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# Safety Assessment of *Humulus lupulus* (Hops)-Derived Ingredients as Used in Cosmetics

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Status: Draft Report for Panel Review  
Release Date: September 2, 2016  
Panel Meeting Date: September 26-27, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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**MEMORANDUM**

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.  
Scientific Analyst and Writer

Date: September 2, 2016

Subject: *Humulus lupulus* (Hops)-Derived Ingredients as Used in Cosmetics

Attached is the Draft Report of 6 *Humulus lupulus* (hops)-derived ingredients as used in cosmetics. [HumLup092016Rep] These ingredients are derived from parts of the *Humulus lupulus* (hops) plant. The strobiles (also called cones) of *Humulus lupulus* are known for their use in beer brewing.

In July 2016, the Scientific Literature Review (SLR) was posted for public comment with a request for additional information, including data on the methods of manufacturing, composition, and irritation and sensitization.

Data on method of manufacture, impurities, and dermal and ocular irritation were submitted. Concentration of use data were also updated since the SLR was issued. [HumLup092016Data\_1-4]

Council comments have been addressed. [HumLup092016PCPC]

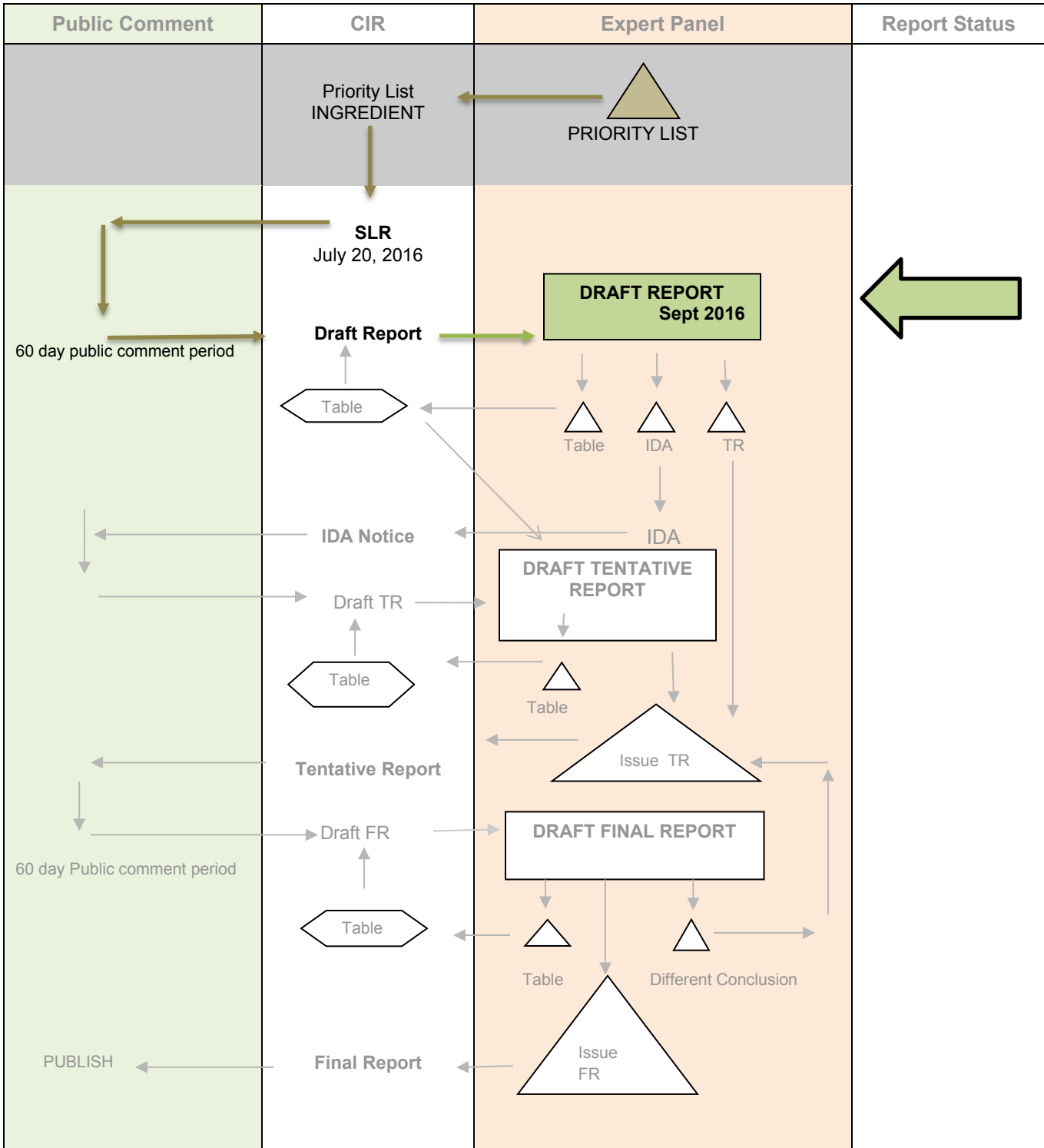
The Panel should note the sensitization data on people who work in the cultivation of the *Humulus lupulus* (hops) plant and in the beer industries as well as the data on the potential estrogenic effects.

If no further data are needed, the Panel should develop the basis for the Discussion and issue a Tentative Report. If more data are required, the Panel should list the data that are needed for the Panel to come to a conclusion of safety, and issue an Insufficient Data Announcement.

# SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Humulus lupulus (hops)-derived ingredients

MEETING Sept 2016



### **History – *Humulus lupulus* (Hops)-Derived Ingredients**

**2015** – The ingredient group was added to the Priority List.

**July, 2016** – Scientific Literature Review posted with a request for additional information.

**September, 2016** – The Panel is to examine the Draft Report.



## **Search Strategy – Humulus lupulus (Hops)**

### **SCIFINDER**

“toxicity of Humulus Lupulus” – “toxicity” and “Humulus Lupulus” closely associated – 22; in same report – 155. 147 combined hits. English – 83. Remove patents – 60. 2 possibly useful.

**CAS Nos.** – 0 hits

“hops” – 323 hits for tissue non-specific alkaline phosphatase.

### **PUBMED**

“Humulus Lupulus” – 374 hits. ~25 possibly useful.

### **ECHA**

“Humulus Lupulus” – 13 hits, 12 of mixtures containing hops. 1 useful (CPL info card).

### **Online Edition: "Combined Compendium of Food Additive Specifications"**

“Humulus” “Lupulus” “Hops” – no hits

**Journal of the Institute of Brewing** – “essential oil”, toxicity, lots of hits, ~15 potentially useful.

### **Internet**

“Humulus lupulus” or “hops” in general and with “FDA”, “NICNAS”, “EU”, “IFRA”, and “toxicity”

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## INTRODUCTION

This is a review of the published scientific literature and unpublished data provided by industry for assessing the safety of six *Humulus lupulus* (hops)-derived ingredients as used in cosmetics. According to the *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)*, the functions of these ingredients in cosmetics include antimicrobial agent, antiperspirant agent, fragrance ingredient, hair conditioning agent, and skin-conditioning agent – miscellaneous (Table 1).<sup>1</sup> There are no reported functions for *Humulus Lupulus* (Hops) Strobile. The ingredients in this safety assessment are:

Humulus Lupulus (Hops) Extract	Humulus Lupulus (Hops) Flower Extract
Humulus Lupulus (Hops) Cone Extract	Humulus Lupulus (Hops) Stem Extract
Humulus Lupulus (Hops) Cone Oil	Humulus Lupulus (Hops) Strobile

All of these ingredients are derived from part or all of the *Humulus lupulus* (commonly called hops) plant. This plant is generally known as an ingredient in the brewing of beer.<sup>2,3</sup>

The terms “cone” and “strobile” are synonymous and refer to the structures formed by the female *Humulus lupulus* (hops) plant after the flowers have bloomed, whether or not they have been fertilized. Thus, “cone oil” is the same as “strobile oil”. Both “cone” and “strobile” are used in the literature. Also, “hops” is used commonly for the plant name as well as for the harvested strobiles; in the literature, it is not always clear if authors are referring to the whole plant or just the strobiles. In this report, it is assumed that the authors are referring to just the strobiles unless otherwise indicated.

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) has reviewed related ingredients. These reviews may provide additional relevant information about *Humulus lupulus* (hops)-derived ingredients. The Panel reviewed the safety of phytosterols (plant-derived sterols that are likely constituents of most of the *Humulus lupulus* (hops)-derived ingredients) in 2013 and concluded that the phytosterols are safe as used.<sup>4</sup> The Panel also reviewed citrus peel oils, which are essential oils like *Humulus Lupulus* (Hops) Cone Oil, in 2014 and concluded that these ingredients are safe for use in cosmetic products when finished products, excluding rinse-off products, do not contain more than 0.0015% (15 ppm) 5-methoxypsoralen (5-MOP), and when formulated to be non-sensitizing and non-irritating.<sup>5</sup>

*Humulus lupulus* (hops) strobile is an ingredient in food (most commonly in beer) and most of the other parts of this plant (shoots, leaves, flowers, seeds, rhizomes, and essential oils) are edible.<sup>6,7</sup> Also, the U.S. Food and Drug Administration (FDA) determined that essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Humulus lupulus* L. (hops) are generally recognized as safe (GRAS) for human consumption.[21CFR182.20] Consumption of these *Humulus lupulus* (hops)-derived ingredients would result in much larger systemic exposures than what is expected from use in cosmetic products, even if there was 100% absorption. Thus, the systemic toxicity potential of *Humulus lupulus* (hops)-derived ingredients will not be the focus of this safety assessment (although toxicity information may be included here). The primary focus of the safety assessment is the review of safety based on local (dermal) effects.

Botanical cosmetic ingredients, such as *Humulus lupulus* (hops)-derived ingredients, may contain hundreds of constituents, some of which could have the potential to cause toxic effects. For example, sesquiterpene lactones present in *Humulus lupulus* (hops) plant may cause Type IV allergic reactions (cell-mediated, delayed-type hypersensitivity) and toxicity when present in sufficient amounts, and  $\beta$ -myrcene may be a dermal irritant and sensitizer.<sup>8,9</sup> In this assessment, CIR is reviewing information available to evaluate the potential toxicity of each *Humulus lupulus* (hops)-derived ingredient as a whole, complex substance. Except for specific constituents of concern, CIR is not reviewing information that may be available to assess the potential toxicity of the individual constituents derived from *Humulus lupulus* (hops).

The names of the ingredients in this report are written in accordance with the *Dictionary*, as listed above, capitalized without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the standard taxonomic practice of using *italics* will be followed (e.g., *Humulus lupulus*).

## CHEMISTRY

### Definition and Structure

The definitions of these *Humulus lupulus* (hops)-derived ingredients are provided in Table 1.

The terms “cone” and “strobile” are synonymous and refer to the structures formed by the female *Humulus lupulus* (hops) plant after the flowers have bloomed, whether or not they have been fertilized. Commonly, hops, when used to make beer, are the fresh or dried ripe strobiles of the female plant.<sup>10</sup>

### Plant Identification

The genus *Humulus* consists of dioecious, perennial, climbing vines and bines (i.e., a twining plant stem or flexible shoot).<sup>11</sup> This genus belongs to the Cannabaceae family of the Urticales order which, in 2003, was incorporated into the natural order of Rosales.<sup>12</sup> The only other genus in the family is *Cannabis*, represented solely by *C. sativa* (i.e., Indian hemp and marijuana).<sup>13,14</sup> The plant, which is native to Europe and western Asia, is now cultivated in North and South America, Africa, Asia and Australia and invasive is in many areas.<sup>3</sup> Cultivation is predominately in the northwestern United States and Germany.<sup>2</sup>

Within *Humulus lupulus* (hops), there are five taxonomic subspecies based on morphological properties and geographical location: *Humulus lupulus* var. *lupulus*, *Humulus lupulus* var. *cordifolius*, *Humulus lupulus* var. *neomexicanus*, *Humulus lupulus* var. *pubescens*, and *Humulus lupulus* var. *lupuloides*.<sup>15</sup> Over 100 cultivars have been named.<sup>16</sup> It is not known whether a single or multiple varieties are used in cosmetics.

The *Humulus lupulus* (hops) plant is dioecious (i.e., the male and female flowers usually develop on separate plants); occasional fertile monoecious individuals have been reported.<sup>14</sup> When grown for beer, viable seeds are undesirable; therefore, only female plants are grown in hop fields to prevent pollination. Female plants are propagated vegetatively, and male plants are culled if plants are grown from seeds. Under natural conditions, the flowers are wind pollinated and the female inflorescence develops to form a strobile (or cone).

*Humulus lupulus* (hops) is a climbing perennial bine; it grows in a helix around a support and uses downward-facing bristles/hooked hairs for grip instead of tendrils or suckers as would a vine.<sup>3,7,17</sup> The bines are trained to 25 ft (7.6 m) or higher and twine clockwise on a trellis. Lateral arms develop at the nodes, producing flowers at their terminal buds. The green to yellowish-brown leaves have three or five lobes, depending on the variety, and are hairy on both sides; the margins of the cordate (heart-shaped) leaves are serrated and the petioles are slightly fleshy with stout hooked hairs. *Humulus lupulus* (hops) is a perennial plant that regrows each spring from the rhizomes of an underground rootstock in commercial hop production.

To harvest, the bines are cut down and the strobiles stripped off; the crown remains in the ground to grow the next year. The strobiles consist of stipular petal-like structures called “bracts” and “bracteoles” around a central axis or strig. At the base of the bracteoles, the lupulin glands are formed as the strobile ripens. Only the strobiles of the female plants are able to develop the lupulin glands that secrete the fine yellow resinous powder.<sup>2</sup> These glands secrete predominantly bitter acids and hop oil, the constituents of which include phytoestrogens such as 8-prenylnaringenin (8-PN) and other prenylflavonoids.<sup>18,19</sup>

### Physical and Chemical Properties

The chemical and physical properties for *Humulus Lupulus* (Hops) Extract are provided in [Table 2](#).

Once harvested, *Humulus lupulus* (hops) strobiles deteriorate upon aging and exposure to atmosphere.<sup>3</sup> The stability of stored strobiles and ethanol extracts, as measured by humulones, lupulones, and xanthohumol content, is optimal in 70% ethanol.<sup>20</sup>

Green *Humulus lupulus* (hops) strobiles have a variety of odors including: citrus, tropical fruit, stone fruit, pine, cedar, floral, spicy, herbal, earthy, tobacco, onion/garlic and grassy.<sup>10</sup>

### Method of Manufacture

One manufacturer reported the method of manufacture of *Humulus Lupulus* (Hops) Cone Extract for use in cosmetics begins with extraction with water and propylene glycol.<sup>21</sup> The extract solution is then pressed, clarified, and decontaminated. Further details were not provided.

In general, when the strobiles are harvested from *Humulus lupulus* (hops) bines, the strobiles are immediately dried by forced hot air, and are often pressed into dense cylindrical pellets, 5 to 8 mm in diameter and up to 25 mm long.<sup>16</sup> The pelletization reduces the overall surface area and therefore reduces the rate of chemical oxidation/degradation, and provides a more compact product for shipping. Not all suppliers dry the strobiles; the strobiles may be harvested fresh as whole, wet cones at the farm, and shipped for immediate use within 36 h of harvest.<sup>10</sup>

Sometimes, hops are treated with sulfur dioxide to improve the color and prevent change of active constituents.<sup>3</sup>

In general, oils are extracted from *Humulus lupulus* (hops) by steam distillation at 100°C.<sup>22</sup>

Methylene chloride is the most common solvent used for the extraction of *Humulus lupulus* (hops) for beer brewing; hexane and methanol are also employed.<sup>23</sup> Typically, at least 95% of the available  $\alpha$ -acids (source of the bitter flavorings) can be extracted from fresh *Humulus lupulus* (hops) strobiles. Methanol is the most efficient solvent for the extraction of  $\alpha$ -acids (approximately 25%), followed by methylene chloride (approximately 20%) and hexane (approximately 18%).

Supercritical fluid extraction (SFE) with carbon dioxide is also used to collect the extract for beer brewing.<sup>24-27</sup> Another modern method is pressurized fluid extraction (PFE), which is employed for extracting different polyphenols.<sup>28-32</sup> PFE has been developed to extract bitter acids.

FDA regulations on the method of manufacture of “modified hop extract”, as a food additive intended for use as a flavoring agent in the brewing of beer, list the allowed solvents (including benzene, light petroleum spirits, methyl alcohol, n-butyl alcohol, and ethyl acetate; [Table 3](#)). Six of the eight listed methods follow extraction with isomerization.

[21CFR172.560]

### Composition

[Humulus Lupulus \(Hops\) Cone Extract](#),

[Humulus Lupulus \(Hops\) Flower Extract](#),

[Humulus Lupulus \(Hops\) Strobile](#)

The principle components of fresh and dried *Humulus lupulus* (hops) strobiles/cones are listed in [Table 4](#) and [Table 5](#).<sup>2,33</sup> Analysis of dried food grade *Humulus lupulus* (hops) strobiles grown for beer production showed  $\alpha$ -acids at 3.0% to

15.5% (w/w) and  $\beta$ -acids at 3.0% to 5.5% (w/w).<sup>10</sup> *Humulus lupulus* (hops) bitter acids are classified as either “ $\alpha$ -acids” or “ $\beta$ -acids” that are, respectively, di- or tri-prenylated phloroglucinol derivatives. In addition, they each contain a 3-, 4-, 5-, or 6-carbon oxo-alkyl side chain.<sup>7,34</sup> Historically, the  $\alpha$ -acids were distinguished because they precipitated from a crude extract of hops with the addition of lead acetate. The  $\beta$ -acids, by definition, would remain in solution. The  $\alpha$ -acids, particularly humulone (35%–70% of total  $\alpha$ -acids), cohumulone (20%–65%), and adhumulone (10%–15%) are regarded as the most important constituents in determining the quality of hops.<sup>7,34</sup>

Flavonoids are composed of different chemical classes such as flavones, isoflavones, flavonols, flavanols, flavanones, and chalcones. These compounds differ in the level of oxidation of the flavane nucleus and in the number and position of hydroxyl, methyl, and methoxyl substituents.<sup>35</sup> Flavonoids, which make up 0.5%-1.5% of the dried strobile, include quercetin and kaempferol glycosides.<sup>36,37</sup> In an analysis of *Humulus lupulus* (hop) samples by high-performance liquid chromatography (HPLC)–diode array detection, over 100 compounds were in the polyphenol fraction of *Humulus lupulus* (hops).<sup>38</sup> Thirty prenylated, geranylated, oxidized and/or cyclized chalcones have been isolated from the secretions of the lupulin glands.<sup>16</sup> The prenylated, geranylated flavonoids are up to 1% of the dried strobile and 80%–90% of total flavonoids.<sup>18,19,39-41</sup> The chalcone xanthohumol is the most abundant prenylated flavonoid in fresh and properly preserved strobiles (approximately 0.01%–0.5%); desmethylxanthohumol, dehydrocycloxanthohumol, and the flavanones isoxanthohumol, 8-PN (25-60 mg/kg) and 6-prenylnaringenin are also found in the strobiles.<sup>18,19,39-42</sup> A majority of the known flavonoids from *Humulus lupulus* (hops) strobiles can be considered to be derivatives of the compound 2',4,4',6'-tetrahydroxy-3'-prenylchalcone (chalcone numbering), commonly known as desmethylxanthohumol. The composition of the polyphenols in *Humulus lupulus* (hops) is provided in [Table 6](#).

The constituents and their concentrations of aqueous *Humulus Lupulus* (Hops) Cone Extracts from 10 different cultivars are provided in [Table 7](#).<sup>43</sup>

### Humulus Lupulus (Hops) Cone Oil

The *Humulus Lupulus* (Hops) Cone Oil comprises secondary metabolites of the *Humulus Lupulus* (hops) plant, and are secreted in the lupulin glands (located on the female flower cones/strobiles).<sup>2</sup> The strobile oil makes up 0.5%-1.5% of the dried inflorescence of *Humulus Lupulus* (Hops) Strobile.<sup>44</sup> The *Humulus Lupulus* (Hops) Cone Oil contains many volatile constituents, including simple oxidized alkanes, monoterpenes, and sesquiterpenes.<sup>16,45-47</sup> It is possible that the *Humulus Lupulus* (Hops) Cone Oil contains over 1000 compounds. The primary volatile constituents are the monoterpene  $\beta$ -myrcene, and the sesquiterpenes  $\beta$ -caryophyllene and humulene, which together were shown to comprise between 57% and 82% of the volatile oil, depending on the cultivar and the method of detection. There are only traces of 2-methyl-3-buten-2-ol found in freshly harvested *Humulus Lupulus* (Hops) Strobile; after drying and storing, the amount is higher, increasing to a maximum of approximately 0.15% of the dry weight (up to 20% of the volatile constituents) after 2 years due to degradation of humulones and lupulones.<sup>44</sup> The constituents in *Humulus Lupulus* (Hops) Cone Oil are not consistent across years or cultivars and not all of constituents are detectable in every essential oil sample;  $\beta$ -myrcene, linalool,  $\alpha$ -humulene,  $\beta$ -caryophyllene, undecanone-2, geranyl acetate, humulene epoxide-2, and  $\alpha$ -selinene are always present.<sup>48</sup> A list of some of the compounds in *Humulus Lupulus* (Hops) Cone Oil is provided in [Table 8](#) and [Table 9](#).

### **Impurities/Constituents of Concern**

The results of an analysis of a product that contained *Humulus Lupulus* (Hops) Cone Extract (0.6% to 1.2%) reported that heavy metals were certified to be present at  $\leq 5$  ppm, microbes at  $< 100$  cfu/mL, yeasts and molds at  $< 100$  cfu/mL, and enterobacteria were absent.<sup>49</sup>

Analysis of dried food grade *Humulus lupulus* (hops) strobiles (possible source material for *Humulus Lupulus* (Hops) Extract, *Humulus Lupulus* (Hops) Cone Extract, *Humulus Lupulus* (Hops) Cone Oil, and *Humulus Lupulus* (Hops) Strobile) produced for beer production had the following results: lead  $< 1.0$  ppm, arsenic  $< 0.5$  ppm, cadmium  $< 0.03$  ppm, and total heavy metals  $< 10$  ppm.<sup>10</sup> Heavy metals, pesticides, herbicides, fungicides, nitrates, and radioactivity are reported to be below tolerance levels. Another analysis of leaves and strobiles of *Humulus lupulus* (hops) plants had the following results: copper, 102.3 and 81.1 ppm; vanadium, 0.07 and 0.05 ppm; molybdenum, 0.07 and 0.12 ppm; iron, 49.3 and 54.2 ppm; tin, 1.4 and 1.2 ppm; lead, 3.1 and 2.3 ppm, and nickel, 7.9 and 5.5 ppm, respectively.<sup>50</sup>

The levels of residual solvent present in commercial hop extracts used for brewing beer are reported to be  $< 100$  ppm.<sup>51</sup>

Multiple fungi and bacteria may be found on *Humulus lupulus* (hops) plants.<sup>3</sup> Analysis of the airborne dust in air samples performed during harvest showed total concentrations of airborne microorganisms ranged between 2.08 to  $129.58 \times 10^3$  cfu/m<sup>3</sup>; the concentrations of airborne endotoxin ranged between 26 to 6250 ng/m<sup>3</sup>.<sup>52</sup> In samples of the settled dust after harvest, the concentrations of total microorganisms ranged from  $0.25 \times 10^6$  to  $2.87 \times 10^8$  cfu/g; the concentrations of endotoxin ranged between 312.5 to 6250  $\mu\text{g/g}$  (median 6250  $\mu\text{g/g}$ ).

*Humulus lupulus* (hops) plants are reported to contain linalool, quercetin,  $\beta$ -myrcene, and 8-PN (or hopein) and other prenylated flavonoids.<sup>8,36,37,47,53,54</sup> *Humulus Lupulus* (Hops) Cone Oil is reported to contain sesquiterpene lactones.<sup>16,45-47</sup> *Humulus Lupulus* (Hops) Extract is reported to contain geraniol (0.2%), limonene (1%), and linalool (0.6%).<sup>55</sup> The potential adverse effects of exposures to these constituents are summarized in [Table 10](#).

FDA regulations restrict the amounts of residual solvents in the manufacture of “modified hop extract” as a food additive ([Table 3](#)).[21CFR172.560] These restrictions include: boron, 310 ppm; benzene, 1.0 ppm; light petroleum spirits,

1.0 ppm; methyl alcohol, 250 ppm; hexane, 125 ppm; ethylene dichloride, 150 ppm; methylene chloride, 250 ppm; trichloroethylene, 250 ppm; and isopropyl alcohol, 250 ppm.

## USE Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated based on data received from the FDA and the cosmetic industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentration by product category.

According to the VCRP survey data received in 2016, *Humulus Lupulus* (Hops) Extract was reported to be used in 362 formulations, including 299 leave-on formulations and 60 rinse-off formulations (Table 11).<sup>56</sup> *Humulus Lupulus* (Hops) Cone Extract and *Humulus Lupulus* (Hops) Strobile were reported to be used in 4 and 7 cosmetic formulations, respectively.

The results of the concentration of use survey conducted by the Council in 2016 indicate that *Humulus Lupulus* (Hops) Extract has the highest reported maximum concentration of use; it is used at up to 0.6% in face and neck products.<sup>57</sup> The maximum concentration of use for *Humulus Lupulus* (Hops) Cone Extract and *Humulus Lupulus* (Hops) Flower Extract are reported to be 0.00055% (face powders) and 0.001% (hair conditioners and other hair preparations), respectively.

In some cases, reports of uses were received in the VCRP, but no concentration of use data are available. For example, *Humulus Lupulus* (Hops) Strobile was reported to be used in 7 formulations, but no use concentration data were available. In some cases, no uses were reported in the VCRP, but concentration of use data were received from industry; *Humulus Lupulus* (Hops) Flower Extract had no reported uses in the VCRP, but use concentrations in two hair product categories and bath soaps and detergents were provided in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported.

The ingredients not in use according to the VCRP and the industry survey are *Humulus Lupulus* (Hops) Cone Oil and *Humulus Lupulus* (Hops) Stem Extract.

*Humulus Lupulus* (Hops) Extract (up to 0.13%), *Humulus Lupulus* (Hops) Cone Extract, and *Humulus Lupulus* (Hops) Strobile are reported to be used in formulations that are used around the eyes. *Humulus Lupulus* (Hops) Extract (up to 0.084%), *Humulus Lupulus* (Hops) Cone Extract (no concentration of use reported), and *Humulus Lupulus* (Hops) Flower Extract (up to 0.00055%) are reported to be used in formulations that come in contact with mucous membranes (e.g., bath soaps and detergents, bubble baths).

*Humulus lupulus* (Hops)-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, *Humulus Lupulus* (Hops) Extract is reported to be used at up to 0.0002% in hair sprays. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles <10 µm compared with pump sprays.<sup>58,59</sup> Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.<sup>60,61</sup> *Humulus Lupulus* (Hops) Cone Extract is used in face powders at up to 0.00055%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits established for talc particles and nuisance dusts in the workplace.<sup>62-64</sup>

The International Fragrance Association (IFRA) restricts the amount of geraniol, a constituent of *Humulus Lupulus* (Hops) Oil, to <0.2% in fragrance products.<sup>65</sup>

None of the *Humulus lupulus* (hops)-derived ingredients named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union.<sup>66</sup>

## Non-Cosmetic

*Humulus lupulus* (hops) strobiles are predominantly used to make beer.<sup>2,3</sup> They were originally added to beer for their antimicrobial properties. Brewers then began using strobiles to add bitterness, flavor, and aroma. Brewers also use *Humulus lupulus* (hops) strobile extracts for the same purposes.<sup>23</sup>

FDA determined that essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Humulus lupulus* L. (hops) are GRAS for human consumption.[21CFR182.20] Modified hop extract may be safely used in beer in accordance with the following prescribed conditions: (a) the food additive is used or intended for use as a flavoring agent in the brewing of beer, and (b) the food additive is manufactured by one of the prescribed processes (Table 3).[21CFR172.560]

Most parts of the *Humulus lupulus* (hops) plant (shoots, leaves, flowers, seeds, rhizomes, and essential oils) are edible.<sup>6,7</sup> The shoots are eaten as a delicacy and resemble asparagus.

In Europe, *Humulus lupulus* (hops) is administered as an herbal supplement in the form of powders, liquid extracts (ethanol extract drug extract ratio/dry extract ratio [DER] 1:1; sweet wine extract DER 1:10), tinctures (ethanol extract DER 1:5), and dry extracts (50% methanol extract DER 4 to 5:1) of the inflorescence of the plant.<sup>44</sup> It is also administered as a tea. *Humulus lupulus* (hops) strobiles are used in traditional medicinal in Europe and Native American traditional medicines for

the relief of insomnia, excitability, and specifically for restlessness associated with nervous tension, headache and/or indigestion. Lipophilic extracts are used for the preparation of bath oils whereas hydroalcoholic liquid extracts are prepared for internal use as sedatives, mostly in combinations with other sedative plant extracts.

In Native American traditional medicines, *Humulus lupulus* (hops) is also used as a sedative, anti-rheumatic, analgesic, gynecological aid for breast and womb problems, and kidney and urinary aid for “gravel” and inflamed kidneys.<sup>67</sup>

In Indian-Ayurvedic medicine, *Humulus lupulus* (hops) has been recommended for restlessness associated with nervous tension, headache, and indigestion.<sup>67</sup> It is reported to act as a sedative, hypnotic, and antibacterial.

*Humulus lupulus* (hops) byproducts, after harvesting of the strobiles, can be used to absorb lead from contaminated waters.<sup>68</sup>

### **TOXICOKINETIC STUDIES**

Data on the toxicokinetics of *Humulus lupulus* (hops)-derived ingredients would not be practical because these ingredients are complex mixtures. Exposure to the components of these ingredients in cosmetics is expected to be lower than that from dietary exposure because these ingredients are consumed as food and drink.

### **TOXICOLOGICAL STUDIES**

#### **Acute Toxicological Studies**

Acute toxicity data on *Humulus lupulus* (hops)-derived ingredients were not found in the published literature and no unpublished data were submitted.

#### **Short-Term Toxicity Studies**

##### **Oral**

Wistar rats (n=7/group) were fed a low-fat diet, a high-fat diet, or high-fat diet supplemented with 1% xanthohumol-rich *Humulus Lupulus* (Hops) Cone Extract for 41 days.<sup>69</sup> There were no mortalities or other adverse effects observed in any of these groups. The addition of the *Humulus Lupulus* (Hops) Cone Extract reduced the effects of the high-fat diet with regard to weight gain from days 21 to 41 of the study. The weights of livers of rats fed the supplemented high-fat diets were similar to the controls, as were the plasma glucose levels, at the end of the test period. There were no effects on the mesenteric and epididymal adipose tissues.

#### **Subchronic Toxicity Studies**

##### **Oral**

Male C57BL/6J mice (n=10/group) were fed a normal diet, a high-fat diet, or a high-fat diets supplemented with 2% or 5% of various *Humulus Lupulus* (Hops) Cone Extracts for 20 weeks.<sup>70</sup> The high-fat diets were supplemented with one of the following:

- an aqueous *Humulus Lupulus* (Hops) Cone Extract,
- an ethyl acetate-soluble fraction of the aqueous *Humulus Lupulus* (Hops) Cone Extract,
- an ethyl acetate-insoluble fraction of the aqueous *Humulus Lupulus* (Hops) Cone Extract,
- a methanol-soluble fraction of the ethyl acetate-insoluble fraction of the aqueous *Humulus Lupulus* (Hops) Cone Extract,
- a methanol-insoluble fraction of the ethyl acetate-insoluble fraction of the aqueous *Humulus Lupulus* (Hops) Cone Extract.

There were no mortalities or adverse effects reported for any group. The additions of any of the *Humulus Lupulus* (Hops) Cone Extracts reduced the effects of the high-fat diet with regard to weight gain. The weights of livers and mesenteric and epididymal adipose tissues of mice fed the supplemented high-fat diets were similar to the controls, as were plasma glucose levels, at the end of the test period.

### **DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES**

Developmental and reproductive toxicity data on *Humulus lupulus* (hops)-derived ingredients were not found in the published literature and no unpublished data were submitted.

### **GENOTOXICITY STUDIES**

#### **In Vitro**

An aqueous *Humulus Lupulus* (Hops) Cone Extract (10 to 400 mg/μL in ethanol) was weakly mutagenic (an increase in induced revertants of 2 to 4 times the controls) to *Salmonella typhimurium* (strains TA 98 and TA100) with and without metabolic activation.<sup>71</sup> No further details were provided.

A *Humulus Lupulus* (Hops) Cone Extract (0, 1000, 2500, 5000, 7500, and 10,000 μg/plate; extract solvent not specified; water control) was not mutagenic to *S. typhimurium* (strains TA98 and TA100) and *Escherichia coli* (strain pKM101), with and without metabolic activation.<sup>72</sup> The controls had the expected results.

### **In Vivo**

*In vivo* genotoxicity data on *Humulus lupulus* (hops)-derived ingredients were not found in the published literature and no unpublished data were submitted.

### **CARCINOGENICITY STUDIES**

Carcinogenicity data on *Humulus lupulus* (hops)-derived ingredients were not found in the published literature and no unpublished data were submitted.

### **OTHER RELEVANT STUDIES**

#### **Possible Estrogenic/Endocrine Effects**

Historically, there is circumstantial evidence of potential estrogenic activity connected to *Humulus lupulus* (hops) exposure, including menstrual disturbances reported to be common among female *Humulus lupulus* (hops) harvesters.<sup>73,74</sup> In an investigation of the folk legend that women who normally live “a distance” from hop gardens regularly begin to menstruate two days after arriving to pick hops, it was reported that hops contain “the equivalent of 20 to 300 µg estradiol/g”.<sup>44</sup> *Humulus lupulus* (hops) extracts have been reported to reduce hot flashes in menopausal women and, in Germany, hop baths containing approximately 30% *Humulus lupulus* (hops) extracts (which have been discontinued) were used to treat gynecological disorders.<sup>44,75</sup> However, early studies to confirm this activity experimentally were inconclusive or contradictory because of inadequate sensitivity of the methods used.<sup>73,76</sup>

More recently, 8-PN has been shown to be the source of the estrogenic activity of *Humulus lupulus* (hops). It mimics the action of 17β-estradiol, albeit with less (10- to 20,000-fold) potency.<sup>77-81</sup> It is a potent ligand for the α-estrogen receptor (ER) with an IC<sub>50</sub> value in the nanomolar range; it stimulates the production of alkaline phosphatase in Ishikawa cells, and stimulates the growth of estrogen-dependent MCF7 breast cancer cells.<sup>39,82</sup> It was reported that 8-PN has a greater affinity for the ERα (where it is 70-fold less potent than estradiol) than for ERβ (reported to be 20,000-fold less potent than estradiol).<sup>83</sup>

In a screening for drugs derived from plants for estrogenic activity, an ethanolic *Humulus Lupulus* (Hops) Cone Extract (50%; 0.2 g/mL) exhibited binding to ERs in intact, estrogen-dependent [ER(+)], human breast cancer MCF-7 cells with a potency equivalent to 0.5 µg of estradiol per 2 g of dried *Humulus Lupulus* (Hops) Strobile (for comparison, the potencies of 2 g of thyme or red clover were equivalent to 0.5 or 3 µg of estradiol, respectively).<sup>84</sup> *Humulus Lupulus* (Hops) Cone Extract also showed significant ability to stimulate cell proliferation in ER (+)T47D, but not in ER(-) MDA 468, breast cancer cells.<sup>84</sup> In contrast, in a different series of experiments, a similarly prepared *Humulus Lupulus* (Hops) Cone Extract at concentrations of 0.01%-1.0% v/v was found to inhibit serum-stimulated growth of ER(+)T47D breast cancer cells.<sup>85</sup> Ovarian cells isolated from immature female rats, which 48 h previously had been injected (primed) with pregnant mare’s serum gonadotrophin, were incubated with follicle-stimulating hormone to induce estradiol secretion. The addition of purified water-soluble fractions F1 or F2 from defatted *Humulus Lupulus* (Hops) Cone Extract to the culture medium reduced the estrogen E<sub>2</sub> released from the ovarian cells with a probably related decrease in cyclic adenosine monophosphate (cAMP) release.<sup>44</sup>

A *Humulus Lupulus* (Hops) Cone Extract demonstrated transiently transfected estrogen response element (ERE)-luciferase, quantitative reverse-transcription-polymerase chain reaction (RT-PCR) of an estrogen-inducible gene, and alkaline phosphatase (AP)-enzyme induction assays (EC<sub>50</sub> of 1.1 µg/mL).<sup>86</sup> This *Humulus Lupulus* (Hops) Cone Extract consisted of a chloroform partition of a methanolic extract from a previously SFE-CO<sub>2</sub>-extracted Nugget *Humulus lupulus* (hops) cultivar; the individual constituents included prenylated flavanones and isoflavonoids. The estrogenic activity proved to be considerably greater than that of established phytoestrogens such as coumestrol (present in red clover) and genistein and daidzein (present in soy).

### **DERMAL IRRITATION AND SENSITIZATION STUDIES**

#### **Irritation**

#### ***Human***

##### **Humulus Lupulus (Hops) Extract**

In a 2-week cumulative irritation test (n=26) of a formulation containing *Humulus Lupulus* (Hops) Extract (0.125%), the test formulation did not demonstrate a significant irritation potential in human skin.<sup>87</sup>

##### **Humulus Lupulus (Hops) Cone Extract**

A formulation containing *Humulus Lupulus* (Hops) Cone Extract (0.6% to 1.2%; 20 µL) was patch tested (n=12) at 10% (final concentration 0.06% to 0.12%) using 8-mm aluminum cups covering 50 mm<sup>2</sup>.<sup>88,89</sup> The patches were administered to the upper back for 24 h. Controls were water and sodium lauryl sulfate (1%). The test sites were examined at 30 min to 1 h and 24 h after patch removal. One subject had a reaction at the site of the negative control and was not used in the final results. No reactions to the test material were observed in 9 subjects; two subjects showed very slight erythema. The controls had the expected results in the rest of the subjects. The irritation index was 0.04 (out of 5) and was rated a non-irritant.

### Humulus Lupulus (Hops) Plants

The causative agents of *Humulus lupulus* (hops) plant-induced contact skin reactions have not been established.<sup>90,91</sup> Both irritant and allergic effects have been described. In *Humulus lupulus* (hops) harvesters, the dermatitis has been attributed to mechanical abrasion by the rough hairs on the climbing stem. It has also been suggested that lupulin, the yellow powdery secretion of the glandular hairs on the scales of the strobiles, may be responsible for the irritation.

#### **Sensitization**

In a human maximization test (n=26) of a product containing *Humulus Lupulus* (Hops) Extract (0.125%), the test product did not demonstrate contact sensitization potential.<sup>87</sup>

### OCULAR IRRITATION STUDIES

#### **In Vitro**

##### Humulus Lupulus (Hops) Cone Extract

A product containing *Humulus Lupulus* (Hops) Cone Extract (0.6% to 1.2%) was tested in a hen's egg test-chorion-allantoic membrane (HET-CAM) assay at 10% (final concentration 0.06% to 0.12%).<sup>88,89</sup> There were no signs of potential irritation in any form of hyper-anemia, hemorrhage, or coagulation. The primary irritancy index (IP-CAM) score was 0.00 and the product was rated a practically non-irritating under these conditions.

The same product containing *Humulus Lupulus* (Hops) Cone Extract (0.6% to 1.2%) was tested in a cornea fibroblast (CFIO) assay at 10% (final concentration 0.06% to 0.12%). The ocular irritation index (IOeq) was 2.8 with a mean cytotoxicity index (MCI) of 0.0; the test substance was rated at the lowest irritation level (IOeq=0 to 15) as a slight ocular irritant.

When combining the results of these two *in vitro* HET-CAM/CFIO assays, the author concluded that this cosmetic formulation containing *Humulus Lupulus* (Hops) Cone Extract (0.6% to 1.2%) was a slight ocular irritant.<sup>88,89</sup>

#### **Human**

##### Humulus Lupulus (Hops) Extract

In a 4-week use study (n=48) of an eye cream that contained *Humulus Lupulus* (Hops) Extract (0.125%), the test material did not demonstrate potential for eliciting ophthalmic irritation.<sup>87</sup>

### CLINICAL STUDIES

#### **Occupational Exposure**

##### **Dermal**

Farmers (n=73) who cultivated *Humulus lupulus* (hops) plants and other crops from 18 randomly selected farms filled out a questionnaire on their skin diseases and were administered skin prick tests (SPT) for allergens of *Humulus lupulus* (hops) as well as grain dust, straw dust, hay dust, storage mites, and antigens of microorganisms typical of farm environments (only the results of the *Humulus lupulus* (hops) are reported here).<sup>92</sup> Fresh strobiles and leaves were cut into small pieces, and extracted with glycerol and saline at 1:2 (w/w) for 48 h at 4°C. The extracts were centrifuged and clear supernatants were used in the testing. The subjects consisted of 42 males and 31 females, aged 16 to 84 (median 46) years, with duration of exposure ranging from 2 to 73 (median 31) years.

The questionnaire showed that *Humulus lupulus* (hops) was reported to cause the greatest number of skin problems; 14 farmers (19.2%) reported work-related skin symptoms, 11% of which were caused by *Humulus lupulus* (hops). There were no reported skin problems from working with *Humulus lupulus* (hops) by 65 subjects. The reported skin symptoms were mostly mild: four reported rashes on uncovered skin (the description of which was sufficient to diagnose airborne dermatitis), two subjects reported hand dermatitis, and two reported pruritus without visible skin changes. One case of airborne dermatitis to hops was severe enough to be classified as debilitating.

Positive skin reactions to four *Humulus lupulus* (hops) allergen preparations, i.e., cone extract in glycerol, cone extract in saline, leaf extract in glycerol, and leaf extract in saline, were found in one, two, three, and four subjects, respectively. In all, six subjects (8.2%) reacted to at least one extract. Among the subjects reporting skin problems related to *Humulus lupulus* (hops), SPTs gave positive results in two subjects, and the tests were negative in six subjects. The tests were also positive in four persons who did not report any *Humulus lupulus* (hops)-related skin problems. The predictive values for SPT of the extracts (skin reaction to at least one of the preparations) were: positive predictive value (PPV)=0.33 and negative predictive value (NPV)=0.91.<sup>92</sup>

##### **Inhalation**

Washington State Workers' Compensation claims filed by *Humulus lupulus* (hops) workers for respiratory disease between 1995 and 2011 were systematically identified and reviewed in a study of occupational respiratory disease in *Humulus lupulus* (hops) workers.<sup>93</sup> Incidences of respiratory disease in *Humulus lupulus* (hops) workers were compared with rates in field vegetable crop farm workers. A total of 57 cases of respiratory disease associated with *Humulus lupulus* (hops) dust inhalation were reported. The attending health care practitioner diagnosed 61% of these cases as having work-related

asthma. Chronic obstructive pulmonary disease was diagnosed in 7% of these cases; the remaining cases were diagnosed as allergic respiratory disorders (e.g., allergic rhinitis [18%] or asthma-associated symptoms [e.g., dyspnea; 14%]). All cases were associated with *Humulus lupulus* (hops) harvesting, secondary hop processing, or indirect exposure. The incidence of respiratory disease in *Humulus lupulus* (hops) workers was 15 cases per 10,000 full-time workers, which was 30 times greater than the incidence for field vegetable crop workers. A strong temporal association between *Humulus lupulus* (hops) dust exposure and respiratory symptoms and a clear association between an increase in hop dust concentrations and the clinical onset of symptoms were apparent in 3 cases. The authors concluded that occupational exposure to *Humulus lupulus* (hops) dust is associated with respiratory disease; respiratory disease rates were higher in hop workers than in a comparison group of agricultural workers.

In a study of occupational exposure of brewery workers to organic dusts such as *Humulus lupulus* (hops), barley, and brewery yeast, the potential to affect respiratory function and immunological status was examined.<sup>94</sup> Male subjects (n=97) employed in a brewery plant had a mean age of 40 years, and the mean duration of employment was 16 years. The control group consisted of unexposed workers (n=76). Respiratory symptoms were recorded. Lung function was measured by recording maximum expiratory flow-volume (MEFV) curves. Immunological testing was performed on all brewery workers and 37 of the control volunteers using SPTs with *Humulus lupulus* (hops), barley, and yeast antigens as well as other non-occupational allergens, and by determining total serum IgE levels. There was a higher prevalence of most of the chronic respiratory symptoms in brewery workers compared to controls. Occupational asthma was recorded in only 2 (2.1%) of the brewery workers; smoking was reported to be the major factor (that was examined in this study) responsible for the high prevalence of chronic respiratory symptoms in workers, not exposure to dust of the brewing ingredients, including *Humulus lupulus* (hops). A large number of brewery workers complained of acute symptoms that developed during the work shift. Lung function test scores were decreased compared to predicted levels. Multivariate analysis of these respiratory function parameters suggested the importance of workplace exposure in explaining lung function abnormalities. There was a greater instance of positive SPTs in brewery workers for *Humulus lupulus* (hops) than in controls (15% vs 3%). There were increased serum levels of total IgE in 34 out of 97 (45.1%) brewery workers compared to controls, 1 out of 76 (2.7%). However, workers with positive SPTs had a prevalence of chronic respiratory symptoms and lung function changes similar to those of workers with negative SPTs. The authors concluded that the data suggests that both smoking and dust exposure in the brewery industry may be responsible for the development of respiratory impairment and immunological reactions.

### Case Reports

There were multiple case studies of irritation and sensitization to *Humulus lupulus* (hops) or the constituent  $\beta$ -myrcene while working with the plant on farms, laboratories, and in breweries (Table 12).<sup>8,95-98</sup>

### SUMMARY

This is a review of the scientific literature and unpublished data provided by industry relevant to assessing the safety of six *Humulus lupulus* (hops)-derived ingredients as used in cosmetics. The functions of these ingredients in cosmetics include antimicrobial agent, antiperspirant agent, fragrance ingredients, hair conditioning agent, and skin-conditioning agent – miscellaneous. All of these ingredients are derived from part or all of the *Humulus lupulus*, commonly called hops, plant. This plant is mostly known as an ingredient in the brewing of beer. The terms “cone” and “strobile” are synonymous and refer to the same part of the plant.

*Humulus lupulus* (hops) strobile is an ingredient in food (most commonly in beer) and most of the other parts of this plant (shoots, leaves, flowers, seeds, rhizomes, and essential oils) are edible. The FDA determined that essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Humulus lupulus* L. (hops) are GRAS for human consumption. The systemic toxicity potential of *Humulus lupulus* (hops)-derived ingredients will not be the focus of this safety assessment (although toxicity information may be included here). The primary focus of the safety assessment is the review of safety based on local (dermal) exposure.

*Humulus lupulus* (hops) plants are reported to contain linalool, quercetin,  $\beta$ -myrcene, and 8-PN (and other prenylated flavonoids). *Humulus Lupulus* (Hops) Extract is reported to contain geraniol (0.2%), limonene (1%), and linalool (0.6%). *Humulus Lupulus* (hops) Cone Oil is reported to contain sesquiterpene lactones.

According to the VCRP survey data received in 2016, *Humulus Lupulus* (Hops) Extract was reported to be used in 362 formulations, 299 in leave-on formulations and 60 in rinse-off formulations. *Humulus Lupulus* (Hops) Cone Extract and *Humulus Lupulus* (Hops) Strobile are reported to be used in 4 and 7 cosmetic formulations, respectively. *Humulus Lupulus* (Hops) Extract has the highest reported maximum concentration of use; it is used at up to 0.6% in face and neck products. The maximum concentration of use for *Humulus Lupulus* (Hops) Cone Extract and *Humulus Lupulus* (Hops) Flower Extract are reported to be 0.00055% and 0.001%, respectively.

Rats fed a low-fat diet, a high-fat diet, or high-fat diet supplemented with 1% xanthohumol-rich extract of *Humulus Lupulus* (Hops) Cone Extracts for 41 days and male mice were fed a normal diet, a high-fat diet, or high-fat diets supplemented with 2% or 5% of various extracts of *Humulus Lupulus* (Hops) Cone Extracts for 20 weeks had no mortalities or adverse effects reported for any group. The additions of any of the *Humulus lupulus* (hops) extracts reduced the effects of the high-fat diet with regards to weight gain. The weights of livers and mesenteric and epididymal adipose tissues of mice fed the supplemented high-fat diets were similar to the controls as were the plasma glucose levels at the end of the test period.

An aqueous *Humulus Lupulus* (Hops) Cone Extract (10 to 400 mg/ $\mu$ L in ethanol) was weakly mutagenic (an increase in induced revertants of 2 to 4 times the controls) to *S. typhimurium* with and without metabolic activation. In another assay, a *Humulus Lupulus* (Hops) Cone Extract was not mutagenic to *S. typhimurium* and *E. coli* at up to 10,000  $\mu$ g/plate, with and without metabolic activation.

8-PN has been shown to be the source of the estrogenic activity of *Humulus lupulus* (hops) plants. It mimics the action of 17 $\beta$ -estradiol, albeit with a lesser (10- to 20,000-fold) potency.

In a 2-week cumulative irritation test of a product containing *Humulus Lupulus* (Hops) Extract (0.125%), the test product did not demonstrate a significant irritation potential in human skin. In a human patch test of a product containing *Humulus Lupulus* (Hops) Cone Extract at 0.06% to 0.12%, the irritation index was 0.04 (out of 5) and was rated a non-irritant.

The causative agents of *Humulus lupulus* (hops) plant-induced contact skin reactions have not been established. In *Humulus lupulus* (hops) harvesters, the dermatitis has been attributed to mechanical abrasion by the rough hairs on the climbing stem. It has also been suggested that lupulin, the yellow powdery secretion of the glandular hairs on the scales of the strobiles, may be responsible for the irritation.

In a human maximization test of a product containing *Humulus Lupulus* (Hops) Extract (0.125%), the test product did not demonstrate contact sensitization potential.

Combining the complimentary results of the *in vitro* HET-CAM/CFIO assays of a cosmetic product containing *Humulus Lupulus* (Hops) Cone Extract at 0.6% to 1.2% showed that this product was rated as a slight ocular irritant.

In a 4-week use study (n=48) of an eye cream that contained *Humulus Lupulus* (Hops) Extract (0.125%), the test material did not demonstrate potential for eliciting ophthalmic irritation.

In a survey of farmers, exposure to *Humulus lupulus* (hops) was reported to cause the greatest number of skin problems; 14 of 73 (19.2%) of the farmers reported work-related skin symptoms, 11% of which were caused by *Humulus lupulus* (hops). There were one, two, three, and four positive SPTs to the following *Humulus lupulus* (hops) allergen preparations: cone extract in glycerol, cone extract in saline, leaf extract in glycerol, and leaf extract in saline, respectively.

In a study of occupational respiratory disease in *Humulus lupulus* (hops) workers, using Workers' Compensation claims filed by *Humulus lupulus* (hops) workers for respiratory disease, the incidence rate of respiratory disease in *Humulus lupulus* (hops) workers was 15 cases per 10,000 full-time workers, which was 30 times greater than the incidence rate for field vegetable crop workers. The authors concluded that occupational exposure to *Humulus lupulus* (hops) dust is associated with respiratory disease; respiratory disease rates were higher in hop workers than in a comparison group of agricultural workers.

In a study of occupational exposure of brewery workers to organic dusts, including *Humulus lupulus* (hops), the potential to affect respiratory function and immunological status was examined. A large number of brewery workers complained of acute symptoms that developed during the work shift. Lung function tests were decreased compared to predicted levels. There was a greater instance of positive SPTs in brewery workers for *Humulus lupulus* (hops) than in controls (15% vs 3%). There were increased serum levels of total IgE in 34 of 97 (45.1%) brewery workers compared to controls, 1 of 76 (2.7%). However, workers with positive SPTs had a prevalence of chronic respiratory symptoms and lung function changes similar to those of workers with negative SPTs. The authors concluded that the data suggests that both smoking and dust exposure in the brewery industry may be responsible for the development of respiratory impairment and immunological reactions.

There were case studies of subjects becoming sensitized to *Humulus lupulus* (hops) plants or the constituent  $\beta$ -myrcene while working with the plant on farms, laboratories, and in breweries.

## DISCUSSION

*To be developed.*

## CONCLUSION

*To be developed.*

**TABLES****Table 1.** Definitions and functions of the *Humulus lupulus* (hops)-derived ingredients in this safety assessment.<sup>1</sup>

<b>Ingredient</b>	<b>Definition</b>	<b>Functions</b>
Humulus Lupulus (Hops) Extract 8016-25-9 8060-28-4	Humulus Lupulus (Hops) Extract is the extract of the whole plant, <i>Humulus lupulus</i> .	Fragrance ingredient; skin-conditioning agent – miscellaneous
Humulus Lupulus (Hops) Cone Extract	Humulus Lupulus (Hops) Cone Extract is the extract of the cone of <i>Humulus lupulus</i> .	Antimicrobial agent; antiperspirant agent; hair conditioning agent
Humulus Lupulus (Hops) Cone Oil 8007-04-3	Humulus Lupulus (Hops) Cone Oil is the volatile oil obtained from the cones of <i>Humulus lupulus</i> .	Fragrance ingredient
Humulus Lupulus (Hops) Flower Extract	Humulus Lupulus (Hops) Flower Extract is the extract of the flowers of <i>Humulus lupulus</i> .	Skin-conditioning agent – miscellaneous
Humulus Lupulus (Hops) Stem Extract	Humulus Lupulus (Hops) Stem Extract is the extract of the stems of <i>Humulus lupulus</i> .	Skin protectant
Humulus Lupulus (Hops) Strobile	Humulus Lupulus (Hops) Strobile is the strobile obtained from <i>Humulus lupulus</i> .	None reported

**Table 2.** Chemical and physical properties of *Humulus Lupulus* (Hops) Extract.

<b>Property</b>	<b>Value</b>	<b>Reference</b>
<b>Humulus Lupulus (Hops) Extract</b>		
Physical Form	Oil	55
	Viscous liquid <sup>a</sup>	99
Color	Greenish-yellow-reddish brown	55
	Yellow/orange to brown/green <sup>a</sup>	99
Odor	Harsh and bitter	55
	Citrus, tropical fruit, stone fruit, pine, cedar, floral, spicy, herbal, earthy, tobacco, onion/garlic and/or grassy	10
Density/Specific Gravity @ 20°C	0.883-0.900	55
	850-1100 <sup>a</sup>	99
Vapor Density mmHg	>1	55
Melting Point °C	40-60 <sup>a</sup>	99
Water Solubility	Negligible	55
	Insoluble <sup>a</sup>	99

<sup>a</sup> A CO<sub>2</sub> extract of dried cones manufactured for use as a food ingredient

**Table 3.** FDA regulations on the method of manufacture and residual solvents in “modified hop extract”, as a food additive used or intended for use as a flavoring agent in the brewing of beer. [21CFR172.560]

<b>Method of Manufacture</b>	<b>Solvent/Impurities restrictions</b>
(b)(1) The additive is manufactured from a hexane extract of hops by simultaneous isomerization and selective reduction in an alkaline aqueous medium with sodium borohydride, whereby the additive meets the following specifications: A solution of the food additive solids is made up in approximately 0.012 <i>n</i> alkaline methyl alcohol (6 mL of 1 <i>n</i> sodium hydroxide diluted to 500 mL with methyl alcohol) to show an absorbance at 253 m $\mu$ of 0.6 to 0.9/cm. (This absorbance is obtained by approximately 0.03 mg solids/mL.) The ultraviolet absorption spectrum of this solution exhibits the following characteristics: An absorption peak at 253 m $\mu$ ; no absorption peak at 325 to 330 m $\mu$ ; the absorbance at 268 m $\mu$ does not exceed the absorbance at 272 m $\mu$ .	The boron content of the food additive does not exceed 310 ppm (0.0310%), calculated as boron.
(b)(2) The additive is manufactured from hops by a sequence of extractions and fractionations, using benzene, light petroleum spirits, and methyl alcohol as solvents, followed by isomerization by potassium carbonate treatment. The light petroleum spirits and benzene solvents shall comply with the specifications in §172.250 except that the boiling point range for light petroleum spirits is 150°F to 300°F.	Residues of solvents in the modified hop extract shall not exceed 1.0 ppm of benzene, 1.0 ppm of light petroleum spirits, and 250 ppm of methyl alcohol.

**Table 3.** FDA regulations on the method of manufacture and residual solvents in “modified hop extract”, as a food additive used or intended for use as a flavoring agent in the brewing of beer. [21CFR172.560]

Method of Manufacture	Solvent/Impurities restrictions
(b)(3) The additive is manufactured from hops by a sequence of extractions and fractionations, using methylene chloride, hexane, and methyl alcohol as solvents, followed by isomerization by sodium hydroxide treatment.	Residues of the solvents in the modified hop extract shall not exceed 5 ppm of methylene chloride, 25 ppm of hexane, and 100 ppm of methyl alcohol.
(b)(4) The additive is manufactured from hops by a sequence of extractions and fractionations, using benzene, light petroleum spirits, methyl alcohol, <i>n</i> -butyl alcohol, and ethyl acetate as solvents, followed by isomerization by potassium carbonate treatment. The light petroleum spirits and benzene solvents shall comply with the specifications in §172.250 except that the boiling point range for light petroleum spirits is 150°F to 300°F.	Residues of solvents in the modified hop extract shall not exceed 1.0 ppm of benzene, 1.0 ppm of light petroleum spirits, 50 ppm of methyl alcohol, 50 ppm of <i>n</i> -butyl alcohol, and 1 ppm of ethyl acetate.
(b)(5) The additive is manufactured from hops by an initial extraction and fractionation using one or more of the following solvents: ethylene dichloride, hexane, isopropyl alcohol, methyl alcohol, methylene chloride, trichloroethylene, and water; followed by isomerization by calcium chloride or magnesium chloride treatment in ethylene dichloride, methylene chloride, or trichloroethylene and a further sequence of extractions and fractionations using one or more of the solvents set forth in this paragraph.	Residues of the solvents in the modified hop extract shall not exceed 125 ppm of hexane; 150 ppm of ethylene dichloride, methylene chloride, or trichloroethylene; or 250 ppm of isopropyl alcohol or methyl alcohol.
(b)(6) The additive is manufactured from hops by an initial extraction and fractionation using one or more of the solvents listed in paragraph (b)(5) of this section followed by: hydrogenation using palladium as a catalyst in methyl alcohol, ethyl alcohol, or isopropyl alcohol acidified with hydrochloric or sulfuric acid; oxidation with peracetic acid; isomerization by calcium chloride or magnesium chloride treatment in ethylene dichloride, methylene chloride, or trichloroethylene (alternatively, the hydrogenation and isomerization steps may be performed in reverse order); and a further sequence of extractions and fractionations using one or more of the solvents listed in paragraph (b)(5) of this section.	The additive shall meet the residue limitations as prescribed in paragraph (b)(5) of this section.
(b)(7) The additive is manufactured from hops as set forth in paragraph (b)(6) of this section followed by reduction with sodium borohydride in aqueous alkaline methyl alcohol, and a sequence of extractions and fractionations using one or more of the solvents listed in paragraph (b)(5) of this section.	The additive shall meet the residue limitations as prescribed in paragraph (b)(5) of this section, and a boron content level not in excess of 300 ppm (0.0300%), calculated as boron.
(b)(8) The additive is manufactured from hops as a nonisomerizable nonvolatile hop resin by an initial extraction and fractionation using one or more of the solvents listed in paragraph (b)(5) of this section followed by a sequence of aqueous extractions. The additive is added to the wort before or during cooking in the manufacture of beer.	Removal of nonaqueous solvents to less than 0.5%.

**Table 4.** Fresh *Humulus lupulus* (hops) strobile composition.<sup>33</sup>

Principle Components	Concentration (%w/w)
Cellulose + lignin	40.0-50.0
Protein	15.0
$\alpha$ -Acids	2.0-17.0
$\beta$ -Acids	2.0-10.0
Water	8.0-12.0
Minerals	8.0
Polyphenols and tannins	3.0-6.0
Lipids and fatty acids	1.0-5.0
Hop oil	0.5-3.0
Monosaccharides	2.0
Pectin	2.0

**Table 5.** Dried *Humulus lupulus* (hops) strobile composition.<sup>2</sup>

Principle Components	Concentration (%)
Cellulose, etc.	43
Proteins	15
Amino acids	0.1
Moisture	10
Ash	8
Polyphenols (tannins)	4
Essential oil	0.5-3
Waxes and steroids	Trace-25
Monosaccharides	2
Pectins	2
Total resins	15-30

**Table 6.** Composition of polyphenols and their concentrations in *Humulus lupulus* (hops).<sup>2</sup>

Polyphenols and Polyphenol Groups	Concentration (%)
<b>Phenolic carboxylic acids</b>	
Benzoic acid derivatives	<0.01
Cinnamic acid derivatives	0.01-0.03
<b>Flavonoids</b>	
8- or 6-Prenylnaringenin	<0.01
Acylphloroglucinol derivatives (multifidols)	0.05-0.50
Catechins and epicatechins	0.03-0.30
Kaempferol	0.02-0.24
Oligomeric proanthocyanidins	0.20-0.50
Quercetin	0.05-0.23
Xanthohumol	0.20-1.70
<b>Higher molecular substances</b>	
Catechin tanning agents and tannins	2.00-7.00

**Table 7.** Constituents found in the aqueous extract of 10 cultivars of “aroma”-type *Humulus Lupulus* (Hops) Cone Extracts analyzed by GC/MS.<sup>43</sup>

Constituent	Composition range (%) <sup>a</sup>
(2E)-Dodecen-1-ol	ND-0.2
(2E)-Hexenal	0-0.1
(2Z,6E)-Farnesol	0.2-0.9
(6Z)-Pentadecen-2-one	ND-2.5
(E)-Caryophyllene	4.1-11.3
(E)-Nerolidol	ND-0.3
(E)-β-Farnesene	ND-8.1
(E)-β-Ocimene	0-0.2
(E,E)-α-Farnesene	0.1-0.9
(Z)-Caryophyllene	ND-0.1
14-Hydroxy-(E)-caryophyllene	ND-0.8
1- <i>epi</i> -Cubanol	ND-0.7
1-Octen-3-ol	0-0.2
2-Decanone	0-0.5
2-Dodecanone	0-0.4
2-Methylbutanoic acid	0-0.6
2-Methylbutyl 2-methylbutyrate	0-0.3
2-Methylbutyl isovalerate	0-0.1
2-Nonanone	0-0.5
2-Pentadecanone	ND-0.8
2-Tridecanone	ND-1.6
2-Undecanone	0.1-1.6
3-Methyl-2-buten-1-ol	0-0.5
3-Methyl-2-butenal	0-0.9
3-Methyl-2-pentanone	0-1.0
4-Methyl-2-pentanone	0-3.4
4-Methyl-2-pentenolide	0.1-1.5
6,7-Epoxyterpinene	0-0.3
6-Methyl-5-hepten-2-one	0-0.4
9-Decenoic acid	0-0.5
<i>ar</i> -Curcumene	0.2-1.2
Cadalene	ND-0.4
Caryophylla-4(12),8(13)-dien-5-ol	ND-0.7
Caryophyllene Oxide	0.6-3.0
<i>cis</i> -Linalool oxide (furanoid)	0-0.2
<i>cis</i> -Linalool oxide (furanoid)	0-0.6
Decanoic acid	0-trace

**Table 7.** Constituents found in the aqueous extract of 10 cultivars of “aroma”-type *Humulus Lupulus* (Hops) Cone Extracts analyzed by GC/MS.<sup>43</sup>

Constituent	Composition range (%) <sup>a</sup>
Dendrolasin	ND-0.1
Furfural	Trace
Geranial	0-0.2
Geraniol	0-1.1
Geranyl acetate	0-1.8
Geranyl isobutyrate	ND-2.1
Geranyl propionate	ND-1.7
Heptyl isobutanoate	0-trace
Hexanal	0-0.2
Humulene epoxide II	1.4-7.9
Isoamyl isobutyrate	0.3-1.6
Isoamyl propionate	0-0.3
Isobutyl isobutyrate	0-0.3
Isobutyl isopentanoate	0-0.8
Isovaleric acid	0-3.8
Limonene/β-Phellandrene	0-1.2
Linalool	0.2-3.2
Methyl (4Z)-decenoate	0.4-2.2
Methyl decanoate	0-1.0
Methyl geranate	0-0.7
Methyl heptanoate	0-1.1
Methyl nonanoate	0-0.5
Methyl nonenoate	0-0.3
Methyl octanoate	0-0.1
Myrcene	8-52.4
Neral	0-trace
Neryl acetate	0-0.1
Neryl isobutyrate	ND-trace
<i>n</i> -Nonanal	0-0.5
Nonanoic acid	0-0.4
Octanoic acid	0-0.1
Palmitic acid	ND-0.5
Perilla alcohol	0-0.2
Phenylacetaldehyde	0-0.1
Prenyl isobutyrate	0-trace
Tetradecane	ND-trace
<i>trans</i> -Cadina-1(6),4-diene	ND-0.1

**Table 7.** Constituents found in the aqueous extract of 10 cultivars of “aroma”-type *Humulus Lupulus* (Hops) Cone Extracts analyzed by GC/MS.<sup>43</sup>

Constituent	Composition range (%) <sup>a</sup>
<i>trans</i> -Cadina-1,4-diene	ND-0.1
<i>trans</i> -Calamenene	ND-1.2
Unidentified	0-1.5
Unidentified	0-0.7
Unidentified	0.4-9.7
Unidentified	0.1-1.8
Unidentified	0.2-3.5
$\alpha$ -Amorphene	ND-0.1
$\alpha$ -Cadinene	Trace-0.2
$\alpha$ -Cadinol	0.1-1.2
$\alpha$ -Calacorene	Trace-0.4
$\alpha$ -Copaene	0.3-0.9
$\alpha$ -Humulene	12.6-51.2
$\alpha$ -Humulene hydrate	0.3-2.9
$\alpha$ -Muurolene	0.3-0.6
$\alpha$ -Muurolol	ND-0.1
$\alpha$ -Pinene	0-0.4
$\alpha$ -Selinene	ND-1.8
$\alpha$ -Terpineol	0-0.2
$\alpha$ - <i>trans</i> -Bergamotene	ND-1.7
$\alpha$ -Ylangene	Trace-0.3
$\beta$ -Copaene	0.1-0.2

**Table 7.** Constituents found in the aqueous extract of 10 cultivars of “aroma”-type *Humulus Lupulus* (Hops) Cone Extracts analyzed by GC/MS.<sup>43</sup>

Constituent	Composition range (%) <sup>a</sup>
$\beta$ -Pinene	0.2-1.5
$\beta$ -Selinene	0.2-1.2
$\gamma$ -Cadinene	ND-1.5
$\gamma$ -Muurolene	ND-1.7
$\delta$ -Cadinene	1.1-2.4
$\delta$ -Selinene	ND-1.2
$\tau$ -Cadinol	0.2-1.1
Constituent Groups	
Aldehydes	ND-1.3
Aliphatic alcohols	ND-1.1
Aliphatic ketones	0.4-8.9
Carboxylic acids	ND-6.4
Carboxylic esters	1.2-9.1
Monoterpene hydrocarbons	9.4-54.5
Oxygenated monoterpenoids	0.4-3.5
Oxygenated sesquiterpenoids	3.3-18.4
Sesquiterpene hydrocarbons	0.4-3.5

<sup>a</sup> Percent composition determined from total ion current count without correction.  
GC/MS= gas chromatography – mass spectrometry

**Table 8.** Compounds in *Humulus Lupulus* (Hops) Cone Oil.<sup>47</sup>

Classification	Compound
Hydrocarbon, Monoterpene	$\alpha$ -Pinene
	$\beta$ -Pinene
	$\beta$ -Myrcene
	Limonene
Hydrocarbon, Sesquiterpene	$\rho$ -Cymene
	Caryophyllene
	E, $\beta$ -Farnesene
	Humulene
Oxygenated, Ester	Methyl Heptonoate
Oxygenated, Monoterpene Alcohol	Geraniol
	Linalool
Oxygenated, Monoterpene	Citronellol
Oxygenated, Sesquiterpene Alcohol	Farnesol
Oxygenated, Other	Citral
Oxygenated, Monoterpene or Ester	Geranyl Acetate
Oxygenated, Epoxide	Humulene Epoxide 1
	Humulene Epoxide 2

**Table 9.** Composition of compounds in *Humulus Lupulus* (Hops) Cone Oil.<sup>100</sup>

Compound	Percentage
$\alpha$ -Caryophyllene	36.7
$\beta$ -Myrcene	25.4
$\beta$ -Caryophyllene	9.8
$\gamma$ -Cadinene	5.5
$\delta$ -Cadinene	4.1
$\alpha$ -Muurolene	3.0
$\alpha$ -Copaene	1.5
Geraniol	1.5
Sabinene	1.4
$\beta$ -Selinene	1.2
Linalool	1.1
$\alpha$ -Selinene	1.0
( <i>E</i> )- $\beta$ -Ocimene	1.0

**Table 10.** Constituents of concern found in *Humulus Lupulus* (hops).

Constituent	Concern	Reference
8-Prenylnaringenin (8-PN), 6-prenylnaringenin (6-PN), 8-geranylnaringenin (8-GN) and 6,8-diprenylnaringenin (6,8-PN)	Estrogenic activity. 8-PN is found in the strobiles of <i>Humulus lupulus</i> (hops) and has been proposed as a possible treatment for menopausal hot flashes. Subcutaneous administration of 8-PN to rats has estrogenic activity (as measured by the effect on uterine and vaginal weights), but is 20,000-fold less potent than estradiol. <i>In vitro</i> studies showed that 8-PN generally mimicked the action of 17 $\beta$ -estradiol with a lesser (10- to 20,000-fold) potency.	39,54,77-83,101
Geraniol	Potential dermal sensitizer	100,102-104
Limonene	Potential dermal sensitizer	100,105
Linalool	Potential dermal sensitizer. Safe at up to 4.3% (20% in a consumer fragrance)	106
$\beta$ -Myrcene	Potential dermal irritant/sensitizer; dermatitis, conjunctivitis, somnolence, and asthma-like symptoms	8,98,100
Quercetin	Positive genotoxic effect in an Ames assay Consistently genotoxic in <i>in vitro</i> tests and in some <i>in vivo</i> studies of i.p. exposures, but was consistently nongenotoxic in oral exposure studies	107,108
Sesquiterpene lactones	Potential dermal sensitizers	9,109

**Table 11.** Frequency of use according to duration and exposure of *Humulus lupulus* (hops)-derived ingredients.<sup>56,57</sup>

Use type	Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)	
	Uses		Uses		Uses		Uses	
	Humulus Lupulus (Hops) Extract		Humulus Lupulus (Hops) Cone Extract		Humulus Lupulus (Hops) Flower Extract		Humulus Lupulus (Hops) Strobile	
<b>Total/range</b>	<b>362</b>	<b>0.000006-0.6</b>	<b>4</b>	<b>0.00055</b>	<b>NR</b>	<b>0.000055-0.001</b>	<b>7</b>	<b>NR</b>
<i>Duration of use</i>								
Leave-on	299	0.00005-0.6	3	0.00055	NR	0.001	5	NR
Rinse-off	60	0.000006-0.38	1	NR	NR	0.000055-0.001	2	NR
Diluted for (bath) use	3	NR	NR	NR	NR	NR	NR	NR
<i>Exposure type<sup>a</sup></i>								
Eye area	7	0.0024-0.13	1	NR	NR	NR	2	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	2; 178 <sup>b</sup> ; 80 <sup>c</sup>	0.00008-0.0002; 0.00005-0.1 <sup>b</sup>	1 <sup>b</sup> ; 1 <sup>c</sup>	NR	NR	NR	1 <sup>b</sup>	NR
Incidental inhalation-powders	80 <sup>c</sup>	0.0003-0.6 <sup>d</sup>	1 <sup>c</sup>	0.00055	NR	NR	NR	NR
Dermal contact	285	0.0001-0.6	4	0.00055	NR	0.000055	6	NR
Deodorant (underarm)	8 <sup>b</sup>	0.13 <sup>c</sup>	NR	NR	NR	NR	NR	NR
Hair-noncoloring	77	0.00005-0.2	NR	NR	NR	0.001	NR	NR
Hair-coloring	NR	0.000006-0.00001	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	5	0.0003-0.084	1	NR	NR	0.000055	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

<sup>a</sup> Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

<sup>b</sup> It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

<sup>c</sup> Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

<sup>d</sup> It is possible these products may be powders, but it is not specified whether the reported uses are powders.

<sup>e</sup> Not a spray

**Table 12.** Case reports of sensitization to *Humulus lupulus* (hops).

Presentation	Data, Tests, and Results	Reference
A 57-years-old female farmer presented with occupational airborne dermatitis and hand dermatitis from <i>Humulus lupulus</i> (hops).	Disease appeared at the age of 46, after 30 years of working with <i>Humulus lupulus</i> (hops) without any health problems. Patient had erythema of the skin of face, neck and upper chest, edema of eyelids, conjunctivitis, as well as acute dermatitis of hands. Symptoms were provoked by exposure to fresh or dried <i>Humulus lupulus</i> (hops). Symptoms appeared after 30 min of work and persisted over 1 to 2 days. There were no other skin or allergic problems. Skin tests were conducted with <i>Humulus lupulus</i> (hops) leaves (saline extract: prick positive, patch negative; glycerol extract: prick positive, patch negative) and hop strobiles (saline extract: prick positive, patch negative; glycerol extract: prick negative, patch positive after 48 and 72 h). Despite discontinuing work, patient experienced several relapses of her dermatitis. A cream and an herbal sedative, both containing <i>Humulus lupulus</i> (hops) extract, were identified as causing her dermatitis. During next <i>Humulus lupulus</i> (hops) cultivation period it also turned out that physical proximity to her husband was provoking relapses of the patient's dermatitis. Husband said that sometimes he did not wash thoroughly after working with the plant.	95
An atopic 35-year-old male brewery worker with rhinoconjunctivitis diagnosis due to grass and olea pollen presented with occupational rhinoconjunctivitis after 3 years of exposure to <i>Humulus lupulus</i> (hops).	Subject had no symptoms when he was away from his work place. He was able to drink beer without symptoms. An SPT with a common commercial inhalants battery including pollens, mites, animal dander, molds, and latex was performed. Additionally, SPTs were performed using <i>Humulus lupulus</i> (hops) and barley extracts. Assays for specific IgE to barley, malt, corn, wheat and hops were also carried out. To demonstrate the patient's symptoms, a nasal challenge with <i>Humulus lupulus</i> (hops) extract was performed. SPTs were positive to grass, olive pollen, and <i>Humulus lupulus</i> (hops). Specific IgE was positive only to <i>Humulus lupulus</i> (hops). Nasal challenge with <i>Humulus lupulus</i> (hops) extract reproduced an immediate nasal response. SPTs with <i>Humulus lupulus</i> (hops) controls subjects (n=10) were negative.	96
A 29-year-old male subject, who had three episodes of urticaria-angioedema immediately after ingestion of peanuts, chestnuts, and banana over the last 4 years, the latter requiring emergency treatment.	Subject presented with urticaria on both hands while working with ripe dried <i>Humulus lupulus</i> (hops), though not with fresh <i>Humulus lupulus</i> (hops). SPTs were negative for common aeroallergens (soy, latex, rapeseed, and the fish nematode <i>Anisakis simplex</i> ) and positive for wheat and corn; controls (histamine and normal saline) had expected results. SPTs for banana, chestnut, walnut, almond, kiwi, avocado, and ripe dried <i>Humulus lupulus</i> (hops) were positive. Two additional atopic subjects served as controls; they had negative results for ripe dried <i>Humulus lupulus</i> (hops). Specific IgE to chestnut was 1.69kU/L, and ripe dried hops: 1.00 kU/L; total IgE: 64 IU/mL. Authors commented that <i>Humulus lupulus</i> (hops) rash as skin irritation has been known for several decades, but this subject could not be included in this category. A diagnosis of immunological contact urticaria due to dried <i>Humulus lupulus</i> (hops) by was made because: 1) work-related symptoms from handling dried <i>Humulus lupulus</i> (hops), but not fresh, 2) positive SPT, and 3) positive specific IgE. Authors hypothesized that <i>Humulus lupulus</i> (hops) drying process may transform certain proteins into allergens. Authors were not able to conclude if cross-reactivity between various fruits and dried <i>Humulus lupulus</i> (hops) was feasible.	8
A 43-year-old female subject who worked in a laboratory that investigated <i>Humulus lupulus</i> (hops), presented with conjunctivitis, rhinitis, bronchitis, and dermatitis of the face.	She had no history of asthma or hay fever or previous dermatitis or inflammation of the mucous membranes. In her workplace, the dried plant strobiles were pulverized in a mill, some of which became airborne; she had no exposure to <i>Humulus lupulus</i> (hops) pollen. The results of a patch test of the <i>Humulus lupulus</i> (hops) dust was ++ and an intradermal test of 0.1 mL aqueous <i>Humulus lupulus</i> (hops) extract was +++. She was able to drink beer with no symptoms.	97
A 28-year-old male subject who was a chemist for a brewery presented with sneezing, itching, hives, closed feeling in his throat, wheezing, shortness of breath, abdominal bloating, watering eyes, and irregular heartbeat.	His job required exposure to <i>Humulus lupulus</i> (hops) plants in the field and laboratory. In laboratory, he crushed and rubbed strobiles in his hands and inhaled for aroma. Laboratory also used pure $\beta$ -myrcene, which is a volatile oil. He had never had hay fever or asthma, but had a former allergy (watering eyes) to Siamese cats. As a child, milk ingestion would produce hives. Walnuts induced a burning feeling in his throat and stomach. Patch tests with crushed, dried <i>Humulus lupulus</i> (hops) flowers (two varieties) were negative. A patch test of $\beta$ -myrcene was positive after 4 h and strongly positive after 48 h. Strongly positive reactions were observed in scratch and intradermal tests to most pollens, house dust, pyrethrum, orris root, and grain dust; moderate reactions were observed to some molds and horse dander. Tests were negative for other molds and other animals. Drinking a beer did not produce symptoms unless he had been exposed to $\beta$ -myrcene.	98

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## 2016 VCRP Data for *Humulus lupulus* (Hops)-Derived Ingredients

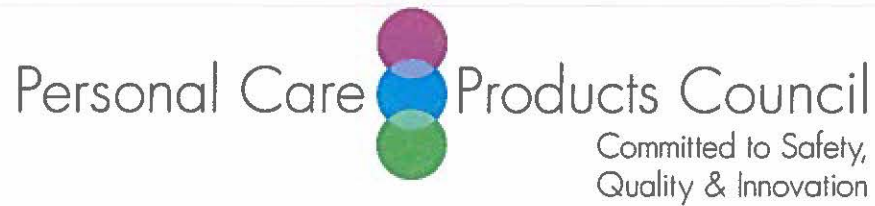
03G - Other Eye Makeup Preparations	Humulus Lupulus (Hops) Cone Extract	1
10A - Bath Soaps and Detergents	Humulus Lupulus (Hops) Cone Extract	1
12C - Face and Neck (exc shave)	Humulus Lupulus (Hops) Cone Extract	1
12G - Night	Humulus Lupulus (Hops) Cone Extract	1
		<b>4</b>

02B - Bubble Baths	Humulus Lupulus (Hops) Extract	3
03D - Eye Lotion	Humulus Lupulus (Hops) Extract	3
03G - Other Eye Makeup Preparations	Humulus Lupulus (Hops) Extract	4
05A - Hair Conditioner	Humulus Lupulus (Hops) Extract	20
05B - Hair Spray (aerosol fixatives)	Humulus Lupulus (Hops) Extract	2
05C - Hair Straighteners	Humulus Lupulus (Hops) Extract	2
05F - Shampoos (non-coloring)	Humulus Lupulus (Hops) Extract	21
05G - Tonics, Dressings, and Other Hair Grooming Aids	Humulus Lupulus (Hops) Extract	20
05I - Other Hair Preparations	Humulus Lupulus (Hops) Extract	12
07A - Blushers (all types)	Humulus Lupulus (Hops) Extract	4
07C - Foundations	Humulus Lupulus (Hops) Extract	1
10A - Bath Soaps and Detergents	Humulus Lupulus (Hops) Extract	2
10B - Deodorants (underarm)	Humulus Lupulus (Hops) Extract	8
12A - Cleansing	Humulus Lupulus (Hops) Extract	9
12C - Face and Neck (exc shave)	Humulus Lupulus (Hops) Extract	26
12D - Body and Hand (exc shave)	Humulus Lupulus (Hops) Extract	54
12F - Moisturizing	Humulus Lupulus (Hops) Extract	146
12G - Night	Humulus Lupulus (Hops) Extract	9
12H - Paste Masks (mud packs)	Humulus Lupulus (Hops) Extract	6
12I - Skin Fresheners	Humulus Lupulus (Hops) Extract	1
12J - Other Skin Care Preps	Humulus Lupulus (Hops) Extract	7
13A - Suntan Gels, Creams, and Liquids	Humulus Lupulus (Hops) Extract	1
13B - Indoor Tanning Preparations	Humulus Lupulus (Hops) Extract	1
		<b>362</b>

03D - Eye Lotion	Humulus Lupulus (Hops) Strobile	1
03F - Mascara	Humulus Lupulus (Hops) Strobile	1
07C - Foundations	Humulus Lupulus (Hops) Strobile	1
11G - Other Shaving Preparation Products	Humulus Lupulus (Hops) Strobile	2
12G - Night	Humulus Lupulus (Hops) Strobile	1
12J - Other Skin Care Preps	Humulus Lupulus (Hops) Strobile	1
		<b>7</b>

**There were no uses in the VCRP for:**

Humulus Lupulus (Hops) Cone Oil  
Humulus Lupulus (Hops) Flower Extract  
Humulus Lupulus (Hops) Stem Extract



**Memorandum**

**TO:** Lillian Gill, D.P.A.  
Director - COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Lange, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** July 26, 2016

**SUBJECT:** Humulus Lupulus (Hops) Extract

Anonymous. 2016. Summary information: Studies on an eye cream containing 0.125% Humulus Lupulus (Hops) Extract.

July 2016

**Summary Information - Studies on an Eye Cream Containing 0.125% Humulus Lupulus (Hops) Extract**

Study Type: Human maximization test  
Study Year: 2006  
Number of Subjects: 26  
Conclusions: The test product did not possess a detectable contact-sensitizing potential.

Study Type: Two-week cumulative irritation patch test  
Study Year: 2006  
Number of Subjects: 26  
Conclusions: The test product did not possess a significant irritation potential in human skin.

Study Type: Four-week use study - ocular irritation  
Study Year: 2006  
Number of Subjects: 48  
Conclusions: The test product did not demonstrate a potential for eliciting ophthalmic irritation.



**Memorandum**

**TO:** Lillian Gill, D.P.A.  
Director - COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Lange, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** July 26, 2016

**SUBJECT:** Humulus Lupulus (Hops) Cone Extract

Greentech. 2013. Regulatory data sheet: Hops Phytellene EG136.

Greentech. 2016. Certificate of analysis: Hops Phytellene EG136.

Greentech. 2013. Manufacturing process: Hops Phytellene EG136.

Greentech. 2016. Toxicological tests on Houblon Phytellene EG136 (Humulus Lupulus (Hops) Cone Extract) (summaries).



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**FICHE REGLEMENTAIRE**  
**REGULATORY DATA SHEET**

**HOUBLON PHYTELENE EG136 /  
HOPS PHYTELENE EG136**

Référence produit / Product reference : 320049

Nom INCI CTFA / CTFA INCI name	Propylene Glycol, Water, Humulus Lupulus (Hops) Cone Extract
Nom INCI EU / EU INCI name	Propylene Glycol, Aqua, Humulus Lupulus Cone Extract
N° CAS / CAS number	57-55-6, 7732-18-5, 8060-28-4
N° EINECS / EINECS number	200-338-0, 231-791-2, 232-504-3

***COMPOSITION CENTESIMALE FINALE / FINAL CENTESIMAL COMPOSITION***

<b>Propylene Glycol</b>	47.5-52.5%
<b>Water</b>	46.3-51.9%
<b>Humulus Lupulus Cone Extract</b>	0.6-1.2%

***REGLEMENTATION COSMETIQUE / COSMETIC REGULATION***

<b>REACH</b>	Extrait de houblon non concerné quantité produite par an inférieure à 1 tonne (matière sèche) / Hops extract not concerned quantity produced per year lower than 1 ton (dry matter)  Propylene Glycol enregistré REACH n° 01-2119456809-23 / Propylene Glycol registered REACH n° 01-2119456809-23
<b>USA</b>	Autorisé en cosmétique avec le nom INCI CTFA et le n° CAS / Approved for use in cosmetic with INCI CTFA name and CAS number
<b>Canada</b>	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name
<b>Japan</b>	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name
<b>Australia</b>	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name

***DONNEES TOXICOLOGIQUES / TOXICOLOGICAL DATA***

**Irritation cutanée / Skin  
irritation**

**Irritation oculaire / Eye  
irritation**

**Non irritant / Not irritant**

**Légèrement irritant /  
Slightly irritant**

**Produit testé à 10% /  
Product tested at 10%**

**Produit testé à 10% /  
Product tested at 10%**

**Patch Test**

**Het cam  
CFIO Test**

**Jean-Yves BERTHON  
PDG / CEO**

**Po / For and on behalf**



**Noémie MORETTON  
Chargée réglementaire**

Doc 06-11 Ind.1



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**FICHE DE SPÉCIFICATION / SPECIFICATION DATA SHEET**  
 **BULLETIN D'ANALYSES / CERTIFICATE OF ANALYSIS**

**HOUBLON PHYTELÈNE EG 136 /  
HOPS PHYTELENE EG 136**

Référence du produit / Product reference : 320049

**DLUO : 36 mois / months**  
Conservation dans le contenant d'origine, sans ouverture, dans les conditions de stockage préconisées. Agitation conseillée avant utilisation / Keep in the original packaging, without opening, in the recommended storage conditions. Agitation advised before use  
**STOCKAGE / STORAGE : température ambiante (15-25°C)**  
room temperature (15-25°C)  
Pourcentage de plante mise en œuvre à l'extraction / Percentage of plant implemented during the extraction : approx. 10%

**COMPOSITION**

Houblon / Hops (*Humulus lupulus*)  
Propylène glycol / Propylene glycol  
Eau / Water

Cône / Cone

**PROCÉDURES**

**SPÉCIFICATIONS**

**CARACTÉRISTIQUES ORGANOLÉPTIQUES / ORGANOLEPTIC CHARACTERISTICS**

Aspect / Sight	GT001	Liquide limpide / Limpid liquid
Couleur / Color	GT002	Jaune ambré à brun rosé / Amber yellow to pink brown
Odeur / Odor	GT003	Aromatique / Aromatic

**CARACTÉRISTIQUES PHYSICO-CHIMIQUES / PHYSICAL AND CHEMICAL CHARACTERISTICS**

Solubilité : 10 % dans l'eau / Solubility 10 % in water	GT004	Soluble
Solubilité : 10% dans l'éthanol / Solubility 10% in ethanol	GT004	Partiellement soluble / Partially soluble
pH (direct)	GT005	5.0-5.8
Matière sèche / Dry matter (%)	GT006	0.6-1.2
Indice de réfraction / Refraction index	GT007	1.388-1.394
Densité / Density	GT071	1.040-1.043

**QUANTIFICATIONS**

Identification réaction colorée : flavonoïdes / Identification colored reaction : flavonoids	GT360	Conforme / Conform
Identification réaction colorée : dérivés phénoliques / Identification colored reaction : phenolic derivatives	GT360	Conforme / Conform
Identification CCM : flavonoïdes / Identification TLC : flavonoids	GT360	Conforme / Conform
Identification CCM : acides aminés / Identification TLC : amino acids	GT360	Conforme / Conform
Propylène glycol / Propylene glycol (%)	GT022	47.5-52.5
Métaux lourds / Heavy metal (ppm) (*)	Ph. Eur. 2.4.8 proc C	≤5

**ANALYSES MICROBIOLOGIQUES / MICROBIOLOGICAL ANALYSIS**

Germes aérobies totaux / Total germs (ufc/mL - cfu/mL)	GT100	<100
Levures et moisissures / Yeasts and moulds (ufc/mL - cfu/mL)	GT101	<100
Enterobactéries / Enterobacteria (ufc/mL - cfu/mL)	GT102	Absence

(\*) Analyses effectuées tous les 10 lots / Analysis realised every 10 batches

Version n°5 (28/01/16)

Version précédente / Precedent version : n°4 (08/12/09)

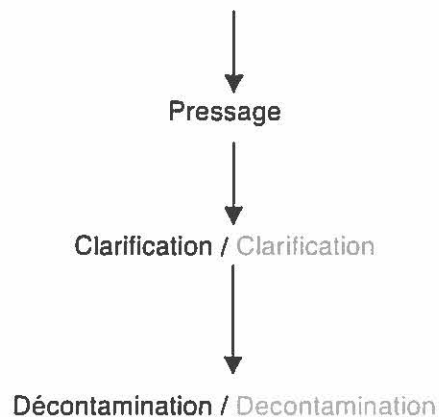
Version 2 (27/05/2013)



## PROCEDE D'OBTENTION / MANUFACTURING PROCESS

Nom Commercial / Trade Name : **HOUBLON PHYTELÈNE EG 136 (320049)/ HOPS PHYTELENE EG 136 (320049)**

Extraction des cônes de houblon dans de l'eau et du propylène Glycol /  
Extraction of hops cones in water and Propylene Glycol



Jean-Yves BERTHON  
PDG / CEO

Po / For and on behalf

A handwritten signature in black ink, appearing to read "Noémie Moretton".

Noémie MORETTON  
Chargée réglementaire

**TOXICOLOGICAL TESTS**  
**HOUBLON PHYTELENE EG136**

*Test done by BIOHC  
In May 2006*

**TOXICOLOGICAL TESTS BY ALTERNATIVE METHODS**

**HOUBLON PHYTELENE EG136**

*Propylene glycol, water, Humulus Lupulus (Hops) Cone Extract (0.6-1.2%)*

**Evaluation of cutaneous irritation (patch test)**

The study was performed according to the protocol referenced HICV of 31/07/2000.

12 volunteers (10 females and 2 males), from 24 to 56 years old were enrolled.

The product was applied 10% diluted in distilled water, on the upper back of the volunteers during 24 hours.

The area to be patched is examined prior to the application in order to verify the absence of dermatological disease. The occlusive epicutaneous test technique involves the use of aluminium cups of 8mm in diameter and 20 microliters in volume. Each cup covers about a 50mm area. They are affixed by two on an adhesive tape.

The patch is applied on the upper back of every subject and then covered with an adhesive tape. The product is left in contact with the skin during 24 hours.

Two control cups are applied in parallel. One receives a 1 % solution of sodium lauryl sulfate, the other receives distilled water.

The test product is generally applied as supplied.

After 30 minutes to 1 hour after patch removal, the panelist are subjected to a cutaneous examination. The aim of this examination is to point out any objective signs of irritation.

Six parameters ( Erythema, Edema, Vesicles, Cutaneous Dryness, Wrinkling, Glazing) will be researched and scored according to a 5 level score scale (0 through 4).

Depending on the index obtained, the product will be classed according to the following table

Index HICV	CLASSIFICATION
below 0.1	No irritant
From 0.1 to less than 0.3	Slightly irritant
From 0.3 to less than 0.5	Moderately irritant
Higher than 0.5	Irritant

A reading was performed 30 minutes after patch removal and 24 hours later in order to assess possible delayed reactions.

One subject developed a slight erythema to negative control so he was excluded from the interpretation of results.

The irritation index was calculated from the 11 subjects who were retained.

On test product site, no skin reaction was found on 9 subjects and very slight erythema was found on 2 subjects.

The score attributed allow to obtain an irritation index of: 0,04 which would class the test product as non irritant.

**To conclude, under the experimental condotions adopted, the product HOUBLON PHYTELENE EG136 10% diluted appeared non irritant to skin.**

### **Evaluation of ocular irritation (HET-CAM / CFIO tests)**

The studies were performed according to the experimental protocol referenced IOP of 11/23/2005.

The potential irritancy of a cosmetic compound is detected, on the one hand, by observing adverse changes which occur in the chorionallantoic membrane of the egg after exposure to test product (HET CAM assay) and, on the other hand by recording cytotoxicity obtained after contact with cornea fibroblasts (CFIO assay). This assay is proposed as an alternative test to the Draize Rabbit Eye test to assess the ocular irritancy potential of cosmetics and toiletries.

The results of a previous study on 107 cosmetics and toiletries have shown a good correlation between both alternative methods and the Draize test and the simultaneous use of both methods CFIO and HET CAM gave a satisfactory assessment of the ocular irritation potential of the cosmetics and toiletries. As there were no false negatives common to both methods, the risk of underestimating the ocular irritation potential was avoided.

#### **Chorion-allantoic membrane assay**

The ocular irritating potential is determined on embryonar eggs of White Leghorn of chicken. The product is put on the chorioallantoic membrane.

0,3 ml of the test product was applied on the CAM and eliminated by irrigation with 5 ml of saline solution, after 20 seconds.

The CAM is observed through a magnifying glass 30 seconds, then 2 and 5 minutes after application. This macroscopic examination consists in monitoring the appearance of the following phenomena : hyperaemia, haemorrhage, coagulation.

The observations are scored as follows depending on the time for each reaction to occur :

APPARITION TIMES	HYPERAEMIA	HAEMORRHAGE	COAGULATION
30 secondes	5	7	9
2 minutes	3	5	7
5 minutes	1	3	5

The score obtained for the 3 parameters are summed to give the irritation index for each egg. The mean score is calculated to obtain the primary irritancy index (IP-CAM).

The table below allows to classify the product depending on the index obtained :

Medium score	Classification
0 to $\leq$ 0.9	Pratically not irritant
1 to $\leq$ 4.9	Slightly irritant
5 to $\leq$ 8.9	Moderately irritant
9 to $\leq$ 21	Very irritant

The results obtained with « HOUBLON PHYTELENE EG136 » are referenced in the following table:

Assay	Concentration	Score/egg	IP-CAM	Classification
HOUBLON PHYTELENE EG136	10% (in distilled water)	0/0/0/0	0,00	Pratically not irritant

The positive control (3% SLS) tested in parallel induced clear irritating phenomena on every membrane and confirmed the good reactivity of eggs.

The results of the chorio-allantoic membrane assay allowed to obtain an IP-CAM of 0,00 which should class the tested product as **Pratically not irritant**.

#### CFIO test

(in Hank's Balanced Salt solution)

The product was studied 10% diluted. Cell viability was assessed at the end of the study by a MTT test.

After three contact times, cell viability intreated and control plates is evaluated by a colorimetric method, either MTT or neutral Red test.

After an incubation period of 2 to 3 hours with MTT or NR solution, the absorbance of the resulting coloured solution is measured at 570 nm(MTT) or 540nm (NR) using a microplate reader (Dynatech MR 5000).

From the optical densities (OD) measured for each contact time, a cytotoxicity percentage is calculated according to the formula :

$$\% (t) = ((OD_{CO} - OD_{TR}) / OD_{CO}) \times 100$$

where

OD<sub>CO</sub> = mean « control » OD

OD<sub>TR</sub> = mean « treated » OD

A mean cytotoxicity Index (MCI) is calculated according to the formula :

$$MCI = (\% (30mn) + 0.5 \times \% (1h) + 0.125 \times \% (4h)) / 3$$

From the value of MCI, an equivalent ocular irritation index (IO eq) is calculating according to the equations established from results obtained from in vivo/in vitro correlations studies.

$$IOeq = 0,922 \times MCI + 2,787$$

The IOeq index obtained allows to classify the test product according to the classification proposed by the « Journal de la République Française » dated July the 10<sup>th</sup>, 1992, for assessment of primary ocular irritation

IOeq	CLASSIFICATION
IOeq ≤ 15	Slightly Irritant
15 < IOeq ≤ 30	Moderately Irritant
30 < IOeq ≤ 50	Irritant
50 < IOeq	Very Irritant

The results obtained with « HOUBLON PHYTELENE EG136 » are referenced in the following table

	Control	Contact 30min	Contact 1 hour	Contact 4 hour
D.O.1 (O.D.1)	0,999	0,985	1,010	0,928
D.O.2 (O.D.2)	0,971	0,985	1,042	0,899
D.O.3 (O.D.3)	0,842	1,161	1,186	1,009
<b>Mean</b>	<b>0,937</b>	<b>1,044</b>	<b>1,079</b>	<b>0,945</b>
<b>Viability (%)</b>	<b>100</b>	<b>111</b>	<b>115</b>	<b>101</b>
<b>Cytotoxicity (%)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Mean cytotoxicity index (IMC-c)</b>	<b>0,0</b>			
<b>Ocular irritation index (IOeq)</b>	<b>2,8</b>		<b>Slightly irritant</b>	

The calculated scores MCI = 0,0 and IOeq = 2,8 would class the product as Slightly irritant.

Taking into account the complementary results of these two In Vitro methos, the ocular irritation potential of the test product is calculated according to the following table :

IP-CAM	Oleq		
	0 to 15	15 to 30	>30
0 to 4,9	Slightly irritant	Moderately iritant	Irritant / very irritant
5 to 8,9	Moderately irritant	Moerately irritant	Irritant / very irritant
9 to 21	Irritant / very irritant	Irritant / very irritant	Irritant / very irritant

With regard to the results obtained during both assay, and in compliance with the classification criteria retained, the test product « HOUBLON PHYTELENE EG136 » must be considered as slightly irritant to eye.



**Memorandum**

**TO:** Lillian Gill, D.P.A.  
Director - COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Lange, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** August 2, 2016

**SUBJECT:** Updated Concentration of Use by FDA Product Category: *Humulus lupulus*-Derived Ingredients

**Concentration of Use by FDA Product Category – *Humulus lupulus* (Hops)-Derived Ingredients\***

Humulus Lupulus (Hops) Extract

Humulus Lupulus (Hops) Flower Extract

Humulus Lupulus (Hops) Cone Extract

Humulus Lupulus (Hops) Stem Extract

Humulus Lupulus (Hops) Cone Oil

Humulus Lupulus (Hops) Strobile

<b>Ingredient</b>	<b>Product Category</b>	<b>Maximum Concentration of Use</b>
Humulus Lupulus (Hops) Extract	Eye lotion	0.0024-0.13%
Humulus Lupulus (Hops) Extract	Hair conditioners	0.0002-0.2%
Humulus Lupulus (Hops) Extract	Hair sprays Aerosol Pump spray	0.0002% 0.00008%
Humulus Lupulus (Hops) Extract	Rinses (noncoloring)	0.0002%
Humulus Lupulus (Hops) Extract	Shampoos (noncoloring)	0.002-0.2%
Humulus Lupulus (Hops) Extract	Tonics, dressings and other hair grooming aids Not spray	0.00005-0.1% 0.0002-0.0022%
Humulus Lupulus (Hops) Extract	Other hair preparations (noncoloring)	0.0002-0.15%
Humulus Lupulus (Hops) Extract	Hair dyes and colors	0.000006%
Humulus Lupulus (Hops) Extract	Hair rinses (coloring)	0.00001%
Humulus Lupulus (Hops) Extract	Foundations	0.0013-0.0028%
Humulus Lupulus (Hops) Extract	Bath soaps and detergents	0.0003-0.084%
Humulus Lupulus (Hops) Extract	Deodorants Not spray	0.13%
Humulus Lupulus (Hops) Extract	Aftershave lotions	0.001%
Humulus Lupulus (Hops) Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0001-0.001%
Humulus Lupulus (Hops) Extract	Face and neck products Not spray	0.006-0.6%
Humulus Lupulus (Hops) Extract	Body and hand products Not spray	0.0003-0.084%
Humulus Lupulus (Hops) Extract	Moisturizing products Not spray	0.001-0.2%
Humulus Lupulus (Hops) Extract	Paste masks and mud packs	0.0029-0.38%
Humulus Lupulus (Hops) Extract	Skin fresheners	0.0006-0.02%
Humulus Lupulus (Hops) Extract	Other skin care preparations	0.0003-0.013%
Humulus Lupulus (Hops) Extract	Suntan products Not spray	0.0006%
Humulus Lupulus (Hops) Extract	Indoor tanning preparations	0.0006%
Humulus Lupulus (Hops) Cone Extract	Face powders	0.00055%
Humulus Lupulus (Hops) Flower Extract	Hair conditioners	0.001%
Humulus Lupulus (Hops) Flower	Other hair preparations (noncoloring)	0.001%

Extract		
Humulus Lupulus (Hops) Flower Extract	Bath soaps and detergents	0.000055%

\*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2015


Table prepared October 5, 2015

Updated July 26, 2016: Eye lotion high concentration changed from 0.5% to 0.13%; body and hand products from 0.84% to 0.084%



## Memorandum

**TO:** Lillian Gill, D.P.A.  
Director - COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Lange, Ph.D.  
Industry Liaison to the CIR Expert Panel 

**DATE:** August 2, 2016

**SUBJECT:** Comments on the Scientific Literature Review: Safety Assessment of *Humulus lupulus* (Hops)-Derived Ingredients as Used in Cosmetics (released July 20, 2016)

### Key Issues

Table 8 and Tissarand and Young, *Essential Oil Safety*<sup>1</sup> indicate that  $\beta$ -myrcene is a major component of hop essential oil. Therefore, throughout the text, rather than myrcene, it should state  $\beta$ -myrcene.

The oil in this report is an essential oil. The reference to the plant oil report (a review of the safety of fixed oils from plants) in the Introduction is not appropriate.

### Additional Considerations

Introduction, Summary - Please correct "*lupus*"

Plant Identification - If "bine" is the correct term for hops, why is vine used in the first paragraph of the Plant Identification section?

Cosmetic Use - It is *Humulus Lupulus* (Hops) Flower Extract that was reported to be used up to 0.001% not *Humulus Lupulus* (Hops) Strobile. Please state the product categories in which *Humulus Lupulus* (Hops) Cone Extract was used at 0.00055% and *Humulus Lupulus* (Hops) Flower Extract was used at 0.001% (this also needs to be corrected in the Summary). Since the mucous membrane contact products were both bath soaps and detergents, please be specific and state, "bath soaps and detergents".

Non-Cosmetic Use - The labeling information from ECHA does not belong in the Non-Cosmetic Use section.

Genotoxicity - Reference 71 indicates that the vehicle control was water. Therefore, it is not correct to state "solvent not specified".

Table 2 - Please indicate that reference 95 concerns a CO<sub>2</sub> extract of dried cones manufactured for use as a food ingredient.

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<sup>1</sup>2<sup>nd</sup> edition, Churchill Livingstone Elsevier, 2014

Table 9 - Only listing "dermal sensitizer" as concerns for Geraniol, Limonene, Linalool and  $\beta$ -Myrcene is misleading and implies that no additional information is available. For example, there is an NTP bioassay on  $\beta$ -myrcene and a nomination background document that reviews numerous studies on this constituent. At minimum, a reference should be provided to a general review for each compound so that the reader could find more information about potential effects on other endpoints. Perhaps the constituent profiles in *Essential Oil Safety* would be helpful.

Table 10 - Please correct the concentration range in the spray row for Humulus Lupulus (Hops) Extract (it is currently stated as "0.0000-0.1").

Table 11 - It is not clear why Table 11 includes "irritation" in the title as the case reports concern sensitization.