the ocular surface and adnexa, because this compound has also been shown to induce hepatotoxicity, renal toxicity and hemolysis in multiple species [229]. Given these phenoxyethanol actions, and the fact that it has a high dermal absorption rate for leave-on formulations, it has been recommended that this compound be avoided in products that come into contact with the eyes [177].

5.1.5. Chlorphenesin

Chlorphenesin, a chlorophenol derivative, is an antibacterial and antifungal biocide, which is approved for use at up to a 0.3% concentration in more than 1300 rinse-off and leave-on cosmetics [177,230]. But, at a 300-fold lower concentration (0.001%), chlorphenesin significantly reduces the survival of human meibomian gland epithelial cells [215]. Chlorphenesin is also known to irritate the eyes [230]. Considering that chlorphenesin is well absorbed through the skin, this property may have contributed to its classification as being moderately hazardous in eye-related products [177].

5.1.6. Ethylhexylglycerin

Ethylhexylglycerin is used as a cosmetic preservative, in addition to its effects as a surfactant, emollient and skin-conditioner. As indicated in a clinical case series, leave-on products containing ethylhexylglycerin are not inert and were identified as having potential to cause contact dermatitis [231] as well as eye irritation [232,233].

5.1.7. Methylisothiazolinone

Methylisothiazolinone is a preservative used in liquid cosmetics and personal care products to inhibit bacterial contamination. There is an increased risk of sensitization to this compound [234,235], as well as possible toxicity [236,237]. The European Scientific Committee on Consumer Safety has declared that there is no safe concentration of methylisothiazolinone in leave-on products, and that concentrations in rinse-off products must be less than 16 parts per million [238]. Because of its toxic adverse effects, this compound has been banned in Canadian cosmetics [239].

5.1.8. Thimerosal

Thimerosal is a mercury derived preservative. Although it has been removed from contact lens solutions, it is still found in some cosmetics such as makeup remover, eye moisturizer, mascaras and bleaching creams. It is the fifth most common allergen found on patch testing in North America, eliciting a reaction in 11% of patch tested patients [240]. Evidence also indicates that this compound is a neurotoxin [241] and an endocrine disruptor [242].

Thimerosal is banned in Canada [239], but very low levels (0.0065%) are allowed by the US FDA in makeup used around the eyes if no other effective and safe preservative is available [243].

5.2. Additional ingredients

Aside from preservatives, many additional ingredients in eye makeup may elicit adverse reactions on the ocular surface and adnexa. A number of these are discussed below.

5.2.1. Acrylates

Acrylates are the salts, bases and conjugate bases of acrylic acid and are used to form polymer plastics. These polymers are commonly found in cosmetics, artificial nail and nail adhesive, nail polishes, artificial eyelashes and hair fixatives. Because these polymers can easily form a film, they are added to many products, such eyeliner, liquid makeup, mascaras, sunscreens, lipsticks, creams and lotion skin care [244] (Table 2).

There are many types of acrylates. Methacrylate and polymethyl methacrylate (PMMA) are recognizable and known to eye care professionals for their safe use in soft and hard contact lenses and intraocular lenses. PMMA can be used in makeup to give a matte and less greasy application that can absorb sweat. Hydroxyethyl methacrylate (HEMA) and poly(2-hydroxyehtyl methacrylate) (PHEMA) are both also used to make soft contact lenses as well as artificial cornea prostheses. Ethyl acrylate is also used in paints, textiles, pharmaceuticals, and cosmetics. 2-ethyl hexyl acrylate and butyl acrylate are used as important adhesives.

The International Agency of Research on Cancer funded by the World Health Organizations published monographs about some acrylates as being possibly carcinogenic to humans (group 2B) [245]. Methyl acrylates were also found to trigger allergic contact dermatitis [246].

5.2.2. Carnauba wax

Carnauba wax, derived from the tropical palm, *Copernicia Cerifera*, is an excellent emulsifier, binds oils, raises the melting points of gels, and is hydrophobic. It is often added to mascaras, eyeliners, and eyeshadows to create a glossy, smooth finish. Sixty percent of commercial mascaras contain carnauba wax. This is the hardest known plant wax on the market [247,248]. Use of carnauba wax has been linked to the development of eyelid contact dermatitis [249,250]. For comparison, it has been found that eyeliners containing other common waxes, candelilla and microcrystalline, when mixed with human meibum, can alter the

phase transition and increase the melting point of this secretion [251].

5.2.3. Castor oil

As listed in Table 2, castor oil is used as an eyelash conditioner, and is also an ingredient in around-eye-cream, eyeliner, eyeshadow, glitter, makeup primer, makeup remover, mascara and serum. Anecdotal evidence suggests that castor oil stimulates eyelash growth, but there is no research indicating that eyelash cilia or follicles are either positively or negatively impacted by topical application to the eyelash line. There is evidence that ricinoleic acid, the main mono-α hydroxy mono-unsaturated fatty acid contained in castor oil, can help to inhibit prostaglandin D2 [252]. Prostaglandin D2 has been linked with androgenic alopecia [252,253]. More research needs to be conducted to determine whether this effect can be generalized to eyelash growth.

Castor oil is not a significant skin irritant, sensitizer, or photosensitizer in humans, but individuals with occupational dermatoses may have a positive reaction to castor oil or ricinoleic acid. Ocular surface exposure to a castor oil solution leads to mild and transient discomfort and may promote corneal epithelial cell death and disrupt the epithelium [254]. Ricinoleate is also known to cause a dose-dependent (0.1–2.0 mM) cytotoxicity of other epithelial cells [255].

5.2.4. Cocamide diethanolamine

Diethanolamine is commonly used as an emollient, thickener and dispersant. It is found in personal care products that contain cocamide diethanolamine which comes from reactive products from diethanolamine and coconut oil derived fatty acids [256].

It can be found in concentrations ranging from 0.5% to 50%. The CIR panel judged it to be safe in 1986, and deemed it an eye irritant, but not a sensitizer or photosensitizer [257]. Since then, California Department of Health has listed cocomide diethanolamine as a carcinogen [258]. Cocomide diethanolamine may contain diethanolamine. The International Agency for Research on Cancer has categorized both diethanolamine and coconut oil diethanolamine condensate as possibly carcinogenic to humans (Class 2B) [259].

5.2.5. Cocamidopropyl betaine

Cocamidopropyl betaine is also coconut-derived and is used as a surfactant in personal cleansers. Since the 1980's, cocamidopropyl betaine has been found to cause contact dermatitis. Some of this effect may be a crossover reaction to 3-(dimethylamino)propylamine, which is used in its manufacture [260]. Additionally, patients may be allergic to amidoamine which is also used in the manufacturing of cocamidopropyl betaine [261]. Cocamidopropyl betaine is also an ingredient in some contact lens cleaners and caused eyelid dermatitis [262].

5.2.6. Fragrances

Fragrances, such as linalool, when left to oxidize can cause skin dermatitis [263]. Synthetic musks are used as fragrances but may interfere with cell function and hormone regulation and have been banned in Europe but not in the USA [264].

5.2.7. Gold

Gold was listed as the 2001 Contact Allergen of the Year by the American Contact Dermatitis Society [265]. In the past 20 years, not much has changed in the use of gold in cosmetics even with this 2001 designation. Many cosmetic products on the market currently tout the use of gold as an added benefit without labeling the allergy risk. In a series of patch testing in North American almost 10% of patients had a Type IV hypersensitivity reaction to gold [266]. Patch testing to gold sodium thiosulfate usually confirms the gold allergy [267].

5.2.8. Heavy metals

Though lead is known to be toxic, heavy metals like lead are found in small amounts in cosmetics including lipsticks that can be ingested. To achieve the metallic sparkle effect, eyeshadows, blushes, and compact powders contain heavy metals that can cause irritation and allergy [268].

Heavy metals (for example, nickel, lead, arsenic, mercury, zinc, chromium, cobalt, cadmium and iron) are known allergens (i.e., sensitizers), and some are considered toxic such as lead. Nickel is a common reactant found in cosmetics and jewelry worn on ears and hands and also found on metal parts of glasses. Nickel-free makeup contains less than 1 part per million nickel and is usually tolerated by nickel-allergic patients [269].

The US FDA lists results of testing online on its website [270]. Additionally, black iron oxide in mascara was reported to result in eyelid contact dermatitis [271].

5.2.9. Lanolin

Lanolin is made from sheep wool and derived from the sebaceous glands. It is used as an emollient in cosmetics. Though it is considered a lesser sensitizer compared to other products, it has been found to be related to periorbital contact allergy when a lanolin product was applied to damaged skin [272].

5.2.10. Nylon

Nylon is included in cosmetics as a bulking and opacifying agent [273]. The most common forms are nylon-6 in mascara and eyebrow pencils (for example, 20% concentration), and nylon-12 in eyeshadows and face powders (for example, 35% concentration).

Initial research concluded that an eyeshadow containing 5% nylon-12 "did not produce ocular irritation and was considered safe for use by contact and non-contact lens wearers, individuals with self-perceived sensitive eyes, and individuals with normal eyes" [273]. However, there has been a documented case report of 1 mm cosmetic nylon fibers embedding in the ocular surface tissues (conjunctiva), resulting in an inflammatory reaction. These embedded nylon fibers were ingredients in "fiber-lash" mascara [274]. Contact dermatitis to nylon fibers in other products in proximity to the ocular surface and adnexa have also been documented with glasses frames [275] and nail polish (with touching/rubbing the eyes) [276].

5.2.11. Phenylethyl resorcinol

Phenylethyl resorcinol is an agent used for skin-whitening, as it reduces both melanin content and tyrosinase activity in the skin [277]. Phenylethyl resorcinol is often utilized in combination with other whiting agents, such as retinol, disodium glycerophosphate and L-leucine [278-280]. One study showed no negative effects with phenylethyl resorcinol application under the eye for intra-orbital dark circles, or when used in combination with microneedling [281]. However, contact dermatitis has been identified in case reports with the use of phenylethyl resorcinol in cosmetics used for skin lightning and as an additive to sunscreen [282,283].

5.2.12. Phthalates

Phthalates are common ingredients used as solvents in cosmetic makeup removers or fragrances. Phthalates are also found as plasticizers in plastic cosmetic packaging and can leach unintentionally into cosmetics themselves [284]. While small levels of some cosmetic phthalates have been approved in different markets globally, approved concentrations can easily be exceeded due to unintentional contamination [284].

Phthalates are lipophilic, meaning they exhibit the ability to potentially penetrate through to the corneal stroma and into the corneal endothelial cell layer. Phthalates (dibutyl phthalate [DBP], benzyl butyl phthalate [BBP], and diethylhexyl phthalate [DEHP]) have been shown to adversely affect the growth and viability of a human corneal endothelial cell line [285].

Phthalate exposure has also been linked to endocrine disruption, reproductive disorders [286,287], cardiovascular disease [287,288], early onset of puberty [289], hepatoxicity [288], neurotoxicity [288],

and sleep problems [290]. Another study found that cosmetic and perfume sale clerks had exceeded the cumulative risk of phthalate exposure for anti-androgenic effect [291].

Interestingly, research has indicated higher exposure to phthalates in females in comparison to males [292]. Females who reported recent use of specific makeup products, such as foundation, blush and mascara, had higher urinary concentrations of monoethyl phthalate and mono-*n*-butyl phthalate (MBP) [292].

Based on current evidence, Europe has banned the use of DBP in cosmetics [293]. The USA has not banned phthalates in cosmetics, but the US Consumer Product Safety Commission has banned certain phthalates (DEHP, DBP, and BBP) from children's toys [294].

5.2.13. Prostaglandin analogues

Eyelash elongation and darkening resulted as unexpected side effects with use of the topical glaucoma medication, bimatoprost (Lumigan 0.03%, Allergan). Bimatoprost (FDA approved in 2001 to lower intraocular pressure), along with other topical prostaglandin analogues (PGA), target the anagen phase of the eyelash growth cycle. This phase is responsible for eyelash growth and melanin deposition [295]. PGAs may increase the number of eyelashes in the growth phase, resulting in a "thicker" eyelash appearance on the eyelid margin.

The manufacturer (Allergan) took advantage of these eyelash-effects and re-branded bimatoprost as Latisse® with US FDA approval in 2008. Latisse® was originally FDA approved for the treatment of hypotrichiasis, but later gained approval in the treatment of trichotillomania, chemotherapy-induced eyelash loss and alopecia areata eyelash loss [295]. Unlike the glaucoma medication formulation, Latisse® is not an eyedrop, but rather supplied as solution that is applied with a small brush to the eyelid margin prior sleep. Sixteen weeks of use is required for maximal efficacy for eyelash growth [296].

The beauty industry took note of the financial success of the pharmaceutical industry's release of Latisse®. Latisse® had one of the most successful pharmaceutical launches in history with $47.7 million dollars in prescriptions the first year on the market [297]. The beauty industry began to incorporate synthetic PGAs into over-the-counter eyelash growth serums, obtainable without a prescription. While pharmaceutical companies must list all potential side effects of medications on the packaging, the beauty industry does not have to adhere to this standard [243]. The consumer may be unaware that the over-the-counter eyelash growth serums may have similar side effects to Latisse®, given that eyelash enhancement is not the only effect. Documented side effects of PGAs are conjunctival hyperemia, skin or iris pigmentation, pruritus (itching), eyelash loss, fall or ptosis, trichiasis, malar hypertrichosis, and lowered intraocular pressure [298-301]. Meibomian gland dysfunction (MGD) and dry eye disease have also been positively correlated with topical PGA use [300,302-307]. These effects may relate to a direct bimatoprost action on human Meibomian gland epithelial cells. Exposure of such cells to an amount (10 μM) of bimatoprost 24-times smaller than the topical clinical 0.01% (i.e., 240 μM) concentration significantly decreased the intracellular phosphorylation of AKT, a mediator of cell survival [308].

PGAs in eyedrop formulations are also known to cause variable degrees of ophthalmopathy including acquired blepharophimosis (narrowing in palpebral aperture) and thinning of eyelid skin and orbital fat [300,309,310]. There have not been any clinical studies to show the safety or tolerability of PGA in over-the-counter eyelash growth serums. A survey of 154 current and past over-the-counter eyelash growth serums users indicated that users experienced side effects with the OTC products. In this survey, 40% of respondents ceased over-the-counter eyelash growth serums use, primarily because of side-effects (noted by 43% of dropouts)" [311].

Some cosmetic manufacturers have chosen (voluntarily or via regulations in non-USA countries) to re-formulate their over-the-counter eyelash growth serums considering the potential for side effects. A report in 2013 by the Swedish Medical Products Agency led to the ban of PGAs in over-the-counter cosmetics and mandated re-formulation of products sold in Sweden [310].

Isopropyl cloprostenate is one of the most common active ingredients in over-the-counter eyelash growth serums, but there are others. To identify a synthetic PGA in an over-the-counter eyelash growth serum, it helps to look for ingredients that contain "prost."

PGAs are not single-ingredient products in over-the-counter eyelash growth serums. These serums can include other ingredients (preservatives, fragrances, etc.) that may cause adverse effects, so it is important to review the full ingredient list of all cosmetics prior to use.

5.2.14. Systematic review: Is the use of eyelash growth products associated with symptoms or signs of ocular surface disease?

5.2.14.1. Background. The use of eyelash growth serums and products is commonplace [312]. The indication of these products is typically to enhance eyelash growth (including their length, thickness and darkness), either for patients with hypotrichosis, or for aesthetic purposes [313].

As described in Section 5.2.13, prostaglandins and their PGAs are usually the primary active ingredients in these products. Latisse® (bimatoprost ophthalmic solution 0.03%, Allergan Inc) is the only US FDA approved product for eyelash growth in patients with eyelash hypotrichosis [295,313], and is a prescription-only product. Alternative over-the-counter eyelash growth serums have rapidly become available which similarly claim to enhance growth and lengthen eyelashes. In 2011, the US FDA issued warning letters to several manufacturers of eyelash growth products for including PGAs, such as isopropyl cloprostenate, in these products [314]. These warnings were issued due to the manufacturers' clinical claims, and the inclusion of a compound in the same category as US FDA-approved drugs meant these products should be categorized as drugs, rather than a cosmetic product [315].

Some eyelash serums that avoid the inclusion of prostaglandins may use ingredients that may maintain or condition the eyelashes, making the eyelashes appear longer and thicker rather than promoting their growth [313,316].

The side effects of bimatoprost in the management of glaucoma are recognized, as reported in Section 6.2.13. However, the ocular effects of over-the-counter eyelash growth serums that contain PGAs, synthetic or naturally derived peptides and/or natural products are less well characterized. A systematic review that critically appraises the currently available data on the potential adverse effects of over-the-counter eyelash growth serums, regardless of their chemical ingredients, can provide clinicians, consumers, and policy makers with rigorous and updated evidence for anticipatory care and prevention. The findings of this review may also highlight evidence gaps and indicate future directions for research to focus on ocular surface outcomes that may have been overlooked.

The aim of this review was to evaluate the risks of the development or progression of signs or symptoms of ocular surface diseases associated with the use of eyelash growth products.

5.2.14.2. Methods. Methods applied to conducting the current review were previously described in the review protocol submitted to PROSPERO [317], with details outlined in Appendix A and briefly summarized below. The Subcommittee members SHL, AN and PN conducted this systematic review.

Ovid MEDLINE, Embase (January 1947 to 8 December 2021), and PubMed (1946–8 December 2021) were searched using database-specific search strategies (Appendix B). No limits to the search dates or languages were imposed on the electronic searches. Additional manual searching through the reference lists of included reports was performed but no eligible trials were further identified. Database search results were imported into the web-based review management software, Covidence (Veritas Health Innovation, Melbourne, Australia), for title/

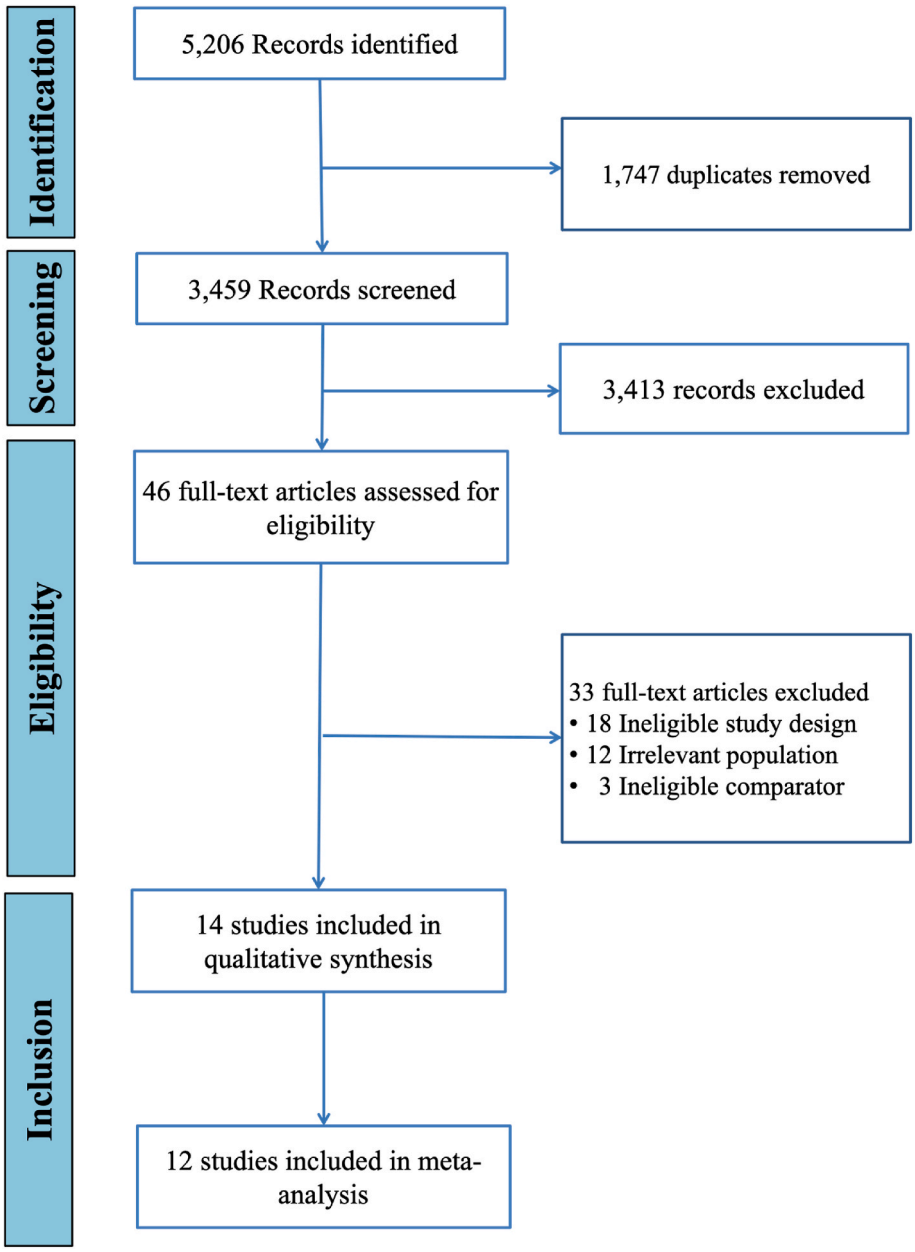

Fig. 2. Flow diagram of studies included in the systematic review.

abstract screening and then duplicate records were removed after full-text reviews.

Initially, randomized controlled trials (RCTs), quasi-RCTs, and observational comparative studies were considered for inclusion. After reviewing eligible full-text publications, only RCTs were included in the data extraction stage, in recognition of the sufficient number of RCTs identified (>2) and the generally poor reporting by observational studies screened for eligibility.

Eligible study populations included participants who were exposed to eyelash growth products (Appendix A) indicated for eyelash growth or extension. 'Control' participants were those randomly assigned to a comparison therapy, either a placebo (the vehicle of the intervention treatment) or another active treatment. Trials that examined safety outcomes of topical glaucoma medications in glaucoma patients were excluded.

5.2.14.2.1. Two primary outcomes were planned

. • Subjective outcome: participant-reported symptoms, based on a validated scale or scoring system such as the Ocular Surface Disease Index (OSDI), visual analog scale (VAS), or others.
• Clinical outcomes: in the form of ocular surface parameters, such as fluorescein corneal staining scores, tear film break-up time, tear osmolarity.

The following secondary outcomes were planned: eyelash length, eyelash thickness as one of the quantifiable changes of eyelash consistency, incident ocular adverse events and incident non-ocular adverse events. Among the various ocular adverse events reported, proportions of participants (or eyes) with incident "conjunctival hyperemia" and other "ocular surface symptoms" were extracted and compared between comparison groups; these specific adverse events were not listed in the protocol [317].

Table 5
Characteristics of included trials.

Study ID	Country, setting	Target population	Age, years mean ± SD (range)	Female, n/N (%)	Major race/ethnicity, n/N (%)	Intervention (formula)	Comparison	Treatment duration	No. randomized/analyzed, Intervention group	No. randomized/analyzed, Comparison group	No. analyzed for AE, Intervention/Comparison	Note
Parallel design												
Borchert 2016	USA & Brazil, multi-site	Mixed[a]	14.5 (5–17)/ 14.6 (8–17)	53/71 (75)	White, 46/71 (65)	Bimatoprost 0.03% (soln)	Vehicle	4 months	48/48	23/23	48/23	Eyelash parameters measured by DIA; industry-funded; NCT01023841 (clinicaltrials.gov); additional 1-month follow-up period after DC treatment
Glaser 2015	US & UK, multi-site	Clinical patients	49.3 ± 11.1	235/238 (98.7)	White, 202/238 (84.9)	Bimatoprost 0.03% (soln)	Vehicle	6 months[e]	179/179	59/59	118/59	Eyelash parameters measured by DIA; industry-funded; NCT00907426 (clinicaltrials.gov); reported data for participants with idiopathic hypotrichosis; 3-arm study[b]
Wirta 2015	US & UK, multi-site	Clinical patients	50.7 (26–76)	129/130 (99.2)	Caucasian, 103/130 (79.2)	Bimatoprost 0.03% (soln)	Vehicle	6 months[e]	96/96	34/34	96/33	Eyelash parameters measured by DIA; industry-funded; NCT00907426 (clinicaltrials.gov); reproted data for participants with post-chemotherapy hypotrichosis
Harii 2014 (study1)	Japan, multi-site	Clinical patients	40.1 (28–76)/ 41.4 (20–64)	155/173 (89.6)	Asian, 173/173 (100)	Bimatoprost 0.03% (soln)	Vehicle	4 months	88/88	85/85	NR/NR	Eyelash parameters measured by DIA; industry-funded; reported results of two trials: study 1 with an initial target enrollment of 126 participants; "the safety population, which consisted of all the subjects who received at least one dose of study medication"
Harii 2014 (study2)	Japan, multi-site	Clinical patients	46.3 (31–61)/ 54.9 (39–74)	36/36 (100)	Asian, 36/36 (100)	Bimatoprost 0.03% (soln)	Vehicle	4 months	18/18	18/18	NR/NR	Eyelash parameters measured by DIA; industry-funded; reported results of two trials: study 2 was a safety trial, "not powered for efficacy"; "the safety population, which consisted of all the subjects who received at least one dose of study medication"
Smith 2012	US & Canada, multi-site	Healthy volunteers	49.9 (22–77)/ 49.7 (22–78)	270/278 (97.1)	White, 225/278 (80.9)	Bimatoprost 0.03% (soln)	Vehicle	16 weeks	137/137	141/141	137/141	Eyelash parameters measured by DIA; industry-funded; NCT00693420 (clinicaltrials.gov); additional visit at week 20 (4 weeks after DC treatment)
Woodward 2010	US, single site	Healthy volunteers	49.2 (27–69)	51/52 (98)	NR	Bimatoprost 0.03% (gel)	Vehicle	6 months	36/36	16/16	36/16	Eyelash parameters measured by DIA; funded by Research to Prevent Blindness, Inc. and Duke University Eye Center; mean IOP at baseline and month 6 were compared between two groups
Fabbrocini 2019	Italy, single site	Clinical patients	42.25 ± 16 (Range 25–69)	40/40 (100)	NR	15-keto fluprostenol isopropyl ester (gel)	Vehicle	60 days	20/30	20/20	20/20	Eyelash parameters measured by DIA; sources of funding NR
Paired-eye design												

(*continued on next page*)

Table 5 (*continued*)

Study ID	Country, setting	Target population	Age, years mean ± SD (range)	Female, n/N (%)	Major race/ethnicity, n/N (%)	Intervention (formula)	Comparison	Treatment duration	No. randomized/analyzed, Intervention group	No. randomized/analyzed, Comparison group	No. analyzed for AE, Intervention/Comparison	Note
Wester 2010	US, single site	Healthy volunteers	46 (23–69)	19/19 (100)	NR	Bimatoprost 0.03% (gel)	Normal saline mixed 1:1 with Gonak[d]	6 weeks	19/15 (eyes)	19/15 (eyes)	15	Eyelash parameters measured by DIA; funded by Research to Prevent Blindness, Inc. and NEI; NCT00773136 (clinicaltrials.gov); mean changes in IOP at week 6 were reported for both groups with no differences (P = 1.00)
Morris 2011	US, single site	Clinical patients	Median 50 (Range 31–66)	20/20 (100)	Caucasian, 16/18 (89)	Bimatoprost 0.03% (gel)	No treatment	3 months	20/13 (eyes)	20/13 (eyes)	13	Eyelash parameters measured by DIA; funded by Duke University; NCT01200251 (clinicaltrials.gov); "two patients withdrew from the study unrelated to the eyelash gel" and were excluded from the analysis
Qualitative synthesis only												
Cohen 2013	US, multi-site	Clinical patients	NR	NR	NR	Bimatoprost 0.03% (soln)	Placebo	16 weeks	44/NR	44/NR	NR/NR	Industry-funded; a conference proceeding
Roseborough 2009	US, single site	Clinical patients	NR	NR	NR	Latanoprost (soln)	Bimatoprost (soln)	16 weeks	NR/NR	NR/NR	NR/NR	Eyelash parameters measured by DIA; funding source none reported; a Research Letter; overall, "11 patients completed the study"
Choy 2008	US, single site	Healthy volunteers	(Range 20–56)	33/34 (97)	NR	Dechloro ethylcloprostenolamide (soln)[c]	Placebo	4 weeks	23/NR (eyes)	11/NR (eyes)	34	La Canada Ventures, Inc; all authors reported conflicts of interests with the testing product
Faghihi 2009	Iran, single site	Clinical patients	22.5 ± 7.6 (Range 11–40)	12/26 (46)	NR	Latanoprost (soln)	No treatment	4 months	26/26 (eyes)	26/26 (eyes)	26	None reported; a Brief report

Abbreviations: AE, adverse events; DIA, digital image analyzer; DC, discontinue; No., number; NR, not reported; SD, standard deviation; soln, ophthalmic solution.

[a] Mixture of clinical patients and healthy volunteers.

[b] Randomization ratio of 2:1 to bimatoprost 0.03% vs vehicle, with one intervention arm receiving bimatoprost for 12 months and the other for 6 months followed by a cross-over to vehicle in the second 6-month period.

[c] MD Lash Factor contains no prostaglandin analogue, and was provided in full strength, half-strength, or quarter strength in (intervention) groups A, B, D; group C was placebo.

[d] Gonake (Akorn Inc., Lake Forest, IL).

[e] Outcome and safety data were extracted from the end of the first 4 or 6 month after randomization.

During data extraction, the Cochrane risk of bias tool was applied by review authors in pairs to independently assess study-level risks of bias [318] in addition to collect study-level information. Any disagreements were resolved by discussion. Continuous variables were extracted as means and standard deviations (SD). Reported median values were treated as means; standard error (SE) estimates were derived by back-calculation from the reported p-values from the comparison test, as suggested by the Cochrane Handbook [319]. For trials that had more than two comparison groups, only data relevant to the pre-specified exposure comparisons were extracted. Information about funding sources and authors' declaration of interest was also extracted. To assess the potential sources of clinical and methodological heterogeneity, study characteristics, particularly the study design and the study population, were assessed and I^2-statistics were quantified to estimate proportions of the overall variability in effect measures that could be attributable to heterogeneity, rather than random sampling errors [320].

Random-effects models were used to combine outcome results from two or more trials. Quality assessment using the risk of bias 2 tool on the two primary outcomes were initially planned [317], but none of the included trials reported on these two outcomes. Instead, each included trial was assessed for risk of bias at the study level using the previous risk of bias tool [318]. Each secondary outcome was graded for the level of certainty of the evidence as "high", "moderate", "low", or "very low" according to the GRADE approach [321].

5.2.14.3. Results. A total of 5206 records were identified by searches in three electronic databases (Appendix B). After duplicates were removed, 3459 titles and abstracts were independently screened by two review authors. At the full-text review stage, 46 articles were assessed for eligibility by two independent reviewers and 33 were excluded, with reasons documented (Fig. 2). Ultimately, 14 trials (13 reports) were included in a qualitative synthesis, 12 of which were also included in one or more meta-analyses.

Ten of the 14 trials used parallel group design (71%), whereas the other three used paired-eye design [322-324]. One trial involved the randomization of participants to four comparison groups yet only the left eye of each participant allocated to different interventions, including placebo, while the right eye of each participant received the same intervention medication [325]. Half of these trials were single-site studies conducted in the USA, Italy, or Iran; others were multi-site trials in the USA, UK, Brazil, Japan, or Canada. Industry funding was reported by eight trials as the sole funding source (57%); no source of funding was reported by two trials (14%).

Overall, these 14 trials enrolled and randomized 1196 participants to receive the intervention or the control treatment. The active ingredients in the intervention treatments included: bimatoprost (11 trials), latanoprost (1 trial), 15-keto fluprostenol isopropyl ester (1 trial), and dechloro ethylcloprostenolamide (1 trial); the comparison treatments included: vehicle (8 trials), placebo (including saline, 3 trials), or no treatment (1 trial). Two active treatments were compared in only one trial, in which latanoprost was tested head-to-head against bimatoprost [326]. Other study-level characteristics are summarized in Table 5.

5.2.14.4. Risk of bias or quality assessment in included studies. None of the trials were judged to be at low risk across all the domains assessed; nine were considered as having high risk of bias (64%); the others were judged to have some concerns (Fig. 3).

5.2.14.4.1. Randomization and allocation (selection bias). Eleven of the included 14 trials (79%) were judged to have unclear risk of bias with regard to either proper random sequence generation or appropriate allocation concealment. Other trials were at low risk for both domains (Fig. 4).

5.2.14.4.2. Masking (performance bias and detection bias). Seven of the 14 trials (50%) were judged to be at low risk of performance bias and detection bias. In one of the three paired-eye trials, participants were aware of which eye was the study eye (i.e., the eye receiving the intervention) versus the control eye that did not receive any treatment [327]. While it was unclear whether the study personnel were masked or not, clinicians who assessed the participants were unlikely masked due to the likely skin hyperpigmentation effects caused by the intervention medication. This trial was thus judged to be at unclear risk for performance bias and high risk for detection bias (Fig. 4). The other six trials had unclear risk of bias in either domain relating to masking (43%).

5.2.14.4.3. Incomplete outcome data (attrition bias). Four trials (29%) were judged to have high risk of bias due to reporting of incomplete outcome or safety data overall, or for the control group only [323,324,327,328]. Another four trials were considered as having unclear risk of bias due to providing descriptive results for the study outcomes without reporting numeric data [326,329-331]. The remaining five trials were assessed as having low risk of bias in this domain (Fig. 4).

5.2.14.4.4. Selective reporting (reporting bias). Nearly half of the included trials (43%) were judged to be at high risk of under-reporting, selective analytic approaches, or reporting adverse events at certain threshold levels. Five trials were considered at low risk of bias in this domain (Fig. 4). Others were judged to have unclear risk of bias because no numeric data were reported [326] or inconsistent reporting [324].

5.2.14.4.5. Other bias: source of funding. Half of the 14 trials were considered to be at high risk of bias due to potential conflicts of interest as reported by the authors. Two trials were judged to have unclear risk of bias due to the lack of information [332] or insufficient information disclosed [326]. Trials judged to be at low risk of bias included those that reported no commercial funding sources [322,323], government funding alone [324], or that the industry 'had no roles in the design or conduct of the study', except for donating the intervention medications [331].

The overall assessment for each trial did not consider the source of funding as a predisposing or protective factor for risk of bias.

5.2.14.5. Effects and harm of interventions

5.2.14.5.1. Primary outcomes

Participant-reported ocular surface-associated symptoms

None of the included trials reported these measures as study outcomes.

Changes in ocular surface measures

None of the included trials reported measures in this outcome domain.

5.2.14.5.2. Secondary outcomes

Quantifiable growth or extension of eyelash length

Eight of the 10 parallel-group trials reported changes in eyelash lengths from 60 days to 6 months post-intervention (n = 1016); the other two trials did not report numeric outcome data [326,329]. Among parallel-designed trials that lasted 2–4 months, the combined estimate suggested that the use of bimatoprost may increase eyelash length by 1.32 mm (95% CI: 1.12 to 1.52) compared with a control intervention; results were similar when combining 6-month data of the two parallel-group trials (Fig. S1) [328]. Two of the four paired-eye trials also yielded a comparable estimate (MD 0.94 mm, 95% CI: 0.49 to 1.39; n = 56 eyes). One study presented pre-versus-post comparison results within each intervention group, which were not useable for meta-analysis [325]. The certainty level of the evidence was downgraded one level from being high to moderate due to risk of bias.

Quantifiable thickness changes of eyelashes

Six trials contributed data to this outcome at 4- or 6-months or both (Fig. S2); another study stated that "any increase in eyelash length, thickness/fullness and darkness was registered" but did not report any findings on this outcome [332].

The combined estimate at 4 months indicated that bimatoprost-containing products was likely to increase eyelash thickness by 0.47 mm^3 (95% CI: 0.37 to 0.56; n = 922). When considering 6-month data

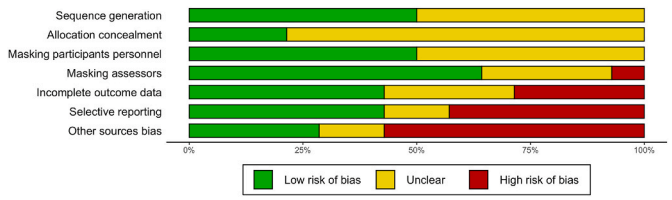

Fig. 3. Risk of bias or quality assessment in included studies.

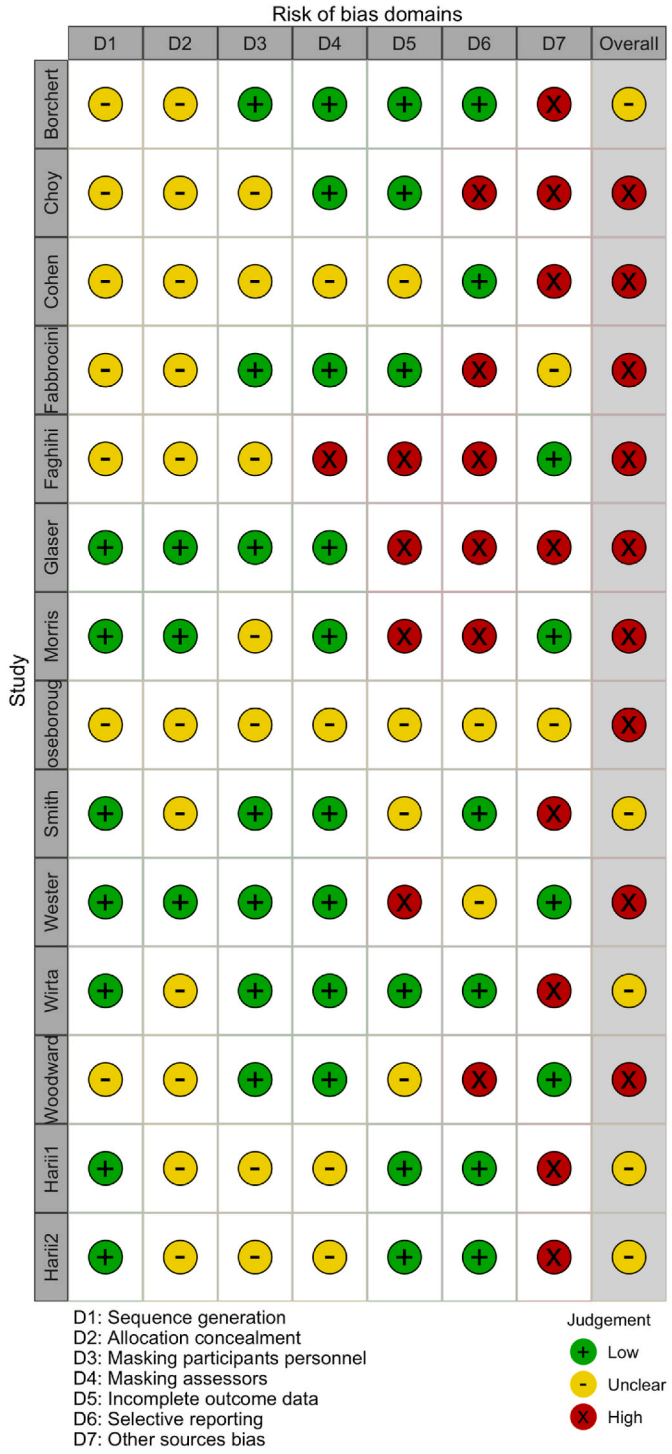

Fig. 4. Risk of bias judgements for randomized controlled trials included in the systematic review.

from two of the 6 trials [328,333], eyelash thickness also was likely to increase (MD 0.56 mm; 95%CI: 0.40 to 0.73). In contrast, the single-study estimates of a paired-eye trial [323] provided indirect support for the participant-level evidence (median difference 1.00 mm^3, interquartile range [IQR] −1 to 2.5; n = 26 eyes) (Table 6). Overall, the certainty level of the evidence was judged to be low because of risk of bias (downgraded for one level) and inconsistency (downgraded for one level).

Incidence of ocular adverse events

Incidence of conjunctival hyperemia: Combining data from five parallel-group trials (n = 828) for this outcome, the estimates suggested that bimatoprost might increase the risk of conjunctival hyperemia by five-fold when compared to control intervention (RR 6.09; 95% CI: 1.88 to 19.67) (Fig. 5), although the evidence was very uncertain (Table 6). Only one of the four paired-eye trials reported on this outcome (n = 36 eyes) with a brief statement that "there were no episodes of conjunctival hyperemia" [323]. Overall, the certainty level was considered very low due to high risk of bias (downgraded for two levels) and imprecision (downgraded for one level).

Incidence of adverse ocular surface symptoms or signs: Several symptoms and signs, including ocular irritation, pain (or stinging), and pruritis, were judged to be relevant to the ocular surface and included for this outcome. Data reported by six parallel-group trials and three paired-eye trials were separately combined according to study design (Fig. 6). Participant-level estimates based on 60-day to 4-month data suggested that bimatoprost-containing eyelash products may not increase the risk of ocular surface symptoms or signs (RR 2.38, 95%CI: 0.59 to 9.61; n = 579) when compared with a control intervention. Pooled results of 6-month data were similar (RR 2.77, 95% CI: 0.77 to 10.01; n = 306); so were eye-level estimates (RR 2.12, 95%CI: 0.23 to 19.40; n = 108 eyes). The certainty level of the evidence was judged as very low due to high risk of bias (−2) and imprecision (−1) (Table 6).

Incidence of ocular adverse events leading to treatment cessation: Nine of the 10 parallel-group trials reported incidents of ocular adverse events during the trial period, leading to participants stopping the intervention (Fig. 7). For trials lasting 4 months or shorter, the pooled results suggested no evidence that the use of eyelash growth products may affect participants' risk of local adverse events leading to treatment termination (RR 1.68, 95% CI: 0.59 to 4.81; n = 686); the evidence was very uncertain. Results were comparable when considering participant-level data reported by trials lasting 6 months (n = 420) and trials of paired-eye design (n = 72 eyes).

One trial documented a total number of 10 such adverse event episodes but did not specify whether all these incidents occurred in the intervention group [328]. Assuming all adverse events were in the intervention group [328], no evidence suggested that the use of bimatoprost might affect the risk of ocular adverse events resulting in treatment cessation (RR 3.41, 95% CI: 0.62 to 18.65; n = 420). In a sensitivity analysis that assumed all relevant adverse events happened in the control group of the Glaser 2015 trial, the combined results were similar (RR 0.40, 95% CI: 0.01 to 12.99). Overall, the certainty of the evidence was judged as very low because of imprecision (downgraded for one level) and high risk of bias associated with biased outcome measurement and selective reporting (downgraded for two levels).

Incidence of non-ocular adverse events

A total of seven non-ocular adverse events were reported in four of the 14 trials. These non-ocular adverse events included.

- facial eczema [334].
- cancer recurrence [333].
- facial pain (n = 1) and dissociative disorder (n = 1) [335].
- eczema (n = 1), contact dermatitis (n = 1) and lymphoma (n = 1) [330].

Due to the low number of reported non-ocular adverse events across the trials, no further analyses were conducted for this outcome.

Table 6
Summary of findings table.

Outcomes	Relative effect (95% CI)	No. of participants (RCT)	Quality of evidence (GRADE)	Comments
Primary				
Patient-reported dry eye symptoms	None of the included trials reported this outcome			–
Ocular surface signs	None of the included trials reported this outcome			–
Secondary				
Eyelash length (mm)	**≤ 4 months:** MD 1.32 (1.12–1.52)	964 (7)	**Moderate**[a]	Combined results from paired-eye trials (56 eyes, 2 RCTs) suggested comparable treatment effects (MD 0.94, 95% CI: 0.49 to 1.39).
	6 months: MD 1.21 (0.90–1.51)	418 (3)		
Eyelash thickness (mm^3)	**4 months:** MD 0.47 (0.37–0.56)	922 (6)	**Low**[a,b]	Estimates from the single paired-eye trial (26 eyes) provided indirect evidence (median difference 1, IQR: 1 to 2.5).
	6 months: MD 0.56 (0.40–0.73)	366 (2)		
Incident conjunctival hyperemia (AE)	RR 6.09 (1.88–19.67)	828 (5)	**Very low**[c,d]	–
Incident ocular surface symptoms (AE)	**≤ 4 months:** RR 2.38 (0.59–9.61)	579 (4)	**Very low**[c,d]	Combined results from 3 paired-eye trials (108 eyes) suggested a similarly uncertain risk associated with the intervention (RR 2.12, 95% CI: 0.23 to 19.40).
	6 months: RR 2.77 (0.77–10.01)	306 (2)		
Incident ocular AE leading to treatment cessation	**≤ 4 months:** RR 1.68 (0.59–4.81)	686 (6)	**Very low**[c,d]	Results from 2 paired-eye trials (72 eyes) were similar (RR 0.71, 95%CI: 0.08 to 6.50).
	6 months: RR 3.41 (0.62–18.65)	420 (3)		

Abbreviations: AE, adverse events; CI confidence interval; MD, mean difference; No., number; RCT, randomzied controlled trial; RR, relative risk.
[a] Downgraded for risk of bias (−1).
[b] Downgraded for indirectness (−1).
[c] Downgraded for imprecision (−1).
[d] Downgraded for high risk of bias (−2).

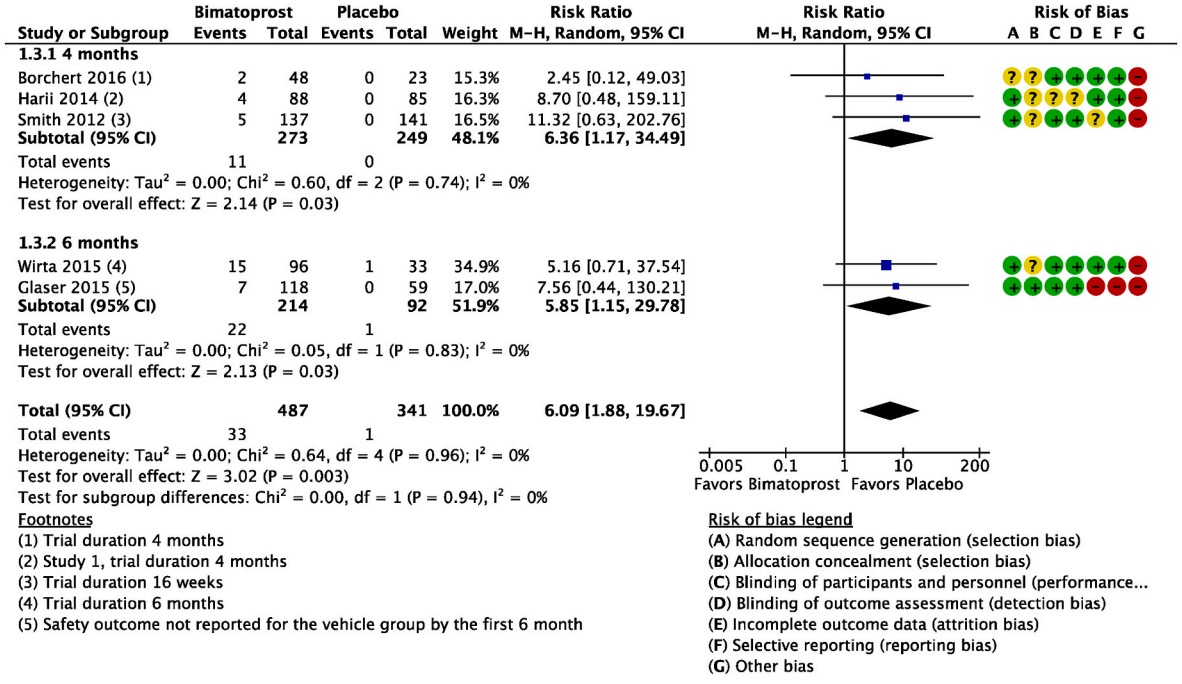

Fig. 5. Incidence of conjunctival hyperemia.

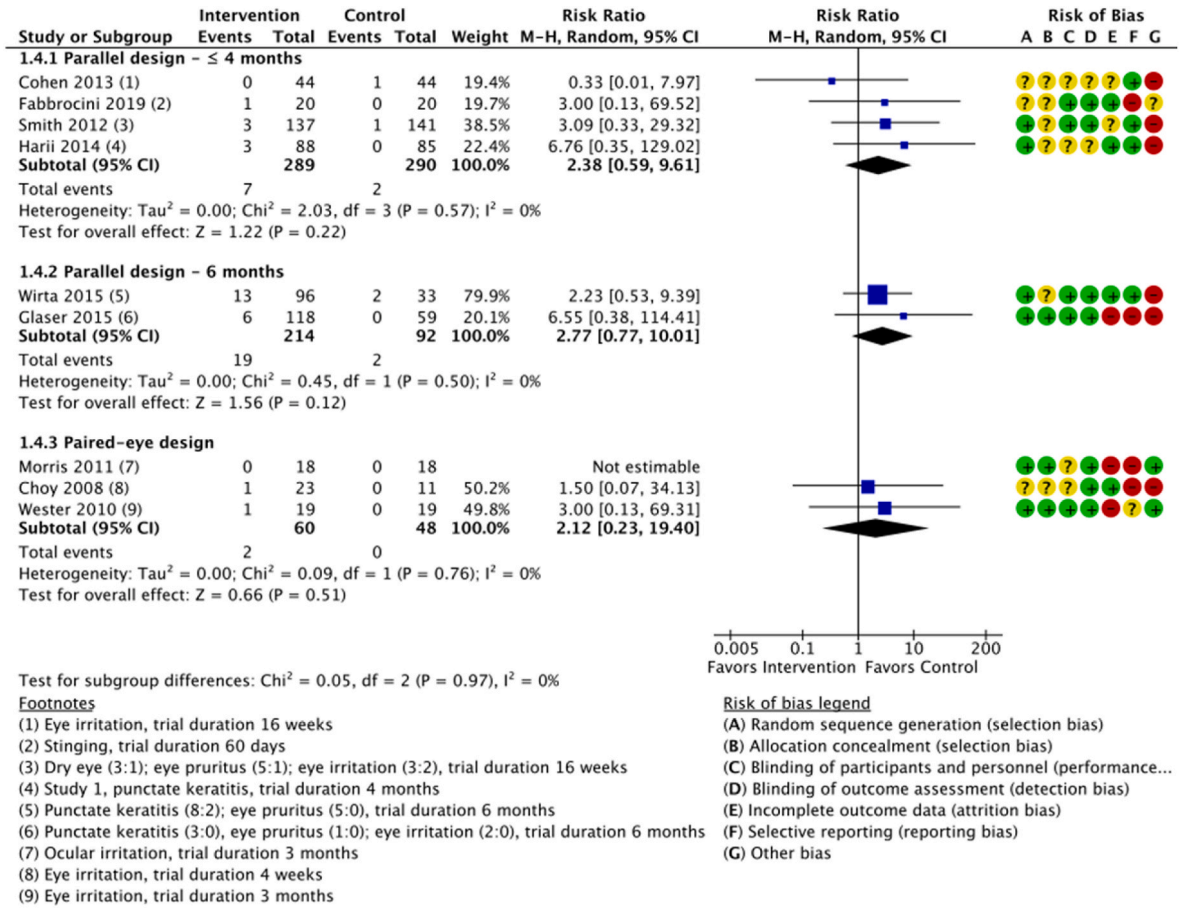

Fig. 6. Incidence of adverse ocular surface symptoms or signs.

5.2.14.6. Discussion. None of the 14 trials eligible for inclusion in this systematic review reported on either of the two pre-specified primary review outcomes associated with ocular surface disease symptoms and signs based on a validated questionnaire, scoring system or routine ophthalmic examinations. Consequently, given the lack of available literature, it was not possible to answer the key question of this systematic review ("Is the use of eyelash growth products associated with symptoms or signs of ocular surface disease?").

Over-the-counter eyelash growth serums, notably containing bimatoprost, were efficacious in increasing eyelash length and thickness. However, eyelash growth products likely increased the risk of ocular adverse events such as conjunctival hyperemia, compared to use of a placebo, after 4–6 months of use; this finding was consistent with the literature [314] though the evidence was of very low certainty. Although not measured as study outcomes, most included trials reported adverse incidents of ocular surface disease-related symptoms or signs, such as ocular irritation, stinging sensation, pruritus, or MGD; these are common adverse effects found in patients using PGAs [174,260,261] as described in Section 5.2.13.

Because other non-prostaglandin medications for glaucoma are also known for increasing risks of dry eye, only RCTs that examined efficacy and safety of PGA-containing eyelash growth serums were included to avoid carry-over effects from past usage of other anti-glaucoma medications. To reduce biases associated with patient-reported symptoms or measurements of clinical signs associated with ocular surface disease, this current review included only RCTs and excluded quasi-RCTs and observational studies, which deviated from the original protocol. The absence of evidence in patient-reported symptoms (measured by structured questionnaires) or ocular surface signs determined by clinical examinations, either as efficacy or safety outcomes, in RCTs involving eyelash growth products points to the large evidence gap in the current understanding about the safety and efficacy those products. To date, only one clinical study, though not a randomized trial, has attempted to assess the effect of bimatoprost as an eyelash growth product specifically on the ocular surface using a validated dry eye questionnaire and a suite of ocular surface assessments including non-invasive tear break-up time, ocular surface staining, ocular redness grading and tear osmolarity [336].

Of all trials eligible for inclusion in this review, bimatoprost was the most commonly studied eyelash growth product, highlighting its dominance in the trial setting and the limited breadth of the evidence on other eyelash growth products. Very few studies that examined other PGAs in over-the-counter eyelash growth serums met the review eligibility criteria. Of the studies that met the eligibility criteria, the active ingredients included: latanoprost [322,326], 15-keto fluprostenol isopropyl ester [337], and dechloro ethylcloprostenolamide [325]. Like bimatoprost, latanoprost is commonly used in the pharmacological management of glaucoma, and in this indication, reports of burning sensation, bulbar and limbal hyperemia are commonplace [338], however no ocular adverse effects were reported in the trials using latanoprost that were used for lash growth [322,326]. The PGA, 15-keto fluprostenol isopropyl ester, has similar potential side effects to bimatoprost (eye pruritus, conjunctival hyperemia, skin hyperpigmentation, ocular irritation, dry eye symptoms, and erythema of the eyelid) [337]. However the 4-week exposure to this active ingredient yielded only 1 ocular adverse event out of the small sample of 20 participants. Outside of anecdotal data and the one included trial in this review, no other published data exists for the ocular or periocular adverse event profile for dechloro ethylcloprostenolamide. A lack of evidence does not imply increased safety for these compounds; regardless of the chemical

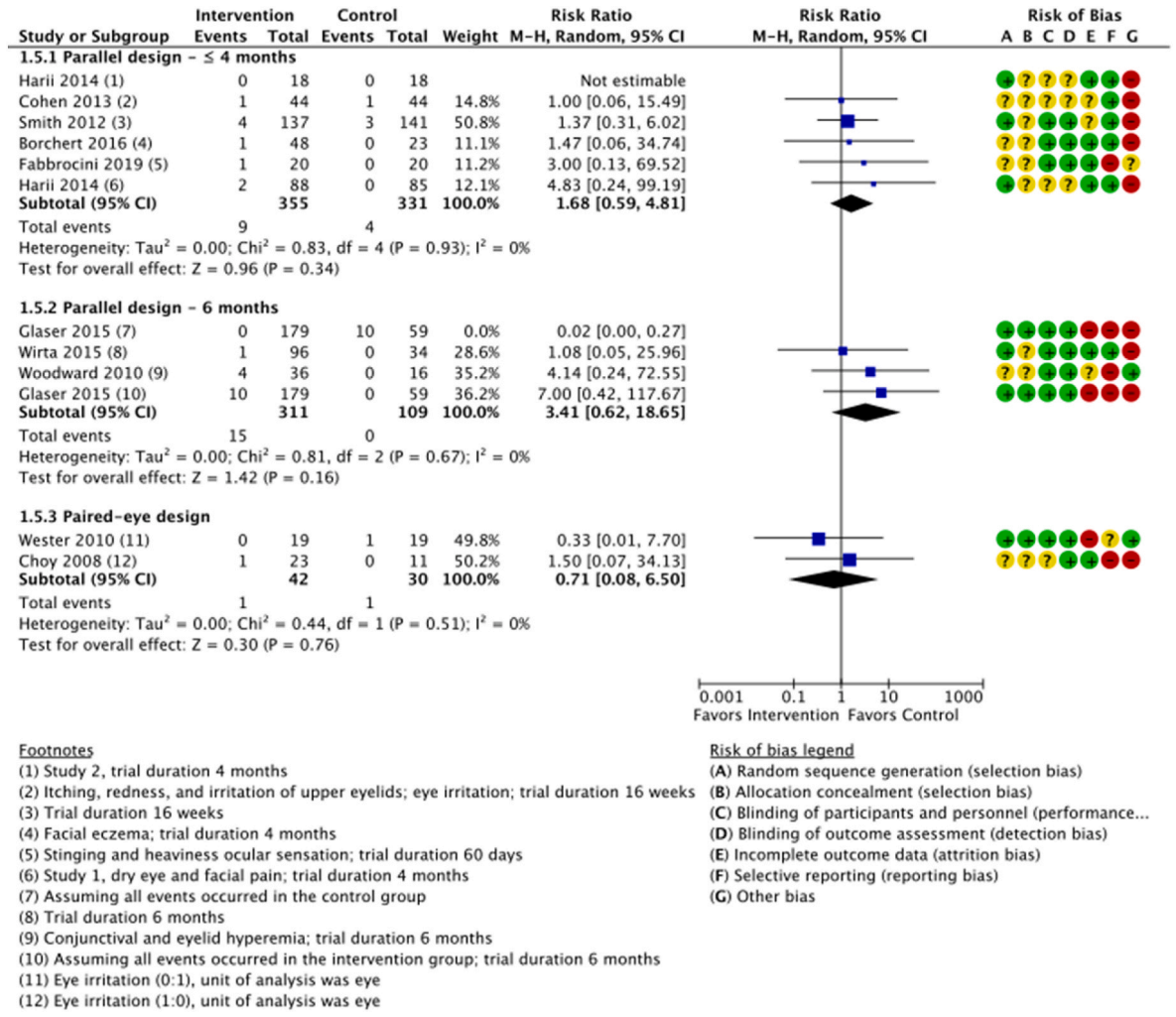

Fig. 7. Incidence of ocular adverse events leading to treatment cessation.

structure, PGAs are compounds that have the ability to alter the structure and function of the body, which results in their classification as drugs. Certain countries, such as Canada, prohibit the inclusion of prostaglandins in cosmetic products [239].

In a recently published review article, the safety profile of PGA eyelash growth products, particularly of its association with iris pigmentation, was narratively reviewed based on findings of randomized trials and observational studies [314]. Similarly, under-reporting of ocular adverse effects was common in both study designs. Validated and sensitive instruments to detect and monitor ocular or periocular changes were also advocated by the review authors [314].

Based on the current, best available evidence, patients should be counseled that they are at a higher risk, at least, of conjunctival hyperemia if they elect to use an eyelash growth product.

5.2.14.7. Implications for research. To better inform patients, clinicians, and policy makers if eyelash growth products are associated with the development or progression of ocular surface symptoms or signs, future trials should.

- quantify patient-reported symptoms using reliable and valid questionnaires [339];
- assess tear film parameters using standardized clinical techniques and standard (or consensus) scoring systems [339];
- mask participants, trial personnel, and investigator physicians who assess participants at follow-up visits with respect to treatment allocations;
- consider sample size and statistical power based on changed scores in symptoms.

Further, additional points that may delved into for future research may include head-to-head comparisons of safety and efficacy of other PGAs; gel versus solution formulations of products; preserved vs. unpreserved products (or different preservatives in these products; longer-term effects (>6 months) as well as reversibility of ocular surface signs and symptoms after cessation of treatment.

5.2.14.8. Conclusions. Using valid and reliable measurement tools, there is currently an absence of evidence based on high-quality RCTs examining the signs or symptoms of ocular surface disease associated with the use of eyelash growth products. Future trials are needed to better clarify the effects of eyelash growth products on the signs and symptoms of ocular surface disease.

5.2.15. Retinoids

Retinoids are a derivative of vitamin A and can be natural or synthetic. There are many retinoid formulations, ranging from over-the-counter products to those that must be prescribed by an eye care professional. One of the major reasons for their use is to reduce wrinkles [340].

However, one of the vitamin A metabolites, isotretinoin (13-*cis* retinoic acid), has been shown to be detrimental to the health of the meibomian glands [341,342]. This compound inhibits cell proliferation, increases cell death, alters gene expression, changes signaling pathways, and promotes inflammatory mediator and protease expression in meibomian gland epithelial cells. These effects may be responsible, at least in part, for the 13-*cis* RA–related induction of MGD [223,342].

5.2.16. Salicylic acid

Topical salicylic acid is a cosmetically available keratolytic or dermatologic peeling agent. It is marketed to treat acne and dandruff (both seborrheic or psoriatic), and to remove corns, calluses, and warts on the skin [343]. It has also been studied to lighten the skin in Asian patients [344] and to treat post-inflammatory hyperpigmentation in dark skin [345]. Products containing salicylic acid should not be placed near the eye due to risk of serious allergic reactions, ocular surface toxicity and chemical burn [343,346,347]. Similarity in packaging between ocular lubricants and topical salicylic acid has been indicated as a potential issue and cause for mistaken application of salicylic acid to the eye [346,347].

5.2.17. Shellac

Shellac is made from scraping tree bark for tunnel-like secretions of the female lac beetle Kerria lacca. It is heated and then dried to isolate the secretions and mixed with ethyl alcohol to make liquid shellac. It is used in eye makeup to bind mascara and emulsify moisturizers [348].In one publication six patients were reported to have developed allergic contact dermatitis from mascara containing shellac, which was confirmed with patch testing [349].

5.2.18. Talc

Talc, a hydrous silicate mineral, is a bulking agent used in cosmetic powders. It is a common element found in eyeshadows, creating a silky texture [350]. While allergic contact dermatitis can be directly attributable to talc, there is a far more concerning issue, which is contamination. Talc has been confirmed to be contaminated with different types of asbestos (anthophyllite tremolite, actinolite asbestos) across the global market [350,351]. The asbestos-forming minerals are created in similar geologic conditions as talc, which can account for contamination prior to product production when proper mining precautions are not taken. Cosmetic facial powder products are considered an asbestos inhalation risk [350,351]. Asbestos has been identified as a causative agent in severe lung disease (cancer, mesothelioma, pleural effusion/fibrosis/plaques, asbestosis), and cancers (renal, oropharyngeal, gastrointestinal, ovarian) [350-352]. Of particular concern is that asbestos has been identified in modern cosmetics marketed to children [350,353-355]. While there normally are no specific federal regulatory boards tasked with checking cosmetic ingredients, the US FDA was prompted to conduct regular reviews for talc contamination, which began in 2019. The repeated detectable presence and cosmetic industry's lack of self-regulation promoted these reviews [353]. The latest update was posted on October 21, 2021 [356]. Talc can go by a few different names on product labels: cosmetic talc, talcum, talcum powder, French chalk, magnesium silicate talc, and talc (MG3H2(SIO3)4) (1068–1069). Consumers should be aware that products labeled "asbestos-free" can legally contain up to 1% asbestos according to USA government definitions [353]. For those concerned about asbestos-talc risks, there are other bulking agents on the market that can be used, including cornstarch, mica, boron nitride, silica, rice powder, oat flour and silk powder [357].

5.2.19. Tea tree oil and terpinen-4-ol

As described in the Elective Medications and Procedures Subcommittee report [358], tea tree oil and its most active ingredient, terpinen-4-ol (T4O), effectively reduce mite counts in *Demodex* blepharitis [359-363]. *Demodex* mites are killed within 88 min of exposure *in vitro* to 1% T4O and within 40 min in 4% T4O [363,364]. These findings have led to the development of eyelid products containing up to 4% tea tree oil or T4O for use in treating ocular demodicosis [362,364,365]. Indeed, American Academy of Ophthalmology recommends, "Typically, a daily lid scrub with 50% tea tree oil and lid massage with 5% tea tree oil ointment will take care of ocular Demodex infestation" [366].

Tea tree oil products are not only sold for the management of *Demodex* blepharitis. Tea tree oil and T4O, at concentrations up to 1%, are also advertised as eye makeup removers, moisturizers, toners, and cleansers for eyelids, eyelashes and eyelash extensions [367-370]. However, such cosmetic use, especially chronically, may exert adverse effects on the ocular surface and adnexa. To explain: [a] exposure of human meibomian gland epithelial cells to 1% T4O killed all the cells within 90 min *in vitro*. Decreasing the T4O concentration 10-fold to 0.1% killed most of the cells within 24 h, and exposing the cells to 0.01% T4O for five days significantly reduced cellular survival [371]; [b] Tea tree oil is an endocrine disruptor and possesses anti-androgen (for example, 0.005% tea tree oil) and estrogen (for example, 0.025% tea tree oil) activities [372-374]. Androgen deficiency is a major risk factor for the development of MGD and dry eye disease [375,376], whereas estrogen may promote these conditions [223,375,376]; [c] tea tree oil at sub-lethal concentrations (0.1–0.25%) may contribute to the development of antibiotic resistance [377]; [d] tea tree oil causes allergic contact dermatitis with an 0.7% prevalence in patch-tested patients [378]; and [e] tea tree oil has been reported to induce prepubertal gynecomastia in boys [374].

T4O is known to increase skin permeability and rapidly penetrate the epidermis [379-383]. After application about 2–4% of tea tree oil ingredients pass through the skin, and approximately 0.23–0.37% of these products are retained after 24 h [371,381]. If such pharmacodynamics occurs in the eyelid, this would generate amounts of T4O between 0.2% (permeation) and 0.02% (retention). These T4O levels either kill, or significantly decrease the survival of human meibomian gland epithelial cells [371]. Consequently, the chronic use of eye makeup products containing tea tree oil and/or T4O may lead to toxic sequelae. Clinical research is necessary to determine the impact of daily application of tea tree oil and T4O on the eyelid margins. Further, as recently recommended, the eye care practitioners should be aware of the potential for endocrine disruption and should caution patients about repeated exposure to tea tree oil or T4O [371].

5.3. Summary

Although pharmacokinetic data may be absent for many cosmetic ingredients, it is important to note that the eyelid skin is relatively thin and permits the easy penetration or absorption of chemicals [371,384]. In addition, externally applied eye cosmetics may migrate onto the ocular surface, move into the tear film, and elicit negative effects [53,60,63,169,385-388]. For example, migrating compounds may obstruct meibomian gland terminal orifices and decrease meibum delivery to the eyelid margin and tear film, thereby increasing tear film hyperosmolarity, triggering symptoms of discomfort, and promoting ocular surface inflammation and damage [169,385-387]. Given that people may apply several types of eye makeup multiple times a day, every day, it is quite possible that these chemicals accumulate and affect eye health.

6. Eye cosmetic products

6.1. Eye makeup brushes and sponges

In addition to makeup itself, makeup applicators may have an impact on ocular surface and adnexal health. The principal types of makeup applicators are brushes and sponges. The main concern with makeup applicators is the potential for these instruments to act as reservoirs for microbial growth. Skin oils, skin debris and moisture can create a

breeding-ground for microbes. Sponges were identified to have the largest surface area and therefore pick up the most skin cells of any applicator [389]. One study reported that all brushes and sponges sampled from 100 different beauty salon tools were contaminated with *Staphylococcus aureus*; 69.6% of sponges and 81.8% of brushes had *Pseudomonas aeruginosa*; *and* fungus was found in 51.5% of sponges and 30.3% brushes examined [390]. *Staphylococcus aureus* and *Escherichia coli* have been found in cellulose and nylon sponges [391]. Yet another study found *Enterobacteriaceae* and *fungi* species in addition to *Staphylococcus aureus*, *Escherichia coli* and *Citrobacter freundii* on beauty blenders (a type of sponge) [392].

To minimize the likelihood of cross-contamination and the spread of infection, the use of disposable, single-use applicators (such as mascara wands, brushes and sponges) are commonplace and strategies for disinfecting contaminated applicators and sponges include the use of 60–80% isopropyl alcohol or ethanol alcohol [393]. Disinfection by UV/UVC systems is also being further explored [393]. However, its effectiveness in turbid materials (for example, lipsticks or thick gels) is limited [394].

Some sponges can be made from latex, so it is important for those with latex allergies to choose latex-free versions [395]. "Rubber" makeup sponges, in turn, have been associated with contact dermatitis in the past. Modern sponges use mostly polyester- and silicone-based materials [396,397]. It is recommended to clean sponges after each use, with a mild facial cleanser or baby shampoo [395] and store cleaned sponges in a dry place to avoid microbial contamination [391].

A makeup brush consists of three main parts: the bristles, the ferrule, and the handle. The ferrule is the metal portion of the brush that holds the bristles in place [398,399]. Makeup brushes can be made from synthetic fibers (nylon, polyesters) or animal hair. Contact allergies can occur with animal hair or nylon allergies [400]. Contact allergies have also been documented to occur in those with nickel allergies when the ferrule of the brush is made with nickel [401].

The website acne.org recommends the use of clean fingers to apply makeup, when possible, to avoid excessive irritation from coarse applicators [400]. Another recommendation is to clean makeup brushes regularly, at weekly intervals with baby-shampoo or a mild facial cleanser [400]. It has been reported that cleansers, including alcohol-based, surfactants, wipes, and shampoos of all types were successful at removing *Staphylococcus aureus* from makeup brushes. This simplifies cleaning, in that it can be done successfully with a variety of products [402].

6.2. Eyelash curlers

Use of eyelash curlers has been associated with adverse events. Contact dermatitis secondary to nickel in eyelash curlers has been described [403,404], as has dermatitis secondary to an antioxidant in the rubber fillers of eyelash curlers [405]. There has also been a report of penetrating eye injury from an eyelash curler [406]. For more information about eyelash curling, see Section 7.1.1.

6.3. False eyelashes & metallic eyeliners

Given the challenges associated with eyelid glues (see Section 7.1.5), companies have sought to find alternatives in order to avoid using glues altogether. One such innovation has been the development of magnetic eyelashes – stuck either to a thickly applied eyeliner containing metal or magnets on either side of the natural eyelashes. Several articles describe MRI artifacts related to magnetic eyelashes and metallic eyeliners [407,408], as well as a mechanical effect on the eyelids [409]. Using magnets and metallic makeup near the eye has been associated with loss of eyelashes (due to the weight applied), allergic reactions to the metal as well as corneal abrasions. False eyelashes, in turn, may cause entropion [410].

6.4. Foundation

Foundation is a cosmetic used to even out skin tone, act as a base for other cosmetics, and to cover blemishes [411-414]. Smoothed skin has been reported to be a marker of enhanced beauty [415]. While foundation is made to be applied to the face, it is also often applied to the eyelids as a base for eye shadows. Foundations can be marketed under a variety of different categories, but are mostly supplied as liquid or cream emulsions, anhydrous cakes, sticks and pressed or loose powders [411-414]. The main components of foundations are described in Table 7. Sunscreen is also a common additive to foundations [411-414].

While foundation is intended to stay on the skin, migration of cosmetics into the tear-film is a commonly observed phenomenon [416,417]. Some concerns with foundation ingredients ending up in contact with the ocular surface are the risks associated with its contained ingredients, including contact dermatitis [418], and microbial and heavy metal contamination [419].

6.5. Eye shadows

Eye shadows are pigmented products applied to eyelids to promote the appearance of larger eyes or used for color for fashion. Eye shadows are supplied as powders, creams and pencils [420-422]. Powders are composed primarily of a bulking agent such as talc or mica, mixed with pigments. Cream eye shadows are made of pigments in an emollient such as petrolatum, lanolin, or cocoa butter. They could be anhydrous or contain water [420-422]. Both powder and cream eye shadows are typically applied with a dry soft sponge-tipped applicator or brush. They can also be applied with a clean fingertip [420-422]. Stick eye shadows contain pigments based in petrolatum with added waxes to hold the consistency required for formation into a rod. These can be applied directly to the eyelid but are then commonly blended *in situ*, using brushes or sponge tools [420,421].

The cosmetic irritants in eye shadow include pigments, glitters and metallic particles, which are covered in other sections of this report [420-422]. All types of eye shadows are susceptible to microbial growth, even powders [129,422]. "Testers" at beauty salons with open cosmetics should be avoided [422]. As an example, one study demonstrated that 67% of 1345 individual eye shadow samples obtained from retail stores were contaminated with one or more species of microorganisms representing the genera *Staphylococcus* sp., *Micrococcus* sp., *Corynebacterium* sp., *Acinetobacter* sp., *Bacillus* sp. *and Moraxella* [129]. Application of powder eye shadow has been associated with the severe corneal staining and subjective irritation scores [423].

The potential for trauma exists in the case of any cosmetic applied with an applicator. A documented case showed powder eye shadow deposition under the edge of post-LASIK flap created 6.5 years prior. The patient was accidentally "bumped" while applying the shadow. This required the flap to be lifted, the cosmetic removed, and the flap replaced [424]. Care should always be taken to remain stationary while applying cosmetics near the eye.

6.6. Eye makeup primers

Eye makeup primers are marketed to help eye shadows be applied more smoothly and be retained longer, minimize migration of eyeliner product, prevent creasing, and help brighten eyes by covering skin deficiencies [425]. Primers create an adherence base for the other eye cosmetics. Eye makeup primers usually contain silicone or silicone-based ingredients like dimethicone and siloxanes D4 and D5. The former is a recognized skin irritant that can cause dryness, acne breakouts, and allergic reactions; the latter are endocrine disruptors that may cause liver damage [426,427]. Other common ingredients are natural or synthetic mica, which are used to create shimmer [428]. The silicate material that makes up mica can cause eye irritation, allergic reactions, and migrate into delicate tissues [53].

Table 7
Common foundation ingredients [411-414].

Type	Definition	Examples
Pigments	Colorants	titanium dioxide, zinc oxide, kaolin, iron oxides
Opacifying Agents	Substances that reduce the clear or transparent appearance of cosmetic products. Some opacifying agents are used in skin makeup for hiding blemishes.	myristic acid, palmitic acid, cellulose succinate, potassium cellulose succinate
Surfactant Emulsifying Agent	Surfactants that help to form emulsions by reducing the surface tension of the substances to be emulsified.	stearic acid, palmitic acid, lecithin, cellulose gum
Solvents/Viscosity Decreasing Agents	Substances that decrease the thickness of liquid cosmetic products.	water, butylene glycol, hexylene glycol, ethoxydiglycol, dipropylene glycol, mineral oil, propylene glycol, cellulose gum
Antioxidants	Ingredients that prevent or slow deterioration due to chemical reaction with oxygen.	tocopherols/vitamin E, vitamin C, ferulic acid, niacinamide, green tea
Skin Conditioner/ Smoothers/Emollient	Ingredients that act as lubricants on the skin surface, which give the skin a soft and smooth appearance	tocopherols/vitamin e, squalane and squalene, mineral oil, cyclomethicone, propylene glycol, dimethicone, cellulose succinate, potassium cellulose succinate, coco-caprylate
Skin Protectant		mineral oil, glycerin, dimethicone
Humectant	Ingredients that slow the loss of moisture from a product during use	glycerin, propylene glycol, cellulose succinate, potassium cellulose succinate
pH adjuster	Ingredients that are used to control the pH of cosmetic products.	triethanolamine (tea)
Bulking agents/Shine control	Non-reactive, solid ingredients that are used to dilute other solids, or to increase the volume of a product.	talc, silica, magnesium aluminum silicate, cellulose, mica, bismuth oxychloride
Fragrances	Scents	unidentified/proprietary, propylene glycol
Anti-foaming agent	Ingredients that reduce the tendency of finished products to generate foam when shaken.	dimethicone
Preservatives		methylparaben, paraben, phenoxyethanol, ethylhexylglycerin

6.7. Mascara

A traditional means by which to accentuate the periocular area is with the application of mascara. There is a panoply of products on the market that can contain various pigments, waxes, talc and resin. When applied to the eyelashes they give the eyelashes a darker and thicker appearance. With liquid mascara, these ingredients adhere to the eyelashes on drying and result in a temporary enhancement of the eyelashes. Mascara ingredients can migrate onto the ocular surface with blinking. In some cases the makeup is applied to the mucous membrane at the mucocutaneous junction of the eyelid margin, potentially blocking meibomian glands and contributing to dry eye disease [135,416] Dry eye treatments can then in turn make migration of makeup more likely – contaminating the ocular surface and resulting in increased blink frequency – a positive feedback loop which may render the user unable to continue with their periocular cosmetics [388,416]. Mascara has been documented to obstruct the nasolacrimal duct and canaliculi [429], cause pigmentation of, and a mascaroma (mass composed of keratin with mascara) in, the palpebral conjunctiva [47,430] and is associated with milphosis (loss of eyelashes) or madarosis (loss of eyebrows or eyelashes) [431,432]. Contamination of cosmetics, either by shared usage or poor manufacturing or formulation will further increase infection risk [126,130,433,434]. Choice of preservatives for example is very important for manufacturers – the oils in cosmetics can otherwise promote infestation with *Demodex* mites that may contribute to blepharitis [53,435]. Overall, use of eye cosmetic products and the associated need for eyelid manipulation results in a higher risk of ocular symptoms [135,416,436].

Corneal trauma is a recognized complication of mascara applicator wands [437], and has been associated with *Pseudomonas* corneal ulcers [438]. Contact dermatitis to various chemicals including preservatives, antioxidants, emollients, resins, nickel-containing pigments and pearlescent additives, shellac in mascara [439] and mascara wax has also been reported [249].

6.8. Makeup with high water content

Water is used in cosmetics as a solvent and carrier agent for other ingredients. It is found almost universally in cosmetics [440,441]. Cream formula cosmetics are composed 60–85% of water, a lotion up to 90%, and shower gel or shampoos up to 95% [442]. Tap, deionized, distilled, and demineralized water can all be included in cosmetics [443]. The choice of which type of water to use depends on the goal of the product. Tap water is not appropriate for soap formulations due to the metal and mineral ions disrupting formulations [443]. Deionized, and demineralized waters have sodium, calcium, and magnesium, plus metal ions removed from the water, which make them better choices. Distilled water has a lower pH (4.5–5.0), which is desirable for some cosmetic formulations [443].

One environmental concern is the amount of water it takes to clean and process aqueous-based cosmetic products. These thousands of liters/gallons of water are often referred to as, “virtual water [442,444]. Some companies have started utilizing “grey water,” fresh water mixed with wastewater, in elements of cosmetic production that are not incorporated directly into the product itself [444].

“Water activity” is the term given to describe the water availability in a product. The higher the water activity, the higher the potential for microbial growth [434,445,446]. In a study of cultured microorganisms from open beauty counter cosmetics, mascaras had the broadest bacterial diversity. The higher water activity of mascara leads to a greater chance of microbial deposits originating from the environment and from the surface of the eyelashes, which may make the product more susceptible to infections [434]. Many cosmetic companies have employed “anti-water activity” packaging to help lower the microbial growth in products. These precautions include the use of vapor-resistant bottles, filmstrip, vapor-repellent film coatings, or polyacrylamide hydrogels to coat packaging and discourage microorganism growth [447-449].

There are also ingredients that can be added to cosmetics to lower the water activity. These ingredients include glycerin, propylene glycol, polyethylene glycol, salts (Dead Sea Salts), and mixtures of these ingredients. To date, there has been no linear relationship identified between specific levels of these ingredients and water activity [447-449].

6.9. Eyeliner

Application of eyeliner directly to the eyelid margin at the mucocutaneous junction may predispose individuals to the migration of cosmetic material to the ocular surface [416], as well as to meibomian gland dysfunction [450]. Lipid-containing eye drops and liposomal sprays may be more likely to migrate across the eyelid margin promoting ocular surface contamination with cosmetic product [451,452] Delivery of topical therapies may themselves be compromised by interaction with eyeliner; the lipid rich lubricating effect of instilled drops may be countered by cosmetic products mixing into the tear film [388]. A study

from New Zealand found that cosmetic glitter particles could be identified in the tear film with use of a cosmetic eyeliner containing a hydrophobic waxes, oils and pigments, peaking at 10 min after product application [63].

For removal, waterproof eyeliner and mascara require more stringent eye makeup removers, which may pose additional risks to the ocular surface [453]. Also, cosmetic products are often not used in isolation, and the application of eyelash extensions may be combined with mascara and eyeliner use. The additive effect of multiple products further increases the risk of inflammation, immune-mediated allergic reactions or infection due to bacterial and fungal contamination [454]. One means by which to mitigate this risk is with the use of hypochlorous acid, a safe cleaning solution with broad anti-viral, anti-fungal and anti-microbial properties and an option that does not compromise functionality of the various glues used for extensions [455].

6.10. Eyelash growth serums

See sections 5.2.13 about prostaglandin analogues, and section 5.2.14 for the systematic review of eyelash growth serums.

6.11. Facial bleaching creams

Sun exposure and the associated photodamage that ensues are an aspect of aging that people attempt to reverse with the application of specific products. Cumulative photodamage of the skin can present in a number of ways but one significant way is hyperpigmentation. Consumers commonly seek out ways to minimize this photodamage and other hyperpigmentation disorders such as melasma to lighten affected areas of the skin. In some cultures, uniform skin is highly desirable and in others it is considered beautiful, gives the appearance of youth, as well as higher socio-economic status [456]. These factors lead people to utilize skin-lightning agents to give the perception of flawless skin beauty and higher socio-economic status.

Hydroquinone and topical corticosteroids are both utilized to combat hyperpigmentation of the skin with success but have some serious consequences. Hydroquinone is known to cause ochronosis, a marked discoloration of the skin [457]. With more than 2 weeks of consecutive use, topical corticosteroids thin the skin [458]. As greater regulation of hydroquinone has taken place, including banning the sale of products in which it is contained, its use might be expected to diminish. Banishment and illegal sales have done little, however, to stop the use of these agents. It is important for users and prescribers to recognize the limitations of these products, the adverse events associated with them and seek other alternatives [456,459].

6.12. Glitter

Glitter is an ingredient found in eye makeup, the remnants of which may appear on the ocular surface, stuck to a contact lens, distributed across meibomian gland orifices, and even within conjunctival tissue. Cosmetic grade glitter, which is typically made from polyethylene terephthalate, synthetic fluorphlogopite or borosilicate, is sprayed with aluminum in varying colors to create the “sparkle” [53,460]. Glitter edges are a concern, because they can cause a corneal abrasion [461]. Glitter may also induce allergic contact dermatitis, usually due to the ingredient methylisothiazolinone [460]. The US FDA has not given approval for glitter in eye makeup [462], and there are no regulations for glitter’s use around the eyes.

6.13. Eye makeup remover

The three main types of eye makeup removers, including oil, oil-free, and micellar, all migrate under the eyelid and increase tear film evaporation; the oil-based remover causes the greatest decrease in tear film stability.

Oil-free removers use different surfactants to solubilize makeup for removal. Unfortunately, this category of makeup remover can also solubilize eyelid skin sebum, causing the periocular skin to become drier, leading to eyelid irritation and flares of skin conditions like eczema [63, 463-466]. Surfactants have also been documented to penetrate the skin and remain even after rinsing [467].

Micellar removers utilize the oily properties of makeup to attract the cosmetic. The hydrophobic tails of the remover molecules aggregate around insoluble oily makeup residue, while the hydrophilic heads point outward, trapping the makeup residue inside, forming a small micelle, which can be rinsed away [63,463-466]. While the micellar concept is effective, micellar removers often contain harsh preservatives including formaldehyde derivatives and methyldibromo glutaronitrile [467,468].

Preservatives are not the only irritating agent contained in removers. CAPB is an amphoteric synthetic detergent that has been associated with contact dermatitis and was even named “Allergen of the Year” in 2004 by the American Contact Dermatitis Society [469,470]. Other surfactants in makeup removers, including sodium cocoamphoacetate, have been associated with contact dermatitis [471]. As excessive eyelid skin-rubbing during the makeup removal process is also associated with worsening atopic dermatitis, the method of makeup removal should be gentle [472].

6.14. Toner

Toners are designed to remove residual waterproof makeup and to prepare the skin for moisturizers [473,474]. Toners are liquid formulations, target various skin types (dry, oily, anti-aging) and contain assorted ingredients [473-476]. Certain of these ingredients help to maintain proper skin pH and barrier function, or possess anti-inflammatory (for example, aloe vera [477]) and antimicrobial properties (for example, rose water [478,479]). However, other ingredients may cause harm. A search of the poorest-rated toners for health (scores from 7 to 10 out a scale of 1–10) on the Environmental Working Group’s SkinDeep Database, revealed toners can include ingredients such as phthalates, alcohols, parabens, fragrance (proprietary, lilal/butylphenyl methylpropional), dyes (red CI 16035, blue CI42090, yellow CI19240) and retinyl palmitate [480-482] that may have adverse effects on the ocular surface and adnexa (See Section 5).

7. Eye cosmetic procedures

7.1. Eyelashes and eyelids

Humans have evolved to pay particular attention to the eyes and periocular area when they first meet someone. Gaze tracking studies from the 1960’s demonstrate this preoccupation and focus of the observer’s eyes on the subject’s eyes and surrounding periocular area [483]. The eyelashes contribute significantly to the whole aesthetic and have spawned entire industries for their enhancement. To discuss the impact of cosmetics for eyelash enhancement on the ocular surface and periocular area, the function and physiology of eyelashes is first considered.

Our lower eyelids sport around 80 hairs in three rows and about twice that number in the upper eyelid in about six rows [484]. The eyelashes have a dense array of sensory terminals which are believed to function in the elicitation of the blink reflex and thereby protect the cornea [485]. As with other hairs, eyelid cilia have sebaceous glands (glands of Zeis) to maintain lubrication and flexibility but they lack the erector pilori muscles; eyelashes do not therefore change position in response to changes in emotion or temperature for example [486]. Though notoriously difficult to eradicate, once follicles are lost they do not regenerate – the follicle number is fixed during embryonic development [487]. The natural life cycle of eyelashes involves three phases, as with all hair, anagen, catagen and telogen, but with a short anagen growth phase and long resting telogen phase. This means that they grow

only to about 10 mm and then shed naturally. We lose about 1–4 eyelashes per day and replace them. Eyelashes are more robust than other hairs – they are usually the most darkly pigmented and may lose their color (poliosis) due to a variety of genetic and nongenetic conditions [488,489].

Based upon anatomical measurements, aerodynamic scaling analysis, numerical simulation and wind tunnel experiments, the optimal eyelash length equals 0.35 ± 0.15 times the eye width. This length accrues the greatest benefit in diverting airflow, and minimizing shear stress, shear rate, evaporation and contamination at the ocular surface [490,491].

7.1.1. Eyelash curling

The desire for more 'expressive' eyes led to introduction of the first eyelash curler by William J Beldue, who called it the "Kurlash" in 1931. His invention has been a commercial success, with the heated eyelash curler market forecast to approximate US$1.6 billion by the end of 2032 [492]. However, use of curlers may lead to complications, such as nickel allergy and contact dermatitis [404,493,494]. Breakage of a curler during use also led to a penetrating corneal injury, traumatic cataract formation and vitreous disturbance [406].

7.1.2. Eyelash perming and solutions

Eyelash perming (lift) is a chemical procedure that changes the curvature of the eyelashes for a period of 6–8 weeks. The perming process consists of 4–5 steps and requires a special mold (rod made of silicone, metal or plastic) that is coated with adhesive, or requires adhesive to be painted on and the eyelashes wrapped round to achieve the desired shape. Chemicals for perming, neutralization and conditioning are then applied to finalise the procedure [495,496]. This procedure can be self-performed or applied in a cosmetic studio. In both situations, there are risks to the ocular surface and periorbital tissue in the short-term and long-term.

The short-term effects are usually the direct result of the curling and fixing lotion chemicals applied, most commonly thioglycolic acid or peroxide. Toxic keratoconjunctivits and contact dermatitis to adhesives and perming solutions are known to occur [497]. Although there are limited publications in the literature about possible chemical injuries, those might be left unreported or not correlated to the eyelash lift [498].

The long-term consequences may be more serious as the anatomy of the eyelashes is changed. Eyelash "curling" can change the air movement on the ocular surface and an increase in evaporation [490].

7.1.3. Eyelash dyeing/tinting

Eyelash dyeing/tinting is used to reduce the need for mascara and is a semi-permanent procedure. Usually, a mixture of hair dye and a hydrogen peroxide developer, which aids in the dyeing process, is applied to the eyelashes and rinsed afterwards [499]. The dyes used during eyelash dyeing usually include black henna and paraphenylene diamine, which have been related to severe blepharoconjunctivitis, contact and periorbital dermatitis and eyelid edema [500-503].

Henna is a reddish-brown dye prepared from the dried and powdered leaves of the mignonette tree (*Lawsonia inermis*), commonly mixed with a coal-tar hair dye containing paraphenylene diamine to strengthen and darken the color (black henna or blue henna) [504]. Henna was US FDA-approved in 1965 for hair pigmentation, but not for use in the periocular area (i.e., eyelids, eyelashes and eyebrows) [505].

Because black henna blends are often prepared with non-standardized ingredients, the precise amount of paraphenylene diamine and other substances may fluctuate [504]. Some marketed products have been reported to contain sodium picramate, amaranth, silver nitrate, carmine, pyrogallol, disperse orange dye and chromium [506]. A large number of aromatic compounds have been isolated from 10 'natural' hennas (black, dark brown, chestnut, and red) and 25 'commercial' hennas (black, dark brown, chestnut, burgundy, red, golden blonde, and yellow): *m*-phenylenediamine (2.16%), *o*-phenylenediamine (1.13%), *p*-nitroaniline (0.88%), aniline (0.85%), *m*-aminophenol (0.51%), *p*-aminophenol (0.37%), 3,4-toluenediamine (0.12%), *p*-chloroaniline (0.11%), *o*-aminophenol (0.10%), and o-toluidine (0.10%) [507]. These substances have been reported to cause allergic and inflammatory reactions [504,508].

Irrespective of product used for dying the eyelashes, the most common side effects are allergic reactions (for example, dermatitis), blepharoconjunctivitis, and permanent silver staining (argyrosis) of the ocular adnexa [499]. Less frequently, xanthelasma palpebrarum and corneal erosions may occur [509]. A five-year prospective study of 544 participants found that 82.6% of all dye users reported worsening of their allergic eye diseases [510]. Aside from discoloration of the eyelids, conjunctiva and cornea, silver exposure during eyelash dyeing may stimulate benign and malignant lesions, such as conjunctival melanoma [511,512]. Occasionally, measures are taken to "protect the eye" during eyelash dyeing, such as applying petroleum jelly to the periorbital skin to coat the surface from excessive dye applied to the eyelashes [500].

Eyelash tinting products are not sold exclusively by licensed professionals, which may lead to more frequent clinical complications due to inappropriate use [499].

7.1.4. Eyelash extensions

Eyelash extensions are an alternative means by which to enhance the periocular appearance. Hairs or synthetic eyelashes are individually fixed to a native host's eyelashes. This is time-consuming, as applying up to 200 extensions individually can take several hours. This procedure is not risk free. Eyelash extensions have been associated with allergic contact dermatitis, eyelash loss, eyelash base calcification, blepharitis, conjunctivitis, corneal abrasions and keratitis [513,514]. This is because the glues involved contain sensitizing ingredients such as formaldehyde, cyanoacrylate, ammonia, lead and latex [515-517], all of which are known to be able to trigger allergies [518]. Post-application irritation is common [515-517]. Glue typically takes 5–6 h to solidify during which time it can migrate to the ocular surface. Vapors from the glue may also lead to dermatitis days after the application. There are several case reports of accidental gluing of the eyelids shut [519].

The procedure must be repeated on an almost monthly basis to follow the natural eyelash life cycle. Subconjunctival migration of nylon fibers from eyelash extensions has been described, requiring surgical removal [274]. Eyelashes will be at different phases of growth, with a single eyelash lifespan of 4–11 months depending on the ocular health [517]. Some applied eyelashes will need to be removed in order to make room for new ones that are to be placed further back on the emerging eyelash. This process can necessitate use of solvents which themselves can be irritants alongside nylon or hair remnants. Misapplication of eyelash extension remover has led to bilateral chemical conjunctivitis and diffuse lamellar keratitis secondary to epithelial defects [463,520]. Both eyelash extensions and the glue are known to be flammable, and another report describes eyelashes being set alight during a minor oculoplastic procedure [521].

In a recent survey of 205 Japanese women, 55 (26.8%) experienced a complication such as redness, discomfort or itch or edematous eyelids following the application of eyelash extensions [522]. Another survey conducted of 310 Nigerian women in 2017, indicated "itching" as the most common negative complication of extension wear, in 45.8% of those surveyed [523].

7.1.5. Eyelid glue & tape for double-eyelid creation

The monolid is an anatomical variation of eyelid structure common throughout Asia. Double eyelids have a supra-tarsal eyelid crease between the eyelid margin and eyebrows, whereas monolids do not have this crease [524-527]. Varying studies have determined this structure to have a prevalence of approximately 67–81% in Chinese populations studied [524]. Overall rates throughout Asia are approximately 50% [524-527]. The single eyelid is due to the lack or absence of fibrous attachments between the levator aponeurosis and the orbicularis and

eyelid skin [527,528]. While these are healthy variations of eyelid anatomy, cosmetically, a double-eyelid structure is preferable to some [524,525].

Surgical double eyelid blepharoplasty is the most common surgical procedure performed throughout Asia [527,529]. Surgical complications from removing too much tissue include lagophthalmos, dry eyes, scleral show, and cosmetic asymmetry [527,529]. Chemosis, granulomas, ectropion, ptosis, and retrobulbar hemorrhaging are also documented complications in any kind of blepharoplasty [527,529,530].

Cosmetics interventions are readily available as an alternative to surgery. The double eyelid appearance is achieved largely via adhesives [524,529-531]. Adhesive glue, a strip of tape (either lace or solid), or a long fiber is placed on the exterior eyelid and then the skin is positioned to create the appearance of a double eyelid. The positioning of tape or fibers is often achieved with the use of a flat, plastic, double-pronged applicator. This applicator is placed over the skin and pushed towards the orbit to press the tape or fibers into place [524,530-532]. Tapes can be supplied as single or double-sided. Glues are offered as "paint-on" products. Fibers are single strips of synthetic materials of varying weights and lengths.

The use of adhesive tape is not without risk. The constant application and removal have been associated with skin irritation, eyelid thickening, loss of elasticity and inflammation [531]. The constant pulling and stretching of the eyelid skin can also lead to decreased elasticity over time, which can eventually lead to poor cosmesis of loose skin on the eyelid [531]. With constant movement of the eye, most glue products will only hold the eyelid in place for between 2 and 4 h and require re-application [529].

It has been documented that the artificial creation of a double eyelid with eyelid tape can lead to ocular surface complications. In a pilot study 29 participants of Chinese ethnicity, aged 18–29, were required to apply double eyelid tape for at least 8 h a day, five days a week, for four weeks [524]. Those with ocular surface disease, including meibomian gland dysfunction, were excluded. This study found a significant increase in conjunctival and corneal staining, and meibomian gland dysfunction, with a significant decrease in tear break-up time and intraocular pressure. By week 3, all participants had incomplete blinks, which may have been responsible for the alterations in signs. In contrast, symptoms did not change significantly. This illustrates the potential for asymptomatic ocular surface damage with double eyelid taping [524].

Adhesives are also known to cause an allergic reaction and contact dermatitis [499]. Investigation of package ingredients on eyelid tape and glues reveal the same ingredients as those used for false eyelash and eyelash extension glues [515-517]. Possible ocular surface irritants in eyelid adhesives include, rubber latex, parabens, ammonium hydroxide, fragrance, and the combination of both ethylhexylglycerin and phenoxyethanol as preservatives, and acrylates.

It should be noted that eyelid tape is not exclusively used for double-eyelid creation. Eyelid tape has also been employed in cases of dermatochalasis and ptosis for eyelid "lifting," particularly in cases with hooding [530].

7.2. Periocular rejuvenation

The periocular region is one of the earliest areas of the body to indicate aging. This manifests principally in three ways: a) skin changes such as photoaging (i.e., due to sun damage), hyperpigmentation and skin atrophy, b) reduction in skin and ligament tension resulting in tissue descent and sagging, and c) volume loss as seen with infraorbital hollowing, rhytids, deep upper eyelid sulci and eyebrow thinning.

As a result, the eyes receive the most attention for enhancement, restoration and rejuvenation, with blepharoplasty coming second only to rhinoplasty for aesthetic surgical procedures and periocular botulinum toxin treatments first, followed closely by facial fillers and energy devices for aesthetic non-surgical rejuvenation [533]. The demand for non-surgical facial skin and volume restoration has risen by almost an order of magnitude over the past 15 years [534]. This has fueled and also resulted from innovations in energy-based devices such as intense-pulsed light therapy, ultrasound, advanced lasers, thermal and radiofrequency devices. Lasers previously were the main modality for tightening skin and accomplished this by inducing new collagen formation and remodeling after damaging the epidermis with heat [535]. Particularly with the early lasers this came with the cost of significant recovery time and risk of permanent pigment changes, particularly in darker skin types [535]. Ocular adverse events with ablative energy devices have also been reported, including exposure keratopathy [536], corneal injury [537], retinal injury [538] and macular neovascularisation [539].

7.2.1. Botulinum toxin injections

Botulinum neurotoxin (BoNT) was first introduced to ophthalmology in the 1970s as a non-surgical treatment for ocular misalignment (strabismus) [540]. Following this BoNT was approved to be safe and effective for the treatment of strabismus, blepharospasm [541], hemifacial spasm, autonomic dysfunction (e.g., gustatory lacrimation) [542], and facial wrinkles, although there are also off label uses [543]. BoNT is an exotoxin from the bacterium *Clostridium botulinum* and has seven subtypes, designated A-G [544]. Its mechanism of action is through interfering with SNARE proteins that orchestrate the docking and release of neurotransmitter-containing vesicles in the synaptic boutons of neurons. Without acetylcholine release, the neuromuscular junction is bereft of signal and contractions are inhibited, resulting in a temporary muscle paralysis [544] Adverse events are rare in the aesthetic setting as complications will inevitably resolve when the effect wears off, usually within 3–4 months; blepharoptosis, reduced lacrimal function, brow ptosis, lagophthalmos, ectropion and diplopia are therefore temporary and only rarely seen in the aesthetic setting.

When used to treat facial dystonia or dyskinesis greater units are used than for aesthetic periocular treatments, and side effects from treating blepharospasm have been reported at 13.5% for blepharoptosis, microbial keratitis in 4.1%, epiphora in 3.5%, dry eyes in 2.5%, facial weakness in 0.9% and lagophthalmos in 3.0% [545]. The main cause is thought to be due to spread of the toxin beyond the target region, relating to a greater volume of more dilute toxin injection, which may be avoided with low volume, high concentration injections [546]. Upper eyelid ptosis can occur as a result of toxin infiltrating through the orbital septum into the levator complex, which is more likely with too low and deep injections to the corrugator supercili tail [547]. Ptosis of other facial muscles and the lip have been reported with treatment to the lateral canthal wrinkles or so called 'crow's feet,' when the injection has been placed too inferiorly and has affected the zygomaticus major muscle [548]. Dry eye disease induced by BoNT is dependent on the site of injection and may be caused by incomplete blink, reduced aqueous tear production due to the effect on the lacrimal gland, or meibomian gland dysfunction and tear film instability [549,550]. BoNT injections particularly to the lateral canthal area may result in incomplete blink in up to 78.9% of patients compared to 56.5% in the normal population [551], lagophthalmos, lateral canthal laxity, lower eyelid retraction and paralytic ectropion with secondary corneal exposure and evaporative dry eye disease [551-553]. In order to avoid lagophthalmos, the recommendation is to ensure injections to the lateral brow are over 1 cm above the orbital rim [554] and also avoiding treating lateral pretarsal orbicularis oculi [548]. BoNT spread to the lacrimal gland from lateral canthal injections affects tear production, resulting in aqueous deficiency [549,555-557], this effect is used as a treatment modality for crocodile tears after facial nerve palsy [542].

Interestingly, BoNT injections to the medial upper and lower eyelid may improve dry eye symptoms and signs [558-561], thought to be due to inhibition of the orbicularis muscle pump medially and increased tear retention [560]. Tear film instability due to MGD and evaporative dry eye disease following BoNT injections is reported and thought to occur due to two mechanisms [223]. Firstly, chemodenervation of pretarsal

orbicularis oculi impairs secretion of the lipid layer of tears from meibomian glands. Secondly, BoNT may also disrupt the regulation of meibomian gland function via its effect on the parasympathetic nervous system [562]. There is limited evidence however and although two studies suggest a link between BoNT and tear film instability due to meibomian gland dysfunction [549,562], other studies were equivocal or demonstrated an improvement in the lipid layer thickness with BoNT treatment [556,563-566]. Although BoNT related adverse events are rare and transient, the long-term effect on the ocular surface is not known. With increased demand for cosmetic procedures, especially amongst increasingly younger consumers and so-called 'Teen-toxing', even before rhytids are visible, there is a potential risk of significant future ocular surface sequelae.

7.2.2. Filler rejuvenation

7.2.2.1. Filler injections. Globally over 8 million filler injections are administered every year [567]. A hyaluronic acid-based fillers are the most popular as they have an excellent safety profile and are reversible with the enzyme hyaluronidase if required.

The use of fillers for facial rejuvenation is not new. The earliest use was with injection of paraffin wax as early as the 1800's. Not unsurprisingly this resulted in significant complications given the rudimentary understanding of infection and lack of antibiotics. Such treatments were replaced by fat injections but by the 1980's, these had been superseded by injectable collagen [568]. As a semi-permanent material it was much safer than, for example, silicone but still resulted in allergic responses and inflammation [569]. The market is now dominated by hyaluronic acid fillers which were first FDA-approved in 1996 [570], and although new innovations in filler technology continue, hyaluronic acid fillers continue to dominate, particularly for use in the periocular area.

Hyaluronic acid was first identified in 1934 by Kendall and Palmer as a component of the vitreous gel of cows' eyes as "a uronic acid and amino sugar' – hence the name hyaluronic acid from 'hyaloid' (or glass-like), and 'uronic acid' [571]. Three years later, Kendall reported that this same substance could also be isolated from *Streptococci* bacteria. This paved the way for the industrial production of hyaluronic acid fillers using a bacterial source, for the molecules are highly conserved in evolution. To this day, hyaluronic acid continues to be manufactured from *Streptococci* species and as there is no inter-species difference, there is little chance of an immunological rejection other than from contaminants.

Synthetic hyaluronic acid is stabilized after synthesis by cross-linking. In most-market leading products, this is achieved using 1,4-butanediol diglycidyl ether [572]. The degree of cross-linking alters the physical properties of hyaluronic acid, for example slowing its degradation, changing its viscosity and cohesiveness. These forms of hyaluronic acid can remain *in situ* for 6–24 months, though recent studies have found that they can persist for more than a decade in areas – such as the periocular area – where there is less hyaluronidase expression. MRI evidence is suggestive however of much longer potential longevity, with hyaluronic acid seen on imaging 12 years after injection [573]. Autologous fat, polymethylmethacrylate, polyalkylimide, calcium hydroxylapatite and polylactic acid confer greater longevity than hyaluronic acid, but hyaluronic acid-based products offer advantages such as being dissolvable (with the enzyme hyaluronidase) and having differing properties depending on variations in molecular size, degree of crosslinking and concentration. Resulting changes in filler rheology such as cohesivity, extrusion force, viscous modulus and elastic modulus affect their safety profiles and ability to achieve volumizing and improve tension or tissue integration [574]. Permanent and semi-permanent fillers for example, calcium hydroxylapatite and polyacrylamide have the advantage of longevity, with fewer treatments required to maintain voluminization. They are not reversible, not suitable for the treatment of fine lines, and may migrate. The last decade has also seen a paradigm shift in the way soft tissue fillers are used, from filling superficial lines to reduce the appearance of wrinkles to multi-planar 'lifting' with restoration of tension of deflated tissues.

A survey by the American Society of Aesthetic Plastic Surgeons in 2020, recorded the administration of 3.4 million soft tissue filler procedures, in the USA alone though this was 11% lower than the year before due to global coronavirus pandemic [567]. Before that the industry was growing very rapidly, with a more than 40% increase in the number of injectables administered over a 5 year period [575]. In the USA soft tissue fillers are regulated by the US FDA as medical devices [576]. In Europe soft tissue fillers are also classed as medical devices and regulated under Annex XVI of the Medical Devices Regulations (EU 2017/745) [577]. In most of the world fillers can only be legally administered by a medical professional, however in many countries currently, including the UK, soft tissue fillers injections do not need to be performed by a medical practitioner.

With the increased demand, deeper and larger volume treatments and variability in regulation and training, complications are inevitable. Filler complications should be differentiated from unwanted aesthetic effects due to inappropriate use of fillers with the latter being much more common. True adverse events are rare, often delayed, poorly reported and poorly documented. Most available data are based on small case series and case reports. The main types of adverse events are better described by time of onset, than cause, and can be divided into immediate (within 24 h), early-onset (within 4 weeks) and delayed (more than 4 weeks).

7.2.2.2. Immediate and early-onset filler complications

7.2.2.2.1. Bruising/ecchymosis/haematoma. Bruising is a common complication of fillers. This is observed more frequently after injection into the superficial subcutaneous tissues and particularly with techniques involving repeated and multiple needle passes [578]. Cannulas have been suggested as a safer alternative to needles for soft tissue fillers injections as they are blunt and less likely to penetrate into the vessel lumen and cause embolism. However, inadvertent vessel entry can still occur, particularly with finer cannulas above 22 gauges, which can act like needles and penetrate vessel walls, at least in studies conducted with fresh frozen cadaveric vessels [579-581]. Counterintuitively, needles may be safer as they allow for cleaner penetration to appropriate tissue levels, including onto periosteum. In the eye area any bruises become apparent quickly as the skin is thin and the bloody supply is rich with anastomoses. The delicate vessels are either punctured or can be stretched and tear as the filler is injected or swells [578].

Occasionally there is persistent skin discolouration with hemosiderin staining following resolution of bruising which can be improved with pulsed dye light, intense pulsed light and potassium titanyl phosphate lasers [582]. The light emitted from these devices is better absorbed by haemoglobin than structures of other colors.

7.2.2.2.2. Edema. Some swelling is expected following soft tissue fillers, however the degree and timing will vary depending on the product, volume and technique used, and will usually settle within a few weeks [582]. Swelling is more common with periocular treatments that affect the lymphatic drainage when injected too superficially in the orbicularis muscle where the lymphatic channels lie [583].

7.2.2.2.3. Antibody-mediated angioedema. An immunoglobulin E (IgE)- mediated type 1 hypersensitivity response to soft tissue fillers is rare but may occur after the initial or repeated exposure. As hyaluronic acid and other filler material is synthetically manufactured it can stimulate an IgE response with mast cell degranulation, release of inflammatory mediators and edema. This is characterised by facial itching, swelling, erythema and pain, characteristic of an allergic response and can result in airway obstruction. Angioedema occurs within hours of exposure and may last for several weeks. This mast cell mediated edema is usually responsive to antihistamines. When edema persists, or when

there is no response to antihistamine, these cases may be difficult to treat and have variable response. Oral prednisolone is the mainstay, though other treatment options include intra-lesional steroid and immunosuppressive agents, used in a step-wise fashion dependent on the treatment response [582,584].

7.2.2.2.4. Overcorrection, painless nodules and contour irregularity. Overcorrection is particularly common in the periocular area when treating the 'tear trough'- an area of depression in the medial lower eyelid demarcated by the lower eyelid crease, inferior orbital rim [585], and laterally by the mid pupillary line. Without detailed expert knowledge of the periorbital anatomy and how it changes with age, too much filler may be injected in an incorrect location, in-an-attempt-to obliterate this 'under eye circle', for instance within the confines of the orbitomalar ligament, above the orbital rim or even in the retroseptal space. The thin periocular skin coverage over the bone is very unforgiving with filler treatment and may result in worsening of 'under eye bags', that as discussed before may last for longer than the usual duration of hyaluronic acid. One hypothesis is that the periocular area has reduced breakdown of hyaluronic acid with natural anti-hyaluronidase activity to protect the hyaluronic acid within the vitreous body of the eye [586] However, there is no current evidence to support this hypothesis.

Overfill with injection of soft tissue fillers, particularly hyaluronic acid in too superficial a plane can lead to a bluish appearance under the skin, the so-called Tyndall effect. There is debate as to whether this is due to Rayleigh scattering of light or due to filler pushing subcutaneous veins to a more superficial location so they are visible through the thin periocular skin [587]. Treatment of overcorrection is with hyaluronidase if it is a hyaluronic acid filler or if superficial, by surgical expression by puncturing the skin, massage and release [588].

7.2.2.2.5. Infection. With every pass of the needle or cannula, skin commensals are introduced under the skin and fillers provide a culture medium for their colonisation with formation of populations of biofilms [589]. Overall, infections after soft tissue fillers treatment are uncommon [590], but the risk is increased in certain skin conditions such as rosacea, dermatitis, herpetic infections or prior colonisation with viruses, bacteria or fungi [591,592].

Excessive amounts of *Propionibacterium acnes* may also make patients unsuitable for soft tissue fillers augmentation. A consensus review of dermal filler complications suggest that the presence of resistant *P. acnes* at the edges of topically treated areas may play a role in the formation of infective biofilms, and also that the "safe distance" for filler placement relative to an area of acne is unknown [584]. Infections require early identification and treatment with broad-spectrum antibiotics, to prevent progression to cellulitis and orbital cellulitis risking vision and abscess formation requiring surgical incision and drainage.

7.2.2.2.6. Nerve damage. Damage to nerves during soft tissue fillers facial augmentation is rare and even more rarely permanent. Trauma can occur during injection causing dysesthesia, paraesthesia or anaesthesia, with the infraorbital nerve most commonly affected; less commonly the facial nerve or marginal mandibular nerve may be affected. Injection into the nerve, transection or tissue compression by product or edema is possible. From the ocular perspective, lagophthalmos from facial nerve paresis should be managed with ocular lubricants [593].

7.2.2.2.7. Vascular occlusion. Inadvertent injection of soft tissue fillers into a vessel leading to vascular compromise is almost always the result of injection into an artery causing embolization and occlusion of blood flow. It is the most feared of all complications, potentially leading to tissue necrosis, vision loss, stroke or death. Venous occlusion may also occur, from external compression by filler or edema and haematoma. Vascular occlusion is not a rare event unfortunately, with an estimated incidence of up to 3 in 1000 for calcium hydroxylapatite compared to 3–9 per 10,000 for hyaluronic acid injections [594]. The most commonly affected areas described in the literature are the glabella, alae nasi and the upper lip, perhaps due to the confined space and high vascularity or due to reporting bias as these are the most frequently treated areas in the reviews [594]. Arterial occlusions are typically immediate, associated with severe pain and blanching of the skin followed by a mottled, dusky purple-lace-like pattern called livedo reticularis due to swelling of venules from obstruction of capillaries. As the ischaemia progresses there is marked delineation of the necrotic area and small white pustules may appear on the skin surface. These should not be mistaken for herpetic vesicles [595].

Venous occlusion may be associated with less severe dull pain, or with no pain. Recommendations for the management of vascular occlusion are based on expert opinion [596] and consensus guidance [593]. Treatment in the case of vascular occlusion from hyaluronic acid is with hyaluronidase, delivered according to a pulsed high dose protocol dependent on the area of blanching and livedo reticularis [597]. Other strategies to reduce the risk of skin necrosis include systemic steroid, low molecular weight heparin, hyperbaric oxygen and sildenafil (1 per day for 3–5 days) [598].

7.2.2.2.8. Retinal artery occlusion. Although retinal artery occlusion is the most serious of all complications due to soft tissue fillers, unlike other vascular occlusions, it is extremely rare.

In a review of medical literature published in 2019, there were 190 cases of filler-induced vision loss, 28% were due to hyaluronic acid [599] but as the market share of hyaluronic acid has increased, reviews limited to cases reported since 2010 [600] show that hyaluronic acid now accounts for 81.3% of 146 reported cases. Still, the numbers are extremely low and this is considered a rare albeit devastating occurrence. Adverse events due to autologous fat appears to have a lower likelihood of recovery in comparison to hyaluronic acid filler-related sight loss [601]. Symptoms can be delayed but are usually almost immediate: with blood flow speeds between 20 and 42 cm/s, filler emboli can reach the ophthalmic circulation from any part of the face in a fraction of a second [602].

Larger calibre avalvular veins in the orbit also permit flow in multiple directions and anastomoses between the external and internal carotid artery territories allow the ophthalmic artery to be compromised despite injections to the external carotid circulation [603,604]. As the retina does not have nociceptors, pain associated with vision loss arises secondary to ischaemic changes in the skin, ocular anterior segment, extraocular or levator palpebrae superioris muscles. Theoretically therefore, pain should suggest a more proximal location of any embolus as seen in ocular ischaemic syndrome [605]. Despite this, clinically, pain at presentation is not a good prognostic indicator for a poorer visual outcome. This may be because proximal obstruction also provides access to more collateral circulations [606].

7.2.2.3. Late onset complications

7.2.2.3.1. Delayed hypersensitivity reactions & chronic infection/biofilm. Type IV hypersensitivity reactions can present weeks, months and even years after initial treatment and have been reported to occur in 0.5% of all hyaluronic acid treatments [582]. We know that soft tissue fillers may still be present over a decade after treatment when the patient has forgotten about previous treatment, and presents with edema and/or nodules [573]. Without a thorough aesthetic history, these nodules can result in unnecessary investigation for a suspicious mass. Often a trigger can be identified, such as systemic or local infection or immune challenge [582]. High molecular weight hyaluronic acid is anti-inflammatory but the low molecular weight HA may be pro-inflammatory; a shift over time with filler degradation will present low molecular weight fragments to the immune system, which may account for delayed inflammation [584]. Laboratory studies have also shown that addition of *Proprionibacterium acnes* with hyaluronic acid can trigger an immune response to it not seen in uncontaminated hyaluronic acid. This suggests that later aesthetic treatments which introduce *P acnes* may be responsible for delayed onset nodules [607]. The implications from these studies are that care should be taken when retreating

areas where filler may be starting to degrade (and thus be more immunogenic) and that peri-treatment sterility and antiseptic measures are key even when performing non filler injections such as BoNT due to the risk of introducing commensals [592]. Avoiding contamination is key to a successful clinical practice, since certain bacteria, once established, are able to form biofilms which make eradication most challenging as the free diffusion of antibiotics is restricted [608]. As culture of such nodules is often negative treatment algorithms have evolved empirically and usually include treatment with macrolides or tetracyclines that have additional anti-inflammatory properties. Additionally, it may be necessary to dissolve hyaluronic acid filler with hyaluronidase to aid antibiotic spread or to employ oral or locally injected steroid (or 5-fluorouracil) to reduce inflammation. In certain parts of the face, such as the highly active periocular area, fillers can migrate and lead to the presentation of new masses at sites distant from the original placement location, even years later [609].

7.2.2.3.2. Malar edema. Malar edema is a very common sequel of tear trough filler treatment and has been estimated to occur in 11% of such procedures [610]. It can occur even months or years later due to the particular anatomy of the sub orbicularis oculi fat compartment that has a superficial and deep aspect separated by the malar septum. Whilst the superficial layer has poor lymphatic drainage (in keeping with the periocular area in general – hence the marked swelling and delayed resolution of eyelid swelling in boxers for example) the deeper sub orbicularis oculi fat component is well established with lymphatic channels draining into the cheek that has excellent drainage. If filler is placed too superficially it can compress the feeble lymphatics and cause accumulation of fluid. Furthermore, as the filler begins to degrade it can block the few lymphatic channels that are present, or attract more water helping to compress those channels, explaining why malar edema can present even years later. The best treatment course can be to dissolve the remaining filler with hyaluronidase and replace it with fresh filler after a fortnight [610].

High quality studies on complications and adverse effects of periocular treatments are mainly available for procedures performed in a clinical setting such as BoNT. Data for treatments performed in the aesthetic setting are scarce and adverse outcomes likely under-reported. Furthermore, outside of registries, many physicians may be reluctant to report serious adverse events.

7.2.3. Platelet-rich plasma injection

Intradermal/subdermal injection of autologous platelet-rich plasma into the eyelids is used as a cosmetic treatment for decreasing periorbital hyperpigmentation and wrinkles [611,612]. The rationale for this approach is that platelets are enriched with a number of growth factors, such as insulin-like growth factor, transforming growth factor-β1, vascular endothelial growth factor, basic fibroblastic growth factor and epidermal growth factor [613,614], that play a major role in promoting tissue regeneration [615].

The platelet-rich plasma injections reportedly improve skin texture, color homogeneity, firmness and elasticity, lessen wrinkles, erythema and melanin, and increase patient satisfaction [612,616]. Some complications of platelet-rich plasma injections are pain in the application area, possible infection, blood clots and skin discoloration [617].

7.2.4. Microdermabrasion

Microdermabrasion is an exfoliation procedure, which involves abrading and resurfacing outer skin layers with chemical products (for example, inert aluminum oxide or sodium chloride crystals) [618]. The intention is to stimulate dermal collagen and elastic fiber production [619], thereby removing fine wrinkles and superficial irregularities [620,621]. Ocular complications, may occur, such as corneal irritation [622] or erythematous eyelids [623]. There is also a risk of autoinoculation with certain viral diseases, such as warts or molluscum contagiosum [624], and an increased risk of flares in patients with a history of recurrent herpes simplex infection [624]. Microdermabrasion is contraindicated, or should be performed very carefully, in patients with thin, photodamaged skin [623].

7.2.5. Microneedling

Microneedling is a cosmetic procedure that involves repetitive puncturing of the stratum corneum, the outermost layer of the epidermis, with sterile microneedles to induce collagen production. The procedure is designed to reduce periorbital hyperpigmentation beneath the lower eyelids and regenerate the dermis [625]. When combined with a topical kojic acid treatment, microneedling was reported to lead to a significant improvement in skin texture and under eye dark circles in a patient with periorbital melanosis [626]. Risks associated with microneedling may include bleeding, bruising, and itching [627].

7.2.6. Plasma pen

Plasma is a state of matter which can be formed by superheating a gas or passing it across a strong magnetic field [628]. In the cosmetic industry, the plasma used is referred to as 'cold plasma', which is generated at around room temperature by creating a potential difference between the skin and the device. The subsequent ionization creates an arc, which causes sublimation of the cell membranes. The epidermis is therefore converted from solid to gas without cutting and this creates free radicals which in turn can injure surrounding cells [629]. Non-surgical upper eyelid blepharoplasty using plasma is proclaimed as an alternative to surgery with potential advantages of less treatment time, no anesthetic requirement, reduced risk of scarring, and low cost. Often 3 or more treatments are performed spaced every 4–6 weeks. The recovery period is described as 7–15 days and in one study of 1000 patients over a 2-year period, no adverse events were reported [628]. The risks to the ocular surface are yet to be quantified; one report describes bilateral chemical injury and corneal burn following topical skin anesthetic for plasma treatment [630]. Animal studies have shown that plasma has no adverse effect on the conjunctiva [631] and has been used recently to treat conjunctival cysts [632]. Because the technology is relatively new, and due to a likely lack of reporting there is a paucity of data describing adverse events. The plasma pen is also not able to address underlying fat prolapse, septal dehiscence, skin crease position and asymmetry, with recovery time likely greater than with uncomplicated surgical blepharoplasty.

7.2.7. Radiofrequency skin tightening

Radiofrequency energy is a form of electromagnetic current that, when in contact with the impedance (resistance) of tissues converts the energy into heat [633]. It will target any tissue and is not restricted to certain pigments absorbing energy, as is the case with light-based devices such as lasers or intense pulsed light. An early application, dating back to the 1920's, saw it being used for electrocautery [634]. It has since been found that adipose tissue, due to its high impedance, will produce a 7-fold higher temperature differential relative to the overlying skin, allowing the technology to be used for fat reduction without damage to the epidermis [635]. The tightening effect of the technology arises from the heat altering the structure of the existing collagen as well as stimulating new collagen formation and strengthening of the elastin fibres in the tissues [636]. Unlike light based therapies, the amount of pigment will not affect the generation of heat and it is thus a predictable treatment in patients regardless of pigmentation and with an ability to penetrate deeper without absorption of the energy [637]. Monopolar radiofrequency energy has been demonstrated to tighten periorbital skin and was approved by the US FDA for this indication in 2002 [638]. But those early iterations of radiofrequency technology were associated with significant side effects – including tissue necrosis – because the energy output was less controlled, likely due to reduced capacitance in the devices [639]. The latest device generations are much safer and have proven particularly helpful for facial rejuvenation and neck tightening [640]. In the periocular area, improvement has been demonstrated on the Fitzpatrick Wrinkle Classification System, eyebrow lift of >/ = 0.5

mm, and low complication rates, with only mild transient erythema and edema reported [633,639]. In the periocular area this may result in worsening of pre-existing lymphoedema [641]. Development of fractional radiofrequency has allowed for islands of untreated normal tissue to improve recovery time. One such example is the Morpheus8 (InMode, Lake Forest, Calif) which uses needles to deliver highly anatomically localised tissue injury; this specificity does not discriminate between tissue type though and can result in adverse effects (for example, transient burning, blistering or erythema) [642]. For this reason, great care must be taken when using radiofrequency near sensitive structures such as the eyelids or eyes. On its own radiofrequency also appears to be less effective at treating wrinkles in the periocular area compared with ablative fractional laser technology [643]. Combining modalities with toxin and fillers has been proposed to achieve tissue re-contouring [644], however this also comes with the risk of adverse events to the ocular and periocular area associated with these modalities.

7.2.8. Carbon dioxide (CO_2) laser skin resurfacing

7.2.8.1. CO_2 laser technical aspects. CO_2 lasers have been used in dermatology since the early 1960s. The CO_2 laser emits an invisible infrared beam at 10,600 nm which is absorbed by water-containing tissues, resulting in skin vaporization [645]. CO_2 lasers were initially used in continuous wave mode in order to ablate tissue to a depth of 400–500 μM. To minimize thermal injury to deep tissues a high-energy pulsed CO_2 laser was developed to ablate tissue between 20 and 100 μM of tissue. This innovation repositioned CO_2 lasers in the algorithm of cosmetic treatments. Further advances led to the introduction of the fractional CO_2 laser delivery systems that split the laser beam into numerous microbeams to create columns of ablation through the skin. This refined modality improved the safety of CO_2 applications and minimized side effects, such as dyspigmentation or delayed wound healing [646-648].

7.2.8.2. Biological rationale. The main collagens in the dermis are type I and III [649-651]. Dermatologic conditions such as acne scars and aging result in dermal alterations that cause a permanent loss of, or a diminished, collagen synthesis and an altered balance between fibroblast collagen production and degradation [652]. CO_2 laser application results in contraction of the skin through dissolution of hydrogen bonds of the collagen fibrils and subsequent collagen remodeling in the dermis [653]. Recently, confocal microscopy studies have reported on the long-term efficacy of CO_2 procedures in increasing collagen deposition and remodeling [653-655].

7.2.8.3. Indications, efficacy and outcomes. CO_2 resurfacing was primarily used for skin rejuvenation of face and neck including the treatment of photoaging and chronoaging [654,656-660]. Several studies have reported the efficacy and safety of this method alone or in combinations with other topical drugs and/or devices [660-664]. More recently, positive results have been published on the use of CO_2 resurfacing for sensitive areas such as the eyelids and periocular region [665, 666].

The resurfacing CO_2 laser has been widely used also for the treatment of acne scars, alone and in combination with other treatments [647, 667-679]. Fractional CO_2 laser has proven therapeutic efficacy of over 40% in treating acne scars, with minor and transient side effects, and well-tolerated pain [668,672].

Recent studies explored the use of resurfacing lasers for new therapeutic applications such as the treatment of actinic keratoses of the eyelids [680,681]. Several studies have shown that CO_2 lasers, used alone or in combination, are effective and safe for the treatment of non-melanoma skin cancers, offering new therapeutic options for patients with extensive actinic damage [681-686]. An histology study also supported the potential use of CO_2 resurfacing for the treatment of basal cells carcinomas confirming lack of malignant tissue in the treated areas [687]. However, more studies are needed to assess the long-term efficacy of this technique.

7.2.8.4. Contraindications and side effects. Patient selection for CO_2 resurfacing treatment is important. Periocular burns, corneal ulcers due to metal shield overheating or to direct damage of the eye are the most serious complications [688-690]. Moreover, the presence of active acne lesions, tendency of hyperpigmentation, inflammatory skin diseases, viral infection reactivations, and/or use of oral isotretinoin within the previous 6–12 months may lead to delayed wound healing or undesirable scarring [648,691,692]. The typical post-procedure course involves the development of erythema, peeling, and skin fragility, which can last for up to 3 months after treatment [693]. Dyschromia is also an adverse event linked to CO_2 laser procedures and hypopigmentation is more frequently observed in Fitzpatrick skin types III-VI compared with types I-II [694]. Further studies are needed, but these results suggest that ablative lasers are superior to non-ablative lasers to treat damaged skin [695].

7.2.9. Lasers and light therapy

7.2.9.1. Biological rationale. Laser and light are widely used for cosmetic purposes as well as for the treatment of dermatologic conditions [696]. These light-based technologies transmit in either a single or broad wavelength to the skin, resulting in tissue damage and/or remodeling [697]. Laser specificity is called "selective photothermolysis" as the light beam selectively targets a chromophore (for example, melanin, hemoglobin, water) causing minimal damage to surrounding tissue [698,699]. Recently non-thermal laser therapy in the form of light-emitting diodes (LED) emerged in the cosmetic field. These LEDs use the principle of photobiomodulation in which light is purported to excite a target such as the iron- and copper-containing enzyme cytochrome C oxidase located in the mitochondrial respiratory chain resulting in an increase of reactive oxygen species production and, subsequently, in cellular migration and proliferation [700].

7.2.9.2. Indications, efficacy and outcomes. Laser can be used for cosmetic purposes or to treat several skin conditions. Wavelength, fluence, intensity and other parameters must be chosen carefully according to the desired depth of penetration in the skin, the targeted chromophore and the dermatological characteristics of the individual patient.

7.2.9.3. Skin rejuvenation. Ablative and non-ablative lasers, in pulsed or fractional modality, are the most commonly applied techniques for skin rejuvenation of face and eyelids. Ablative CO_2 (10,600 nm) and Er:YAG (2940 nm) lasers emit in the far-infrared spectrum and the mode of action is through the ablation of tissues. Several studies have shown the safety and efficacy of the ablative CO_2 and Er:YAG laser in high-pulse or fractional modalities to treat skin aging as well as acne scars [693, 701-705]. On the other hand, non-ablative lasers (Nd:Yag 1320 nm, Nd: Yap 1340 nm, Nd:Yag 1064 L P., Erbium Glass 1550 nm, Diode 1450 nm, Infrared 750–1800 nm) emit in the mid-infrared and are used for non-ablative resurfacing of the skin [706]. Non-ablative lasers are able to modify the dermal structure with fibroblastic activation, production of elastin and extracellular collagen, and release of angiogenetic factors responsible for dermal perfusion [707,708]. Recently a new device emitting a red light at a wavelength of 675 nm has been evaluated for skin rejuvenation. This wavelength shows high affinity to collagen fibers and minimal interaction with the vascular component directly acting on remodeling collagen fibers in dermis [709]. In acne scars this method offers minimum pain and the absence of side effects such as hyperpigmentation, hypopigmentation, and blistering [710].

7.2.9.3.1. Benign hyperpigmentation and tattoo removal. Pigmentation disorders are among the most common cutaneous changes and

occur in up to 60% of people [711]. The most common indications for which laser treatment is recommended include genetically predisposed nevi [712] and pigmentation (for example, lentigines, post-inflammatory hyperpigmentation, nevus spilus, hypermelanosis, exogenous pigments, tattoos and cosmetic pigments) [711,713,714]. Lasers that treat hyperpigmentation target melanin, contained in the melanosomes. Q-switched lasers such as the QS Ruby, QS Nd: YAG, and QS Alexandrite emit pulses of very short duration (nanoseconds) with peak powers in the order of megawatts and represent an effective solution for the treatment of benign hyperpigmentation and tattoo removal [711,715-723]. There now exist picosecond 532-nm, 694-nm, 755-nm, and 1064-nm devices available to target a wide array of tattoo pigments [724,725].

7.2.9.3.2. Vascular lesions. In recent years, several laser systems have been developed for the treatment of vascular lesions (dye laser 585–595 nm, Nd:Yag 1064 nm, KTP 532 nm, Diode 810, 940 nm). Those lasers target oxyhemoglobin, such that the absorbed energy results in thermal damage to vascular structures. Several vascular lesions can be effectively treated with laser therapy such as telangiectasias, spider nevi, cherry angiomas and port-wine stain lesions [726-732]. A retrospective analysis for facial telangiectasia treatment showed that pulsed dye laser (595 nm) and intense pulsed light with M22 vascular filter (530–650 nm and 900–1200 nm) had similar results and optimal clinical efficacy as compared to intense pulsed light with other wavelength bands [733].

7.2.10. Intense pulsed light (polychromatic non-laser light)

Intense pulsed-light systems emit light in a broad spectrum with wavelengths between 500 and 1200 nm. It is a non-coherent, non-collimated, nonselective high-energy light, with fluence ranging between 3 and 40 J/cm^2 and pulse durations that can vary from 10 to 340 msec with single, double or triple pulses and extremely variable pauses between pulses (2–100 msec) [734].

With the help of suitable filters that exclude unwanted wavelengths it is possible to selectively target a specific tissue or pigment, allowing the intense pulsed light to be effective for the treatment of several skin conditions (for example, superficial hyperchromic lesions, vascular lesions, hair removal, rejuvenation and photoaging) [735-739]. Large, controlled trials are needed to standardize the use of intense pulsed light [740,741].

7.2.11. Photodynamic therapy and other light sources

Photodynamic therapy involves the use of a topical photosensitizer, light irradiation, and oxygen to generate cytotoxic reactive oxygen species that may destroy damaged cells while leaving normal skin intact [742,743].

However, photodynamic therapy emerged as an off-label treatment modality used with different sensitizers for a range of dermatological and aesthetic conditions [744]. New protocols including laser mediated photodynamic therapy significantly improved results for several indications such as acne vulgaris and photorejuvenation [745-748]. Recently, low-level light therapy, termed "photobiomodulation," has emerged as a safe and effective method of skin rejuvenation and body contouring, but corroborative, more standardized clinical trials are still needed [749-752]. Photobiomodulation has also been proposed as a possible treatment for MGD and dry eye disease [753].

7.3. Tanning beds

Solar beds are a popular way to enhance appearance, especially among young women with lighter skin complexion [754-756]. Recent data indicate that the global prevalence on indoor tanning is 10.4% in adults and 6.5% in adolescents [757]. The use and possible dependence on the artificial sun tanning exposure may relate to reported increased endorphin levels after several sun tanning sessions [758]. However, tanning beds also increase the risk of developing squamous cell and basal cell carcinoma by 58% and 24% respectively, and use of these beds before the age of 20 increases the risk of developing melanoma by 47% [759].

During a sun tanning session, every person must wear eye protection [760]. However, various internet blogs note that many people do not use eye protection, or instead of goggles they use a towel over the face [761, 762].

Solar beds have potentially harmful effects on the eyes, and especially the ocular surface [763]. A recent study found that exposure to indoor tanning (10 sessions of 10 min duration over a 15 day period) resulted in significant microstructural changes in the cornea and the bulbar conjunctiva [764]. These alterations were detected by using *in vivo* confocal microscopy, but not the slit lamp, and included reductions of epithelial cells and circumscribed cystic lesions [764]. Although reversible, sub-dermal cysts are well correlated with the development of skin cancer [763].

7.4. Tattooing and jewelry

Tattoos are non-medical procedures that involve injecting colored inks into the dermis with solid or multiple fine needles or by inserting colorants with microblades [765]. These tattoos may be for cosmetic purposes, such as to create permanent makeup.

7.4.1. Tattoo pigments and dyes

The International Organization for Standardization defines “colorants” as pigments consisting of insoluble particles, usually dispersed in vehicles or substrates for application, as well as dyestuffs, which are soluble in a medium. A colorant can contain the pure chemical substance and/or a surface treatment and/or additives, as well as traces of impurities, which can originate from raw materials and/or the production processes. Pigments can be further described on the basis of their chemical composition and optical or technical properties (for example, inorganic, organic, colored, corrosion-inhibiting, magnetic) [766].

Organic pigments are carbon based, while inorganic pigments comprise metallic salts including those of iron, titanium, zinc and chromium. They show dull and non-brilliant shadows of color, while organic pigments present a more strengthened and vivid color, especially when containing barium sulfate and titanium oxide, resulting in a wider color spectrum [767].

A dull surface texture is created through the inclusion of titanium dioxide, while a pearled shine is created by bismuth oxychloride, mica, or fish-scale essence (guanine). A metallic iridescent finish is provided by copper, brass, aluminum, gold, or silver powders [135].

Commercial products usually contain additives to enhance specific characteristics such as fluidity and dispersibility for better application, but the dyes or pigments that will produce the final color of the product are the essential colorants. These are listed in the Color Index™ (Generic Names and Constitution Numbers), wherein each pigment has a generic index number that makes it possible for anyone to ascertain the specific dye or pigment present in cosmetic products [768]. The Color Index™ contains over 13,000 color names, classified according to their chemical structure [769].

Color additives are any substances that can modify the color of a product, and they must comply with individual listing regulations, some of them with a tightly restricted use [25]. Some traditional pigments used to contain toxic heavy metals such as lead, mercury, and cadmium, which could cause severe health issues. In the USA “color additives that are permitted for general use may not be used in the area of the eye unless such use is specified in the color additive listing regulation” [505].

Inorganic pigments contain metal salts to provide better color opaqueness and broaden the hue variety [770]. Lighter shades usually derive from titanium dioxide, whereas darker shades are mostly made of iron oxides [765]. With organic pigments, the risk of allergic reactions and sunlight transformation is generally reduced, and the insolubility

helps prevent blurring and color relocation [765].

Organic pigments are more affected by sunlight exposure since they absorb the light, causing earlier color changes and fading [765,771]. They are usually byproducts of carbon, oxygen and hydrogen, and are considered to be semi-permanent [765]. The polycyclic (or azo pigments) are commonly used in tattoo inks (for example, quinacridone for red and violet and phthalocyanines for green and blue), and can also be mixed with metal inorganic elements, such as iron, cobalt, copper and nickel for more color variations [772-776].

To reduce the potential for allergic reactions, the so-called "lake pigments" have been developed, in which a protective membrane of alumina hydroxide is formed around the organic molecules, avoiding a direct reaction with the human body [777]. Also, botanic water-based "vegan" pigments without iron oxides have been used in permanent makeup inks more recently [765,778].

Carbon black is largely used worldwide, with an annual global production of 5–10 million tons per year, mostly used for automobile tires (70%) and black plastic (20%), but also for inks, paints, cosmetics and others [779]. One of the main concerns regarding carbon black production is the formation of carcinogen polycyclic aromatic hydrocarbons. Studies have reported that there are many brands of black tattoo ink with high levels of polycyclic aromatic hydrocarbons, but also that there are some products in the market with polycyclic aromatic hydrocarbons levels that are below the Council of Europe recommendation of <0.5 μg/g (500 parts per billion), proving that very low polycyclic aromatic hydrocarbons products can be produced [779].

7.4.2. Tattoos: general concerns

Permanent makeup has biosafety issues with respect to untrained professionals and the inks used, which may generate infectious and inflammatory reactions due to toxicity or contaminated material [767]. In addition, tattoo/permanent makeup products and practices lack national and international regulatory harmonization. There are different policies for tattooing procedures and biosafety worldwide, with little regulation regarding the chemical ingredients within inks [767].

For toxicological risk assessment, tattoo and permanent makeup inks must be considered differently from cosmetic products because of differences in terms of their routes of exposure as well as their chemical and physical compositions [780]. Tattoo and permanent makeup inks are usually composed of combinations of organic and inorganic pigments and a medium containing additives, preservatives, byproducts and impurities [767].

As noted above, ink colorants can be classified into pigments or dyes. Characteristics of the former are insolubility and photostability, while those of the latter are soluble and decomposable. Whenever dyes are used in tattoo inks, they are manipulated to form lake pigments, coated with an inorganic substance (for example, barium sulfate and aluminum hydroxide), making them more resistant to light and degradation [767].

Several complications have been reported following tattoo/permanent makeup procedures, namely blisters, aseptic inflammation due to needle trauma, site infection, hypersensitivity and autoimmune type reactions (such as dermatosis reactivated by tattooing), pigmentary disorders, keloid development, tumors and medical diagnostic and treatment interference [410,767]. Inorganic pigments are less likely to cause allergic reactions and are commonly used in permanent makeup procedures [765]. However, some components may not be regulated by the local sanitary agency, increasing the risks involved [772].

7.4.3. Eyelid tattooing

Tattoos are often applied to the eyelid margin near the eyelashes in order to create a permanent makeup eyeliner [765]. Since the eyelid skin is very delicate and the components of the inks used are not always safe or known, some ocular disorders associated with blepharopigmentation have been reported: allergic granulomatous reactions, conjunctivitis, inadvertent pigmentation of the cornea and limbus, eyelid penetration, diffuse lamellar keratitis, tear film instability and meibomian gland loss, as well as widespread ink fanning or distant ink deposition, fading and scarring [499,781-785].

Histopathological examination of specimens after eyelid tattooing demonstrates "persistence of pigment implants as free granules in the epidermis and dermis, and most of the residual pigment can be found within the macrophages in the dermis and, focally, in the endomysial connective tissue of the superficial orbicularis oculi muscle" [786]. Ocular complications have been associated with lysis of cells containing phagocytosed pigment after tattoo pigment-induced mast cell activation [783].

Eyelid tattooing has been reported to promote eyelid inflammation, meibomian gland loss and tear film instability [781,787]. Investigators [788] reported a case of "delayed-hypersensitivity granulomatous reaction following blepharopigmentation," presumed to be caused by the aluminum-silicate pigment used. They recommended that the pigments used should meet high quality manufacturing standards by creditable companies.

7.4.4. Conjunctival/episcleral tattooing

Cosmetic tattoos may be used to change conjunctival color. A successful conjunctival tattooing after evisceration for a patient who was unable to wear an artificial eye has been reported [789]. Also, combined corneal and ingrowing conjunctival tissue tattooing by micropigmentation has been used for cosmetic purposes with satisfactory results and with no postoperative complications [790].

However, the "eyeball tattooing" (conjunctiva and episcleral tattooing), first described in 2007 [791], has emerged as an extreme and rare form of body modification, consisting of multiple injections of subconjunctival ink to color the whole eye surface, frequently performed by artists with no medical training [792]. Procedure complications have been reported to include globe penetration with the tattoo needle device, such as vitreous or subretinal hemorrhage, retinal detachment, endophthalmitis, and traumatic cataract) [793-799].

From reported cases to the date, 11/17 (68%) were complicated by inadvertent globe puncture, with more serious visual consequences whenever ink was accidentally injected inside the eye [800,801]. When ink reaches intraocular structures, early removal is recommended as a first treatment. Inflammatory reactions and ink particles may cause transparency loss, toxicity, and trabecular damage with ocular hypertension and eventual secondary glaucoma [793]. Additionally, both local and systemic immune hypersensitivity reactions to the tattoo ink used can occur, including delayed onset uveitis [801]. Reports have also associated the tattooing of eyeballs with the development of episcleral nodules, posterior scleritis, orbital cellulitis, necrotizing scleritis and uveitis, conjunctival swelling, and conjunctival lumps [792,797,800, 802,803].

Remarkably, multiple cases of "tattoo-associated uveitis" exist in the literature in the setting of systemic sarcoidosis or a delayed-type hypersensitivity reaction, in which simultaneous tattoo inflammation and uveitis occur, yielding potentially vision-threatening ocular complications [804,805].

Unintended pigmentation of the conjunctiva and nasolacrimal sac has been reported to occur from usage of kohl eyeliner and mascara, and to simulate a melanocytic tumor [48,806,807]. Conjunctival pigmentation occurs when macrophages ingest pigmented exogenous material that then settles within the substantia propria of the epithelium. Mascara-laden dacryoliths may also be generated [806,808,809].

7.4.5. Eyelid and conjunctiva piercing

Piercing is a modality of body modification in which holes are created through any part of the body to insert decorative adornments (for example, rings, studs or pins) usually made of stainless steel, titanium, gold, niobium or acrylic, and is especially common among adolescents and young adults [810]. Individuals are often unaware of the risks involved [811].

The wound and presence of a foreign body facilitate bacterial

Table 8
Examples of cosmetics regulations in various regions.

Product notification/ in-market surveillance program	Regulation of chemicals	List of prohibited or restricted substances	Legal requirement to conform with Good Manufacturing Practices	Membership in the International Cooperation on Cosmetic Regulation	Surveillance of dangerous/ non-compliant goods	Reporting of adverse reactions
European Union						
Online notification to Cosmetics Products Notification Portal	EU Registration, Evaluation & Authorization of Chemicals (REACH)	Annex II and III. Positive lists under Annexes IV, V and VI lists permitted colors, preservatives and UV filters	Yes	Yes	EU Safety Gate	Consumer reports directly to manufacturer. Manufacturer needs to report to the national Competent Authority of the EU Member State in the event of a serious undesirable effect within 20 days of awareness
Great Britain (post-Brexit; EU regulations may apply for Northern Ireland)						
Online notification to the Office for Product Safety and Standards using the Submit Cosmetic Product Notification portal	UK REACH	As per EU regulations, as implemented on 31 Dec 2020. UK will make independent decisions on ingredients from 01 Jan 2021 and may differ from EU in the future	Yes	TBD – no ICCR meeting since Brexit	UK Product Safety Database	Consumer reports directly to manufacturer or distributor. Distributor or named responsible person in Product Information File notifies the UK Competent Authority of any serious undesirable effects without delay
Canada						
Online notification using the CNF (Cosmetic Notification Form)	Review of chemicals under the Chemicals Management Plan of existing substances (listed on the Domestic Substances List) and new substances	Cosmetic Ingredient Hotlist for Prohibited and Restricted Ingredients	No, but encouraged	Yes	Consumer Product Safety Program	Industry must report health or safety incidents to Health Canada within 2 or 10 days (number depends on who is reporting)

infections of the skin and soft tissues and increase the risk of viral hepatitis transmission [812,813]. Allergic reactions to metals (especially nickel) are common [812,814]. Eyebrow piercing may be followed by swelling of the eyebrow and cheek, redness of the eyelid, anterior and posterior cellulitis [815,816]. Eyelid piercing carries the risks of irritation or scratches to the eyeball, eye perforation during the procedure and eyelid abscess [817].

Eyeball jewelry (JewelEye) was developed first in the Netherlands as a “radical new form of body modification” in 2004, in which a 3.5 mm, curved platinum cosmetic extraocular implant was positioned inside the conjunctiva [818]. There is still no evidence about the safety of the procedure and the American Academy of Ophthalmology warns customers about the risks of "eyeball jewelry” implantation, such as ocular infection, sub-conjunctival bleeding, perforation of the eye and blindness, and urges consumers to “avoid placing in the eye any foreign body or material that is not proven to be medically safe or approved by the US FDA” [819].

7.4.6. Eyeliner tattoo removal

Individuals may seek “permanent” eyeliner to typically save time, cost, and application challenges due to dexterity or arthritis [787]. However, they may also choose to remove the tattoo. One approach is to use a Q-switched, ND: YAG or Alexandrite picosecond laser. Both lasers are effective in removing pigment from eyeliner tattoos and eyebrow tattoos [820,821]. It is not currently known how these lasers might affect the meibomian gland and the ocular surface. Severe eye damage can occur if the placement of metal corneal shields is not utilized during the treatment [822,823].

8. Cosmetics regulations

Multiple laws, programs and/or governing bodies regulate cosmetics and cosmetic ingredients in many countries, such as in the European Union (EU), Canada, USA, China, Korea, India, Japan, Brazil and Australia [824]. These regulations address the safety and quality of eye makeup, and assess the product risk profiles, hazardous substance criteria, label information, test methods, manufacturing, registration, and/or the good manufacturing practice qualifications of manufacturing sites [824-826]. Examples of such regulations are shown in Table 8.

Significant differences exist between countries in their regulations. Canada and the EU, for example, have stringent and protective parameters for ocular cosmetics that are far stricter than those required in the USA [826]. The EU Cosmetics Directive mandates pre-market safety analysis of cosmetics, necessitates registration of cosmetic products, prohibits animal testing for cosmetic development, and bans many chemical compounds from cosmetics that are known or suspected to cause health hazards, such as genetic mutations, cancer, reproductive toxicity or birth defects [825,826]. In contrast, the USA does not require safety information or premarket approval of cosmetic products and ingredients, except for color additives, and has banned or restricted very few chemical ingredients from cosmetics [826,827].

The following sections briefly describe the cosmetic regulations in various regions of the world. This information is accurate at the time of writing and is subject to change at any time.

8.1. USA

The USA Federal Food, Drug, and Cosmetic Act (abbreviated as FFDCA, FDCA, or FD&C) is a set of laws passed by Congress in 1938 giving authority to the US FDA to oversee the safety of cosmetics, as well as food, drugs and medical devices [828]. However, under this law, cosmetic manufacturers are not required to: [a] test their products for safety prior to distribution; and [b] obtain FDA approval for cosmetic products and ingredients, other than color additives, before making them available to consumers [828]. In addition, although the FDA does hold cosmetic manufacturers responsible for the safety and proper labeling of their products, they cannot force a manufacturer to recall unsafe products. Such recalls are voluntary (21 CFR 7.40(a)).

There are 11 banned chemicals in the USA, because of known toxic effects. These include bithionol, chlorofluorocarbon propellants,

chloroform, halogenated salicylanilides, hexachlorophene, mercury compounds, methylene chloride, prohibited cattle materials, vinyl chloride and zirconium-containing complexes [243]. Of interest, the FD&C makes an exception for mercury in eye makeup products. Despite this element's toxicity, mercury compounds are permitted up to 65 parts per million in cosmetics, if no other effective preservative is available (21 CFR 700.13).

Cosmetics produced or distributed for retail sale to consumers in the USA for personal care are required to bear an ingredient declaration (21 CFR 701.3). The ingredients must be listed in descending order of concentration, except for those present at one percent or less (21 CFR 701.3 (f)(2)). Color additives may be declared in any order, not concentration dependent, after all other ingredients (21 CFR 701.3(f)(3)). Cosmetic products that may be unsafe to consumers when misused must contain appropriate label warnings, as well as directions for safe use and application.

8.2. Canada

In Canada, cosmetic products are regulated under the Cosmetics Regulation (C.R.C, c. 869) of the Food and Drugs Act (R.S·C., 1985, c.F-27). Similar to the cosmetic regulations in other jurisdictions, the Food and Drugs Act states that all cosmetics manufactured, imported or offered for sale in Canada must be safe for use.

To assist manufacturers of cosmetic products, Health Canada has drawn up the Cosmetic Ingredients Hotlist, which is an administrative tool that lists substances that are prohibited or restricted for use in cosmetics. This evidence-based resource is updated periodically, guided by new scientific data and decisions made under the Chemicals Management Plan.

All cosmetic products for sale in Canada must notify Health Canada within 10 days after the product is first sold.

8.3. European Union

European Cosmetics Regulation ((EC) No. 1223/2009) is the overarching regulation relating to the manufacture of cosmetics in the European Union, which is comprised of 27 member states. The regulation also applies to European Economic Area (EEA) countries and Northern Ireland. Amendments to this regulation are made regularly and supporting technical documents have been added to further ensure human safety. Opinions on health and safety risks of ingredients are provided by the Scientific Committee on Consumer Safety (SCCS), which is made up of experts who specialize in the evidence-based assessments of chemicals, toxicology and pharmacology.

Annex II in the EU Cosmetics Regulations lists over 1300 substances which are prohibited in cosmetic products, while Annex III lists substances which are restricted in cosmetic products but can be used, only within specific conditions as laid out in the document.

All cosmetic products for sale in the EU must be registered into the Cosmetics Products Notification Portal before their sale in the market.

8.4. UK

With the UK formally withdrawing from the EU in 2020, the manufacture of cosmetics is now regulated under the Product Safety and Metrology Statutory Instrument (Schedule 34), which has been in force since January 2021. The UK regulation is transposed from the EU regulation, with many elements remaining the same as the EU legislation, with some amendments made relating to the Northern Ireland protocol of the withdrawal agreement. In line with the EU legislation described above, the UK has also adopted the same lists of prohibited and restricted substances. Going forward, updates to these lists will be made by the UK Cosmetics Ingredients Safety panel, a group of independent scientists who will provide expert opinion on the safety of cosmetic ingredients, and thus may change Annexes II and III laid out by the EU.

All cosmetic products for sale in the UK must be registered into the Office for Product Safety and Standards before sale in the market.

8.5. Brazil

In Brazil, the National Health Surveillance Agency (Anvisa) is the federal agency responsible for establishing the rules for the registration (marketing authorization), manufacture, labeling and sale of cosmetic products, while regional and municipal health surveillance teams carry out inspections in the production chain, from manufacture to commercialization, evaluating the techniques and methods used in the manufacture of these products. Health surveillance bodies are also responsible for monitoring and disseminating information on the safety of cosmetics, personal care products and perfumes [829].

The Resolution of the Collegiate Board of Directors - RDC N^{o} 332, of December 1, 2005 establishes that the companies that own cosmetic products must implement a cosmetovigilance system comprising activities relating to the detection, assessment, understanding and prevention of adverse effects and any other problems associated with the use of cosmetics, and to collect information on problems arising from the use of the products that are under their legal responsibility [830].

8.6. Global comparisons and efforts

Common rhetoric in the "clean beauty" movement suggests that certain geographical regions prohibit or restrict a long list of ingredients in cosmetics while others prohibit or restrict very few. Focusing only on long lists of restricted ingredients is a distraction from the overarching principles of safety and poor indicators of the quality and safety of cosmetic products. The EU list of restricted substances includes named drug compounds and substances that are not historically used in cosmetic products, such as carbon monoxide and chloroform. What is often omitted from the rhetoric is the requirement to conform with Good Manufacturing Practice (GMP). Both the EU and the UK legally require the manufacture of cosmetic products to conform with GMP. This extends to having procedures to ensure that products are prepared in a clean environment and do not allow final products to become contaminated in production to protect human safety [831]. If contaminated, an innocuous ingredient such as water can cause great harm to a consumer, which might not be detected from merely reading an ingredient label on the packaging of a cosmetic product.

From a manufacturer's perspective, many multinational companies choose to uphold the principles of GMP and observe prohibited and restricted lists, even if the requirement is not a legal requirement, as their products may be sold in different regions of the world. Second, the potential negative impact from not performing safety assessments can be significant. Problematic products can result in reputational damage of a company and the erosion of consumer confidence not only for one specific product, but an entire range of products they offer, translating to lost sales [832]. Ultimately, it is not in the manufacturers best interest to allow harm to be caused to consumers in a highly competitive market [832].

The International Cooperation on Cosmetic Regulation (ICCR) is a voluntary international group of cosmetics regulatory authorities that meet annually. The ICCR aims to, "maintain the highest level of consumer protection, while minimizing barriers to international trade". Established in 2007, members include the cosmetic regulatory authorities from the USA, Canada, Japan, the European Commission, Brazil, Taiwan and the Republic of Korea. This global cooperation facilitates dialogue, which includes industry-represented organizations, to ensure regulatory alignment to protect consumers. Different working groups discuss a wide range of topics, such as allergens, safety assessments, microbiology, nanotechnology and product preservation.

9. Eye cosmetic safety and terminology

9.1. Safety

Most jurisdictions have in-market surveillance programs to monitor dangerous and non-compliant products that enter the markets. Depending on the jurisdiction, this may involve the prevention of non-compliant products entering the market or involve a recall of products that no longer meet the required standard. Similarly, reporting mechanisms are in place for consumers to report concerns relating to cosmetic products. This might be to the manufacturer to then forward onto the regional databases, or direct reporting mechanisms may be in place. Table 8 summarizes a number of these reporting pathways.

The following organizations provide searchable data for consumers and clinicians about the ingredient composition and safety of eye makeup and personal care products.

- Environmental Working Group (https://www.ewg.org/skindeep/) is a non-profit USA based organization focused on environmental safety including toxic chemicals
- The US Cosmetic Ingredient Review (CIR) Expert Panel conducts independent testing and publishes in the International Journal of Toxicology and on the CIR website (https://www.cir-safety.org). This Washington DC organization works closely with FDA to set priorities and evaluate ingredient safety data.

Another website, SkinSAFE (www.SkinSafeProducts.com), was developed in collaboration with the Mayo Clinic and serves as a free resource to search for commonly known ingredients that may elicit an allergic reaction. However, SkinSAFE approved ingredients may not necessarily be safe for the eyelid. A number of products rated as 100% safe on this website contain ingredients (e.g., phenoxyethanol, chlorphenesin, parabens) that, as discussed in this report, may be toxic to the ocular surface and adnexa.

9.2. Terminology

Many terms commonly seen on labels of cosmetic products lack definitions set out by regulatory bodies and do not have standard testing methodologies for such claims [136]. Table 9 summarizes terms that are regularly seen on personal care products, including cosmetics. These terms are used as part of marketing strategies for brands to position their products.

Usually product testing claims imply that qualified medical professionals (a medical doctor, dermatologist, ophthalmologist) were involved in the assessment of safety [833], unless they specifically indicate their involvement in tests of efficacy or tolerance [834]. “Clinically tested” implies that the product was tested on humans, under the supervision of a qualified medical profession [834] but does not imply efficacy (unless stated and ideally substantiated).

The rapid increase in ingredient "free-from" claims has been in response to requests from specific consumers (or end-users) to make informed decisions or possibly drawing attention to a specific product’s perceived advantage in a competitive marketplace. For example, “free from animal-derived ingredients” may be considered appropriate if the product were targeted towards groups that abstain from animal products [834]. However, "free-from" claims have been misused in an unethical manner that leads consumers to negatively perceive demonstrably safe and legally permitted ingredients [834]. Consumers may even be led to believe that labels that do not feature a “free-from” claim are unsafe compared to products that do have such labels, which may not be true or accurate.

One of the longest-standing terms is “hypoallergenic” which has no legal standard or scientific definition [833-835]. While the term tends to imply that the product has been formulated to minimize its allergenic potential, it does not guarantee a complete absence of risk [834]. To illustrate this, in one study that evaluated 187 products labeled as “hypoallergenic”, “dermatologist recommended/tested”, “fragrance free” or “paraben free”, 167 (89%) products contained at least 1 contact allergen and 117 products (63%) contained 2 or more contact allergens present in the North American Contact Dermatitis standard screening series [836].

In conjunction with ingredient “free-from” claims is the trend in products marketed under the categories of “clean beauty” and “natural skincare” [837,838]. There are no standardized definitions of these terms. However reactionary responses from both manufacturers and retailers include changing their formulations or product portfolios to keep up with the clean beauty movement [837]. Concerns have been raised by dermatologists that “clean” products are not uniformly less toxic or reactive for a particular patient.

Globally, regulations governing marketing claims vary. The European Union (EU) has regulated cosmetic product claims since 2013 (Commission Regulation EU No 655/2013) and individual member states within the EU can take action within their own national levels. For example, in 2020, the UK’s Advertising Standards Authority ordered the amendment or withdrawal of over 36,000 advertisements, with health and beauty advertisements making up the largest proportion of advertising complaints [839]. In Canada, cosmetic marketing terms fall under the Consumer Packaging and Labelling Act and Competition Act [833] however the Cosmetic Regulations under the Food and Drugs Act permits Health Canada to inspect any labelling or advertising material [840]. Lastly, the US FDA regulates cosmetic labelling claims which must be ”truthful and not misleading” and must avoid drug claims [841]. In 2011, the US FDA issued a warning letter to Lifetech Resources LLC for making drug claims on three eyelash serums (RapidLash, NeuLash and NeuveauBrow). The claims included “this formula is designed to lengthen and thicken eyelashes in 30 days” and “helps promote cell regeneration” on the company’s website and promotional materials led the US FDA to classify the product as a drug as the products were intended to “affect the structure or function of the body” rather than as a cosmetic product [842].

Table 9
Examples of marketing terms frequently seen on labels of personal care products, including cosmetic products, categorized according to the type of terminology.

Product endorsement	Products with specific ingredients	Product features or properties
Dermatologist tested	Preservative-free	Hypoallergenic
Ophthalmologist tested	Paraben-free	pH balanced
Clinically tested	Formaldehyde-free	Organic
	Silicone-free	Vegan/plant-based
	Gluten-free	Herbal
	Sulfate-free	Natural
	Fragrance-free	Clean
	Non-toxic	Medical grade
	Chemical-free	Cosmeceutical
	Synthetic-free	
	Filler-free	

10. Conclusions and recommendations

The use of eye cosmetics represents a lifestyle challenge. Eye cosmetic products and/or procedures may be associated with multiple adverse effects. These may cause harm and/or exacerbate or promote the development of ocular surface and adnexal disease.

For the future, the authors support the recommendation [843] that ocular cosmetics sold commercially list concentrations of all chemical components, as well as provide information about the product’s function, toxicity, indications, contraindications, durability and expiration date. The authors also recommend the.

Table 10
Ten eye makeup ingredients that may have very significant adverse effects on the ocular surface and/or adnexa.

Ingredient	Products	Concerns	Report section
Benzalkonium chloride	eyeliner, makeup remover, mascara	toxic, allergen, irritant	5.1.1.
Chlorphenesin	around-eye cream, eyeliner, eyeshadow, eyelash glue, makeup primer, makeup remover, mascara, moisturizer, serum	toxic, allergen, irritant, immunosuppressant	5.1.5.
Formaldehyde-releasing compounds	serum, eyelash glue	toxic, mutagen, carcinogen and allergen	5.1.2.
Parabens	moisturizer, mascara, eyeshadow, eyeliner, around-eye cream, serum, glitter	toxic, endocrine disruptor, allergen, genotoxic	5.1.3.
Phenoxyethanol	eyeshadow, moisturizer, mascara, serum, eyeliner, makeup primer, around-eye cream, makeup remover, glitter, eyelash glue	toxic, allergen, irritant	5.1.4.
Phthalates	fragrances, makeup remover	cytotoxic, endocrine disruptor, neurotoxic, sleep problems; dibutyl phthalate is banned in Europe	5.2.12.
Prostaglandin analogues (for example, isopropyl cloprostenate)	eyelash growth serum	periorbitopathy, periorbital discoloration, hyperemia, pruritis, eyelid ptosis, meibomian gland dysfunction, blepharophimosis, thinning of eyelid skin and orbital fat	5.2.13.
Retinoids (Vitamin A metabolites)	serum, around-eye cream, moisturizer, makeup primer, makeup remover, mascara, eyeliner	toxic for meibomian glands	5.2.15.
Salicylic acid	around-eye-cream, makeup primer, makeup remover, moisturizer, serum	restricted use in Canada, Europe and Japan, irritant	5.2.16.
Tea tree oil (for example, terpinen-4-ol)	eyelash cleanser, eye makeup remover, moisturizer, toner	toxic to human meibomian gland epithelial cells, endocrine disruptor, allergen, may contribute to antibiotic resistance	5.2.19.

- performance of well-controlled and high-quality studies to examine the acute and chronic effects of eye cosmetic ingredients and procedures on the ocular surface and adnexa
- development of guidelines to assess the safety and tolerability of eye cosmetic products
- determination of the influence of layered cosmetics and multiple preservatives on periocular skin, especially after long-term use
- sharing of data publicly for adverse events associated with eye cosmetic product and procedure treatments in aesthetic settings
- establishment of more stringent and rigorous oversight (for example, US FDA) of the eye makeup industry in general, and eye cosmetic ingredients in particular
- development of standardized and universally accepted definitions of the words "natural" and "clean," as they relate to cosmetics
- education of eye care providers and consumers about the risks associated with ingredients within eye cosmetic products. Ten eye makeup ingredients that may have very significant adverse effects on the ocular surface and adnexa are listed in Table 10.
- creation of evidence-based substitution lists of safe ingredients to replace possible toxic compounds in eye cosmetics

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2023.04.005.

Appendix A. Detailed methods

Search results were imported into the web-based review management software, Covidence, to screen for potentially eligible title and abstracts after removing duplicate references. Based on the eligibility criteria, review authors worked in pairs to classify each citation as 'relevant (yes),' 'maybe relevant,' or 'not relevant (no)' for subsequent full-text review. We listed all excluded studies with the reasons for their exclusion. We reached consensus by discussing the discrepancies at the screening stages.

For each eligible trial, review authors worked in pairs to independently extract data using a structured data collection form developed in Covidence. Trial investigators or sponsors were also asked for detailed information or to clarify information reported in the publication. When the trial investigators or sponsors do not respond within two weeks, we extracted relevant data available to us from trials registers or the published reports. The following information was collected from each included trial: study design, setting, countries where participants were recruited, considerations for sample size and power calculation, study duration, participants' mean age, sex and race/ethnicity composition, and proportions of major medical co-morbidities (if available); specific products for eyelash growth or extension exposed and duration of relevant exposure(s). For outcome variables, outcome metrics were extracted in mean, standard deviation or the associated 95% confidence intervals (95% CI) and number of participants for which the outcome was measured for continuous variables; number of events and number of participants for which outcome data were collected for dichotomous variables. For trials that had more than two comparison groups, we only used data relevant to our exposure comparisons. Information about funding sources and authors' declaration of interest was also extracted.

It was initially proposed to apply Cochrane Risk of Bias 2 tool [318] to assess risk of bias on the two primary review outcomes. Yet none of the included trials reported either outcome. Therefore, it was decided to apply risk of bias tool to assessing study-level risks of bias [318]. Based on assessment results for each domain, an overall assessment was provided on each included trial and any disagreements were resolved by discussion.

We synthesized evidence by either person or eye, depending on the

unit of data analyzed and reported. We examined the consistency and robustness of the review findings by conducting sensitivity analyses as planned in the protocol.

It was not planned to impute data, but used data imputed by the study authors with appropriate methods. Trials were not found to have a substantial amount of missing data due to lost-to-follow up. However, trials that did not report sufficient data to be used for meta-analysis were qualitatively described. When assessing the certainty of relevant evidence on a specific outcome, both descriptive and quantitative data available were considered.

The overall study characteristics were evaluated, particularly the study design and the study population, to assess the potential sources of clinical and methodological heterogeneity. It was estimated the I-squared statistics to quantify proportions of the overall variability in effect measures that could be attributable to heterogeneity, rather than random sampling errors [320].

Random-effects models were used to combine results from two or more trials. When the studies review judged the evidence to be of considerable heterogeneity (I^2-statistics >75%), the evidence was synthesized in a structured narrative summary, rather than performed meta-analysis.

The planned subgroup analysis by design on either safety outcome was not performed since it was decided to include only RCTs for the current review. Planned sensitivity analysis by excluding trials that reported primary outcome data at the eye level was not performed, because none of the trials reported either primary outcome. However, the proposed sensitivity analysis was performed by excluding trials judged to be at high risk of bias.

In the protocol, it was planned to grade the certainty of the overall evidence for each primary outcome. Because none of the included trials reported on either primary outcome, we decided to grade the certainty of the evidence for all secondary outcomes as “high”, “moderate”, “low”, or “very low” according to (1) risk of bias assessment, (2) indirectness of the evidence, (3) unexplained heterogeneity or inconsistency of results, (4) low precision, and (5) risk of publication bias according to the GRADE approach [321]. Discrepancies were resolved about the GRADE assessment by discussion.

Appendix B. Database-specific search strategies

Ovid Embase.

1 exp ophthalmology/
2 exp eye/
3 exp eye disease/
4 exp eye injury/
5 diagnostic procedure/and eye examination/
6 exp visual system function/
7 exp light related phenomena/
8 (vision or sight* or ocular or occular or limbus or limbal or orbit* or blink* or brow or canthus or canthal or conjunctiv* or cornea* or corneo* or eyel* or eye-lid* or eye-lash* or eyeb* or eye-brow* or episcler* or lacrima* or goblet-cell* or lid-wiper or meibomi* or orbicularis or Palisades-of-Vogt or subconjunctiva* or tear or tears).af.
9 (blepharitis or blepharospasm or blindness or cataract* or chalazi* or chemosis or chemotic or CLADE or CLIDE or CLAPC or dacryo* or Demod* or distichiasis or DLK or dry eye* or ectropi* or entropi* or epiphora or ecchymosis or exophthalm* or eye-pruritis or eye-strain or globe-rupture* or hordeola* or keratitis or keratopath* or lid-parallel or limbitis or LIPCOF or keratoconjunctivit* or keratocon* or keratoplasty or lagophthalmos or madarosis or mascaroma or oculopathy* or periorbital-fat-herniation or (periocular and carcinoma*) or photalgia or photophobia or photopsia or pinguec* or poliosis or preseptal-cellulitis or orbital-cellulitis or postkeratoplasty or post-keratoplasty or pteryg* or ptosis or ptotic or scleral-disease* or scleritis or sicca* or symblepharon or trichiasis or xanthelasma or xerophthalmi or onchocercias* or trachoma*).af.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 (eyelash OR cilia OR cilium).af.
12 (exten* OR grow* OR length* OR stimulat* OR increas* OR enhanc* OR bristl* OR elongat* OR dens* OR thick* OR serum*).af.
13 (alprostadil or cloprostenol or dinoprostone or epoprostenol or fluprostenol or misoprostol or Treprostinil or Isopropyl Cloprostenate or dehydrolatanoprost or Ethyl Travoprostamide or Myristoyl Pentapeptide-17 or Myristoyl Hexapeptide-16 or Acetyl tetrapeptide-3 or Biotinoyl tripeptide-1 or Copper tripeptide 1 or Castor oil or sage oil).af.
14 11 and (12 or 13)
15 10 and 14

Ovid MEDLINE(R) ALL <since 1946> (Basic Search function)

1 exp Diagnostic Techniques, Ophthalmological/
2 exp Eye Diseases/
3 exp Eye Injuries/
4 exp Eye/
5 exp Ocular Physiological Phenomena/
6 exp Optical Phenomena/
7 1 or 2 or 3 or 4 or 5 or 6
8 (vision or sight* or ocular or occular or limbus or limbal or orbit* or blink* or brow or canthus or canthal or conjunctiv* or cornea* or corneo* or eyel* or eye lid* or eye lash* or eyeb* or eye brow* or episcler* or lacrima* or goblet cell* or lid wiper or meibomi* or orbicularis or Palisades of Vogt or subconjunctiva* or tear or tears).af.
9 (blepharitis or blepharospasm or blindness or cataract* or chalazi* or chemosis or chemotic or CLADE or CLIDE or CLAPC or dacryo* or Demod* or distichiasis or DLK or dry eye* or ectropi* or entropi* or epiphora or ecchymosis or exophthalm* or eye pruritis or eye strain or globe rupture* or hordeola* or keratitis or keratopath* or lid parallel or lid-parallel or limbitis or LIPCOF or keratoconjunctivit* or keratocon* or keratoplasty or lagophthalmos or madarosis or mascaroma or oculopathy* or periorbital fat herniation or (periocular and carcinoma*) or photalgia or photophobia or photopsia or pinguec* or poliosis or preseptal cellulitis or orbital cellulitis or postkeratoplasty or post-keratoplasty or pteryg* or ptosis or ptotic or scleral disease* or scleritis or sicca* or symblepharon or trichiasis or xanthelasma or xerophthalmi or onchocercias* or trachoma*).af.
10 7 or 8 or 9
11 (eyelash or cilia or cilium).af.
12 (exten* or grow* or stimulat* or increas* or enhanc* or length* or bristl* or elongat* or dens* or serum*).af.
13 (alprostadil or cloprostenol or dinoprostone or epoprostenol or fluprostenol or misoprostol or Treprostinil or Isopropyl Cloprostenate or dehydrolatanoprost or Ethyl Travoprostamide or Myristoyl Pentapeptide-17 or Myristoyl Hexapeptide-16 or Acetyl tetrapeptide-3 or Biotinoyl tripeptide-1 or Copper tripeptide 1 or Castor oil or sage oil).a.f.
14 11 and (12 or 13)
15 10 and 14

PubMed.

1. ("Diagnostic Techniques, Ophthalmological"[Mesh] OR "Eye Diseases"[Mesh] OR "Eye Injuries"[Mesh] OR "Eye"[Mesh] OR "Ocular Physiological Phenomena"[Mesh] OR "Optical Phenomena"[Mesh])
2. (vision[all] OR sight*[all] OR ocular[all] OR occular[all] OR limbus [all] OR limbal[all] OR orbit*[all] OR blink*[all] OR brow[all] OR

canthus[all] OR canthal[all] OR conjunctiv*[all] OR cornea*[all] OR corneo*[all] OR eyel*[all] OR "eye lid*"[all] OR "eye lash*"[all] OR eyeb*[all] OR "eye brow*"[all] OR episcler*[all] OR lacrima*[all] OR goblet cell*[all] OR "lid wiper"[all] OR meibomi*[all] OR orbicularis[all] OR "Palisades of Vogt"[all] OR subconjunctiva*[all] OR tear[all] OR tears[all])

3. (Blepharitis[all] OR Blepharospasm[all] OR blindness[all] OR cataract*[all] OR chalazi*[all] OR chemosis[all] OR chemotic[all] OR CLADE[all] CLIDE[all] OR CLAPC[all] OR dacryo*[all] OR Demod*[all] OR distichiasis[all] OR DLK[all] OR "dry eye*" OR Ectropi*[all] OR Entropi*[all] OR Epiphora[all] OR ecchymosis[all] OR Exophthalm*[all] OR "eye pruritus"[all] OR "eye strain"[all] OR "globe rupture*"[all] OR Hordeol*[all] OR Keratitis[all] OR Keratopath*[all] OR "lid parallel"[all] OR "lid-parallel"[all] OR Limbitis [all] OR LIPCOF[all] OR Keratoconjunctivit*[all] OR Keratocon*[all] OR keratoplasty[all] OR lagophthalmos[all] OR madarosis[all] OR mascaroma[all] OR Oculopath*[all] OR Periorbital Fat Herniation[all] OR (Periocular[all] AND carcinoma*[all]) OR Photalgia [all] OR Photophobia[all] OR Photopsia[all] OR pinguec*[all] OR poliosis[all] OR "preseptal cellulitis"[all] OR "orbital cellulitis"[all] OR postkeratoplasty[all] OR post-keratoplasty[all] OR pteryg*[all] OR ptosis[all] OR ptotic[all] OR Scleral Disease*[all] OR Scleritis [all] OR Sicca*[all] OR Symblepharon[all] OR trichiasis[all] OR Xanthelasma[all] OR Xerophthalmi*[all] OR onchocercias*[all] OR trachoma*[all])
4. #1 OR #2 OR #3
5. (eyelash[all] OR cilia[all] OR cilium[all])
6. (exten* or grow* or stimulat* or increas* or enhanc* or length* or bristl* or dens* or elongat* or serum*)
7. "alprostadil"[MeSH Terms] OR "alprostadil"[All Fields] OR ("cloprostenol"[MeSH Terms] OR "cloprostenol"[All Fields]) OR ("dinoprostone"[MeSH Terms] OR "dinoprostone"[All Fields] OR "dinoproston"[All Fields]) OR ("epoprostenol"[MeSH Terms] OR "epoprostenol"[All Fields]) OR ("fluprostenol"[Supplementary Concept] OR = "fluprostenol"[All Fields]) OR ("misoprostol"[MeSH Terms] OR "misoprostol"[All Fields] OR "misoprostol s"[All Fields]) OR ("treprostinil"[Supplementary Concept] OR "treprostinil"[All Fields]) OR "isopropyl cloprostenate"[All Fields] OR "acetyl tetrapeptide 3"[All Fields] OR ("Biotinoyl"[All Fields] AND "tripeptide-1"[All Fields]) OR (("copper"[MeSH Terms] OR "copper"[All Fields] OR "coppers"[All Fields] OR "copper s"[All Fields]) AND "tripeptide-1"[All Fields]) OR ("castor oil"[MeSH Terms] OR ("castor"[All Fields] AND "oil"[All Fields]) OR "castor oil"[All Fields]) OR "sage oil"[All Fields]
8. #5 AND (#6 OR #7)
9. **#4 AND #8**

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