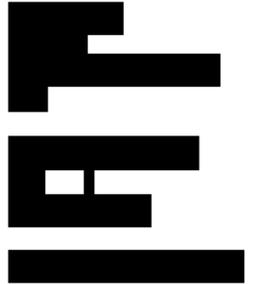


Cardno ChemRisk



**Screening-Level Toxicological Hazard Assessment of WEN by Chaz Dean, Inc.
Cleansing Conditioner**

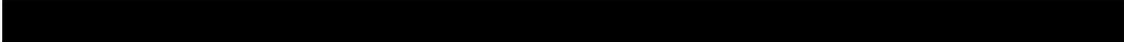


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1. INTRODUCTION

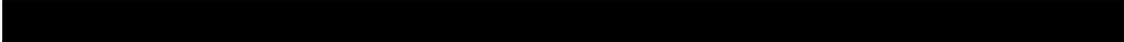
Cardno ChemRisk was requested by WEN[®] by Chaz Dean, Inc. (WCD) to perform a comprehensive risk and safety assessment to evaluate the potential for adverse dermal health effects, including the potential for hair loss or any other adverse dermal event, associated with the topical use of WCD Cleansing Conditioner hair care products (the “WEN Products”), which evaluation was triggered by complaints and allegations that the Products caused hair loss in a very small percentage of consumers. As part of that comprehensive risk and safety assessment, we performed a screening-level human health hazard assessment on the ingredients of the three top selling versions of the WEN Products (Sweet Almond Mint, Lavender, and Pomegranate Cleansing Conditioners), which are also the three most complained about versions of the WEN Products. WCD confirmed to us that the formulations for these three versions of the WEN Products, as manufactured by WCD, have not changed since entering the marketplace (although WCD has informed us that its licensee, the direct marketing company, Guthy-Renker, LLC, which separately manufactures the WEN Products made one change to their formulations that replaced Kathon CG with phenoxyethanol and ethylhexylglycerine, but our analysis only involved the WEN Products manufactured by WCD). These three versions of the WEN Products contain most of the ingredients used in all versions of the WEN Products.

2. METHODOLOGY

2.1 Literature Search For Screening-Level Assessment

A systematic review of the chemical ingredients list for the WEN Products (Sweet Almond Mint, Pomegranate, and Lavender Cleansing Conditioners) was conducted by collecting peer-reviewed literature, as well as information in regulatory and governmental databases. Information on the chemical ingredients were collected and incorporated from various databases and textbooks, many of which are created and maintained by regulatory agencies and all are the authoritative sources relied upon by the scientific community in determining human health risks from exposures to chemicals, cosmetic ingredients, food, and drugs. These include the following:

- PubMed, U.S. National Library of Medicine
- Google Scholar
- Hazardous Substances Data Bank, TOXNET
- Agency for Toxic Substances and Disease Registry (ATSDR)
- U.S. Food and Drug Administration Chemical-Specific Guidance (FDA)
- OECD eCHEM Portal Toxicity Criteria and Regulatory Guidance
- California Proposition 65
- Cosmetic Ingredient Review (CIR)

- 
- The European Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH)
 - Avalos, J. and H.I. Maibach. 2000. *Dermatologic botany*. Boca Raton: CRC Press.
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 - Jellin, J.M., P.J. Gregory, F. Hitchens, et al. 2006. *Pharmacist's letter/Prescriber's letter natural medicines comprehensive database*. 8th ed. Stockton, CA: Therapeutic Research Faculty.
 - Marzulli, F.N. and H.I. Maibach. 1987. *Dermato-toxicology*. 3rd ed. New York: Taylor & Francis.
 - Mitchell, J. and A. Rook. 1979. *Botanical dermatology: Plants and plant products injurious to the skin*. Vancouver: Greengrass Ltd.

3. RESULTS OF HAZARD SCREENING ASSESSMENT

3.1 Primary Route for Exposure

The ingredients of each of the WEN Products are listed in **Table 1**. According to product packaging¹, consumers should use these products to cleanse their hair in 3 steps:

- Step 1: “Rinse hair thoroughly. Apply WEN® into your palms and rub together. Use 10-16 pumps for short hair, 16-24 for medium length hair and 24-32 pumps for long hair. If your hair is longer/thicker you may need to increase the amount of pumps”
- Step 2: “Apply to scalp and hair, adding a splash of water to evenly distribute. WEN® has no harsh sulfates like sodium lauryl sulfate, so it won't lather. Massage thoroughly into hair and leave on for the remainder of your shower.”
- Step 3: “Rinse thoroughly and completely, massaging scalp and running fingers through to the ends.”

In addition, the WEN Products' instructions further provide: “After you have finished rinsing, while your hair is still soaking wet, apply a small amount of the Cleansing Conditioner to the ends of your hair as a leave-in conditioner.”

¹ Upon review of the company website, negligible variation was noted in the use instructions of the products.

Based on the intended use of the product, dermal exposure is clearly the primary route of concern for consumers. As a result, dermal toxicity information in addition to oral toxicity was collected for each constituent, if available.

4.2 Constituents Generally Recognized as Safe by the FDA

Many of the botanical ingredients in WCD Sweet Almond Mint, Pomegranate, and Lavender Cleansing Conditioners are generally recognized as safe (GRAS) for use in food by the FDA (**Table 1**). Despite the historical safe use of many of these botanicals and their derived extracts and oils in foods, the evidence on the safety of topical or dermal preparations containing botanical extracts is limited. Many reports of contact allergies to botanical ingredients have been described, in particular, for some of the botanical ingredients listed as GRAS by the FDA.

According to a study evaluating the presence of allergens in 11 different types of essential oils, 22 different allergens recognized as contact allergens in humans were reported to be present in varying amounts in the different essential oils evaluated (Dornic, Ficheux et al. 2016). Essential oils derived from *Citrus*, *Lavanda* and *Rosmarinus* were reported to contain 12, 11 and 10 different types of allergens, respectively (Dornic, Ficheux et al. 2016). However, it was unclear whether the presence of these allergens result from specific extraction methods. According to Dornic et al. (2016) the contact allergens in these oils included limonene, pinenes, linalyl acetate, cineole, and camphor (Dornic, Ficheux et al. 2016). Additionally, *Compositae* plants, which include *Calendula officinalis* (marigold) and *Chamomilla recutita* (German chamomile), and lavender oil from *Lavandula augustifolia* have been implicated in causing contact allergic dermatitis in sensitive or occupationally exposed individuals (Paulsen 2002; Paulsen, Chistensen et al. 2008; Jack, Norris et al. 2013). The sensitizing compounds include sesquiterpene lactones in *Compositae* plants and linalool, linalyl acetate, and camphor in *Lavandula* (lavender) (Jack, Norris et al. 2013). The CIR panel reported that *Chamomilla recutita* (matricaria) flower oil did not show evidence of contact sensitization in predictive maximization tests in humans; however, provocative testing in *Compositae*-sensitive individuals demonstrated that 1% or 2.5% *Chamomilla recutita* extracts caused positive skin reactions in greater than 50% of subjects (Belsito, Klaassen et al. 2013). Furthermore, the CIR panel reported that dermal sensitization studies in animals and clinical studies in humans did not suggest that *Calendula officinalis* extract is a sensitizer (Andersen, Bergfeld et al. 2010).

The CIR panel addresses the concern that, because botanical ingredients, derived from natural plant sources, are complex mixtures, multiple botanical ingredients may each contribute to the final concentration of a single constituent (Burnett 2016). Therefore, when formulating products, CIR recommended that manufacturers avoid reaching concentrations in final formulation of plant constituents that may cause sensitization or other adverse effects (Burnett 2016). Specific examples of constituents

[REDACTED]

that could possibly induce sensitization are linalool or monoterpenes, and those that could possibly cause adverse effects are caffeic acid and terpenes, such as thujone, limonene, and methyleugenol (Burnett 2016).

Household products that contain botanical ingredients found in the WEN Products with a chemical abstract service (CAS) registry number (n = 57) were searched for in the U.S. Department of Health & Human Services Household Products Database. Four of 57 botanical ingredients in WCD have reported safe levels, which were borage seed oil, ginseng root extract, jojoba seed oil, and evening primrose oil (Becker, Bergfeld et al. 2008; Belsito, Hill et al. 2011; Becker, Bergfeld et al. 2015). Consumer products containing these four constituents include, but are not limited to, automotive grease/lubricant products, wallpaper strippers, lip balms, cosmetic products, body washes, body oils, body lotions and creams, shampoos, conditioners, hair balms, hair colorants, and pet care products. Similarly, household products that contain botanical constituents found in WCD with no reported safe levels include, but are not limited to, shampoos, conditioners, hair gels and mousses, hairsprays, hair colorants, dish soap, diapers, body washes, antibacterial wipes, cosmetic products, and mouthwash.

4.3 Toxicological Hazard Assessment for Each Undiluted Ingredient

A screening level human health hazard assessment was completed to assess the dermal hazard of the individual ingredients used in the WEN Products.

- Aloe Barbadensis Leaf Juice and Leaf Extract

Overview:

Aloe barbadensis is commonly referred to as Aloe vera (IARC 2016). The physical and chemical constituents of the products derived from Aloe vera plants differ depending on the source (IARC 2016). The leaves of the aloe plant consist of two main parts: the bitter latex, produced by the pericyclic cells found just below the plant's skin, and the clear, slightly viscous gel, produced by parenchymal cells in the inner central area of the leaf. The aloe gel is used in cosmetics and personal care products for emollient and moisturizing effects (Panel 2007; IARC 2016). Aloe vera gel extract is composed of polysaccharides, consisting of linear chains of glucose and mannose molecules; the major polysaccharide is acetylated mannan (IARC 2016). Isolated compounds from the aloe latex include the phenolic compounds, anthraquinones C-glycosides, anthrones, and free anthraquinones, aldehydes and ketones; aloin A, a C-glycosyl anthrone, and also referred to as barbaloin is the major component of aloe latex (IARC 2016). Treatment of whole leaf Aloe vera extract by activated carbon can remove the anthraquinone compounds responsible for the bitterness and color of the latex, resulting in a "decolorized whole leaf extract"; the properties of the decolorized leaf differ from those of the whole leaf (IARC 2016). An industry standard

[REDACTED]

for aloin content in decolorized Aloe vera whole leaf extracts is <10 ppm (IARC 2016). Decolorized whole leaf, similar to the Aloe vera gel, contains little to no later anthraquinones (IARC 2016).

Toxicology:

An estimated oral LD₅₀ for aloe vera extracts was reported to be 120.65 mg/kg in mice, although another study reported that no signs of toxicity were observed in mice administered 500 mg/kg, 1 g/kg or 3 g/kg of aloe vera extracts (Panel 2007). No significant systemic effects were observed in rats fed a 1% or 10% preparation of *Aloe barbadensis* charcoal-filtered extracts for 1.5 or 5.5 months (Panel 2007).

Dermal Hazard:

In a human study, one individual out of ten exhibited a very slight erythema following application of 0.02 ml of *Aloe barbadensis* leaf water to the skin and occluded for 48 hours. No other reactions or pathological irritation was observed. There was no available information in animals on the acute dermal toxicity of *Aloe barbadensis* leaf juice or extracts (Panel 2007). In an animal study, 0.5 ml of *Aloe ferox* leaf extract was applied to shaved skin of rabbits. One of the six rabbits had a very slight erythema reaction that cleared after 72 hours. Overall, *Aloe ferox* leaf extract was considered to be nonirritating (Panel 2007). It has been reported that topical use of aloe has not been linked to significant side effects (2012).

Sensitization:

The sensitizing capacity of Aloe vera gel has been reported to be very low or absent (Reider, Issa et al. 2005). In a study of 702 patients, no reactions were observed to the Aloe preparations tested (Reider, Issa et al. 2005).

Association with Hair Loss:

There was no information available on the association between aloe and hair loss.

Agency Data:

The International Agency for Research on Cancer (IARC) has classified whole leaf extract of Aloe vera as “possibly carcinogenic to humans” (Group 2B), based on sufficient evidence in experimental animals for the carcinogenicity of whole leaf extract (IARC 2016). However, IARC characterizes whole leaf extract as filtered or purified products obtained from the entire leaf. Whole leaf extract is distinct from



decolorized whole leaf extract, which has different chemical and biological properties from the whole leaf extract.

- *Bambusa Vulgaris* (Bamboo) Extract

Overview:

Bambusa Vulgaris extract is used as a conditioning agent in personal care products (SpecialChem 2016). Extracts of *Bambusa Vulgaris* reportedly also contain over 70% of natural silica, which provides strength and resilience to collagen and elastin (Institute 2016). Preliminary phytochemical analysis of the aqueous leaf extract also revealed the presence of alkaloids, tannins, phenolics, glycosides, saponins, flavonoids, and anthraquinones (Yakubu and Bukoye 2009).

Toxicology:

There was no information available on the potential systemic toxicity of *Bambusa Vulgaris*.

Dermal Hazard:

There was no information available on the dermal hazard of *Bambusa Vulgaris*.

Sensitization:

There was no information available on the sensitization of *Bambusa Vulgaris*.

Association with Hair Loss:

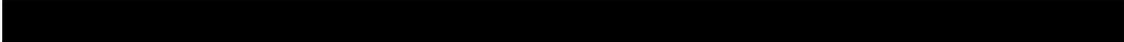
There was no information available on the association between *Bambusa Vulgaris* and hair loss.

Agency Data:

There was no agency data information available for *Bambusa Vulgaris*.

- *Borage* (Organic Starflower) Seed Oil

Overview:



Plant-derived oils are used in a variety of cosmetic products for their skin conditioning, occlusive, emollient, and moisturizing properties (Belsito, Hill et al. 2011). Borage (*Borago Officinalis*) seed oil is a mixture of fatty acids, including linoleic, linolenic, oleic, stearic, and palmitic acids, and appears as a clear, pale yellow-golden oil (Belsito, Hill et al. 2011).

Toxicology:

There was no information available on the potential systemic toxicity of *Borago Officinalis* seed oil.

Dermal Hazard:

Borago Officinalis seed oil was not determined to be a dermal irritant in HRIPT or human primary cutaneous irritation tests using personal care products containing up to 2% the oil (Belsito, Hill et al. 2011).

Sensitization:

Borago Officinalis seed oil was not determined to be a sensitizer in HRIPT or human primary cutaneous irritation tests using personal care products containing up to 2% the oil (Belsito, Hill et al. 2011).

Association with Hair Loss:

There was no information available on the association between *Borago Officinalis* seed oil and hair loss.

Agency Data:

According to a 2011 CIR report, it was used in 180 cosmetic applications at concentrations of 0.001 to 1% (Belsito, Hill et al. 2011). The CIR reported that *Borago Officinalis* seed oil is “safe in the present practices of use” (Belsito, Hill et al. 2011).

- *Camellia Oleifera* Leaf (Green Tea) Extract

Overview:

Camellia Oleifera, also known as “oil tea,” is a tree that serves as an important source of edible oil in China (Tai, Wei et al. 2015). Tea leaves are an important source of biologically active metabolites, such

as flavonoids, theanine, and caffeine, which contribute to its nutritional value and healthful properties (Tai, Wei et al. 2015).

Toxicology:

Toxicity testing on the water extract of the fruit hull of *Camellia Oleifera* did not demonstrate any toxic effects in a subacute, 30 day, oral study conducted in rats and mice (Zhang, Chen et al. 2011). The NOAEL for fruit hull water extract was 2 g/kg bw (Zhang, Chen et al. 2011). Additionally, the oral maximum tolerated dose of fruit hull water extract was greater than 20 g/kg body weight in both rats and mice (Zhang, Chen et al. 2011). There was no information available on the potential systemic toxicity of *Camellia Oleifera* leaf extract.

Dermal Hazard:

There was no information available on the dermal hazard of *Camellia Oleifera* leaf extract.

Sensitization:

There was no information available on the sensitization of *Camellia Oleifera* leaf extract.

Association with Hair Loss:

There was no information available on the association between *Camellia Oleifera* leaf extract and hair loss.

Agency Data:

There was no agency data information available for *Camellia Oleifera* leaf extract.

- *Crambe Abyssinica* (Abyssinian) Seed Oil

Overview:

Plant-derived oils are used in a variety of cosmetic products for their skin conditioning, occlusive, emollient, and moisturizing properties (Belsito, Hill et al. 2011). *Crambe Abyssinica* seed oil is a mixture of fatty acids, including primarily erucic, oleic, linoleic, linolenic, and palmitic acids (Belsito, Hill et al.

2011). It was reported to be used in six cosmetic products; however, information regarding the concentrations used was not reported.

Toxicology:

There was no information available regarding the potential systemic toxicity of *Crambe Abyssinica* seed oil.

Dermal Hazard:

A non-human dermal irritation study (details not provided) found that *Crambe Abyssinica* seed oil is “not a dermal irritant” (Belsito, Hill et al. 2011). In addition, HRIPT studies evaluating products containing 5 to 100% of *Crambe Abyssinica* seed oil found that it was not a dermal irritant (Belsito, Hill et al. 2011).

Sensitization:

HRIPT studies evaluating products containing 5 to 100% of *Crambe Abyssinica* seed oil found that it was not a dermal sensitizer (Belsito, Hill et al. 2011).

Association with Hair Loss:

There was no information available on the association between *Crambe Abyssinica* seed oil and hair loss.

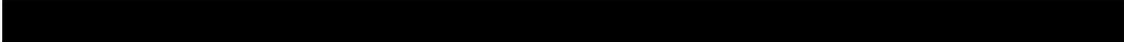
Agency Data:

According to the CIR, *Crambe Abyssinica* seed oil is “safe in the present practices of use” (Belsito, Hill et al. 2011).

- *Cucumis sativus* Fruit Extract

Overview:

Cucumis sativus fruit extract has been reported to function as an emollient skin-conditioning agent in cosmetic products (Fiume, Bergfeld et al. 2014). Cucumber fruit consists of 96% water and the remaining constituents include vitamins, minerals, amino acids, phytosterols, phenolic acids, fatty acids, flavonoids, terpenoids, tannins and cucurbitacins (Fiume, Bergfeld et al. 2014). Cucumber fruit extract is manufactured by extracting cucumber fruit in mixtures of glycerin and water, water and butylene glycol,



or water and propylene glycol or by hydroalcoholic extraction (Belsito, Hill et al. 2012; Fiume, Bergfeld et al. 2014).

Toxicology:

Systemic toxicity studies were not available for cucumber fruit extract (Fiume, Bergfeld et al. 2014).

Dermal Hazard:

Limited dermal toxicity information was available. In one case study, severe eczema was reported to occur in a greenhouse employee that planted, pruned and picked cucumber plants for 5 months (Zachariae 2000). In addition, 10 individuals were patch tested with cucumber leaves, and in two of the cases, slight redness was noted; no reactions were observed in other cases (Zachariae 2000). Irritancy to the hairs on the leaves' surface was provided as a possible explanation for the patch test reactions (Zachariae 2000). Skin irritation was not observed following a clinical study where 21 patients applied a cosmetic eye product containing 1 or 5% cucumber fruit extract to the eye area up to two times daily for 21 days (Fiume, Bergfeld et al. 2014).

Sensitization:

In HRIPTs, cosmetic formulations containing up to 1% cucumber fruit extract were not considered to be skin irritants or sensitizers (Fiume, Bergfeld et al. 2014). In a HRIPT on an eye hydrogel containing 5% cucumber fruit extract, mild irritant responses were observed in 6 out of 100 patients, but there was no evidence of contact hypersensitivity (Fiume, Bergfeld et al. 2014).

Association with Hair Loss:

There was no information available on the association between cucumber fruit extract and hair loss.

Agency Data:

According to a report issued in 2014, the CIR stated that the use cucumber fruit extract was “safe in cosmetic formulations in present practices of use and concentration” (Fiume, Bergfeld et al. 2014).

- *Hamamelis virginiana*

Overview:



Hamamelis virginiana, also known as witch hazel, is a deciduous, tall shrub, or small tree. Natural witch hazel is considered one of the few plant products that meet FDA standards for safety and effectiveness (Agency 2009). The witch hazel preparation used in the WCD Lavender product is a distilled witch hazel product containing 14% alcohol, also known as *Hamamelis* water or *Hamamelis* distillate. *Hamamelis* water is a distillate prepared from the leaves, bark or twigs of the plant (Agency 2009). Witch hazel leaves and bark contain 3-10% and 8-12% of tannins, respectively, which have the capability to bind and precipitate proteins to provide the therapeutic astringent activity characteristic of some witch hazel preparations (Agency 2009). Volatile components, including phenylacetaldehyde, linalool oxide, guaiacol, and geranylacetone, were described as constituents in distilled witch hazel (Agency 2009). Witch hazel is used as an astringent active ingredient in over the counter skin medical products for relief of minor skin irritations, and these over-the-counter products are generally recognized as safe and effective (Agency 2009).

Toxicology:

There was no available information on the systemic toxicity of *Hamamelis* water. Genetic toxicity tests conducted by the National Toxicology Program demonstrated that *Hamamelis* water was negative for genotoxic activity (Agency 2009).

Dermal Hazard:

In a study of over 1,000 patients undergoing patch tests on five popular ointments, only four individuals reacted with an ointment that contained 25% extract of *Hamamelis* (Agency 2009). Witch hazel preparations may cause immunological contact urticaria, although the proposed frequency of sensitization is rare (Agency 2009).

Sensitization:

Witch hazel has been reported to cause contact allergy following topical application in rare cases (Agency 2009). Furthermore, allergic contact dermatitis may occur in sensitive individuals.

Association with Hair Loss:

There was no information available on the association between *Hamamelis* and hair loss.

Agency Data:

According to a report issued by the European Medicine Agency in 2009, the FDA has recognized over-the-counter products containing witch hazel for astringent purposes to be generally recognized as safe and effective for topical administration. In addition, the FDA advised that “based on the evidence currently available, there is inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses” (Agency 2009).

- *Oenothera biennis* (Evening Primrose) Oil

Overview:

Oenothera biennis (evening primrose) oil is a mixture of fatty acids, including primarily linoleic (60-85%), γ -linolenic (7-12%), oleic (5-12%) and palmitic (4-10%) (Belsito, Hill et al. 2011). Primrose oil was used in 150 cosmetic formulations at concentrations between 0.00002 and 58% (Belsito, Hill et al. 2011).

Toxicology:

In a chronic oral toxicity study, 40 dogs were administered 5 mL/kg of primrose oil via gavage daily for 52 weeks and no systemic adverse effects were reported (EMA 2011). Evening primrose oil is generally well tolerated (Bayles and Usatine 2009). Mild adverse effects including gastrointestinal effects, indigestion, nausea, softening of stool and headache have been reported following human exposure via unspecified exposure routes at unspecified doses (Bayles and Usatine 2009; EMA 2011).

Dermal Hazard:

In a HRIPT conducted on 600 subjects with a foundation product containing 1.99% *Oenothera biennis* oil, the oil was found to not be a dermal irritant (Belsito, Hill et al. 2011).

Sensitization:

In a HRIPT conducted on 600 subjects with a foundation product containing 1.99% *Oenothera biennis* oil, the oil was found to not be a sensitizer (Belsito, Hill et al. 2011).

Association with Hair Loss:

There was no information available on the association between *Oenothera biennis* oil and hair loss.

Agency Data:

In a 2011 report, the CIR concluded that *Oenothera biennis* oil was “safe in the present practices of use” (Belsito, Hill et al. 2011).

- *Panax ginseng* Root Extract

Overview:

Panax ginseng root extract is used as a skin conditioning agent in cosmetic ingredients (Becker, Bergfeld et al. 2015). The predominant physiologically active components in ginseng are triterpenoid saponin glycosides, also known as ginsenosides (Carabin, Burdock et al. 2000). Over 40 different ginsenosides have been identified in the root of *Panax ginseng*, and the composition of ginsenosides in ginseng root extracts can vary depending on the method of extraction (Becker, Bergfeld et al. 2015). *Panax ginseng* root extract was reportedly used in close to 300 cosmetic formulations at concentrations between 0.000002 and 0.5% (Becker, Bergfeld et al. 2015).

Toxicology:

The recommended therapeutic dose for *Panax ginseng* extract containing 1.5 to 7% ginsenosides has been reported to be 100 to 300 mg/day (Mahady, Gyllenhaal et al. 2000). Interestingly, according to the NTP, oral LD₅₀ values of 750 mg/kg and 200 mg/kg were reported in the literature for rats and mice, respectively, in 1998; however, NTP’s more recent studies in rats and mice suggest an LD₅₀ greater than 5,000 mg/kg in both rats and mice (NTP 2011). Furthermore, no adverse effects were reported in an oral toxicity study performed in dogs treated with ginseng root extract doses 15 mg/kg/day (NTP 2011; Becker, Bergfeld et al. 2015).

Dermal Hazard:

Information regarding the potential dermal toxicity of *Panax ginseng* root extract was limited. Application of *Panax ginseng* root extract concentrate (0.2 mL; concentration not reported) or of the ginsenoside, Rg2 (1%; 0.2 mL), to the backs of female mice for 14 days did not cause any adverse effects (Becker, Bergfeld et al. 2015). In an in vitro assay, *Panax ginseng* root extract was not cytotoxic to human dermal fibroblast cells at the highest concentration tested (1000 µg/mL) (Becker, Bergfeld et al. 2015).

Panax ginseng root extract was not irritating to humans at concentrations up to 100 mg/mL (Becker, Bergfeld et al. 2015). In addition, inclusion of *Panax ginseng* root extract constituents Rh2 (0.1%) and Rh3 (0.1%) in a dermal test of 2-chloro-1,3,5-trinitrobenzene reduced the appearance of severe

erythema/hemorrhage, edema, excoriation/erosion, and scaling/dryness compared to TCNB in vehicle alone among female mice (Becker, Bergfeld et al. 2015). One case report of allergic contact dermatitis was reported in a human that applied a ginseng extract-containing ointment to her lips; however, it was noted that panaxynol was the potential sensitizer (Avalos and Maibach 1999).

Sensitization:

No indication of sensitization was detected in HRIPTs among humans of products containing *Panax ginseng* root extract at concentrations up to 1% (Becker, Bergfeld et al. 2015).

Association with Hair Loss:

There was no information available on the association between *Panax ginseng* root extract and hair loss.

Agency Data:

The CIR concluded that *Panax ginseng* root extract is “safe in the practices of use and concentration described” in their safety assessment (Becker, Bergfeld et al. 2015).

- *Passiflora incarnate* (Passion Fruit) Flower Extract

Overview:

Passiflora incarnata flower extract is used as a skin protecting and conditioning agent in cosmetic products (CosIng 2016). Interestingly, *Passiflora incarnate* has been used extensively throughout the world for its anxiolytic and sedative effects (Dhawan, Dhawan et al. 2004; Miroddi, Calapai et al. 2013). Additionally, it was reported that moderate doses of *Passiflora incarnata* can act as a narcotic, and excessive doses have produced spasms and paralysis in animals; however, references to specific studies were not available (Patel, Verma et al. 2009). Information on the specific phytochemical composition of *Passiflora incarnata* flower extract was not available; however, it has been reported that the aerial parts of *Passiflora incarnata* plants are characterized by the presence of several primary constituents consisting of flavonoids, maltol, cyanogenic glycosides, and indole alkaloids (Miroddi, Calapai et al. 2013).

Toxicology:

The available toxicology data on *Passiflora incarnata* extracts, including flower extract, was very limited. In an acute toxicity study, oral administration of methanol extracts of *Passiflora incarnata* leaves at doses

of 50, 100, 200, 400, 800 or 1600 mg/kg did not cause mortality in streptozotocin-induced diabetic mice (Gupta, Kumar et al. 2012).

Dermal Hazard:

There was no information available on the dermal hazard of *Passiflora incarnata* extracts.

Sensitization:

There was no information available on the sensitization of *Passiflora incarnata* extracts.

Association with Hair Loss:

There was no information available on the association between *Passiflora incarnata* extracts and hair loss.

Agency Data:

Although *Passiflora incarnata* extract is not listed by the FDA as generally recognized as safe, it is listed as a natural flavoring permitted as a direct food additive for human consumption when used in accordance with good manufacturing practice and in the minimum amount required to produce their intended effect (FDA 2017).

- *Persea gratissima* (Avocado) Oil

Overview:

Persea gratissima oil is a mixture of fatty acids, including primarily oleic, palmitic, linoleic, and palmitoleic acids derived from the fruits/seeds of an avocado tree (Belsito, Hill et al. 2011).

Toxicology:

There was no information available on the systemic toxicity of avocado oil. Avocado oil has historically been used for cooking and consumed in foods. Exposure to the oil from foods would likely result in a much larger systemic dose than that resulting from its use in personal care products (Belsito, Hill et al. 2011).

Dermal Hazard:

No dermal irritation was observed in a HRIPT of a scalp conditioner containing 0.2% *Persea gratissima* oil when the formulation was diluted to 1% (Belsito, Hill et al. 2011). In a four week use test, 10% *Persea gratissima* oil in a skin salve was applied to lips, hands/nails, elbow, knees, and feet did not elicit significant dermal irritation (Belsito, Hill et al. 2011). In a patch test of *Persea gratissima* oil performed on 20 human volunteers, slight erythema was observed in two volunteers, and avocado oil was concluded to have good skin compatibility (ECHA 2016). Furthermore, avocado oil was concluded to be not corrosive in a study using a reconstituted human epidermis in vitro model (ECHA 2016).

Sensitization:

No dermal irritation or sensitization was observed in a HRIPT of a scalp conditioner containing 0.2% *Persea gratissima* oil when the formulation was diluted to 1% (Belsito, Hill et al. 2011). Avocado oil also did not demonstrate any sensitization in the local lymph node assay (ECHA 2016).

Association with Hair Loss:

There was no information available on the association between *Persea gratissima* oil and hair loss.

Agency Data:

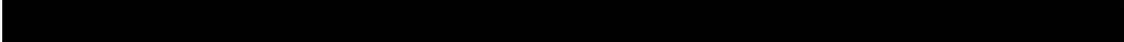
In a 2011 report, the CIR concluded that *Persea gratissima* oil was “safe in the present practices of use and concentration” in cosmetics (Belsito, Hill et al. 2011).

- *Pogostemon Cablin* (Patchouli) Leaf Extract

Overview:

Pogostemon cablin, or patchouli, leaf extract is used as a perfume agent in cosmetic products (CosIng 2016). Patchouli oil is a major constituent extracted from the leaves of *P. cablin* (Swamy and Sinniah 2015). Patchouli oil is rich in sesquiterpene compounds, such as patchouli alcohol (patchoulol), pogostone, and patchoulene, which are responsible for many of the plant’s pharmacological properties and intense aromatic odor (Swamy and Sinniah 2015). Patchouli plant oils and extracts have traditionally been used to relieve infections, headaches, nausea, vomiting, diarrhea, abdominal pain, insect and snake bites, and in aromatherapy to reduce tension, insomnia and anxiety (Swamy and Sinniah 2015).

Toxicology:



No toxicity studies on patchouli leaf extract or case reports describing adverse events following human use of patchouli extract were found. According to the American College of Healthcare Sciences, patchouli has a low toxicity rating; however, details regarding this rating were not available (Sciences 2012). No adverse reactions were reported for patchouli oil in the available literature (2012).

Dermal Hazard:

There was no information available on the dermal hazard of patchouli extract.

Sensitization:

There was no information available on the sensitization of patchouli extract.

Association with Hair Loss:

There was no information available on the association between patchouli extract and hair loss.

Agency Data:

There was no agency data information available for patchouli extract.

- Rooibos (*Aspalathus linearis*) Extract

Overview:

Aspalathus linearis, or more commonly known as rooibos, is largely cultivated and fermented to produce the well-known herbal tea, rooibos, which is marketed as containing no caffeine and very little tannin content compared to black, green, and white teas prepared from *Camellia sinensis* (Joppe, Herrmann et al. 2009). Recently, unfermented or “green” rooibos has been used in preparation of extracts for use in skin and hair cosmetic products (Gruner-Richter, Otto et al. 2008; Joppe, Herrmann et al. 2009; Joubert and de Beer 2011). Green rooibos reportedly contains higher levels of the antioxidant flavonoids, particularly, aspalathin, which is the major flavonoid constituent in rooibos (Joppe, Herrmann et al. 2009; Joubert and de Beer 2011). Rooibos extracts with high aspalathin content have been reported to possess anti-inflammatory, antiallergenic, anti-mutagenic, antimicrobial, antiviral, hepatoprotective, and antioxidative activities (Schlemer and Di Marco 2008; Joppe, Herrmann et al. 2009).

Toxicology:

Limited toxicological information was available regarding rooibos extract. In a short-term and subchronic oral study, rats were fed diets containing 2 mg green rooibos extract per kg milled feed cubes for 28 or 90 days (Van der Merwe, De Beer et al. 2015). No deaths or signs of clinical toxicity were observed in either study (Van der Merwe, De Beer et al. 2015).

Dermal Hazard:

There was no information available on the dermal hazard of rooibos extract.

Sensitization:

There was no information available on the sensitization of rooibos extract.

Association with Hair Loss:

There was no information available on the association between rooibos extract and hair loss.

Agency Data:

There was no agency data information available for rooibos extract.

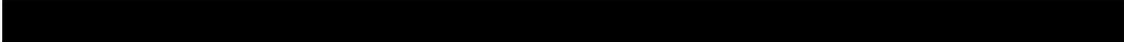
- *Simmondsia Chinensis* (Jojoba) Seed Oil

Overview:

Simmondsia chinensis (jojoba) seed oil is the fixed oil extracted from seeds of the desert shrub, jojoba (Becker, Bergfeld et al. 2008). Wax esters of monounsaturated, straight-chain acids and alcohols with high molecular weights makes up 97% of the oil (Becker, Bergfeld et al. 2008). Eicosenoic acid is the major component of jojoba seed oil (Becker, Bergfeld et al. 2008). Reported impurities include lead up to 0.8 ppm and arsenic up to 0.1 ppm (Becker, Bergfeld et al. 2008). According to a 2008 CIR report, jojoba seed oil was used in over 1000 personal care products at concentrations from 0.000005 to 100% (Becker, Bergfeld et al. 2008).

Toxicology:

In a short term oral toxicity study, rats were fed diets containing 0.5, 1.0, 2.0 or 3.0 g of jojoba seed oil per day for four or seven days (Becker, Bergfeld et al. 2008). One half of the rats fed 1.0 g and all of the rats fed 2.0 and 3.0 g of jojoba seed oil showed signs of toxicity and a 10% mortality rate; none of the rats fed 0.5 g of jojoba seed oil died (Becker, Bergfeld et al. 2008).



Dermal Hazard:

There were no subchronic dermal toxicity studies available for jojoba seed oil; however, a subchronic dermal toxicity study of jojoba seed wax was conducted (Becker, Bergfeld et al. 2008). Jojoba seed wax was applied to shaved dorsal skin of guinea pigs at doses of 0.25 and 0.5 g/kg, six days per week for 20 weeks (Becker, Bergfeld et al. 2008). No systemic or histologic adverse effects were reported for either dose (Becker, Bergfeld et al. 2008). In one skin irritation test, the daily application of 100% refined jojoba seed oil (0.5 mL) for 15 or 30 days did not cause any significant skin reactions in guinea pigs (Becker, Bergfeld et al. 2008). However, a lip balm product containing 20% jojoba seed oil was considered to be minimally irritating in rabbits following the occlusive application of the product for 24 hours; specific composition of the lip balm product was not reported (Becker, Bergfeld et al. 2008). In human clinical studies, pure jojoba seed oil and products containing 0.5%, 20%, and 100% jojoba seed oil were not considered to be irritating (Becker, Bergfeld et al. 2008). However, in a small study of six patients suspected to be sensitive to jojoba seed oil, skin reactions (erythema or erythema and vesicles) were observed in five out of the six patients following patch tests with an oil mixture containing 20% jojoba seed oil (Scott and Scott Jr 1982). Furthermore, the patient that did not show a positive reaction to the patch tests subsequently developed contact dermatitis of the scalp when pure jojoba seed oil was used as a hairdressing (Becker, Bergfeld et al. 2008). It was reported that topically, contact dermatitis could occur with jojoba oil-containing shampoos and hair conditioners (2012).

Sensitization:

In human clinical studies, pure jojoba seed oil and products containing 0.5%, 20%, and 100% jojoba seed oil were not considered to be sensitizing (Becker, Bergfeld et al. 2008).

Association with Hair Loss:

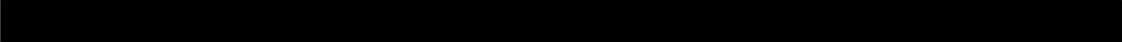
There was no information available on the association between jojoba seed oil and hair loss.

Agency Data:

The CIR concluded that jojoba seed oil is “safe as [a] cosmetic ingredient ... in the practices of use and concentration as discussed” in their safety assessment (Becker, Bergfeld et al. 2008).

- Amino Acids

Overview:



Amino acids are naturally occurring organic compounds that serve as the building blocks of proteins. Amino acids are found in all living organisms and are critical to life. Of the 21 most common amino acids, eight are considered essential in that they cannot be synthesized in the human body and must be obtained through the diet. Aside from their natural occurrence, amino acids can be synthesized or manufactured via fermentation, enzymatic catalysis, or protein hydrolysis. Amino acids are commonly used in cosmetic products at concentrations from 0.0000001 to 2%, primarily as conditioning agents (humectants) in hair and skin conditioners (Burnett, Heldreth et al. 2012). Any potential exposures, including via topical application, to amino acids from cosmetic products are not expected to result in significant doses (Burnett, Heldreth et al. 2012). The most common amino acids used in cosmetic products are reportedly arginine and glycine (Burnett, Heldreth et al. 2012).

Toxicology:

Due to the widespread occurrence of amino acids in living organisms, they are “not considered to pose any significant toxicological safety concern following oral exposure, except to individuals with certain genetic disorders” (Burnett, Heldreth et al. 2012). Individuals with the rare genetic disorder “phenylketonuria” are unable to metabolize the amino acid phenylalanine, which may result in irreversible neurological effects if not identified and properly managed through diet (Burnett, Heldreth et al. 2012). In addition, excess levels of monosodium glutamate (MSG) in foods may cause symptoms including headache and nausea in individuals suffering from MSG symptom complex (Burnett, Heldreth et al. 2012). The CIR panel stated “concentrations of [sodium glutamate and phenylalanine] in cosmetic products are at levels that would not be significantly absorbed through topical application or incidental ingestions, and thus, would not cause systemic reactions in individuals” (Burnett, Heldreth et al. 2012).

Dermal Hazard:

The CIR identified six dermal irritation studies of amino acids including L-arginine, aspartic acid, cysteine HCL, glycine, methionine, and serine in non-human models (Burnett, Heldreth et al. 2012). Negative results were reported in all the aforementioned studies (Burnett, Heldreth et al. 2012). A number of HRIPTs have been conducted with amino acids including alanine, arginine, aspartic acid, aspartate, glutamic acid, glycine, and histidine. Lysine, methionine, phenylalanine, proline, serine, tyrosine, and valine in various cosmetic products including lotions, creams, make-up, eye gels, and hair products (Burnett, Heldreth et al. 2012). No positive results for dermal irritation have been reported (Burnett, Heldreth et al. 2012).

Sensitization:

[REDACTED]

A number of HRIPTs have been conducted with amino acids including alanine, arginine, aspartic acid, aspartate, glutamic acid, glycine, and histidine, lysine, methionine, phenylalanine, proline, serine, tyrosine, and valine in various cosmetic products including lotions, creams, make-up, eye gels, and hair products (Burnett, Heldreth et al. 2012). No positive results for sensitization have been reported (Burnett, Heldreth et al. 2012).

Association with Hair Loss:

There was no information available on the association between amino acids and hair loss.

Agency Data:

In 2012, the IR assessed the safety of amino acids and concluded that they “were safe as cosmetic ingredients in the practices of use” (Burnett, Heldreth et al. 2012).

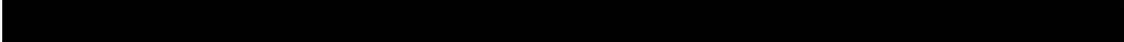
- Amodimethicone

Overview:

Amodimethicone is a member of the dimethicone family of silicone products, which is characterized by their methylated linear siloxane polymer units (Yahagi 1993; Nair 2003). Amodimethicone is produced by partly replacing the methyl groups in the dimethyl siloxane polymers with organic amine groups (Yahagi 1993). Dimethicone, a white odorless fluid polymer, was one of the first commercially available silicone products and was first incorporated into personal care products in the 1950s (Disapio and Fridd 1988; Yahagi 1993; Nair 2003). Dimethicones are widely used in conditioners, hair care, skin care, and other cosmetic products owing to their lubricating and water-insoluble properties (Yahagi 1993). Additionally, dimethicones are used as food additives (Nair 2003).

Toxicology:

The CIR reported that dimethicone was “not acutely toxic following oral exposure” (Nair 2003). Acute oral toxicity studies performed in rats with products containing dimethicone at various concentrations reported oral LD₅₀ values between 1.1 to 27.4 g/kg bw (Nair 2003). However, a LD₅₀ estimate was not reported for humans. Although the specific concentration of dimethicone administered was not specified, “[n]o adverse effects were observed” in one to two year chronic exposure studies conducted in rats and rabbits (Nair 2003). Furthermore, oral ingestion of dimethicone resulted in no absorption in the human body; it was reported to be rapidly excreted from the GI tract (Nair 2003).



Dermal Hazard:

Dimethicone was not absorbed following dermal exposure in humans (Nair 2003). A number of studies conducted in rats and rabbits reported that “[n]o adverse reactions” were observed following exposure to dimethicone at approximately 2000 mg/kg bw (Nair 2003). These authors estimated the dermal LD₅₀ to be in excess of 2000 mg/kg (Nair 2003). Interestingly, a study testing a commercial emulsion containing 15% dimethicone reported a dermal LD₅₀ of 16 mL/kg b.w.; however, other ingredients included in the emulsion were not reported, bringing into question the validity of these results (Nair 2003). A number of studies performed in rabbits demonstrated mixed results on whether dimethicone produced dermal irritation (Nair 2003). The majority of the studies testing doses greater than 90% dimethicone found that there was minor or no irritation produced by dimethicone; however, one study using an unspecified concentration of dimethicone concluded that the material was a severe irritant (Nair 2003). Dimethicone was not found to be an irritant in human studies (Nair 2003).

Sensitization:

“No [sensitization] reactions were observed” in sensitization studies performed in mice and guinea pigs at doses greater than 90% dimethicone (Nair 2003). Dimethicone was also found to not be a sensitizer in human studies (Nair 2003).

Association with Hair Loss:

There was no information available on the association between dimethicone and hair loss.

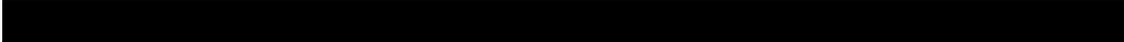
Agency Data:

Dimethicones were reported to be “safe as used in cosmetic formulations” up to or equal to 15% (Nair 2003). The Joint Expert Committee on Food Additives/WHO established an acceptable daily intake level of 0 to 1.5 mg/kg b.w. for dimethicone (Nair 2003). Dimethicone was not considered to be genotoxic or carcinogenic according to a recent publication by the Cosmetic Ingredient Review (CIR) (Nair 2003).

- Behentrimonium methosulfate

Overview:

Behentrimonium methosulfate is a member of the trimonium compound family with a straight alkyl chain 22 carbons in length and is not water soluble due to the length of the alkyl chain (Becker, Bergfeld et al. 2012). Behentrimonium methosulfate is reported to be used in cosmetics as an antistatic and hair



conditioning agent (Becker, Bergfeld et al. 2012). It is reportedly used in over 270 products, primarily hair conditioning products, at maximum concentrations that range from 0.1 to 10% (Becker, Bergfeld et al. 2012).

Toxicology:

Information regarding the potential systemic toxicity of behentrimonium methosulfate was not available. However, an animal study using cetrimonium chloride, another member of the trimonium compound family, performed on rats reported a short-term oral NOAEL of 100 mg/kg (Becker, Bergfeld et al. 2012).

Dermal Hazard:

Limited information regarding the potential dermal toxicity and effects of dermal exposure to behentrimonium methosulfate was available. The dermal absorption of other straight or branched chain alkyl trimonium ingredients was reported to be equal to or less than 3% (Becker, Bergfeld et al. 2012). Interestingly, it was reported that long chain trimonium ions are unlikely to cross the lipid barrier, but may be irritating to the skin (Becker, Bergfeld et al. 2012). However, it was unclear whether behentrimonium methosulfate behaved in a similar fashion. Studies performed using other members of the trimonium compound family reported irritation at concentrations greater than 20% in several animal studies (Becker, Bergfeld et al. 2012).

Sensitization:

Behentrimonium methosulphate was not sensitizing in a guinea pig maximization test with a 5% intradermal induction dose, 50% epidermal induction dose and 3% challenge dose (ECHA 2016).

Association with Hair Loss:

There was no information available on the association between Behentrimonium methosulphate and hair loss.

Agency Data:

The CIR concluded that trimonium compounds, including behentrimonium methosulfate, are “safe in the present practices of use and concentration ... when formulated to be nonirritating” (Becker, Bergfeld et al. 2012). In addition, it was specifically noted that behentrimonium methosulfate is used in cosmetic products at maximum concentrations ranging from 0.1 to 10% (Becker, Bergfeld et al. 2012).

- Carbomer

Overview:

Carbomer resins are synthetic polymers of acrylic acid (98.7-99.9%) cross-linked with a polyalkenyl polyether. Carbomers are commonly used in hair conditioners, hair sprays, shampoos, hair tonics, and other cosmetic products (Bergfeld, Belsito et al. 2001). The carbomer polymers are chemically similar to each other, but differ in molecular weights. Carbomers have been described as “white, fluffy powders, with a slight characteristic odor” (Elder 1982). Carbomer concentrations in cosmetic formulations vary between <0.1% and 50%, with the majority of products containing concentrations below 1% (Elder 1982).

Toxicology:

Acute oral studies with rats, guinea pigs, mice, and dogs have shown that carbomers-910, -934, -940, and -941 have low toxicities when ingested (Elder 1982). No mortalities were observed in rabbits intravenously administered 1%, 2%, or 3% carbomer-934 at a dose of 5 mL/kg (Elder 1982). In a dietary exposure of study of carbomer-934P (5%) administered to rats for 90 days, reduced liver, body, and brain weights were observed; however, no pathological changes were observed (Elder 1982).

Dermal Hazard:

The dermal LD₅₀ of rats exposed to carbomer-910 was found to be more than 3 g/kg (Elder 1982). Animals studies have demonstrated that dermal exposure to 100% carbomer-934 or carbomer-910 to rabbits resulted in “minimal skin irritation” (Elder 1982).

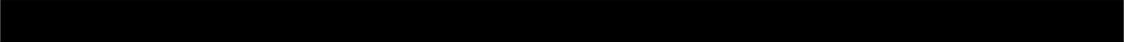
Sensitization:

A series of human studies assessing the potential for carbomer-934, carbomer-940, and carbomer-941 to cause skin irritation and/or sensitization have been conducted (Elder 1982). These clinical studies have found that carbomer-934 polymers “have low potential for skin irritation or sensitization at concentrations of 0.5%, 5.0%, 10%, and 100%” (Elder 1982).

Association with Hair Loss:

There was no information available on the association between carbomers and hair loss.

Agency Data:



In 1982, the CIR panel concluded that “[c]arbomers are safe as cosmetic ingredients in the present practices of use and concentration” (Elder 1982). In 2001, carbomer was re-evaluated by CIR based on new studies, and it was determined that there was no need to reopen the safety assessment of these polymers (Bergfeld, Belsito et al. 2001).

- Cetearyl Alcohol

Overview:

Cetearyl (aka cetostearyl) alcohol is a straight-chain aliphatic alcohol, mostly comprised of cetyl and stearyl alcohols. It is a white, waxy solid that is usually present in a “flake” form (Elder 1988). Cetearyl alcohol was reportedly used in 56 cosmetic products in 1982, based on voluntary reports provided to FDA by industry, with use concentrations ranging from >1% to 25% (Elder 1988). In 2005, an industry survey indicated that cetearyl alcohol was used at concentrations ranging from 0.0002% to 15% (Panel 2008). According to the FDA in 2006, cetearyl alcohol was reportedly used in 1435 cosmetic products (Panel 2008).

Toxicology:

There was no information available on the potential systemic toxicity of cetearyl alcohol.

Dermal Hazard:

An animal study using 3% cetearyl alcohol was conducted in rabbits (Elder 1988). Test sites were evaluated for irritation 8 and 24 hours after application (Elder 1988). Based on the results of the study, it was concluded that the cream was mildly irritating to the skin (Elder 1988). A clinical study involving 25 human subjects was conducted using a cream containing 3% cetearyl alcohol (Elder 1988). Three-tenths of a gram of the product was applied to the forearm, followed by an application of a patch (Elder 1988). Following a 10 day non-treatment period, challenge patches were applied and the test sites were evaluated immediately after and 24 hours after the challenge patch; the product was considered non-irritating (Elder 1988).

Sensitization:

Sensitization reactions were not observed in any subjects during patch testing (Elder 1988).

Association with Hair Loss:

There was no information available on the association between cetearyl alcohol and hair loss.

Agency Data:

In 1988, the CIR panel concluded that “[c]etearyl a[l]cohol ... [is] ... safe as cosmetic ingredients in the present practices of use” (Elder 1988). In 2008, the panel confirmed the safety of cetearyl alcohol in the practices of use at concentrations between 0.0002-15% (Panel 2008).

- Cetyl Alcohol

Overview:

Cetyl alcohol, also known as 1-hexadecanol or n-hexadecyl, is a 16 carbon straight-chain aliphatic alcohol (Elder 1988). It is a white, waxy solid that comes in either a flake or powder form that is soluble in other alcohols and oils, but is not soluble in water (Elder 1988). Cetyl alcohol may contain several impurities, including ash, hydrocarbons, and elemental lead and arsenic; the Cosmetic, Toiletry, and Fragrance Association (CTFA) has set guidelines for the maximum levels of these substances in cetyl alcohol (Elder 1988). Due to its water-binding property, cetyl alcohol is used in cosmetics to prevent drying and chapping of the skin (Elder 1988). It is used as an emulsifying and opacifying agent, emollient, foam booster, and a viscosity-increasing agent in cosmetics and topical pharmaceuticals (Smolinske 1992). According to the FDA, in 2006, 332 conditioners contained cetyl alcohol, at concentrations ranging from 2 to 8% (Elder 1988). Additionally, cetyl alcohol is used as both a direct and indirect food additive (Elder 1988).

Toxicology:

Several oral toxicity studies were conducted in rats to calculate LD₅₀ values for cetyl alcohol (Elder 1988). In the different studies, rats were fed a diet that consisted of 2 to 4% of cetyl alcohol (Elder 1988). Overall, the LD₅₀ ranged from 5 to > 13 g/kg and >7 to >33 ml/kg (Elder 1988).

Dermal Hazard:

Two animal studies were conducted to evaluate the dermal LD₅₀ of cetyl alcohol. In the first study, 100% cetyl alcohol was applied to the skin of 16 rabbits; an LD₅₀ of greater than 2.6 g/kg was reported (Elder 1988). In the second study, lipstick containing 4% cetyl alcohol was applied to the skin of rabbits for a 24 hour period and an LD₅₀ of greater than 2 g/kg was reported (Elder 1988). Several animal studies have been conducted to evaluate subchronic dermal toxicity of cetyl alcohol. When animals were administered a cream containing 11.5% cetyl alcohol, the observed effects included erythema, parakeratosis,



hyperkeratosis, papillary projections of epidermis and exfoliative dermatitis (Elder 1988). In another study, animals were administered a cream containing 2% cetyl alcohol for a three month period; mild inflammation at the application site was observed (Elder 1988). Furthermore, a heated mixture containing 30% of cetyl alcohol in methyl alcohol and propylene glycol was administered to albino rabbits daily for 30 days (Elder 1988). No substantial macroscopic changes were observed, and microscopic infiltrates of lymphomononuclear cells and histiocytes in superficial portions of the dermis were observed (Rantuccio, Sinist et al. 1981; Elder 1988).

A series of animal studies were conducted to evaluate the effect of cetyl alcohol on skin irritation. Products containing anywhere from 2 to 100% cetyl alcohol were applied to the skin of rabbits (Elder 1988). Slight to well-defined erythema was observed in animals receiving 2 to 4% of cetyl alcohol (Elder 1988). Minimal to slight irritation was observed in animals receiving 3 to 100% of cetyl alcohol (Elder 1988). According to the CIR, 14 human studies were conducted to further study cetyl alcohol's effects on skin irritation. In 8 of the studies, subjects were administered a formulation containing 2 to 100% cetyl alcohol and no irritation, or no significant irritation was observed. In five of the studies conducted, subjects were administered a compound containing 2 to 6% cetyl alcohol and mild irritation was observed.

Sensitization:

According to the CIR, a total of 17 studies have been conducted to evaluate skin irritation and sensitization following cetyl alcohol application. In 10 of the studies, subjects were administer cetyl alcohol in concentrations ranging between 1 and 8.4%, and no signs of irritation or sensitization were observed. Other studies reported skin irritation from the application of 1 to 6% cetyl alcohol. Overall, the authors concluded that there was evidence that cetyl alcohol can cause skin irritation. No evidence of sensitization were observed in any of the studies (Elder 1988).

A total of seven clinical studies were conducted to evaluate skin sensitization effects following cetyl alcohol application. Subjects were given a product containing 2 to 30% cetyl alcohol; no sensitization was observed in any of the studies (Elder 1988).

Association with Hair Loss:

There was no information available on the association between cetyl alcohol and hair loss.

Agency Data:

The CIR concluded that cetyl alcohol and other long-chain aliphatic alcohols, were “safe as cosmetic ingredients in the present practice of use” (Elder 1988). An annual report on cosmetic ingredient safety, published in 2006, confirmed that cetyl alcohol is still considered safe and did not warrant any revisions to the safety assessment (Panel 2008).

- Citric Acid

Overview:

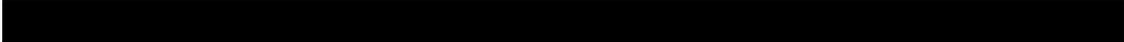
Citric acid is a white solid that is soluble in water and some organic solvents (Soccol, Vandenberghe et al. 2006; Fiume, Heldreth et al. 2014). It is widely used as a flavor, fragrance, pH adjuster, chelating agent, skin conditioning agent, and buffering agent in foods, beverages, cosmetics, pharmaceuticals, detergents and cleaning products, and pesticides due to its low toxicity (Soccol, Vandenberghe et al. 2006; Fiume, Heldreth et al. 2014). Citric acid is used in over 6000 cosmetic leave on and rinse off products at concentrations ranging from 0.0000005 to 10% (Fiume, Heldreth et al. 2014).

Toxicology:

Cases of citric acid intoxication resulting from the use of citrated blood for transfusion were reported in the early 1900s (Gruber and Halbeisen 1948; Bunker, Stetson et al. 1955). A number of studies were performed to evaluate these claims. Gruber et al. (1948) performed estimated an LD₅₀ of 1.75 mmol/kg of citrate administered to a 70 kg man in 15 minutes or less from studies performed in mice, rats, rabbits, and dogs (Gruber and Halbeisen 1948). The authors subsequently concluded that citrate intoxication resulting from massive transfusions “do ... not occur” (Gruber and Halbeisen 1948). Bunker et al. (1955) evaluated signs of clinical citric acid intoxication in patients who received transfusions of citrated blood. The authors determined that citric acid intoxication, leading to hypotension and vascular collapse only occurred at transfusion rates of more than 0.5 mg citrate per kg body weight per minute in patients with compromised liver function (Bunker, Stetson et al. 1955). Limited toxicological information regarding citric acid was available aside from the blood transfusion studies described above. Generally, orally ingested citric acid is readily absorbed and metabolized to serve as a source for energy (Fiume, Heldreth et al. 2014).

Dermal Hazard:

Limited information was available regarding the dermal toxicity of citric acid. A dermal LD₅₀ of more than 5 g/kg for citric acid was reported in an animal study performed in rabbits (Fiume, Heldreth et al. 2014). Although limited dermal toxicity was reported, a number of human and nonhuman skin irritation studies on citric acid have been conducted. An animal study conducted in rabbits found that exposure to



30% citric acid did not lead to irritation; however, exposure to 60% or more citric acid led to erythema and edema (Fiume, Heldreth et al. 2014). It was reported that alpha hydroxyl acids, which include citric acid, are generally well tolerated when topically applied in concentrations at or below 10% (2012). Higher concentrations have been associated with skin irritation, burning, sloughing, and limited frosting and whitening to scar areas (2012).

Sensitization:

A sensitization test using a cuticle cream containing 4% citric acid did not lead to irritation or sensitization in humans (Fiume, Heldreth et al. 2014). Interestingly, 2.5% citric acid in an aqueous preparation produced positive sensitization results in 3 of the 91 patients with urticarial or angioedema (Fiume, Heldreth et al. 2014). These studies suggest that though citric acid is not normally an irritant or sensitizer, it may cause irritation or sensitization in individuals with pre-existing skin conditions.

Association with Hair Loss:

There was no information available on the association between citric acid and hair loss.

Agency Data:

Citric acid is listed as generally recognized as safe (GRAS) by the FDA and Joint FAO/WHO Expert Committee on Food Additives (Soccol, Vandenberghe et al. 2006; Fiume, Heldreth et al. 2014). In addition, the CIR has stated that citric acid is “safe in the present practices of use and concentration” in cosmetics (Fiume, Heldreth et al. 2014).

- Dicyldimonium chloride

Overview:

Dicyldimonium chloride is also known as dicyldimethylammonium chloride; it is a quaternary ammonium salt, and is classified as a surfactant, conditioning agent, emulsifier and antistatic agent for cosmetic use (ChemIDplus 2016; SpecialChem 2016).

Toxicology:

Very limited toxicological information was available on dicyldimonium chloride. An *in vitro* study regarding cell membrane integrity following short-term exposure to dicyldimonium chloride was performed (Korting, Herzinger et al. 1994). The authors reported that dicyldimonium chloride did not elicit a half maximal effect at the highest dose tested and concluded that the chemical was only “slightly

cytotoxic” (Korting, Herzinger et al. 1994). The EC₅₀ of dicetyldimonium chloride for cell membrane integrity was estimated to be 147.84 g/L in human foreskin keratinocytes by extrapolation (Korting, Herzinger et al. 1994). However, in an *in vitro* cell proliferation assay, dicetyldimonium chloride was reported to be “strongly toxic” with an EC₅₀ of 8.05 mg/L for human foreskin keratinocytes (Korting, Herzinger et al. 1994).

Dermal Hazard:

There was no information available on the dermal hazard of dicetyldimonium chloride.

Sensitization:

There was no information available on the sensitization of dicetyldimonium chloride.

Association with Hair Loss:

There was no information available on the association between dicetyldimonium chloride and hair loss.

Agency Data:

There was no agency data information available for dicetyldimonium chloride extract.

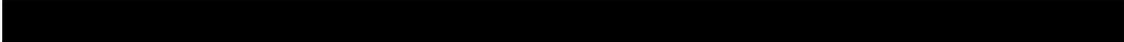
- Ethylhexylglycerin

Overview:

Ethylhexylglycerin, also known as octoxyglycerin, 3-(2-ethylhexyloxy)propane-1,2-diol, is a clear colorless liquid with a “slightly characteristic od[or]” (Leschke 2006; Aerts, Verhulst et al. 2016). It is a well-known multifunctional ingredient, and is commonly used as a medium spreading emollient, to improve the feel of skin care products (Weber and Stoffels 2015). Interestingly, ethylhexylglycerin was also reported to “boost the antimicrobial activity of preservatives or other active substances” (Weber and Stoffels 2015). Aerts et al. (2016) reported that ethylhexylglycerin concentrations up to 2% and 8% have been reported in leave-on and rinse-off products, respectively (Aerts, Verhulst et al. 2016).

Toxicology:

The toxicity of ethylhexylglycerin was determined for both oral and dermal exposures. A 28 day repeated oral dosing study performed in rats found that there was “no treatment-related mortalities” and the NOAEL was determined to be 100 mg/kg (Johnson Jr, Bergfeld et al. 2013).



Dermal Hazard:

The acute dermal toxicity (LD₅₀) of undiluted ethylhexylglycerin, as determined in rats, was reported to be more than 2000 mg/kg (Johnson Jr, Bergfeld et al. 2013). The study showed “[n]o abnormal clinical signs or signs of erythema or edema” in rats and a LD₅₀ of >2000 mg/kg was reported (Johnson Jr, Bergfeld et al. 2013).

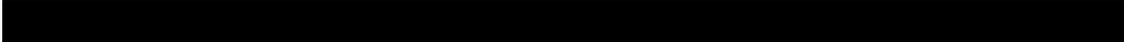
An *in vitro* study using human skin showed that ethylhexylglycerin applied at 2% in cream led to approximately 45% absorption over an unspecified time period. The absorption rate seems to be dose dependent but the delay in absorption was similar between the doses. Interestingly, an *in vivo* study performed in rabbits showed that at the highest dose tested (5% in corn oil), the mean absorption through the skin was 0.02% approximately two hours after application as detected in the animal’s plasma. However, when ethylhexylglycerin was tested at 1% in corn oil, the results were below the limit of detection. In all blood samples collected after the treatment, the concentrations of ethylhexylglycerin were below the level of detection (Johnson Jr, Bergfeld et al. 2013). Based on the available information, the rate of dermal absorption could not be determined.

Sensitization:

Although ethylhexylglycerin was reported to be safe, several case reports of sensitization were published in the peer-reviewed literature (Stausbol-Gron and Andersen 2007; Mortz, Otkjaer et al. 2009; Aerts, Verhulst et al. 2016). These patients reported allergic contact dermatitis caused by the use of ethylhexylglycerin-containing products such as sunscreens, creams, deodorant, and skin care products (Stausbol-Gron and Andersen 2007; Mortz, Otkjaer et al. 2009; Aerts, Verhulst et al. 2016). However, the concentration of ethylhexylglycerin in the aforementioned products were not reported. *In vivo* studies performed in humans with ethylhexylglycerin levels ranging from 0.4 to 1.0% all found that ethylhexylglycerin was neither a skin irritant nor a sensitizer (Johnson Jr, Bergfeld et al. 2013). Animal studies performed in rabbits were in general agreement with human studies, concluding that ethylhexylglycerin was not an irritant or sensitizer (Johnson Jr, Bergfeld et al. 2013). One exception to this was an animal study performed by the Australian National Occupational Health and Safety Commission that classified ethylhexylglycerin to be a “a mild skin irritant” (Johnson Jr, Bergfeld et al. 2013).

Association with Hair Loss:

There was no information available on the association between ethylhexylglycerin and hair loss.



Agency Data:

A recent CIR safety assessment concluded that ethylhexylglycerin was “safe [when used] in the present practices of use and concentration” (Johnson Jr, Bergfeld et al. 2013).

- *Euterpe Oleracei* (Acai) Fruit Extract

Overview:

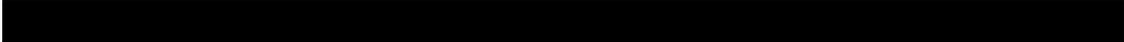
Products derived from the fruit of *Euterpe oleracea* palm plant, more commonly known as acai, have been touted for their anti-oxidant properties and used in traditional Brazilian medicine to treat a variety of diseases (Marques, Froder et al. 2016). Chemical studies of acai have shown that the acai fruit contains many bioactive chemicals including phenolics, flavonoids, and anthocyanins, while fatty acids represent the major compounds found in acai oil extracts (Marques, Froder et al. 2016). According to the CIR, oleic acid represents 60% of fatty acids found in acai fruit oil extract, followed by palmitic acid at 22% , and linoleic acid at 12 % (Belsito, Hill et al. 2011). Anthocyanins, found in high concentrations in acai extracts, have been reported to provide benefits in the prevention and treatment of cutaneous disorders (de Lima Yamaguchi, Pereira et al. 2015). Acai extracts are used in cosmetic products, including shampoos, conditioners, anti-wrinkle creams, and body lotions for the purpose of hydration and hair conditioning. Acai oil extract is used in over 40 cosmetic products at concentrations ranging from 0.00001 to 0.5% (Belsito, Hill et al. 2011).

Toxicology:

Information regarding the potential systemic toxicity of acai fruit extracts was not available. In a 2011 report, the CIR noted that many of the fatty acid oils, including acai fruit oil, reviewed in the assessment are edible and that exposure to the substances via food would result in a systemic dose that would exceed that expected from use in cosmetic products (Belsito, Hill et al. 2011). In addition, the CIR stated allergic responses are rarely observed in refined oil extracts even in individuals with food allergies to the same plant from which the oil was derived (Belsito, Hill et al. 2011). No adverse reactions were reported for acai (2012).

Dermal Hazard:

Limited information regarding the potential dermal toxicity related to acai fruit extracts was available. However, the CIR reported that an unpublished study was conducted on the dermal effects of 0.5% acai fruit oil in an eye treatment cosmetic product (Belsito, Hill et al. 2011).



Sensitization:

The acai fruit extract was reported to not be a dermal irritant nor sensitizer based upon negative HPIRT results (Belsito, Hill et al. 2011).

Association with Hair Loss:

There was no information available on the association between acai fruit extract and hair loss.

Agency Data:

The CIR concluded that the 244 plant-derived fatty acid oils, including *Euterpe oleracea* fruit oil, included in their review of potential dermal effects were “safe as used in cosmetics” (Belsito, Hill et al. 2011).

- Glycerin

Overview:

Glycerin, also known as glycerol, is a clear, syrupy liquid, and is completely miscible with water, methanol, ethanol, and other alcohols (Becker, Bergfeld et al. 2015). It is used in cosmetics as a denaturant, fragrance ingredient, hair conditioning agent, humectant, skin protectant and viscosity decreasing agent (Becker, Bergfeld et al. 2015). According to the FDA’s Voluntary Cosmetic Registration Program (VCRP), glycerin was the third most frequently reported ingredient in the VCRP database, and was reportedly used in over 15,000 cosmetic products, including over 10,000 leave-on products, and over 5,000 rinse-off products in 2014 (Becker, Bergfeld et al. 2015). Maximum uses of glycerin in personal care products was reported to range from 79.2% in leave-on products to 99.4% in rinse-off products (Becker, Bergfeld et al. 2015).

Toxicology:

Systemic toxicity was not observed in neither human nor animal studies (Becker, Bergfeld et al. 2015). No signs of systemic toxicity were observed when human subjects were orally administered glycerin at doses ranging from 1.3 to 2.2 g/kg/d for 50 days; the NOAEL was reported to be greater than 2.2 g/kg/day (Becker, Bergfeld et al. 2015). In a study conducted in rats, orally administered glycerin at doses of 0, 1%, 5%, 10%, or 20% (115, 575, 1150 and 2300 mg/kg) in water for 44 days resulted in no adverse effects for growth curves, lethality, and histological examination of the kidneys, livers and bladders

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(Becker, Bergfeld et al. 2015). The NOAEL was reported to be between 115 and 2300 mg/kg (Becker, Bergfeld et al. 2015).

Dermal Hazard:

Limited information was available regarding the potential dermal toxicity of glycerin. An occlusive dermal application test conducted in rabbits using synthetic or natural glycerol at 18,700 mg/kg bw did not cause any mortality (SIDS 2002). The acute dermal LD₅₀ for glycerol was reported to be greater than 18,700 mg/kg bw in rabbits (SIDS 2002). A clinical study conducted using 25% in a 24 hour semi-occluded human patch test glycerin reported no clinical irritation (ECHA 2016). Although case reports of contact dermatitis to glycerin in humans is rare, a case report identified a 29 year old woman with a seven month history of patchy eczema on her eyelids face, neck and scalp (Preston and Finch 2003). Follow-up patch testing identified positive reactions to the 1% glycerin component of her cream (Preston and Finch 2003).

Sensitization:

Animal and human studies suggest glycerol is not irritating when in contact with the skin. In an animal study conducted in rabbits, dermal application of 0.5 or 4 mL glycerol for 8 hours per day for 45 weeks did not cause irritation (SIDS 2002). No human or animal data indicates glycerol to be a skin sensitizer. Sensitization of natural or synthetic glycerin at 0.1% was also not observed in two week study conducted with guinea pigs (Becker, Bergfeld et al. 2015). A moisturizer containing glycerin at 65.9% was reported to be not sensitizing in a human study (Becker, Bergfeld et al. 2015). Furthermore, no sensitizing effects of glycerol were apparent in skin patch tests conducted on workers regularly exposed to glycerin in a foam rubber factory (Becker, Bergfeld et al. 2015). The low occurrence of case reports of humans showing skin reactions is consistent with glycerol having a “very low skin sensitization potential” (SIDS 2002).

Association with Hair Loss:

There was no information available on the association between glycerol and hair loss.

Agency Data:

The CIR concluded that glycerin was considered “safe in cosmetics in the present practices of use and concentration” (Becker, Bergfeld et al. 2015). Glycerin is also considered generally recognized as safe (GRAS) by the FDA for its use in food packaging and as a multiple-purpose food substance when used in accordance with good manufacturing practices (FDA 2017).

- Glycogen

Overview:

Glycogen is a naturally occurring polysaccharide found in animals. It occurs primarily in the liver and skeletal muscle where it serves as the primary form in which carbohydrates are stored in higher animals. It serves as an energy reservoir, breaking down to glucose for energy as needed (2016).

Toxicology:

There was no information available on the potential systemic toxicity of glycogen.

Dermal Hazard:

There was no information available on the dermal hazard of glycogen.

Sensitization:

There was no information available on the sensitization of glycogen.

Association with Hair Loss:

There was no information available on the association between glycogen and hair loss.

Agency Data:

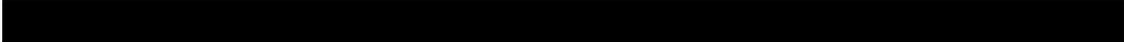
There was no agency data information available for glycogen.

- Guar Hydroxypropyltrimonium Chloride

Overview:

Guar hydroxypropyltrimonium chloride is also known as guar gum, 2 hydroxy-3-(trimethylammonio) propyl ether, chloride (Johnson Jr, Heldreth et al. 2015). It is a quaternary ammonium derivative of hydroxypropyl guar and is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (Johnson Jr, Heldreth et al. 2015). It is used in cosmetic products, including foot powders (at maximum concentration of 0.05%) and hair sprays.

Toxicology:



An acute oral toxicity study on of guar hydroxypropyltrimonium chloride was performed in rats given doses of 7.1, 10, 14, or 20 g/kg via oral intubation (Moyer 1979). Following a 14 day observation period, clinical signs included ataxia, tremors, nasal and oral discharge, and other symptoms (Moyer 1979). Based on the study, the acute oral median lethal dose LD₅₀ 12.5 g/kg was determined (Moyer 1979; Johnson Jr, Heldreth et al. 2015). In a separate study, rats received a single dose of 2000 mg/kg via oral gavage and were observed for 14 days (Johnson and Heldreth 2011). None of the animals died and there were no macroscopic findings at necropsy, an LD₅₀ of > 2000 mg/kg was determined (Johnson and Heldreth 2011).

Dermal Hazard:

Information regarding effects of potential dermal exposure and toxicity was not available. However, it was noted that the “substantial molecular sizes suggest that skin penetration of these ingredients would be unlikely” (Johnson Jr, Heldreth et al. 2015).

Sensitization:

There was no information available on the sensitization of guar hydroxypropyltrimonium chloride.

Association with Hair Loss:

There was no information available on the association between guar hydroxypropyltrimonium chloride and hair loss.

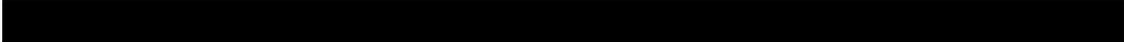
Agency Data:

In 2015, the CIR panel concluded that galactomannans, including guar hydroxypropyltrimonium chloride, are safe in the present practices of use at concentrations between 0.005-2% (Johnson Jr, Heldreth et al. 2015).

- Honey Extract

Overview:

Honey is a sweet, viscous food made by bees (Belcher 2012). It consists of 20% water, 80% sugar, and contains enzymes added by the bees (Belcher 2012). Honey has been used as a medicine throughout the history of the human race, although more recently, it has become available as a sterile, regulated medical-grade honey (Belcher 2012).



Toxicology:

Although toxicological studies were not available for honey or honey extract, reviews of the literature showed that honey is an effective treatment in wounds, burns, cough, and sleep difficulty (Moore, Smith et al. 2001; Wijesinghe, Weatherall et al. 2009; Belcher 2012; Cohen, Rozen et al. 2012).

Dermal Hazard:

There was no information available on the dermal hazard of honey extract.

Sensitization:

There was no information available on the sensitization of honey extract.

Association with Hair Loss:

There was no information available on the association between honey extract and hair loss.

Agency Data:

There was no agency data information available for honey extract.

- Kathon CG (methychlorolisothiazolione and methylisothiazolione)

Overview:

Kathon is the trade name for a cosmetic grade preservative that contains the active ingredients methychlorolisothiazolione (MCI) and methylisothiazolione (MI) in an approximate 3:1 ratio at 14% in a solution of 16% magnesium nitrate, 10% magnesium chloride, and 62% water. Specifically, Kathon CG is a 1.5% dilution of this formulation ((SCCS) 2009). Impurities including 2,2-dichloro-n-methylacetamide, 3-chloro-n-methylpropionamide, and 4,4-dichloro-2-methyl-4-isothiazolin-3-one were reported in various Kathon preparations ((SCCS) 2009).

Kathon is a clear liquid that is light amber in color; it is fully miscible in water (de Groot and Weyland 1988; (SCCS) 2009). It was first used in Europe and subsequently in the United States in 1980 primarily as a cosmetic preservative (de Groot and Weyland 1988). Only four years after its introduction, the utilization of Kathon increased rapidly to the point that it ranked 13th on the list of most frequently used cosmetic preservatives (de Groot and Weyland 1988). Kathon is described as a “highly effective, broad spectrum biocide with excellent compatibility and stability, and low toxicity at in-use levels” (Supleco

1997). It has a shelf life of at least one year at ambient temperatures and at least six months at 50°C (Supleco 1997; Haas 2007). According to the manufacturer's recommendations, the maximum use level for Kathon is 0.1% by weight (15 ppm active ingredient) in rinse-off products such as shampoos and hair conditioners and 0.05% by weight (7.5 ppm active ingredient) in leave-on products such as skin creams and lotions (Haas 2007; DOW 2013). According to the European Commission's Scientific Committee on Consumer Safety (SCCS), a number of reports of allergic contact dermatitis to MCI and MI were initially reported in the 1980s following occupational exposures, while cases in consumers were later identified ((SCCS) 2009). At that time, the recommended levels of Kathon CG's active ingredients was 30 ppm. The revised concentration of 15 ppm in leave-on cosmetic products were based upon the suggestion that a reduction from the prior recommended levels of use of 30 ppm would reduce the risk of sensitization and development of contact dermatitis in sensitized individuals from the use of rinse-off products ((SCCS) 2009). In addition, the European Commission regulates the use of the active ingredients of Kathon used as a cosmetic preservative with the maximum authorized concentration of 15 ppm and have furthermore concluded that Kathon CG does not pose a risk to consumer health up to these concentrations ((SCCS) 2009).

Toxicology:

90 day repeated oral dosing studies for systemic toxicity performed by Rohm and Hass in rats reported that "no systemic toxicity was observed up to and including the highest dose" of 800 ppm of Kathon ((SCCS) 2009). The authors reported that the No Observed Effect Level (NOEL) in this study was estimated to be greater than or equal to 800 ppm ((SCCS) 2009). Due to the lack of mutagenic effects and positive histopathological findings, Kathon was not considered to be carcinogenic or genotoxic (de Groot and Weyland 1988; (SCCS) 2009).

Rohm and Hass performed a number of radiolabel tracer studies on in vitro human skin to determine the dermal absorption of Kathon ((SCCS) 2009). The concentrations tested ranged from 11.25 to 225 ppm. The authors reported that the radiolabeled Kathon was "minimally absorbed during the first 4-6 hours after application" ((SCCS) 2009). However, the absorption increased to 7-56% over 24 hours. The limitation of these studies was that although the absorbed radiolabel was detected, "it was not possible to determine" whether the detected radiolabel was the parent compound or degradation compounds ((SCCS) 2009). Interestingly, the SCCS concluded that due to the large variation in the studies performed, "100% dermal absorption" of Kathon was assumed when evaluating the safety of the substance ((SCCS) 2009).

Dermal Hazard:

Dermal toxicity was evaluated in a 90 day repeat dosing study conducted in rats using acticide 14, containing 10.2% MCI and 4% MI, in distilled water applied to intact skin ((SCCS) 2009). The authors reported that aside from dose-response related erythema, "no other treatment-related clinical changes" were observed ((SCCS) 2009). No histopathological or macroscopic treatment-related lesions were

observed; however, microscopic treatment-related lesions such as inflammation, parakeratosis, and acanthosis was observed at treated sites ((SCCS) 2009). The authors concluded that the Lowest Observed Adverse Effect Level (LOAEL) was 104 mg/kg/day of the active ingredient ((SCCS) 2009).

Kathon may cause contact dermatitis (skin irritation and/or skin sensitization) at concentrations higher than the recommended use level (Haas 2007). Kathon in its undiluted form is reported to be a corrosive substance that is a strong irritant (de Groot and Weyland 1988; Haas 2007; (SCCS) 2009). However, patch test studies revealed that Kathon concentrations up to 100 ppm, which is significantly higher than the maximum recommended use level provided by the manufacturer, did not produce significant skin irritation (Maibach 1985; Björkner, Bruze et al. 1986; de Groot and Weyland 1988; (SCCS) 2009). Furthermore, the SCCS concluded that skin irritation was “not a problem under the conditions of [Kathon’s] use in leave-on and rinse-off products” ((SCCS) 2009). Kathon was reported to be a potential sensitizer in a number of human and animal studies (Chan, Baldwin et al. 1983; Maibach 1985; de Groot and Weyland 1988; Potter and HAZELTON 1995; (SCCS) 2009).

A number of allergic contact dermatitis reports were published shortly after the introduction of Kathon in consumer products, particularly in Europe (de Groot and Weyland 1988; O’Driscoll and Beck 1988; Foussereau 1990). However, the skin condition of these individuals was not reported. Allergy testing of Kathon-containing consumer products (with Kathon concentrations up to 6 ppm) in healthy individuals reported no allergic reactions (Weaver, Cardin et al. 1985; de Groot and Weyland 1988). However, the prevalence of contact allergy increased in eczema patients, suggesting that the risk of eliciting an allergic reaction may be greater in individuals with already damaged skin (Hannuksela 1986; de Groot and Weyland 1988).

Sensitization:

The sensitization potential varied of Kathon with different formulations; nonetheless, it was determined that there were “[n]o signs of induction and elicitation of delayed sensitization” from concentrations below 12.5 ppm (Chan, Baldwin et al. 1983; Maibach 1985; de Groot and Weyland 1988). A recent study showed that the threshold for contact allergy in sensitized individuals was less than 2 ppm of a solution of Kathon active ingredients (Zachariae, Lerbæk et al. 2006).

Association with Hair Loss:

There was no information available on the association between Kathon and hair loss.

Agency Data:

[REDACTED]

In a 2014 report, the CIR stated that MI (a constituent of Kathon) is “safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when ... formulated to be non-sensitizing, which may be determined based on a [quantitative risk assessment]” (Belsito, Klaassen et al. 2014).

- Menthol

Overview:

Menthol is a cyclic terpene alcohol naturally present in the volatile oil of plants from the *Mentha* species including peppermint and cornmint oil; menthol can also be synthesized artificially (Galeotti, Mannelli et al. 2002; Patel, Ishiujji et al. 2007; Kumar, Baitha et al. 2016). It is a waxy clear or white crystalline substance with a distinctive “minty” smell and flavor (Galeotti, Mannelli et al. 2002; Patel, Ishiujji et al. 2007; Sigma 2014). It is widely used in medicine, cosmetics, and food for its antipruritic, antiseptic, analgesic, and cooling properties (Patel, Ishiujji et al. 2007; Kumar, Baitha et al. 2016).

Toxicology:

A small number of cases of menthol toxicity were reported; however, these appear to be rare (Baibars, Eng et al. 2012; Kumar, Baitha et al. 2016). Oral toxicity was reported in an “[u]nusual” case where an 86 year old man who had “chronic exposure to a significant amount of menthol” presented with cutaneous, gastrointestinal, and neurological symptoms (Baibars, Eng et al. 2012). It was reported that the patient ingested “two bags of menthol-rich cough droplets” daily for twenty years; however, the precise dose of menthol that this patient experienced was not reported. After cessation of menthol-rich cough droplets, the patient’s symptoms were reported to improve over time (Baibars, Eng et al. 2012). Interestingly, a more recent case reported the first incident of fatal menthol poisoning, where an individual was found unconscious following exposure to menthol-containing fumes while cleaning a tank in a peppermint factory (Kumar, Baitha et al. 2016). The individual presented to the emergency room with recurrent convulsions and intermittent hematuria; he passed away at a local hospital after ten days of hospitalization and treatment (Kumar, Baitha et al. 2016). The specific exposure level to menthol was not reported.

In a repeat dose study, rats were administered menthol via oral gavage for 28 days at concentrations of 0, 200, 400, and 800 mg/kg bw/day (Thorup, Würtzen et al. 1983). A significant increase in liver weight was reported at all doses, while vacuolization of hepatocytes was reported but did not occur in a dose-dependent manner and was considered an adaptive response (Thorup, Würtzen et al. 1983). The authors determined the “no effect level” to be less than 200 mg/kg/day for menthol ingestion (Thorup, Würtzen et al. 1983). Another study described by Kumar et al. (2016) reported that the oral lethal dose of menthol

was estimated as 50 to 150 mg/kg; however, further details of the study were not provided (Kumar, Baitha et al. 2016). Taken together, the no effect level for menthol is likely to be less than 200 mg/kg/day.

Dermal Hazard:

Dermal absorption was assayed by patch testing in healthy human individuals (Martin, Valdez et al. 2004). Martin et al. (2004) reported that the application of menthol at “unrealistically high” doses of 74.9 to 299.5 mg (levels unlikely to be experienced by an individual at a single time) resulted in “low plasma concentrations that were near the limits of quantification” (Martin, Valdez et al. 2004). Nonetheless, it was concluded that menthol at the concentrations tested undergo dermal absorption resulting in “some degree” of systemic exposure (Martin, Valdez et al. 2004). However, it was unclear whether similar levels of dermal absorption occurred at physiologically relevant doses.

The dermal application of menthol leads to a cooling effect that may lead to hyperalgesia and even pain (Green 1992; Wasner, Schattschneider et al. 2004; Patel, Ishiujji et al. 2007). A cooling sensation was reported after application of 5 and 10% menthol onto the human skin (Green 1992). However, “cold pain” described as a “burning pain sensation” was reported following exposure to more than 30% menthol (Wasner, Schattschneider et al. 2004; Patel, Ishiujji et al. 2007). Furthermore, exposure to may lead to sensitization of the skin resulting in “cold hyperalgesia” where the cold pain threshold is reduced (Green 1992; Wasner, Schattschneider et al. 2004; Patel, Ishiujji et al. 2007).

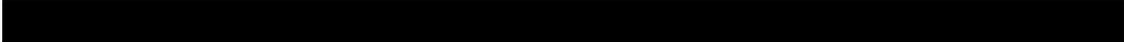
Sensitization:

Although menthol was considered to be safe for topical applications, on rare occasions, it has been associated with sensitization leading to allergic contact dermatitis (Aguirre, Oleaga et al. 1994; Wilkinson and Beck 1994; Patel, Ishiujji et al. 2007). Cases of allergic contact dermatitis following exposure to 1% menthol in petroleum was reported in patients from age 25 to 64 (Aguirre, Oleaga et al. 1994; Wilkinson and Beck 1994). The 25 year old patient was exposed to an undisclosed concentration of menthol in a topical treatment spray; route of exposure for the other aforementioned patients were not reported (Aguirre, Oleaga et al. 1994).

Association with Hair Loss:

There was no information available on the association between menthol and hair loss.

Agency Data:



According to the FDA, menthol is classified a “safe and effective” substance present in over-the-counter topical products with a “low toxicity profile” (Patel, Ishiujii et al. 2007; Baibars, Eng et al. 2012; Kumar, Baitha et al. 2016).

- Palmitoyl Oligopeptide

Overview:

Palmitoyl oligopeptide, also known as Pal-GHK, consists of a short chain of three amino acids that is connected to palmitic acid and functions as a skin and nail conditioning agent and as a surfactant-cleansing agent (Johnson Jr and Heldreth 2012). Palmitoyl oligopeptides have been used in cosmetic products that are applied to the skin and hair including suntan preparations and face powders (Johnson Jr and Heldreth 2012). Palmitoyl oligopeptides have been reported in over 400 cosmetic formulations; however, the concentrations used were not specified (Johnson Jr and Heldreth 2012).

Toxicology:

There was no information available on the potential systemic toxicity of palmitoyl oligopeptides.

Dermal Hazard:

There was no information available on the dermal hazard of palmitoyl oligopeptides.

Sensitization:

There was no information available on the sensitization of palmitoyl oligopeptides.

Association with Hair Loss:

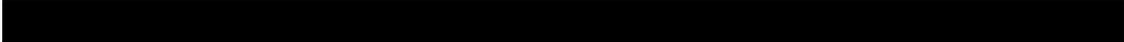
There was no information available on the association between palmitoyl oligopeptides and hair loss.

Agency Data:

There was no agency data information available for palmitoyl oligopeptides.

- Palmitoyl Tetrapeptide-7

Overview:



Palmitoyl tetrapeptide-7, also known as Pal-GQPR, consists of a short chain of four amino acids that is connected to palmitic acid and functions as a skin conditioning agent (Johnson Jr and Heldreth 2012). It is found in cosmetic products and suntan preparations (Johnson Jr and Heldreth 2012). A 2012 CIR safety assessment reported that palmitoyl tetrapeptide-7 have been used in approximately 200 cosmetic formulations; however, the concentrations used were not specified (Johnson Jr and Heldreth 2012).

Toxicology:

There was no information available on the potential systemic toxicity of palmitoyl tetrapeptide-7.

Dermal Hazard:

There was no information available on the dermal hazard of palmitoyl tetrapeptide-7.

Sensitization:

There was no information available on the sensitization of palmitoyl tetrapeptide-7.

Association with Hair Loss:

There was no information available on the association between palmitoyl tetrapeptide-7 and hair loss.

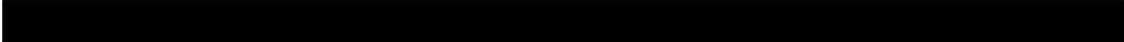
Agency Data:

There was no agency data information available for palmitoyl tetrapeptide-7.

- Panthenol

Overview:

Panthenol is the pro-vitamin alcohol analogue of pantothenic acid that when applied topically, is rapidly converted to pantothenic acid (Vitamin B5), which is important in normal epithelial cell function (Stables and Wilkinson 1998; Camargo Jr, Gaspar et al. 2011). Panthenol is a viscous hygroscopic liquid that is soluble in both water and alcohol (Johnson 1987). It is widely used in the pharmaceutical and cosmetic industry due to its moisturizing, soothing, sedative, and healing properties (Camargo Jr, Gaspar et al. 2011; Chin, Hughes et al. 2013). Topical application of panthenol reportedly aids the healing of burns, fissures, lesions, and allergic dermatitis (Camargo Jr, Gaspar et al. 2011). According to an early review, the concentration of panthenol used in cosmetics predominantly ranged between 0.1 to 1%, although a small number of formulations containing up to 25% panthenol were reported (Johnson 1987). The authors concluded that panthenol was “safe as presently used in cosmetics” (Johnson 1987).


Toxicology:

Limited toxicological information regarding panthenol was available. Several animal studies were conducted to determine the acute oral toxicity of panthenol (Johnson 1987). One study conducted in mice with 100% panthenol reported a LD₅₀ of 15 g/kg b.w.; the other studies did not report significant acute oral toxicity (Johnson 1987). Additionally, no toxicological effects were associated with chronic dermal administration of 2 mg/day of panthenol in rats (Johnson 1987).

Dermal Hazard:

Dermal toxicity was determined in a number of studies in rabbits and rats (Johnson 1987). Two studies conducted in rabbits with a cream containing 0.5% panthenol reported slight to moderate erythema and edema after 90 days of treatment (Johnson 1987). In a study using a cream containing 0.2% panthenol, rats were treated with doses of 227, 420, and 680 mg/kg for 13 weeks (Johnson 1987). Minimal hyperkeratosis of skin was reported in all treatment groups (Johnson 1987). Multiple clinical studies to assess skin irritation were performed using products containing panthenol at concentrations that ranged from 0.1 to 0.5% (Johnson 1987). In one study, 10 female subjects that tested a lotion containing 0.5% panthenol, it was concluded that the lotion was a mild irritant (Johnson 1987). Other studies that tested products containing up to 0.5% panthenol did not report signs of irritation (Johnson 1987).

Sensitization:

Skin sensitization clinical studies conducted with products that contained panthenol concentrations ranging from 0.1 to 0.5% all reported that panthenol had no potential for allergic sensitization (Johnson 1987). Although clinical studies did not report signs of irritation and sensitization, a few cases of allergic contact dermatitis resulting from the use of cosmetic products containing 0.5% to 75% panthenol have been reported in the literature (Stables and Wilkinson 1998; Roberts, Williams et al. 2006; Chin, Hughes et al. 2013).

Association with Hair Loss:

There was no information available on the association between panthenol and hair loss.

Agency Data:

In a report issued in 1987, the CIR stated that panthenol is “safe as presently used in cosmetics” (Johnson 1987). The safety of panthenol in cosmetics was also reviewed in 2006 and the CIR decided against

reopening the safety assessment (CHLORIDE and CHLORIDE 2006). In addition, panthenol is generally recognized as safe (GRAS) by the FDA when used as a dietary supplement (Johnson 1987).

- PCA

Overview:

PCA, also known as pyroglutamic acid, is an internal amide of L-glutamic acid found naturally in vegetables, fruits, grasses, molasses, and mammalian tissue (Fiume 2014). It acts as a skin conditioning agent and humectant in cosmetic formulations (Fiume 2014). According to the CIR report published in 2014, PCA was used in over 100 cosmetic formulations at concentrations between 0.000012 to 1.9% (Fiume 2014).

Toxicology:

No adverse effects were observed in either a short-term study of rats fed 1.5% PCA or in subchronic studies with rats fed diets containing up to 8% PCA (Fiume 2014). Similarly, no observed effects were observed after oral administration to mice (Fiume 2014).

Dermal Hazard:

It was reported that the amount of exogenously applied PCA absorbed through the skin was on the order of 1% of the applied dose, but that up to 5% of the applied dose was distributed between the dermis and epidermis (Fiume 2014). According to CIR, there was concern that the PCA absorbed between the dermis and epidermis would eventually move across the skin and result in a cumulative penetration that could be significant; however, this concern was reportedly mitigated by the low actual penetration through the skin over a 24-hour period and the recognition that PCA is naturally resident in the skin (Fiume 2014).

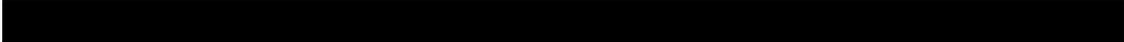
Sensitization:

There was no information available on the sensitization of PCA.

Association with Hair Loss:

There was no information available on the association between PCA and hair loss.

Agency Data:



The CIR Panel concluded in 1999 that PCA was safe to use in cosmetics so long as it was not used in products that contain nitrosating agents (Fiume 2014).

- PEG-60 Almond Glycerides

Overview:

PEG-60 almond glycerides is a polyethylene glycol derivative of the mono- and diglycerides from almond oil with an average of 60 moles of ethylene oxide (Fiume 2015). The predominant fatty acids found in almond oil are oleic and linoleic acid (Fiume 2015). It is used in cosmetics as an emollient skin conditioning agent and surfactant-emulsifying agent (Fiume 2015). PEG-60 almond glycerides are reportedly used in over 160 products, including both leave-on and rinse off products, at maximum concentrations that range from 0.0001 to 6.5% (Fiume 2015).

Toxicology:

Limited information was available regarding the potential toxicity of PEG-60 almond glycerides.

Dermal Hazard:

Limited information was available regarding the effects of dermal exposure to PEG-60 almond glycerides. Undiluted PEG-60 almond glyceride was reported to be irritating in a primary rabbit skin irritation study (Fiume 2015). Human clinical studies reported that PEG-60 almond glyceride concentrations up to 20% was not an irritant (Fiume 2015).

Sensitization:

Human clinical studies reported that PEG-60 almond glyceride concentrations up to 20% was not a sensitizer (Fiume 2015).

Association with Hair Loss:

There was no information available on the association between PEG-60 almond glyceride and hair loss.

Agency Data:

The CIR concluded that PEG-60 almond glycerides were considered “safe in cosmetics in the present practices of use and concentration” (Fiume 2015).

- Phenoxyethanol

Overview:

Phenoxyethanol is a naturally occurring colorless liquid with a mildly rosy and metallic odor (Nakanishi, Wilson et al. 1969; Scognamiglio, Jones et al. 2012). It is used as a fragrance, cooling lubricator, and antibacterial/antifungal preservative in a wide array of cosmetic, pharmaceutical, household, and agricultural products (Schmuck, Steffens et al. 2000; Geier, Jordan et al. 2010; Scognamiglio, Jones et al. 2012). Specific concentrations of phenoxyethanol used in cosmetic products were not available.

Toxicology:

In a 1955 study, researchers reported a “low toxicity of phenoxyethanol in children” when exposed to up to 0.15 g/kg bw of phenoxyethanol (Lowe and Southern 1994). No other adverse effects were reported; however, details regarding the findings in this study were not available (Lowe and Southern 1994). The oral LD₅₀ of phenoxyethanol in rats was reported to be 1.26 to 2.58 g/kg bw in a recent fragrance material review (Scognamiglio, Jones et al. 2012). Autopsy findings included lung hemorrhage, opacity of the stomach and intestines, and congestion of the liver (Scognamiglio, Jones et al. 2012). Additionally, Breslin et al. (1991) reported that hemolytic effects were observed at oral doses of 800 mg/kg bw in rabbits (Breslin, Phillips et al. 1991).

Dermal Hazard:

Roper et al. (1997) studied the absorption of phenoxyethanol on rat and human skin in a series of *in vitro* experiments (Roper, Howes et al. 1997). The authors reported that approximately 60% of the phenoxyethanol applied to rat and human skin was absorbed after 24 hours (Roper, Howes et al. 1997). Dermal toxicity assayed in animal studies using rabbits found that the dermal LD₅₀ was between 3.10 g/kg bw and greater than 5 g/kg bw (Scognamiglio, Jones et al. 2012). A number of clinical human studies reported that no irritation was observed when individuals were exposed to phenoxyethanol at concentrations up to 15% (Scognamiglio, Jones et al. 2012). Findings from animal studies were in general agreement with the aforementioned clinical studies, where no adverse observations were made in rabbits tested with 15% phenoxyethanol; however, slight to moderate erythema was observed in animals who were administered 100% phenoxyethanol (Scognamiglio, Jones et al. 2012).

Sensitization:

[REDACTED]

A number of clinical human studies reported that no sensitization was observed when individuals were exposed to phenoxyethanol at concentrations up to 15% (Scognamiglio, Jones et al. 2012). A study conducted in guinea pigs reported that phenoxyethanol had “no sensitizing potency” at a concentration of 10% ; the authors concluded that the irritancy threshold for phenoxyethanol was more than 10% (Hausen 1993).

Association with Hair Loss:

There was no information available on the association between phenoxyethanol and hair loss.

Agency Data:

In a report issued in 2011, the CIR confirmed the results of a safety assessment conducted in 1990 on phenoxyethanol, that the substance is “safe in the present practices of use and concentration” for cosmetic purposes (Andersen 2011). In addition, a recent fragrance material review reported that phenoxyethanol was generally recognized as safe (GRAS) as a flavor ingredient (Scognamiglio, Jones et al. 2012).

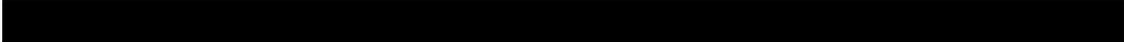
- Polysorbate 20

Overview:

Polysorbates are fatty esters of polyoxyethylated sorbitan, or sorbitol (Becker 2015). Polysorbate 20 is a mixture of laurate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 20 moles of ethylene oxide (Becker 2015). Polysorbate 20, also commonly known as Tween 20, is a yellow oily liquid at 25°C that is used as a fragrance ingredient, surfactant-emulsifying agent, and surfactant-solubilizing agent in personal care products, such as bath soaps and spray deodorants (Rowe, Sheskey et al. 2009; Becker 2015). The reported number of uses of polysorbate 20 increased from 770 in 1998 to 3013 in 2015; it was used in various cosmetic products at concentrations between 0.0000 and 19.6% (Becker 2015). In a 2014 survey, the highest concentration of polysorbate 20 in bath soaps and detergents was 19.6% (a decrease from >50% in 1984).

Toxicology:

The oral NOAELs for polysorbate 20 were reported to be 250 and 500 mg/kg/day for one month and 90 days in rats, respectively, and 10 mg/kg/day for one month in mice (Becker 2015). According to a 22-month feeding study, the NOAEL for polysorbate 20 was 14285.71 mg/kg/day (10% in feed) in mice (Becker 2015). There were no adverse effects or mortalities reported when the same strain of mice were orally administered 1600 mg/kg/d polysorbate 20 in saline for 28 days and after 28 days of a high-fat diet



(Becker 2015). The oral LD₅₀ for hamsters and rats were 18 g/kg and 37 g/kg, respectively (Rowe, Sheskey et al. 2009).

Dermal Hazard:

Dermal toxicity information for polysorbate 20 was not available. Rowe et al. (2009) reported that it was a human skin irritant and is moderately toxic by ingestion; however, information regarding these classifications was not provided (Rowe, Sheskey et al. 2009).

Sensitization:

There was no information available on the sensitization of polysorbate 20.

Association with Hair Loss:

There was no information available on the association between polysorbate 20 and hair loss.

Agency Data:

In 2015, the CIR concluded that polysorbate 20 was safe to use in cosmetics when they are formulated to be non-irritating (Becker 2015). However, the CIR noted that caution must be taken when formulating cosmetic products, especially those intended to be used for infants, which contain polysorbate 20 in combination with other ingredients, since polysorbate 20 may enhance dermal absorption of substances whose dermal safety is not known (Becker 2015).

- Polysorbate 60

Overview:

Polysorbate 60, also known as sorbitan monostearate, ethoxylated, is used in cosmetic and personal care products as a fragrance ingredient, surfactant-emulsifying agent, and surfactant solubilizing agent (Becker 2015). It is a mixture of stearate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 20 moles of ethylene oxide (Becker 2015). It is an oily liquid, yellow/orange in color, and soluble in water (Becker 2015). It was reportedly used in over 1500 products in 2014, primarily in leave-on products, at maximum concentration ranging from 0.0000001 to 6% (Becker 2015).

Toxicology:

[REDACTED]

There was no data available on the systemic toxicity of polysorbate 60. No systemic toxicity was observed at low or moderate doses in several acute and repeated-dose oral exposure studies with polysorbate 20 and polysorbate 80 (Becker 2015). According to ECHA's REACH, a derived no effect level (DNEL) of 51.02 mg/kg bw/day was determined for systemic effects following dermal exposure (ECHA 2016).

Dermal Hazard:

No mortality or clinical signs of intoxication were observed in rats for 14 days following a single dermal treatment with 2000 mg/kg polysorbate 60 for 24 hours (ECHA 2016). In a 30 day skin painting study in rabbits, 5% polysorbate 60 produced moderate skin irritation and 10% polysorbate 60 caused skin necrosis (Becker 2015). However, in a 60 day skin painting study in rabbits, 15% polysorbate 60 did not cause any dermal effects and only mild irritation was observed at 100% Polysorbate 60 (Becker 2015). Local inflammation was also observed at 100% polysorbate 60 in a long-term study of unspecified duration in mice (Becker 2015). In a human patch test, 1% polysorbate 60 was not found to be irritating (Becker 2015). Polysorbate 60 (100%) and a cream containing an unspecified amount of polysorbate 60 caused urticaria when applied to the forehead, but no effects were observed when applied to dorsal and arm skin (Becker 2015).

Sensitization:

There was no information available on the sensitization of polysorbate 60.

Association with Hair Loss:

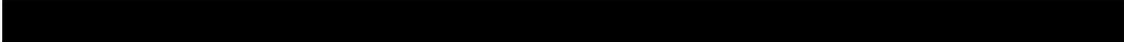
There was no information available on the association between polysorbate 60 and hair loss.

Agency Data:

The US FDA has approved the use of polysorbate 60 as a diluent in color additives for drug use, in all food types as synthetic flavoring, as a multipurpose additive, as a defoaming agent in food for human consumption, and as an indirect addition to all food types as components of adhesives, emulsifiers and/or surfactants (Becker 2015). The Cosmetic Ingredient Review Expert (CIR) Panel concluded that polysorbate 60 was "safe in cosmetics when formulated to be nonirritating" (Becker 2015).

- Sodium Lactate

Overview:



Sodium lactate, the sodium salt of lactic acid, is a colorless or yellowish, odorless syrupy liquid (Andersen 1998). Sodium lactate functions as a buffering agent, skin-conditioning agent, and humectant in a large variety of consumer products including bubble baths, hair conditioners, permanent waves, hair rinses, shampoos, hair grooming aids, cosmetic foundations, deodorants, aftershave lotion, moisturizers, facial cleansers and creams, and suntan products (Andersen 1998). It was reported to the FDA in 1997 that there were 93 cosmetic formulations which used sodium lactate (Andersen 1998).

Toxicology:

The acute oral toxicity of a variety of cosmetic formulations containing 60% aqueous sodium lactate were evaluated in five fasted female rats (Andersen 1998). The rats were dosed at either 5,000 mg/kg or 15,000 mg/kg and no deaths were observed in the study (Andersen 1998). The authors concluded that the formulations containing sodium lactate were either “acceptable” or “prac[tically] nontoxic” (Andersen 1998). Regarding dermal toxicity, a number of animal studies were conducted in rabbits with sodium lactate doses up to 2000 mg/kg (Andersen 1998). The report noted that treated animals experienced slight erythema, slight scaling, desquamation, and drying of the skin; however, no test-related deaths or other adverse effects were reported (Andersen 1998).

Dermal Hazard:

Sodium lactate was evaluated for primary cutaneous irritation potential using occlusive patches at concentrations from 50 to 70% among rabbits; both solutions were found to be nonirritating (Andersen 1998). In addition, two studies evaluated the irritation potential of sodium lactate by immersing guinea pigs in test solutions containing 0.20 and 0.25% of 60% aqueous sodium lactate with a pH of 5.50 and 5.60 for four hours per day for three days (Andersen 1998). The animals were evaluated two days after the last day of immersion; the results were reported to be “practically nonirritating” for both test concentrations (Andersen 1998).

Sensitization:

There was no information available on the sensitization of sodium lactate.

Association with Hair Loss:

There was no information available on the association between sodium lactate and hair loss.

Agency Data:

According to the CIR report published in 1998, sodium lactate is “safe for use in cosmetic products at concentrations $\leq 10\%$ ” (Andersen 1998). In addition, sodium lactate was reported to be safe for use as a food additive and is generally recognized as safe for use beyond infancy (Andersen 1998).

- Sodium PCA

Overview:

Sodium PCA is a salt of PCA; PCA is more commonly known as pyroglutamic acid and is an internal amide of L-glutamic acid found naturally in vegetables, fruits, grasses, molasses, and mammalian tissue [see section on PCA] (Fiume 2014). Sodium PCA is reported to function as a skin conditioning agent and humectant in cosmetic formulations (Fiume 2014). According to a 2014 CIR report, sodium PCA had the greatest reported uses as well as the highest concentration of use amongst PCA derivatives (Fiume 2014). Specifically, sodium PCA was used in over 1200 cosmetic formulations at concentrations from 0.00005 to 3% (Fiume 2014).

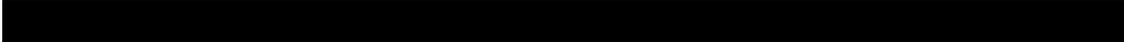
Toxicology:

The oral LD₅₀ of sodium PCA was reported to be 10.4 g/kg for male mice and >2.0 g/kg for rats (Fiume 2014). According to the CIR report, the percutaneous absorption of 5, 10, and 20% sodium PCA through fresh human cadaver skin in a 24 hour period was 5.97, 6.78, and 5.89%, respectively (Fiume 2014). In a dermal toxicity study, 2 g/kg of undiluted sodium PCA was applied to the backs of ten total male and female rats over 24 hours; there were no reported mortalities and the study reported an LD₅₀ of >2 g/kg (Fiume 2014).

Dermal Hazard:

In a reconstructed human epidermis model test, sodium PCA was reportedly non-irritating (Fiume 2014). Further, it was considered non-irritating when applied to the skin of guinea pigs and rabbits at concentrations up to 50% (Fiume 2014). In a human clinical study of dermal irritation using open patch test methods, two of 13 volunteers had reactions to 6.25% sodium PCA applied to their backs and three volunteers developed erythema when concentrations of 12.5% sodium PCA and greater were applied (Fiume 2014). These reactions reportedly dissipated within 30 minutes and no reaction was observed when sodium PCA was applied to the skin of the forehead, cheek, or neck (Fiume 2014). Four other studies of irritation in humans were negative for sodium PCA (Fiume 2014).

Sensitization:



Sodium PCA was not considered a sensitizer in guinea pigs (Fiume 2014). A separate clinical study with 39 subjects indicated that sodium PCA up to 32% in an aqueous solution was not a sensitizer (Fiume 2014).

Association with Hair Loss:

There was no information available on the association between sodium PCA and hair loss.

Agency Data:

The CIR Panel concluded in 1999 that it was safe to use in cosmetics so long as they are not used along with nitrosating agents (Fiume 2014).

- Soluble Collagen

Overview:

Collagen is a naturally occurring substance found ubiquitously in the tissue of humans and animals (Friess 1998). It is the main structural protein in vertebrates and accounts for approximately 30% of all body proteins; over 90% of extracellular protein in the tendon and bone and over 50% of the proteins in skin is comprised of collagen (Friess 1998). It can be derived from many sources including bovine, porcine, sheep, human placenta, and marine sources (Friess 1998). Collagen is used extensively in the medical field to stimulate cellular repair in response to dermatological damage, as well as a biomaterial for the purposes of grafting and drug delivery (Friess 1998). It is also used in cosmetic products for the reported purposes of revitalizing or rejuvenating the skin (Kludas and Borchert 1976). Specifically, it is claimed that soluble collagen in cosmetic products can improve skin's resilience and elasticity while reducing the effects of aging associated with loss of soluble collagen from the skin (Kludas and Borchert 1976). The concentration of soluble collagen in cosmetic cream products was reported to range from 3 to 20% (Kludas and Borchert 1976). Soluble collagen was "considered safe" for use as a biomaterial; however, specific safe levels were not reported (Friess 1998).

Toxicology:

In a 1997 review by Friess, it was noted that collagen shows "excellent biocompatibility due to low toxicity and poor immunogenic reactions" (Friess 1998). It was noted that these characteristics may be due to the similarity in the amino acid sequence between species and low aromatic amino acid content (Friess 1998). However, Gomes et al. (1991) presented a study where collagen injection proved lethal to



rabbits (Gomes, Thomson et al. 1991). Different preparations of soluble collagen obtained from rabbit, rat, and guinea-pig skin, and rat tail tendon were intravenously infused in rabbits the lethal dose of 2 mg/kg; the exposure produced respiratory distress, agitation, convulsions, and death (Gomes, Thomson et al. 1991). Furthermore, increased liver enzymes in the plasma were suggestive of hepatic damage (Gomes, Thomson et al. 1991). Histopathological examination indicated damage to the lungs and livers of exposed rabbits occurred; the heart was observed to be unchanged (Gomes, Thomson et al. 1991).

Given that soluble collagen is a naturally occurring and necessary component in the skin of vertebrates, toxicity and adverse effects on the skin are not expected.

Dermal Hazard:

Due to the large size of collagen molecules, dermal absorption is expected to be minimal from its use in cosmetic products. There was no information available on the dermal hazard of collagen.

Sensitization:

There was no information available on the sensitization of collagen.

Association with Hair Loss:

There was no information available on the association between collagen and hair loss.

Agency Data:

There was no agency data information available for collagen.

- Stearamidopropyl Dimethylamine

Overview:

Stearamidopropyl dimethylamine is physically characterized as a waxy flake (Belsito, Hill et al. 2014). Formulations of stearamidopropyl dimethylamine may contain DMAPA as an impurity from the manufacturing process (Belsito, Hill et al. 2014). DMAPA was reported to have sensitizing potential (Belsito, Hill et al. 2014). Stearamidopropyl dimethylamine reportedly functions as an antistatic agent and hair conditioning agent in cosmetics (Belsito, Hill et al. 2014). According to the FDA's VCRP, it was registered for use in over 400 cosmetic and personal care products; the majority of the products were rinse-off formulations such as hair conditioners (Belsito, Hill et al. 2014). The maximum concentrations

[REDACTED]

of stearamidopropyl dimethylamine reported in personal care products ranged from 0.01% to 5% (Belsito, Hill et al. 2014).

Toxicology:

Limited information regarding the potential systemic toxicity of stearamidopropyl dimethylamine was available. A 14 day dose range finding study conducted in rats tested stearamidopropyl dimethylamine at doses up to 500 mg/kg bw/day (Belsito, Hill et al. 2014). Animals treated with 500 mg/kg bw/day of stearamidopropyl dimethylamine demonstrated fore stomach ulceration, hyperplasia of the fore stomach and intestinal epithelium, thymic atrophy, and adverse effect on the male reproductive system (Belsito, Hill et al. 2014). However, no abnormalities or histopathological changes were observed in animals treated with 50 and 200 mg/kg bw/day of stearamidopropyl dimethylamine (Belsito, Hill et al. 2014).

Dermal Hazard:

The dermal absorption rate of stearamidopropyl dimethylamine was estimated to be 0.04 mg and 0.12 mg after 8 and 12 hours, based on an instantaneous deposition dose of 9,257 mg on a skin area of 2000 cm² (Belsito, Hill et al. 2014). The maximum dermal absorption rate was estimated to be 2.40 x 10⁻⁶ mg/cm²/h (Belsito, Hill et al. 2014). A dermal 90-day repeated dose study of stearamidopropyl dimethylamine doses of 0, 0.25 or 10% w/v (equivalent to 0, 5 and 200 mg/kg/day, respectively) in an ethanol/water vehicle (30/70) was performed in rabbits (Belsito, Hill et al. 2014). The animals were dosed once per day, five days per week for 13 consecutive weeks (Belsito, Hill et al. 2014). The authors concluded that the NOAEL was greater than 10% (200 mg/kg bw/day) (Belsito, Hill et al. 2014). Stearamidopropyl dimethylamine tested at 100% concentration was reported to be not irritating in non-human studies (Belsito, Hill et al. 2014). Contact sensitization was generally not reported with hair conditioners containing up to 2% stearamidopropyl dimethylamine (Belsito, Hill et al. 2014). Three other studies tested 0.6% stearamidopropyl dimethylamine in a hair conditioner reported irritation (Belsito, Hill et al. 2014). It was unclear whether stearamidopropyl dimethylamine or other ingredients were responsible for this finding.

Sensitization:

Contact sensitization was generally not reported with hair conditioners containing up to 2% stearamidopropyl dimethylamine (Belsito, Hill et al. 2014).

Association with Hair Loss:

[REDACTED]

There was no information available on the association between stearamidopropyl dimethylamine and hair loss.

Agency Data:

The CIR concluded that stearamidopropyl dimethylamine was considered “safe in cosmetics when they are formulated to be non-sensitizing” or containing potential impurities, such as DMAPA, that have sensitizing potential (Belsito, Hill et al. 2014).

- Tetrasodium EDTA

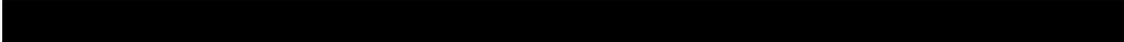
Overview:

Ethylenediaminetetraacetic acid tetrasodium salt (EDTA) is one of many EDTA salts that are commercially available (EPA 2004). EDTA is a white powder that is primarily used as a chelating agent, where it binds and sequesters metals such as lead, mercury, cadmium, and aluminum with high affinity (EPA 2004). EDTA is an approved direct food additive and has also been widely used in pesticides, soaps, liquid products, pharmaceuticals, and cosmetics (Wolf and Gilbert 1992; Whittaker, Vanderveen et al. 1993; Friess 1998; Lanigan and Yamarik 2002; EPA 2004). The permissible levels of EDTA in food was reported to range from 25 to 800 ppm (Whittaker, Vanderveen et al. 1993; EPA 2004). According to a CIR report issued in 2002, EDTA has been used in over 4000 cosmetic products including bath soaps, detergents, deodorants, makeup, lotion, creams, and hair products (Lanigan and Yamarik 2002; EPA 2004). Specifically, tetrasodium EDTA-containing cosmetic formulations had concentrations of EDTA that ranged from 0.004% to 1.3% (Lanigan and Yamarik 2002).

Toxicology:

Limited toxicological information was available for EDTA due to its low toxicity profile. It was reported that the binding of divalent and trivalent cations by EDTA leads to mineral deficiencies, which “seem to be responsible for all known pharmacological effects” to EDTA (EPA 2004). An early chronic toxicity study on calcium disodium EDTA ingestion performed in rats reported that no effects were observed at EDTA doses up to 250 mg/kg/day (Wolf and Gilbert 1992; Whittaker, Vanderveen et al. 1993). This and other studies provided the basis for the Joint FAO/WHO Expert Committee on Food Additives to establish an acceptable daily oral intake of 0 to 2.5 mg/kg in humans (Wolf and Gilbert 1992; EPA 2004). An oral toxicity study performed in rat specified a LD₅₀ of 2400 mg/kg for tetrasodium EDTA (Wolf and Gilbert 1992).

Dermal Hazard:



It was reported that “[a]bsorption [of EDTA and its salts] through the skin [was] essentially zero” (Wolf and Gilbert 1992; Lanigan and Yamarik 2002; EPA 2004). Evaluation of skin irritation studies yielded mixed results. EDTA was classified as a “mild skin irritant” in an EPA report; however, other studies have classified it as a “nonirritant” (Lanigan and Yamarik 2002; EPA 2004). The concentrations of EDTA tested for irritation were not reported. Very few cases of contact allergy to EDTA has been reported in the literature; only one recent case report of a 75 year old man who tested positive to 0.2% EDTA in an aqueous solution was found (Sánchez-Pedreño, García-Bravo et al. 2009).

Sensitization:

Whittaker et al. (1993) reported EDTA to be a “weak sensitizing compound” and Lanigan et al. (2002) reported that “EDTA did not cause sensitization” (Whittaker, Vanderveen et al. 1993; Lanigan and Yamarik 2002). The concentrations of EDTA tested for sensitization were not reported.

Association with Hair Loss:

There was no information available on the association between EDTA and hair loss.

Agency Data:

The CIR concluded that tetrasodium EDTA was “safe as used in cosmetics formulations” (Lanigan and Yamarik 2002). Furthermore, due to the lack of mutagenic effects and positive histopathological findings, EDTA was not considered to be carcinogenic or genotoxic (Whittaker, Vanderveen et al. 1993; Lanigan and Yamarik 2002; EPA 2004).

- Tocopherol (Vitamin E)

Overview:

Tocopherol, together with tocotrienol, represents a major component of vitamin E (Fiume and Heldreth 2014). There are four structural analogs of tocopherol (alpha, beta, gamma, and delta) which differ by the presence and location of methyl groups around the compound’s aromatic ring (Fiume and Heldreth 2014). Alpha-tocopherol is the predominate form of vitamin E in both human and animal tissues; it is present in biological membranes where it serves an important role in protecting skin and other organs due to its lipophilic antioxidant properties (Nada, Zaghloul et al. 2014). Tocopherols are reportedly found naturally in plant materials, vegetable oils and fats, dairy products, meats, eggs, cereals, and nuts (Fiume and Heldreth 2014). Tocopherol can be isolated on a commercial scale from vegetable oils and can be

produced synthetically from the condensing reaction of isophytol with tri-, di-, or monomethylhydroquinone (Fiume and Heldreth 2014).

Tocopherols are reported in both cosmetic and non-cosmetic uses, the latter of which includes in foods as a nutrient supplement or preservative (Fiume and Heldreth 2014). Tocopherols are used extensively as an antioxidant and skin conditioning agent in cosmetics products including lotions, oils, creams, powders, make-up and hair- or deodorant spray products (Fiume and Heldreth 2014). According to the FDA's VCRP, the maximum concentration of tocopherol in leave-on and rinse-off cosmetic products reported in 2013 was 5.4% and 3%, respectively (Fiume and Heldreth 2014).

Toxicology:

Tocopherol, or vitamin E, is considered to have very low acute oral toxicity (Food 2003). The LD₅₀ for alpha-tocopherol is reported as greater than 2,000 mg/kg bw in mice, rats, and rabbits (Food 2003). The CIR reported that the oral LD₅₀ for tocopherol was greater than 4 g/kg bw in rats and greater than 25 mg/kg bw in mice (Fiume and Heldreth 2014).

Dermal Hazard:

In a dermal absorption study conducted in humans, tocopherol acetate was “substantially” absorbed into the skin, but neither systemic availability nor conversion to tocopherol was observed (Fiume and Heldreth 2014). In a study performed in rats, approximately 6% of the applied tocopherol dose penetrated into the epidermis after five days of observation (Fiume and Heldreth 2014). Furthermore, the dermal application of 5 mg/cm² of alpha-tocopherol to the backs of hairless female mice for 24 hours resulted in a 62-fold increase of alpha-tocopherol in the epidermis and a 22-fold increase of the substance in the dermis (Fiume and Heldreth 2014). The CIR reported that dermal LD₅₀ in rats to be > 3 g/kg bw for tocopheryl acetate and > 1,130 mg/kg bw for mixed tocopheryl phosphates in rabbits following acute dosing for 24 h (Fiume and Heldreth 2014). Slight erythema was observed in rats, while well-defined erythema and slight to moderate edema was reported in rabbits (Fiume and Heldreth 2014). It was reported that topically, vitamin E has been associated with contact dermatitis, inflammatory reactions, and eczematous lesions (2012)

Sensitization:

Tocopherol is not considered to be a skin irritant nor sensitizer in human clinical studies (Fiume and Heldreth 2014). Patch-testing was performed with tocopherol, at an unspecified concentration, in 1,136 patients in 1987 and 1997 (Fiume and Heldreth 2014). Six patients or 0.53% had a positive reaction to the patch-test; a similar incidence rate was reported in a total of 1,814 patients tested between 1998 and 2007 (Fiume and Heldreth 2014). Alpha-tocopherol was applied for patch-tested using Finn chambers for

48 hours by the North American Contact Dermatitis Group from 1994 to 2006 (Fiume and Heldreth 2014). The frequency of positive patch-tests varied over time from 0.5% to 1.1% (Fiume and Heldreth 2014). Skin sensitization of tocopheryl acetate was tested in a study where tocopheryl acetate was applied undiluted in 10 applications over a two-week induction period (Fiume and Heldreth 2014). Following two weeks of no treatment, the individuals were challenged with administration of a test substance once daily for three days and no positive reactions were reported (Fiume and Heldreth 2014).

Association with Hair Loss:

There was no information available on the association between tocopherol and hair loss.

Agency Data:

The CIR concluded that tocopherol and related compounds “are safe in the present practices of use and concentration in cosmetics” (Fiume and Heldreth 2014).

- Vanilla Planifolia Fruit Extract

Overview:

Natural vanilla is extracted from the fruits of *Vanilla planifolia* (Dignum, van der Heijden et al. 2004). The bean or pod from the *Vanilla planifolia* plant, a member of the orchid family, is picked while still green and then undergoes a drying and curing process; it is during this process that the aroma and flavor of the vanilla develops (Galetto and Hoffman 1978). The cured beans then undergo an aqueous-alcohol extraction to result in a vanilla extract product (Galetto and Hoffman 1978). Vanillin (4-hydroxy-3-methoxy-benzaldehyde) is the major constituent of the extract and recognized as the major flavor and odor component (Galetto and Hoffman 1978; Khan and Abourashed 2011). Vanilla extract is widely used as a flavoring agent in food, beverages, and pharmaceuticals. In cosmetics, such as perfumes, vanilla is used primarily as a fragrance ingredient (Khan and Abourashed 2011).

Toxicology:

No information was available regarding the potential toxicity or absorption of *Vanilla planifolia* fruit extract.

Dermal Hazard:

An acute dermal toxicity study performed in rats administered 2,000 mg/kg bw of vanillin on shaved skin for 24 hours via semi-occlusive patch (SIDS 1996). No mortality or pathological lesions were observed up to 14 days post treatment (SIDS 1996). Another study administered vanillin to rabbits as a 40%

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solution in corn oil for 24 hours at doses of 3,160, 5,010, and 7,940 mg/kg bw (SIDS 1996). No mortality was reported after 14 days at the low- and mid-dose, while the rabbit receiving the 7,940 mg/kg bw died three days after administration. An LD₅₀ of greater than 5,010 mg/kg bw was derived from this study (SIDS 1996). Topically, vanilla has been associated with allergic responses, including contact dermatitis, at unspecified concentrations (2012). It has been reported that acute contact dermatitis is associated with use of natural vanilla and vanilla extracts at unspecified concentrations (Benezra, Ducombs et al. 1985).

Sensitization:

No information was available regarding *Vanilla planifolia* fruit extract and skin irritation. Two skin irritation studies conducted with vanillin in animals reported negative results (SIDS 1996). In humans, closed-patch tests of vanillin at doses of 20% or 2% in normal subjects, and 0.4% in subjects with dermatitis showed no primary irritation (Opdyke 1977; SIDS 1996). Similarly, no information was available regarding skin sensitization and *Vanilla planifolia* fruit extract. Skin sensitization studies performed with vanillin in animals have reported conflicting results: of 10 identified studies, 5 reported positive results indicating that vanillin may have allergenic potential (SIDS 1996). Negative data from human studies suggest that vanillin is not a human allergen (SIDS 1996). For example, patch testing was performed in workers at a vanillin factory (Wang, Xue et al. 1987). Vanillin was applied undiluted and removed after 48 hours. No skin irritation or sensitization was reported in both groups of workers (Wang, Xue et al. 1987). In a maximization test, where the skin was permeabilized using application of sodium lauryl sulphate for 24 hours prior to a 48 hour repeated application of 2% vanillin, no sensitization reactions were reported (Opdyke 1977).

Agency Data:

There was no agency data information available for *Vanilla planifolia* fruit extract.

- Vanillin

Overview:

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is a naturally occurring chemical found in vanilla pods and several essential oils (SIDS 1996). Vanillin is principally produced from the chemical precursor guaiacol or from lignin, a by-product of the wood pulp industry (SIDS 1996). It is widely used for its characteristic pleasant smell and taste of vanilla (SIDS 1996). Vanillin is mainly used as food and beverage additive (SIDS 1996). It is also added as an odor agent in cosmetics, including perfumes and creams or lotions (SIDS 1996). Normal concentrations as an ingredient in perfumes is 0.2% with a

maximum of 0.8%, while significantly less is found in creams and lotions, 0.005% normal and 0.03% maximum (SIDS 1996).

Toxicology:

Several acute and repeat-dose toxicity studies for vanillin have been conducted in several animal species (SIDS 1996). In a one year study in which vanillin administered in the diet of rats, a NOAEL was derived of 2,500 mg/kg bw/day was determined; this was the highest administered dose and no toxicity was reported (Hagan, Hansen et al. 1967; SIDS 1996).

Dermal Hazard:

An acute dermal toxicity study performed in rats administered 2,000 mg/kg bw of vanillin on shaved skin for 24 hours via semi-occlusive patch (SIDS 1996). No mortality or pathological lesions were observed up to 14 days post treatment (SIDS 1996). Another study administered vanillin to rabbits as a 40% solution in corn oil for 24 hours at doses of 3,160 mg/kg bw, 5,010 mg/kg bw, and 7,940 mg/kg bw (SIDS 1996). No mortality was reported after 14 days at the low- and mid-dose, while the rabbit receiving the 7,940 mg/kg bw died three days after administration (SIDS 1996). An LD₅₀ of greater than 5,010 mg/kg bw was derived from this study (SIDS 1996).

Sensitization:

Skin irritation studies evaluating vanillin conducted in rabbits and guinea pigs reported negative results (SIDS 1996). In humans, patch tests of vanillin at doses ranging between 2% and 20% in normal subjects, and 0.4% in subjects with dermatitis showed no primary irritation (Opdyke 1977; SIDS 1996). Skin sensitization studies performed with vanillin in animals have reported conflicting results: of 10 identified studies, 5 reported positive results indicating that vanillin may have allergenic potential (SIDS 1996). However, negative data from human studies suggest that vanillin is not a human allergen (SIDS 1996). Vanillin was applied undiluted and removed after 48 hours and no skin irritation or sensitization was reported in both groups of workers (Wang, Xue et al. 1987). In a maximization test, where the skin was permeabilized using application of sodium lauryl sulphate for 24 hours prior to a 48 hour repeated application of 2% vanillin, no sensitization reactions were reported (Opdyke 1977; SIDS 1996).

Association with Hair Loss:

There was no information available on the association between vanillin and hair loss.

Agency Data:

Vanillin has been classified as GRAS by the FDA for such use as an additive in foods and beverages (SIDS 1996). In a review of toxicity data and potential sources of exposure for vanillin, the Organization for Economic and Co-operation and Development (OECD) stated that “no particular risk has been identified which should give reason to concern” (SIDS 1996).

4.3.4 Toxicological Hazard Assessment for Each Not Listed Identified Chemical

Several chemicals were identified during separate laboratory analyses of Sweet Almond Mint Cleansing Conditioner (detailed in a separate report). Available information regarding the identified chemical as well as potential toxicity is described below:

- D-Limonene

Due to its wide usage as a fragrance agent in cosmetics, D-limonene identified in WCD Sweet Almond Mint Cleansing Conditioner product during analytical testing, is likely a component of the listed ingredient “Fragrance (Parfum)” in the final product formulation. In fact, MSDS for two fragrance ingredients (Curve Type Functional Fragrance 148431-0297 and Rosemary Mint Fragrance 116713-0695) reportedly used in WCD products reported D-limonene as a component at levels ranging from to <0.1% to <20 to 50% .

Overview:

Limonene, a naturally occurring chemical, is a major constituent of citrus oils found in lemons, oranges, and grapefruits (Kim, Kim et al. 2013). Due to its pleasant lemon-like odor, limonene is widely used as a flavoring and fragrance agent in foods, beverages, perfumes, and cosmetics (Kim, Kim et al. 2013). In Europe, limonene must be included in the list of ingredients for a cosmetic product if the concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products; no such regulations exist in the US (Kim, Kim et al. 2013). Kim et al. (2013) calculated, assuming a concentration of 1% limonene in all cosmetics, the average exposure for an adult was 1.48 mg/kg bw/day, which was considered “marginally safe” (Kim, Kim et al. 2013). Furthermore, the authors concluded that the use of limonene in cosmetics “may be considered as safe under the current regulation on cosmetics” (Kim, Kim et al. 2013).

Toxicology:

Limonene is expected to have relatively low acute toxicity with oral LD₅₀ values greater than 4 g/kg bw reported in rats and mice (WHO 1998). An LD₅₀ value of greater than 5 g/kg bw for limonene was determined in rabbits following dermal application (Kim, Kim et al. 2013). The World Health

Organization (WHO) has concluded that limonene was of “fairly low toxicity” although some concerns exist regarding dermal irritation and allergenic potential at higher doses (WHO 1998).

Dermal Hazard:

Approximately 12% of the dose was absorbed when 5 mg/kg bw limonene was applied to shaved skin of rats using an occlusive patch (Api, Ritacco et al. 2013). In humans, however, only 0.16% of the dermal dose of 12 mg was absorbed (Api, Ritacco et al. 2013). The authors concluded that under conditions of use in cosmetic products, limonene has a low potential for dermal absorption and tissue accumulation (Api, Ritacco et al. 2013).

Limonene is considered a dermal irritant at high concentrations, although it is not allergenic (Kim, Kim et al. 2013). Application of 98% limonene dermally for two hours was reported to induce purpuric rash in one subject (Kim, Kim et al. 2013). Further, volunteers administered perfume-grade limonene via patching testing for 10 to 15 minutes produced strong skin reactions, including irritation that lasted for up to 72 hours, sensory effects, and urticarial responses (Kim, Kim et al. 2013). Skin irritation potential was reported as low to moderate in animal studies (Kim, Kim et al. 2013). Limonene induced a positive response in three of four sensitization tests conducted in guinea pigs, although it did not produce sensitization in mice; the form of purity of limonene was not specified in these tests (WHO 1998). Topically, limonene may cause contact dermatitis at unspecified concentrations (2012).

Sensitization:

Limonene is readily oxidized to limonene oxide and other hydroperoxide products upon exposure to air during handling or storage (Karlberg, Boman et al. 1991). These oxidation products have been shown to be sensitizing and more irritating than the non-oxidized parent compound in guinea pigs (Karlberg, Boman et al. 1991). In addition, while limonene was not found to be sensitizing in a maximization test in humans, approximately 1.5 to 2% of dermatitis patients and 60% of limonene-allergic patients showed positive reactions to oxidized forms of limonene (Matura, Goossens et al. 2003; Kim, Kim et al. 2013). As a result, limonene has been classified as a category 1 skin sensitizer in Europe, and restricted concentrations of peroxide to less than 20 mmol/L (EFSA 2012; Kim, Kim et al. 2013).

Association with Hair Loss:

There was no information available on the association between limonene and hair loss.

Agency Data:

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the skin which was either unoccluded or occluded with a teflon cap (Mint, Hotchkiss et al. 1994). It was reported that approximately 35.9% and 38.4% of the applied dose was absorbed after 72 hours in the occluded and unoccluded treatment respectively (Mint, Hotchkiss et al. 1994). Interestingly, the absorption of the DEP through human skin was reported to be significantly less reaching 3.9% of the applied dose over 72 hours when occluded and 4.8% when unoccluded (Mint, Hotchkiss et al. 1994).

Slight to moderate irritation was reported when rabbit, rat, or guinea pig skin was treated with undiluted DEP (Api 2001). In a 24-hour and 21-day open epicutaneous test on guinea pigs, the application of undiluted DEP reportedly caused irritation effects (Api 2001). The application of undiluted DEP on intact and abraded skin of albino rabbits in a closed patch test caused “slight to moderate” irritation at both sites at 24-hours (Api 2001). However, a 40% irritation reduction was noted at the 72-hours evaluation (Api 2001). In a 4-hour patch test in rabbits, 0.5 mL of undiluted DEP was applied on clipped or intact dorsal skin; the reactions were reviewed at 1, 24, 48, 72, and 168 hours post-patch removal and no irritant effects were observed (Api 2001). Primary dermal irritation of undiluted DEP has not been reported in humans (Api 2001). No primary irritation due to DEP was reported when 45 adult human subjects participated in a closed patch test using 0.5 ml of undiluted DEP (Api 2001). Api 2001 reported that a database maintained by the Research Institute for Fragrance Materials (RIFM) contained over 500 reports of human volunteers exposed to undiluted DEP with no reported adverse dermal reactions (Api 2001).

Sensitization:

It was reported that undiluted DEP has not been shown to be a sensitizer when tested on guinea pig skin (Api 2001). Similarly, no irritation or dermal sensitization due to DEP exposure was reported in two separate maximization tests (Api 2001). Further, little to no irritation and no dermal sensitization was reported in a sensitization potential test in healthy volunteers using undiluted or 50% DEP (Api 2001). However, it was noted that there have been positive findings in some studies and case reports involving patients with dermatitis (Api 2001).

Association with Hair Loss:

There was no information available on the association between DEP and hair loss.

Agency Data:

In the CIR 1985 expert panel report on phthalates, it was concluded that DEP was “safe for topical application in the present practices of use and concentration in cosmetics” (Brandt 1985). A re-review determined that no additional changes were needed to their prior assessment for DEP (Panel 2005). Further, a review by Api 2001 stated that “the potential for dermal exposure to DEP ... [wa]s within the levels of exposure deemed safe by other routes of exposure and is not considered to present any significant toxic liability for its current used as a solvent and vehicle in cosmetic products” (Api 2001).

- Eucalyptol

Due to its wide usage as a fragrance agent in cosmetics, eucalyptol identified in WCD Sweet Almond Mint Cleansing Conditioner during analytical testing, is likely a component of the listed ingredient “Fragrance (Parfum)” in the final product formulation. In fact, MSDS for one fragrance ingredient (Rosemary Mint Fragrance 116713-0695) reportedly used in WCD products reported eucalyptol as a component at levels of <10-20%.

Overview:

Eucalyptol, also known as 1,8-cineole, is a naturally occurring chemical found widely in plants, including those of the *Eucalyptus* species (Food 2002; Higgins, Palmer et al. 2015). Eucalyptol oil is obtained from the distillation of the leaves of such plants, with eucalyptol present in the oil at concentrations of 70 to 90% by volume (Higgins, Palmer et al. 2015). Eucalyptol has a characteristic camphor-like odor described as sweet, fresh, piney, or minty (Burdock 2016). As a result, it is commonly used as a foods flavoring agent and in the pharmaceutical industry (Caldas, Limeira et al. 2016). Maximum concentrations of eucalyptol used in cosmetic products have been reported to be 0.04% in detergents, 0.1% in creams and lotions, and 1.6% in perfumes (Food 2002). Eucalyptol has also been reported to have anti-microbial and anti-inflammatory activities and has been widely in pharmaceuticals used to treat respiratory conditions and arthritis (Xu, Hu et al. 2014).

Toxicology:

Oral LD₅₀ values for eucalyptol of greater than 1500 mg/kg bw were reported in rats (Food 2002). Furthermore, the acute oral LD₅₀ value in mice was reported as greater than 3,800 mg/kg bw (Food 2002; Xu, Hu et al. 2014). No signs of toxicity or death were reported in rats orally administered doses up to 1,000 mg/kg bw for 50 days (Caldas, Limeira et al. 2016). Several cases of acute toxicity to eucalyptol oil but not eucalyptol itself was reported in a European Scientific Committee on Food (SCF) assessment (Food 2002). Information regarding estimates of toxic dose levels of eucalyptol was not provided. More importantly, the SCF noted that the daily intake of eucalyptol from foods would be “much lower than the amount tentatively assumed to be present in the lowest lethal doses of eucalyptus oil reported” (Food 2002).

Dermal Hazard:

In a study conducted in rabbits, administration of eucalyptol to the skin at 5 g/kg bw resulted in slight to moderate skin redness and moderate edema (ECHA 2016).

The skin irritation potential of eucalyptol was evaluated in a reconstructed human epidermis model using a 15 minute treatment followed by a 42 hour incubation period according to OECD 439 guidelines (ECHA 2016). Based on the results, eucalyptol was reported to be non-irritating (ECHA 2016). Vilaplana et al. (2000) reported on a case of contact dermatitis caused by 1% eucalyptus oil in an anti-inflammatory cream (Vilaplana and Romaguera 2000). Other cases of skin irritation caused by eucalyptol

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were not found. Topically, extended exposure or large amounts of eucalyptus oil have been associated with agitation, drowsiness, slurred speech, ataxia, muscle weakness, and seizures (2012).

Sensitization:

Eucalyptol at concentrations of 25, 50, or 100% was assessed for skin sensitization using a mouse local lymph node assay (ECHA 2016). Based on an increase in cellular proliferation, measured via incorporation of radioactive thymidine, eucalyptol was considered to be a sensitizing agent at the doses tested; however, information regarding the sensitizing potential at concentrations below 25% was not available (ECHA 2016).

Association with Hair Loss:

There was no information available on the association between eucalyptol and hair loss.

Agency Data:

In a review of the safety of eucalyptus oil, Higgins et al. (2015) stated that eucalyptus oil is “generally safe” when applied topically and adhering to recommended doses and delivery routes (Higgins, Palmer et al. 2015). In addition, the FDA has approved eucalyptol as a direct food additive that is GRAS when “used in the minimum quantity required to produce [its] intended effect” and in accordance with good manufacturing practices (FDA 2017).

- Menthanol

Menthanol was not specifically listed as an ingredient in the final product formulation of WCD Sweet Almond Mint Cleansing Conditioner nor was it specifically identified as a component of any listed ingredient. However, the identification of methanol as a component of WCD Sweet Almond Mint Cleansing Conditioner during analytical testing is likely due to its similarity in chemical structure to other known ingredients, such as limonene and menthol. Thus, menthanol may represent a minor component of these ingredients or a minor reaction product in the final product formulation. Further analyses would be required to identify the nature of the menthanol in the final product formulation.

Overview:

Menthanol, also known as p-mentan-8-ol, 1-methyl-4-isopropylcyclohexane-8-ol, or dihydro terpineol, is an aromatic chemical with a pine-like odor that is used as a fragrance compound (Vigon 2015; DRT 2016). Menthanol exhibits structural similarity to a class of compounds called cyclic terpenes that are used as fragrance ingredients in cosmetics, including fragrances, shampoos, soaps, and creams (Panel, Belsito et al. 2008). In 2008, an expert panel convened by the Research Institute for Fragrance Materials

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(RIFM) conducted a safety assessment on the use of cyclic terpene alcohols used as fragrance ingredients (Panel, Belsito et al. 2008). Although menthanol was not specifically addressed, many similar compounds including varieties of menthol and terpineol, were included in this evaluation (Panel, Belsito et al. 2008). The authors concluded that cyclic terpene alcohols have a low order of toxicity and “[t]here are no safety concerns ... under the present declared levels of use and exposure” (Panel, Belsito et al. 2008). The RIFM expert panel reported that maximum dermal exposures to terpene alcohols from their use of cosmetic products ranged from “negligible” to 0.32 mg/kg bw/day for high-end users (Panel, Belsito et al. 2008).

Toxicology:

According to the SDS for menthanol, an oral LD₅₀ of greater than 5,000 mg/kg bw was reported in rats (Vigon 2015). No additional information regarding the potential systemic toxicity of menthanol was available. However, clinical signs of systemic toxicity following administration of cyclic terpene alcohols were reported to be non-specific and included transient CNS stimulation followed by CNS depression (Panel, Belsito et al. 2008).

Dermal Hazard:

There was no available information regarding the dermal absorption of menthanol. The RIFM expert panel reported that percutaneous penetration has been observed both *in vitro* and *in vivo* with various cyclic terpene alcohols (Panel, Belsito et al. 2008). An LD₅₀ value of greater than 5,000 mg/kg bw was reported following acute dermal administration of menthanol in rabbits (Vigon 2015). No additional information was available. However, based on reported dermal LD₅₀ values of greater than 5,000 mg/kg bw/day for 15 of 20 cyclic terpene alcohols evaluated, the RIFM concluded that this class of chemicals were “practically not toxic via the dermal route” (Panel, Belsito et al. 2008).

According to the SDS, menthanol may cause mild and temporary irritation following prolonged contact with the skin (Vigon 2015). The RIFM expert panel reported that no skin irritation was observed following a single application of undiluted α -terpineol (Panel, Belsito et al. 2008). They concluded that animal data suggested that most terpene alcohols are likely to be skin irritants when applied topically at undiluted concentrations, but there was little evidence of skin irritation occurring at concentrations in the range of 0.5 to 50% (Panel, Belsito et al. 2008).

Sensitization:

Menthanol is not expected to cause skin sensitization (Vigon 2015). The RIFM expert panel reported that several terpene alcohols are potent skin sensitizers and have been prohibited or restricted from use as fragrance ingredients (Panel, Belsito et al. 2008) However, for the remaining terpene alcohols, the sensitization potential is “generally low” (Panel, Belsito et al. 2008).

Association with Hair Loss:

[REDACTED]

There was no information available on the association between menthanol and hair loss.

Agency Data:

Many cyclic terpene alcohols have been approved for use as flavor ingredients in foods by the FDA and have also been evaluated by the International Joint FAO/WHO Expert Committee on Food Additives (JECFA) to pose no safety concern at current intake levels (Panel, Belsito et al. 2008).

- Stearyltrimethylammonium chloride

Stearyltrimethylammonium chloride (STMAC) was not specifically listed as an ingredient in the final product formulation of WCD Sweet Almond Mint Cleansing Conditioner nor was it specifically identified as a component of any listed ingredient. However, the identification of STMAC as a component of WCD Sweet Almond Mint Cleansing Conditioner during analytical testing is likely due to its similarity in chemical structure to other known ingredients, such as stearamidopropyl dimethylamine. Thus, STMAC may represent a minor component of this ingredient or a minor reaction product in the final product formulation. Further analyses would be required to identify the nature of the STMAC in the final product formulation.

Overview:

STMAC, also known as steartrimonium chloride, is a cationic chemical surfactant (Yam, Booman et al. 1984). It is a member of a large group of quaternary ammonium salts used in cosmetics (Becker, Bergfeld et al. 2012). It functions as an antistatic agent and a hair-conditioning agent (Becker, Bergfeld et al. 2012). Trimoniums are reported to dissociate into their ionic components in aqueous cosmetic formulations (Becker, Bergfeld et al. 2012). Steartrimonium chloride was reported used in a total of six cosmetic formulations at the time of CIR's first safety assessment in 1997 (Becker, Bergfeld et al. 2012).

Toxicology:

The CIR reported that the acute oral LD₅₀ for steartrimonium chloride was reported to be approximately 700 mg/kg (Becker, Bergfeld et al. 2012). Additional information regarding the potential systemic toxicity of steartrimonium chloride was not available. There was no available information regarding the dermal toxicity for STMAC. However, a structurally similar compound, cetrimonium chloride, was reported to induce "mild, transient dermal irritation" based on rat dermal exposure to 54.5% cetrimonium chloride in aqueous isopropanol administered for clipped skin for five days/week for four weeks (Becker, Bergfeld et al. 2012).


Dermal Hazard:

Information regarding the dermal absorption of stearyltrimonium chloride was not available. However, the CIR noted that studies on the percutaneous absorption of a trimonium decorated polymer resulted in no evidence of dermal penetration in rats (Becker, Bergfeld et al. 2012). The CIR reported that when trimoniums are incorporated into cosmetic formulations, the cationic chains are attracted to anionic charges in the protein structure of skin and hair, which results in a conditioning effect (Becker, Bergfeld et al. 2012). It is noted that the charged ingredients are unlikely to cross the lipid bilayer but “tend to be irritating to the skin and eyes” (Becker, Bergfeld et al. 2012). When a single application of stearyltrimonium chloride was tested on rabbits for three minutes and one hour on shaved skin under semioclusion, no mortalities or systemic effects observed (Becker, Bergfeld et al. 2012). Rabbits exposed to stearyltrimonium chloride for one hour were reported to have grade two erythema up to day 22 and grade one erythema up to seven days (Becker, Bergfeld et al. 2012). A Buehler test was performed on guinea pigs using 79.8% stearyltrimonium chloride (Becker, Bergfeld et al. 2012). Although no clinical signs were observed, the treated group was noted to have a slight, well-defined to severe erythema and very slight to well-defined edema at the treatment area during induction (Becker, Bergfeld et al. 2012).

Sensitization:

The authors of the above CIR study concluded that stearyltrimonium chloride was not a sensitizer under the reported test conditions (Becker, Bergfeld et al. 2012).

Association with Hair Loss:

There was no information available on the association between stearyltrimonium chloride and hair loss.

Agency Data:

According to the 2012 CIR report, stearyltrimonium chloride was found to be “safe for use in rinse-off products and safe for use at concentrations of up to 0.25% in leave-on products” (Becker, Bergfeld et al. 2012). However, the CIR noted that there were gaps in the available safety data for some of the trimoniums and therefore data may be extrapolated to support the safety of the entire group from structurally similar trimoniums (Becker, Bergfeld et al. 2012).

3. DISCUSSION AND RECOMMENDATIONS

Based on the review of the chemical ingredients contained in the WEN Products, there is no evidence that the formulation poses a chronic hazard when used in the intended manner. Regarding acute hazards, while some of the chemicals presented were identified as a skin irritants in undiluted form, the concentrations of each of the chemical ingredients in the WEN Products other than water were less than 10% (exact concentrations reported in Table 1) and the concentrations of all chemical ingredients in the WEN Products are at concentration levels that would not be expected to cause an adverse event. According to the GHS regulations, if a mixture is diluted with water or other practically non-toxic materials, the toxicity of the mixture can be calculated from test data on the undiluted mixture. "For example, if a mixture with an LD₅₀ of 1000 mg/kg were diluted with an equal volume of water, the LD₅₀ of the diluted mixture would be 2000 mg/kg." (International Labour Organization n.d.). Therefore, based on this statement, the safe level values in **Table 1** would have to be increased by many fold for each individual chemical based on its weight percentage in the product. Based on this hazard assessment, and the fact that the presence of each of the chemicals (except water) in the final product is significantly less than 10% (exact concentrations reported in **Table 1**), it was determined that the chemical formulation of the WEN Products does not present an acute toxicological hazard when used in the intended manner.

Lastly, if specific concerns arise regarding one of more specific component of the product, individual ingredient testing may be conducted to determine the following: 1) the presence of identified compound in the constituent used in the formulation, 2) preservation of the ingredient in the final product formulation, and 3) the concentration of the compound in the final product formulation.

Based on the results of this assessment, the concentrations reported in **Table 1** all are "practically non-toxic." Cardno ChemRisk concludes that exposure above the reported safe levels in the WEN Products is highly unlikely. Therefore, based on a lack of apparent toxicity and no regulations for any of the ingredients, Cardno ChemRisk believes that the WEN Products would not be expected to be a toxicological hazard at the concentrations present in them.

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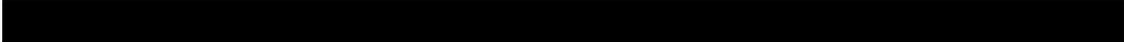
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