SUPPLEMENT

Camellia Sinesis

Hydroquinone & p-Hydroxyanisole

Methylisothiazolinone

2015 Priorities

Tocopherols & Tocotrienols

Tripeptide-1, Hexapeptide-12

CIR EXPERT PANEL MEETING

MARCH 17-18, 2014

Cosmetic Ingredient Review

Commitment & Credibility since 1976

MEMORANDOM

To: CIR Expert Panel and Liaisons

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

Date: March 7, 2014

Subject: Data Submitted for *Camellia sinensis* – Derived Ingredients

To address the insufficient data announcement that was issued at the December, 2013 meeting, the Council has submitted new data which consists of the results of various assays on camellia sinensis leaf extracts in the forms of black tea extract, Chinese tea extract, green tea extract, and oolong tea extract. These data include:

- LD_{50}
- human/animal patch tests/ sensitization tests
- ocular irritation tests
- reverse mutation tests

A summary of the tests is provided but the full reports were not included.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: February 12, 2014

SUBJECT: Summary Safety Information: Camellia Sinensis Leaf Extract

Anonymous. 2014. Summary safety information on various Camellia Sinensis Leaf Extracts.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

● **Camellia Sinensis Leaf Extract** **February 12, 2014**

Black Tea Extract BG (Solids: 1.0%)

Ocular irritation test	Result : negative / Concentration of test solution: 100% / Species : rabbit
RIPT	Result : negative / Concentration of test solution : 100% / Number of subjects : 100 people
Human patch test	Result : negative / Concentration of test solution : 100% / Number of subjects : 10 people

Chinese Tea Extract LA (Solids: 0.85%)

Single dose toxicity test	Result : LD50>2000mg/kg / Species : mouse
Primary skin irritation test	Result : negative / Concentration of test solution : 100, 10% / Species : rabbit
Reverse mutation test (Ames test)	Result : negative / Concentration of test solution : 5000μg/0.1mL/plate / Bacterial strains : TA98, TA100, TA1535, TA1537, WP2uvrA

Green Tea Extract (Solids: 1.6%)

Single dose toxicity test	Result : LD50>2mL/kg / Species : rat
Primary skin irritation test	Result : negative / Concentration of test solution : 100%/ Species : rabbit
Ocular irritation test	Result : negative / Concentration of test solution : 100% / Species : rabbit

Oolong Tea Extract BG (Solids: 1.0%)

Single dose toxicity test	Result : LD50>2000mg/kg / Species : mouse
Primary skin irritation test	Result : negative / Concentration of test solution : 100, 10% / Species : rabbit
Dermal sensitization test	Result : negative / Concentration of test solution : 1st induction ; 50%, 2nd induction ; 25%, challenge ; 10, 5% / Species : guinea pig
Reverse mutation test (Ames test)	Result : negative / Concentration of test solution : 5000μg/0.1mL/plate / Bacterial strains : TA98, TA100, TA1535, TA1537, WP2uvrA

Cosmetic Ingredient Review

Commitment & Credibility since 1976

MEMORANDOM

To: CIR Expert Panel and Liaisons

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

Date: March 7, 2014

Subject: Additional Data on UV Nail Lamps for the Hydroquinone and *p*-Hydroxyanisole Safety Assessments

Additional data have been submitted by industry to further inform the Panel on UV nail lamps. The submissions include:

1) A letter from Dr. Robert M. Sayre discussing the data submitted by industry on the use of UV nail lamps, UV light penetration of nails, and the risk of UV damage of the hand.

2) Markova and Weinstock, 2013. Letter to the Editor discussing the evidence of the carcinogenicity UV lamps.

3) A PowerPoint presentation developed by Mr. Doug Schoon summerizing the submitted data.

4) Olson et al. 1966. Paper concluding that the dorsum of the hand responds less to UV light than other body surfaces.

5) Hui et al 2012, a book chapter on nail penetration enhancement to deliver antifungal drugs through the human nail.

6) Dowdy and Sayre, 2013 – Photobiological safety evaluation of UV nail lamps

RPTL
Rapid Precision Testing Laboratories

P.O. Box 1342, Cordova, TN 38088-1342
Ph (901) 386-0175 Fax (901) 386-7218
e-Mail: RPTL@aol.com Website: RapidPrecision.com

February 22, 2014

To Whom It May Concern:

Rapid Precisions Testing Laboratories, Inc. (RPTL), at the request of the Nail Manufacturers Council on Safety (NMC), evaluated six major brands of UV nail units including three that utilize UV producing LEDs as a primary UV source and three others which use standard fluorescent style lamps (aka bulbs). These UV nail units were chosen and provided by the NMC because they were considered representative of the major US domestic manufacturers that sell these units both domestically and internationally. RPTL's goal was to evaluate potential radiant hazards as defined in: ANSI/IESNA RP-27.1-05-Recommended Practice for Photobiological Safety for Lamps and Lamp System-General Requirements and RP-27.3-07-Risk Group Classification & Labeling.
The evaluation of hazard to skin inside the chamber at the intended use exposure geometry found that these devices fall into Risk Group Class 2-(Moderate Risk) with S (λ) weighted Actinic UV ranging 1.2-1.7 $\mu W/cm^2$ and permissible exposure times of 29.8-129.31 minutes. However, typical salon exposures are much shorter and less often; 10 minutes or less per hand and with exposures occurring only twice per month. At 20 cm on center, and 45° of the opening, radiant output was below maximum levels allowed for Exempt classification for UV risk to skin and eyes. S(λ) weighted actinic UV ranged 0.009-0.078 $\mu W/cm^2$ and unweighted Near UV (320-400 nm) ranged 0.091-0.483 mW/cm^2. Likewise the retinal photochemical blue light hazard was within Exempt range. Meter readings detected negligible IR consequently retinal thermal and cornea/lens IR were also Exempt. For one device however, the aphakic eye hazard (individuals implanted with non-UV blocking intraocular lenses) slightly exceeded this limit, rising into Class 1-(Low Risk). These specific devices were all found to be classified into Risk Group Class 2-(Moderate Risk) for Actinic UV to skin exposed inside the chamber with no other risks to normal individuals. RPTL has concluded that total exposure following typical salon exposure times and exposure steps accumulate to only a small fraction of the permissible daily exposure under ANSI/IESNA RP-27. These risks are further mitigated in realistic use scenarios since it is NOT likely to be a daily occurrence.

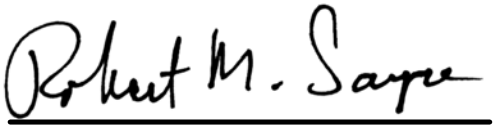
This study provides strong evidence that UV nail lamps are safe as used in professional nail salons. We found the UV nail lamps were even safer than originally expected and we believe the lamps tested are significantly less

hazardous than might have been anticipated based on the initial concerns raise. Also, prior research cited in our paper demonstrates the natural nail plate is a very efficient blocker of UV, protecting the nail bed making the UV exposure risks to the nail bed comparable to that of skin protected by high SPF topical sunscreen. In addition, additional research we have cited demonstrates the dorsum of the hand is 4 times more resistant to UV than the forehead or cheek and 3 1/2 times more resistant than a person's back, making the dorsum of the hand the most UV acclimatized, photo adapted, and UV-resistant body site.

When we compared UV nail lamps together with the UV output of tan bed lamps and found that the UV nail lamps are vastly less hazardous. The results indicate that a person could in their workplace, once every day, put their hand under a UV nail lamp for 25 minutes and remain within the permissible daily occupational exposure limits for workers, according to the applicable international ANSI/IESNA RP-27.1-05 standard. Our study also demonstrates that risks for development of non-melanoma skin cancer (NMSC) are very low when compared to normal noon sunlight. Of the types of UV that can cause NMSC, this study found, "…the UV nail lamps had 11-46 times less NMSC effective irradiance than an overhead 1 atmosphere solar spectrum [normal noon sunlight].

To put things into the proper perspective, it is very unlikely for anyone could become overexposure to UV through normal use of the UV nail lamps tested, since we considered it highly improbably that even the most dedicated nail salon client would approach an unsafe level of exposure. Even so, it is our recommendation after considering the comparatively trivial UV risks associated with UV nail lamps that special care should be taken in cases where potential users are taking medications that increase UV sensitivity. People who have been advised against venturing into natural sunlight without proper protection should also be cautious about using UV nail lamps. Another concern is that the incorrect replacement lamp/bulb may to be inserted into the UV nail unit, e.g. those emitting UV-B or UV-C could be harmful to the skin if accidently inserted. UV lamps/bulb should be replaced with the exactly the same original manufacturer's UV lamp/bulb that was supplied with the UV nail unit when it was purchased.

Thank you.



Robert M. Sayre, Ph.D.

Data2

Markova A, Weinstock MA. Risk of Skin Cancer Associated with the Use of UV Nail Lamp. *Journal of Investigative Dermatology.* 2013; (133): 1097-1099.

CIR Meeting

March 17, 2014

UV Curing in Nail Salons

Doug Schoon, M.S

Co- Chair of Nail Manufacturer's Council on Safety
Professional Beauty Association

Two types of UV Gel services are provided:

UV Gel “Enhancements”

UV Gel “Manicures”

Important to Note

Users should heed manufacturer's instructions/precautions and skin contact should always be avoided with uncured coatings.

Important to Note

Typically three layers of the UV coatings are applied stepwise to each fingernail and each layer is cured:

2-3 minutes under a fluorescent-style UV nail lamp

or

30-60 seconds using an LED-style UV nail lamp

Important to Note

Services are repeated every two or three weeks.

The skin is never burned or tanned even with regular use.

Wavelength ranges from ~410-350 nm

Study 1

"Do UV Nail Lamps Emit Unsafe Levels of Ultraviolet Light?"

Three Experts Rebut Claims that UV Nail Lamps are Unsafe for Skin

Schoon, Bryson and McConnell

Based on a study performed for the NMC by
Lighting Sciences, Scottsdale, Az.

Study 1:

An independent laboratory tested the two most widely used, brand name UV nail lamps, one nail lamp used four 9-watt bulbs, the other nail lamp used two 9-watt bulbs.

Study 1 Results: Assuming 10 minutes of exposure

UVB – less exposure than expected from natural sunlight.

10 minutes exposure = 17 seconds of additional sunlight.

Study 1 Results: Assuming 10 minutes of exposure

UVA – Output equivalent to spending an extra 2 minutes or less under natural sunlight each day between services.

Study 2

"Photobiological Safety Evaluation of UV Nail Lamps"

Dowdy, J., Sayre, R.
Photochemistry and Photobiology, 2013, 89:961-967

Study 2:

Tests conducted by photobiology researchers Dr. Robert Sayre and Dr. John Dowdy who tested six UV nail lamps using two separate internationally accepted standards to determine safety of UV nail lamps.

A. *Recommended Practice for Photobiological Safety for Lamps- Risk Group Classification & Labeling),* ANSI/IESNA RP-27.3-96

Study 2:

Tests conducted by photobiology researchers Dr. Robert Sayre and Dr. John Dowdy who tested six UV nail lamps using two separate internationally accepted standards to determine safety of UV nail lamps.

B. *Photocarcinogenesis action spectrum (non-melanoma skin cancers),* ISO 29077 CIE S 019/E, 2006-12-15

Study 2:

The following table shows the safe daily exposure level expressed as:

A. minutes of allowable exposure per day.

B. the actual percentages of the allowable daily exposure, assuming 10 minutes of salon exposure.

Study 2 Results*:

Lamp 1-	29.8 minutes permissible daily exposure time
(1.676 μW/cm2)	34% of permissible daily occupational exposure
Lamp 2-	36.0 minutes permissible daily exposure time
(1.2-1.4 μW/cm^2)	28% of permissible daily occupational exposure
Lamp 3-	57.1 minutes permissible daily exposure time
(1.02 μW/cm^2)	17.5% of permissible daily occupational exposure
Lamp 4-	129.3 minutes permissible daily exposure time
(0.39 μW/cm^2)	7.7% of permissible daily occupational exposure

** Recommended Practice for Photobiological Safety for Lamps- Risk Group Classification & Labeling"* ANSI/IESNA RP-27.3-96

Study 2 Results*:

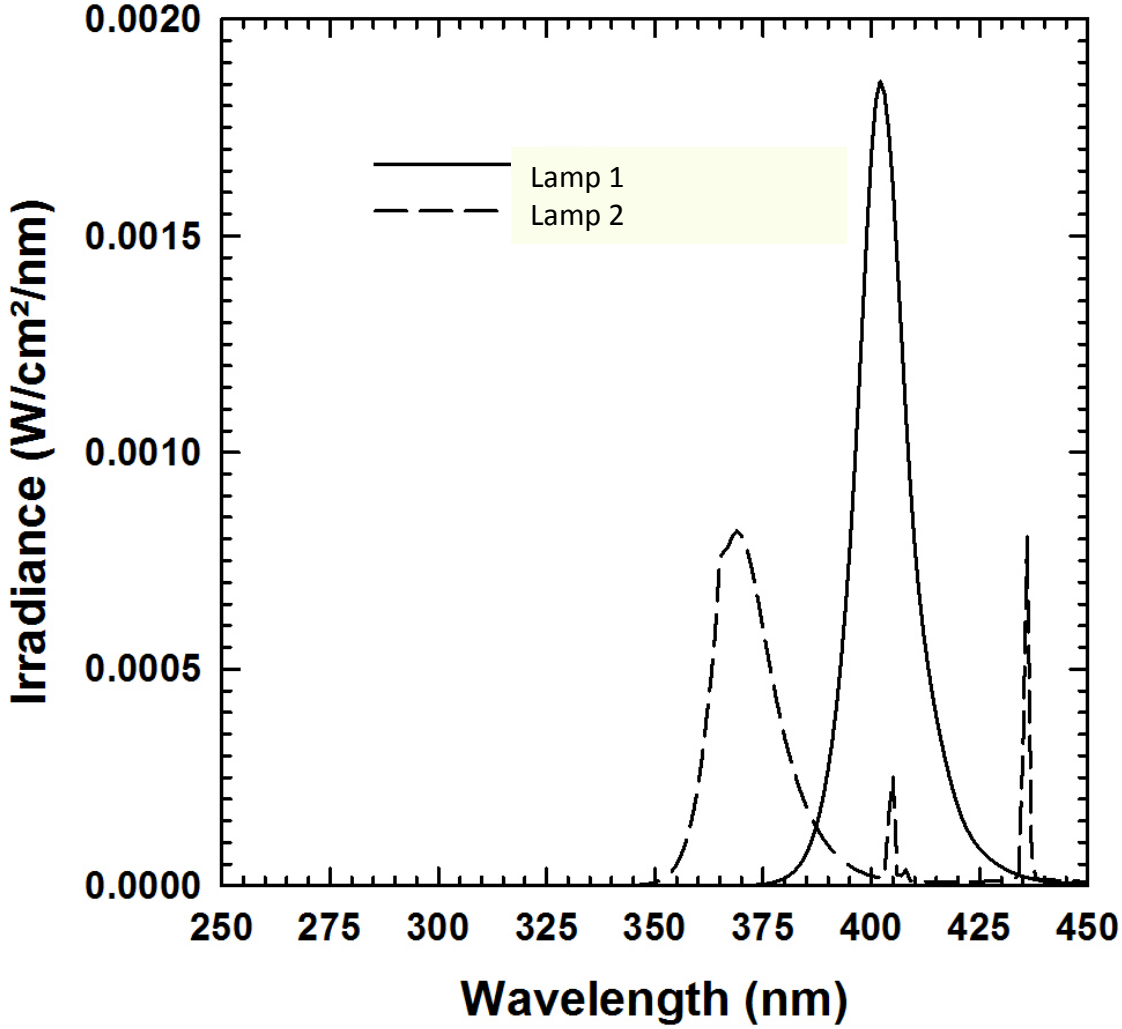
Lamp 1- (1.676 μW/cm2) 2.2% of allowable monthly occupational exposure.

Lamp 2- (1.2-1.4 μW/cm^2) 1.9% of allowable monthly occupational exposure.

Lamp 3- (1.02 μW/cm^2) 1.2% of allowable occupational exposure.

Lamp 4- (0.39 μW/cm^2) 0.5% of allowable occupational exposure.

** Recommended Practice for Photobiological Safety for Lamps- Risk Group Classification & Labeling"* ANSI/IESNA RP-27.3-96



Plot of wavelength vs irradiance of two leading brands of fluorescent-style lamps sold in the US.

Study 2 Conclusions*:

"When the UV nail lamps evaluated in this report are compared together with these earlier sunlamp computations we find the nail lamps vastly less hazardous."

"Using spectral weighting relative to overhead and mid angle sunlight the UV nail lamps had 11–46 times less NMSC effective irradiance than an overhead 1 atmosphere solar spectrum and 3–12 times less than mid angle 1.5 atmosphere sun."

* *"Photocarcinogenesis action spectrum (non-melanoma skin cancers"* ISO 29077 CIE S 019/E, 2006-12-15

Study 2 Conclusions*:

Dowdy and Sayre also cited previous research that demonstrates the dorsum of the hand is four times more UV resistant than the hands or cheeks making it the most UV resistant part of the body, providing a further margin of safety.

Also, the natural nail plate has a natural UV resistance equal to that of a high SPF sunscreen.

Olson, R. L., R. M. and M. A. Everett (1966) *Effect of anatomic location and time on ultraviolet erythema*. *Arch Dermatol* **93,** 211-5.

Stern, D., Creasey Alia, et al.,(2011*), UV-A and UV-B Penetration of Normal Human Cadaveric Fingernail Plate*, Arch Dermatol, Vol.147 (No 4)

“UV nail lamps are safer than natural sunlight or sunlamps.”

“…this UV source properly belongs in the least risky of all categories.”

Dr. Robert Sayre

Study 3

"Risk of Skin Cancer Associated with the Use of UV Nail Lamps"

Markova, A., Weinstock, M.
Journal of Investigative Dermatology, 2013, 89:961-967

Study 3:

Markova and Weinstock tested “three common UV nail lamp device’s”, two fluorescent-style and one LED-style, with peak emission at 368 and 405 nm.

Used collected spectral data to calculate each devices carcinogenic-effective irradiance and compared the UV dose with that of a single course of NBUVB phototherapy.

Study 3 Conclusions:

250 years of weekly UV nail sessions to experience the same risk exposure as a single course of NBUVB

“Dermatologists and primary-care physicians may reassure patients regarding the safety of these devices.”

The Nail Manufacturers Council on Safety (NMC) believes these three studies offer convincing evidence that both fluorescent and LED-style UV nail lamps are safe as used in nail salons and we hope the CIR agrees.

Thank You

Data4

Olson RL, Sayer RM, Everett MA. Effect of Anatomic Location and Time on Ultraviolet Erythema. *Arch Dermatol.* 1966;93(2):211-5.

Data5

Hui X, Wester RC, Barbadillo S, Maiback HI. Nail penetration: enhancement of topical delivery of antifungal drugs by chemical modification of the human nail. In: Baran R, Maibach HI, eds. *Textbook of Cosmetic Dermatology*. 3rd ed. London; New York : Taylor & Francis, 2005: 57-63.

Data6

Dowdy JC, Sayre RM. Photobiological safety evaluation of UV nail lamps. *Photochem Photobiol*. 2013; 89(4):961-7.

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: March 7, 2014
Subject: Wave 2 for Methylisothiazolinone (MI)

The Council has provided HRIPT data of products containing 100 ppm MI with and without the presence of glycols. In 226 subjects, no evidence of induction of allergic contact dermatitis was observed.

Additionally, the Council has provided Cosmetics Europe's recommendation for MI, which states that use of MI should be discontinued in leave-on products and cosmetics wet wipes.

The Council submitted updated concentration of use data for MI, and CIR has just received VCRP data for 2014. Because of the attention that MI is receiving, we wanted you to have the most up-to-date information on this ingredient prior to the Panel meeting. The updated table is attached. Please note the total uses of MI have increased to 3856, with 828 uses in leave-on products, 2907 uses in rinse-off products, and 121 uses in diluted for bath use products. All changes will be reflected in the Use section and in Table 1 of the report.

The Council has also submitted the latest use concentration on the mixture MCI/MI (3:1) for comparison to the MI-only concentration of use data.

All of the data submitted by the Council for wave 2 is presented in this package for your review.

Table 1. Historical and current use and concentration of use data for methylisothiazolinone.

	*# of Uses**		*Max Conc of Use (%)*	
Data Year	**2007**	**2014**	**2007**	**2014**
Totals[1]	**1125**	**3856**	**4×10^{-6}-0.01**	**3.5×10^{-8}-0.01**
Duration of Use				
Leave-On	236	828	0.002-0.01	3.5×10^{-8}-0.01
Rinse-Off	807	2907	4.0×10^{-6}-0.01	2.5×10^{-7}-0.01
Diluted for (Bath) Use	82	121	NR	0.0002-0.01
Exposure Type				
Eye Area	6	52	NR	0.00019-0.01
Incidental Ingestion	NR	1	NR	0.0048
Incidental Inhalation-Spray?[2,5]	144	632	0.005-0.009	0.00018-0.01
Confirmed Spray[3]	NR	NR	NR	0.0002-0.01[a]
Incidental Inhalation-Powder?[4,5]	101	421	NR	NR
Confirmed Powder[3]	NR	NR	NR	NR
Dermal Contact	469	2377	0.0008-0.01	3.5×10^{-8}-0.01[b,c]
Deodorant (underarm)-Spray?[2]	2	NR	NR	NR
Confirmed Spray[3]	NR	NR	NR	NR
Not Spray[3]	NR	NR	NR	0.0095
Hair - Non-Coloring	579	1427	4.0×10^{-6}-0.01	4.0×10^{-6}-0.01
Hair-Coloring	76	29	NR	5.6×10^{-5}-0.0095
Nail	1	6	NR	0.0002-0.006
Mucous Membrane	241	1538	0.0015-0.01	9.0×10^{-7}-0.01[b]
Baby Products	14	17	0.002-0.01[d]	0.0002-0.0075

* Data provided are not clear as to whether uses are MI alone or include uses of MI/MCI.
NR = Not reported
1. 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.
2. It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
3. Use has been confirmed by the Council.
4. It is possible these products may be powders, but it is not specified whether the reported uses are powders.
5. Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
a. 0.01% in an aerosol hair spray; 0.0002-0.01% in a pump hair spray; 0.006-0.0095% in a pump hair tonic or dressing.
b. 0.00023-0.01% in a hand soap; 0.01% in a foot scrub.
c. The Council survey requested that wipe products be identified. One product containing MI was identified as being used as a skin cleansing wipe at a concentration of 0.005%.
d. 0.01% in baby wipes.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: February 5, 2014

SUBJECT: Methylisothiazolinone: HRIPT Data

Anonymous. 2014. Summary of HRIPT of products containing 100 ppm Methylisothiazolinone (MIT), with or without glycols.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

As a result of recent publications suggesting that the MIT reaction rate was higher than expected, a clinical trial was conducted to study the sensitization potential on general and sensitive populations using commercial production lots of MIT.

In most personal care products, MIT at 100 ppm or less is not effective enough to pass industry preservative efficacy testing. Therefore, companies typically incorporate additional preservatives to meet their internal pass criteria based on USP. Due to recent pressure on traditional preservatives companies have been using preservative boosters such as glycols. These types of chemistries have been associated with penetration into the skin; glycols in particular are known to increase dermal penetration. In order to address these combinations and their potential effect on sensitization, MIT was combined with various glycols in these studies.

Below is a summary of human patch studies where 226 subjects were analyzed, among them 56 received 100 ppm MIT alone, the 170 other subjects received 100 ppm MIT in combination with various glycols.

Human Patch Study in Accordance with ICDRG

Induction phase:

- Dermatological examination before each application of the product;
- 48 hours patches application (product and control) on days 1, 3, 5, 8, 10, 12, 15, 17 and 19.

Rest phase (14 days):

During the rest phase, no product will be applied to the induction phase sites or to the contralateral selected for the challenge phase.

Challenge (Reaction) phase:

On day 36, after dermatological examination, patches application (product and control), in the same conditions as used during the induction phase, on the induction site and on the contralateral site for 48 hours. After this period, the patches are taken off. A dermatological examination will be carried out by the investigator 20 minutes after the removal of the patches then 24 and 48 hours later or more if reactions occur (72 and 96 hours after removal of the patches if necessary).

Investigated population:

Number of volunteers, 50 per panel.

Main criteria for inclusion:

18 to 70 years of age, female or male, free of any dermatological lesion especially pigmentary lesions on the investigated site, non-allergic subjects and non-atopic subjects. Sensitive skin subjects were enrolled and represented 50% of the studied population.

Assessment criteria:

Cutaneous reactions which looks allergic during the induction or challenge phase, will be evaluated in accordance with the ICDRG (International Contact Dermatitis Research Group) criteria.

Results:

There was no evidence of induced allergic contact dermatitis in the 226 analyzed subjects.

Discussion and Conclusion:

Based on this data, we are of the opinion that at 100 ppm MIT does not cause a risk in cosmetic products when applied on uncompromised skin in the general population. This is further supported by animal test data and current use data generated by cosmetic companies. However, there is always a sensitive population that will be allergic to specific chemicals including MIT. The cosmetic industry addresses this by disclosing the composition of the products clearly on their labels.

This study also addresses the incorporation of glycols as preservative boosters in combination with MIT which are known to increase dermal penetration. The results confirm that MIT at 100 ppm in combination with various glycols is safe in cosmetic products for use on uncompromised skin in the general population.

Personal Care Products Council
Committed to Safety, Quality & Innovation

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: February 25, 2014

SUBJECT: Methylisothiazolinone

Cosmetics Europe Recommendation

Updated use information Methylisothiazolinone

Use information Methylchloroisothiazolinione/Methylisothiazolinone (3:1)

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Cosmetics Europe
the personal care association

Brussels, 12 December 2013

Recommendation

Cosmetics Europe, following discussions with the European Society of Contact Dermatitis (ESCD), recommends that the use of Methylisothiazolinone (MIT) in leave-on skin products including cosmetic wet wipes is discontinued. This action is recommended in the interests of consumer safety in relation to adverse skin reactions. It is recommended that companies do not wait for regulatory intervention under the Cosmetics Regulation but implement this recommendation as soon as feasible.

Background

Methylisothiazolinone (MIT) is an effective preservative for a wide range of cosmetics and personal care products. The Scientific Committee for Cosmetic Products and Non-food products intended for Consumers (SCCNFP)[i] conducted a safety review and published their opinion in 2004, following which MIT was authorised as a preservative in accordance with the European Cosmetic Products legislation (Directive 76/768/EEC, subsequently Regulation (EC) 1223/2009), for use in leave-on and rinse-off cosmetic products up to a maximum concentration of 0.01% (100ppm).

MIT was introduced to the market as a cosmetic preservative in 2006, and since then has been widely used due to its broad spectrum preservation properties.

Recent publications from the dermatology community report clinical evidence of a sharp increase in positive and relevant patch test reactions to MIT in patients suffering from dermatitis through cosmetic use. Cosmetics Europe took these concerns seriously and, with the support of experts from ingredient suppliers and cosmetic product manufacturers conducted a thorough review of the clinical, toxicological and cosmetovigilance data for MIT. In particular it also updated the risk assessment using a technique called Quantitative Risk Assessment for allergens (QRA), which had not been commonly used when MIT was first assessed by the SCCS in 2004.

Based on the careful assessment of available data, the industry experts concluded that there was evidence to suggest a relationship between the use of leave-on skin products, including cosmetic wet wipes containing MIT, and the induction of contact allergy and allergic contact dermatitis. Therefore the removal of MIT from leave-on

skin products including cosmetic wet wipes is expected to significantly decrease the incidence of induction of contact allergy to MIT.

[1] The SCCNFP is now called the Scientific Committee on Consumer Safety, the SCCS, and is the European Commission's independent committee of scientists which assesses ingredient safety.

Concentration of Use by FDA Product Category
Methylisothiazolinione

FDA Code†	Product Category*	Maximum Concentration of Use
01A	Baby shampoos	0.0002%
01C	Other baby products (hair product)	0.0075%
02B	Bubble baths	0.0002-0.00037%
02D	Other bath preparations	0.0002-0.01%
03D	Eye lotion	0.0038%
03E	Eye makeup remover	0.00019-0.01%
03G	Other eye makeup preparations	0.0095%
04A	Colognes and toilet waters	0.0004%
04B	Perfumes	0.0004-0.008%
04B	Other fragrance preparations	0.00018-0.0076%
05A	Hair conditioners	0.000004-0.01%
05B	Hair sprays aerosol pump spray	 0.01% 0.0002-0.01%
05E	Rinses (noncoloring)	0.00018%
05F	Shampoos (noncoloring)	0.0001-0.01%
05G	Tonics, dressings and other hair grooming aids pump spray	0.0002-0.01% 0.006-0.0095%
05I	Other hair preparations (noncoloring)	0.0095%
06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.000059-0.0082%
06C	Hair rinses (coloring)	0.00027%
06G	Hair bleaches	0.0095%
06H	Other hair coloring preparations	0.000056%
07A	Blushers (all types)	0.000000035%
07C	Foundations	0.0095-0.0097%

07I	Other makeup preparations	0.00037%
08B	Cuticle softeners	0.0002%
08C	Nail creams and lotions	0.006%
09B	Mouthwashes and breath freshener	0.0048%
10A	Bath soaps and detergents	0.0000009-0.01%
10B	Deodorants (underarm) not spray	 0.0095%
10E	Other personal cleanliness products hand soap foot scrub	0.0012-0.0079% 0.00023-0.01% 0.01%
11D	Preshave lotions (all types)	0.0074%
11E	Shaving cream (aerosol, brushless and lather)	0.00011-0.01%
12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads) wipe (not baby wipe)	0.000013-0.01% 0.005%
12B	Depilatories	0.00000025%
12C	Face and neck products not spray	 0.0072-0.01%
12D	Body and hand products not spray	 0.00011-0.01%
12F	Moisturizing products not spray	 0.00001-0.0072%
12G	Night products not spray	 0.0066-0.01%
12H	Paste masks and mud packs	0.0066-0.01%
12J	Other skin care preparations	0.00003-0.00026%
13A	Suntan products not spray	 0.0095%

†Product category codes used by FDA

*This survey requested that wipe products be identified. In this survey, one product containing Methylisothiazolinone was identified as being in the form of wipes.

Information collected in 2013

Table prepared: August 29, 2013

Updated September 6, 2013: Corrected hairspray use from 0.011 to 0.01%

Updated February 24, 2014: Added Other Baby products; Nail creams and lotions corrected 0.0006% to 0.006%; deleted Foot powders and sprays as this product was also correctly presented in Other personal cleanliness products (foot scrub); Moisturizers low concentration changed from 0.0032 to 0.00001%

Concentration of Use by FDA Product Category
Methylchloroisothiazolinone (MCI)/Methylisothiazolinone (3:1)

Product Category*	Maximum Concentration of Use
Baby shampoo	10-12 ppm
Other baby products	0.6 ppm (rinse-off)
Bath oils, tablets and salts	9-14.2 ppm
Bubble baths	10-15 ppm
Other bath preparations	4.2-10 ppm
Eye lotion	7.5 ppm
Other fragrance preparations	10 ppm (rinse-off)
Hair conditioners	6-15 ppm
Hair sprays pump spray	7 ppm
Hair rinses (noncoloring)	14 ppm
Shampoos (noncoloring)	5.2-15 ppm
Tonics, dressings and other hair grooming aids	0.9-11 ppm
Other hair preparations (noncoloring)	7.5 ppm (rinse-off)
Hair dyes and colors	0.34-9 ppm
Hair rinses (coloring)	11 ppm
Hair shampoos (coloring)	4.5-14 ppm
Other manicuring preparations	10 ppm (rinse-off)
Bath soaps and detergents	6-15 ppm
Other personal cleanliness products	3-15 ppm
Shaving cream	0.2-15 ppm
Other shaving preparations	10 ppm (rinse-off)
Skin cleansing	5.2-15 ppm
Face and neck products not spray	0.4 ppm
Body and hand products not spray	6 ppm
Foot powders and sprays	1-10.8 ppm (rinse-off) 4 ppm (leave-on)
Moisturizing products	

not spray	0.2 ppm (rinse-off)
Paste masks and mud packs	0.02-1.1 ppm
Other skin care preparations	2.1 ppm, 10-13 ppm (rinse-off)

*This survey requested that wipe products be identified. No wipes were reported

Information collected in 2014
Table prepared: February 24, 2014

Date: March 7, 2014

From: Bart Heldreth, Ph.D., Chemist CIR

To: CIR Expert Panel Members and Liaisons

Re: Draft 2015 Priority List

The CIR Procedures require that we prepare the Draft 2015 Priority List for public comment by June 1, 2014. The Draft 2015 Priority list has been prepared and is being issued for public comment earlier in the hope of giving more time for the acquisition of data. The list was based on frequency of use data (FOU) from FDA's Voluntary Cosmetic Registration Program (VCRP), received from FDA on February 25, 2014. While this list includes only the lead ingredients, potential groupings for each lead are provided in Attachment 1. The Expert Panel will have the opportunity to review any revisions to this list and any public comments at the June, 2014 meeting at which time a Final 2015 Priority List will be issued. CIR will select about 17 ingredient/ingredient groups, including a proposed hair dye, for review in 2015. Ingredients on the 2015 Draft Annual Priority List are summarized below:

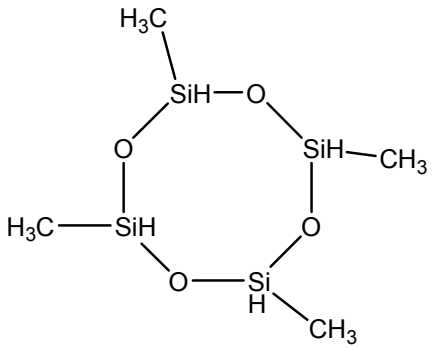
Draft CIR 2015 Priority List (3/17/2014)

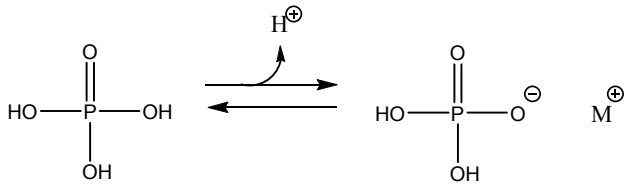
LEAD INGREDIENT	FOU (2014)
YEAST EXTRACT	583
POLYSILICONE-2	515
SEA SALT	498
PHOSPHORIC ACID	443
DICALCIUM PHOSPHATE	353
MAGNESIUM CARBONATE	429
TRIDECYL TRIMELLITATE	426
STEARALKONIUM BENTONITE	403
HDI/TRIMETHYLOL HEXYLLACTONE CROSSPOLYMER	388
AMMONIUM ACRYLOYLDIMETHYLTAURATE/VP COPOLYMER	383
HYDROXYETHYL ACRYLATE/SODIUM ACRYLOYLDIMETHYL TAURATE COPOLYMER	383
PANTHENYL ETHYL ETHER	375
ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER	367
TETRAHEXYLDECYL ASCORBATE	365
POLYGLYCERYL-3 DIISOSTEARATE	358
2-OLEAMIDO-1,3-OCTADECANEDIOL	352
ETIDRONIC ACID	345
HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	344

ROSA CANINA FRUIT EXTRACT	343
SODIUM METHYL COCOYL TAURATE	335
GLYCINE SOJA (SOYBEAN) PROTEIN [Glycine Max (Soybean) Protein]	329
TETRADECENE	327

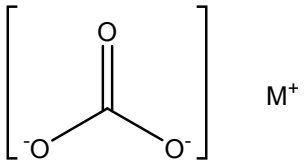
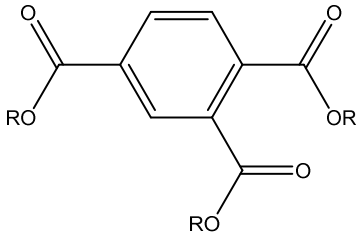
Draft 2015 CIR Priority List with Ingredient Groupings

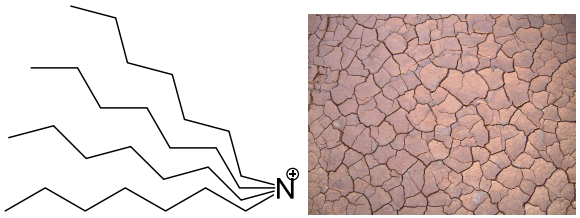
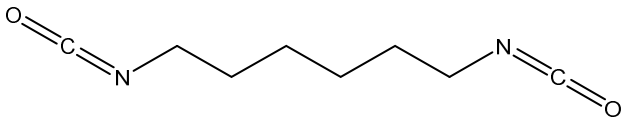
March, 2014

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
Yeast • **YEAST EXTRACT**	583	This group is comprised of yeast products. 	1. Hydrolyzed Yeast Extract 2. Hydrolyzed Yeast 3. Hydrolyzed Yeast Protein 4. Lactic Yeasts 5. Yeast 6. Yeast Beta-Glucan 7. Yeast Polysaccharides (8)
Polymerized Tetramethylcyclotetrasiloxane • **POLYSILICONE-2**	515	This group is comprised of copolymers partially comprised of polymerized tetramethyl-cyclotetrasiloxane.  tetramethylcyclotetrasiloxane	1. Polysilicone-4 2. Polysilicone-5 (3)
Chloride Salts • **SEA SALT**	498	This group is comprised of simple chloride salts, wherein any property difference due to the variable cation can be contrasted. Contrasting these differences in one report is more informative and more efficient than assesing the safety of each salt in separate reports.	1. Aluminum Chloride 2. Ammonium Chloride 3. Barium Chloride 4. Calcium Chloride 5. Cobalt Chloride 6. Cupric Chloride

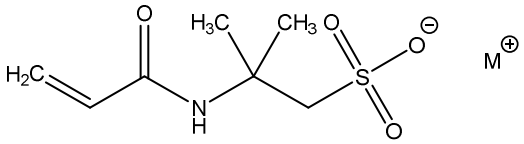
Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			7. Ferric Chloride 8. Gold Chloride HCl 9. Lithium Chloride 10. Magnesium Chloride 11. Manganese Chloride 12. Molybdenum Chloride 13. Potassium Chloride 14. Silver Chloride 15. Sodium Chloride 16. Stannous Chloride 17. Strontium Chloride 18. Strontium Chloride Hexahydrate 19. Zinc Chloride (20)
Phosphoric Acid and Simple Salts • **PHOSPHORIC ACID** • **DICALCIUM PHOSPHATE**	443 353	This group is comprised of phosphoric acid and simple salts thereof. In aqueous solutions (and likely in water containing formulations) there will be a pH dependent equilibrium of phosphoric acid and phosphate. 	1. Aluminum Triphosphate 2. Ammonium Phosphate 3. Calcium Dihydrogen Phosphate 4. Calcium Phosphate 5. Calcium Potassium Sodium Phosphate 6. Calcium Pyrophosphate 7. Diammonium Phosphate 8. Dicalcium Phosphate 9. Dicalcium Phosphate Dihydrate 10. Dipotassium Phosphate 11. Disodium Phosphate 12. Disodium Pyrophosphate 13. Magnesium Hydrogen Phosphate 14. Magnesium Phosphate

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			15. Pentapotassium Triphosphate 16. Pentasodium Triphosphate 17. Phosphate Buffered Saline 18. Potassium Phosphate 19. Potassium Polyphosphate 20. Silver Magnesium Aluminum Phosphate 21. Sodium Calcium Copper Phosphate 22. Sodium Calcium Silver Phosphate 23. Sodium Calcium Zinc Phosphate 24. Sodium Magnesium SIlver Phosphate 25. Sodium Metaphosphate 26. Sodium Phosphate 27. Stannous Pyrophosphate 28. Tetrapotassium Pyrophosphate 29. Tetrasodium Pyrophosphate 30. Tricalcium Phosphate 31. Trimagnesium Phosphate 32. Trisodium Phosphate (34)

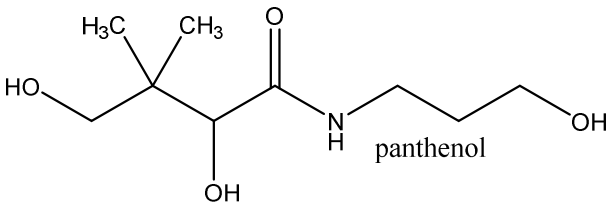
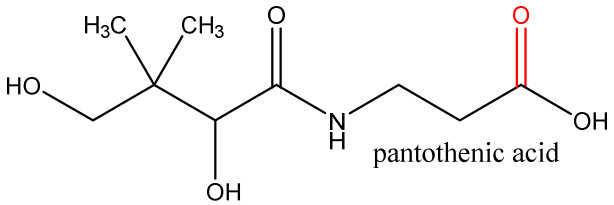
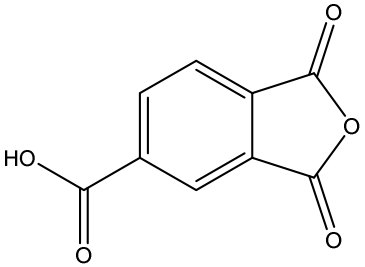
Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
Simple Carbonate Salts • **MAGNESIUM CARBONATE**	429	This group is comprised of simple carbonate salts, wherein any property differences due to the variable cation(s) can be contrasted. Constrasting these differences in one report is more informative and more efficient than assesing the safety of each salt in separate reports. These ingredients are closely related to the recently reviewed ingredients, Sodium Bicarbonate Sodium Carbonate, and Sodium Sesquicarbonate (CIR: [R] IJT-25(SUPPL. 2)2006).  	1. Ammonium Bicarbonate 2. Ammonium Carbonate 3. Calcium Carbonate 4. Copper Carbonate Hydroxide 5. Lithium Carbonate 6. Magnesium/Aluminum/ Hydroxide/Carbonate 7. Magnesium/Aluminum/ Zinc/Hydroxide/Carbonate 8. Magnesium Carbonate Hydroxide 9. Potassium Bicarbonate 10. Potassium Carbonate 11. Propylene Carbonate 12. Silver Bicarbonate 13. Sodium Carbonate Peroxide 14. Zinc Carbonate 15. Zinc Carbonate Hydroxide (16)
Trialkyl Trimelliates • **TRIDECYL TRIMELLITATE**	426	The ingredients in this report are all trialkyl substituted trimellitate moieties.  	1. Tricaprylyl/Capryl Trimellitate 2. Triethylhexyl Trimellitate 3. Triisodecyl Trimellitate 4. Triisotridecyl Trimellitate (5)

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
Alkonium Clays • **STEARALKONIUM BENTONITE**	403	The ingredients in this report are all quaternary ammoinum salts of hydrated colloidal silicate clays. These ingredients are closely related to the recently reviewed ingredient, Stearalkonium Hectorite (CIR: [S] IJT-32(SUPPL. 4)2013). 	1. Hydrogenated Tallowalkonium Bentonite 2. Quaternium-18/Benzalkonium Bentonite 3. Quaternium-90 Bentonite 4. Benzalkonium Montmorillonite 5. Benzalkonium Sepiolite (6)
Hexamethylene Diisocyanate (HDI) Polymers • **HDI/TRIMETHYLOL HEXYLLACTONE CROSSPOLYMER**	388	This group is comprised of copolymers, the monomers of which are partially comprised of hexamethylene diisocyanate. 	1. Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer 2. Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer 3. Bis-Isostearyl 1,4-Butanediol/HDI/Hydrogenated Dimer Dilinoleyl Alcohol Copolymer 4. Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer 5. Bis-Methoxy PEG-10 Dimethyl MEA/HDI/Bis-PEG-10 Dimethicone Copolymer 6. 1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			7. Cholesterol/HDI/Pullulan Copolymer 8. Decyl HDI/PEG-180 Crosspolymer 9. Diethylene Glycol/DMAP Acrylamide/PEG-180/HDI Copolymer 10. HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer 11. HDI/PEI-45/SMDI Crosspolymer 12. HDI/PPG/Polycaprolactone Crosspolymer 13. Methoxy PEG-17/Methoxy PEG-11/HDI Crosspolymer 14. Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer 15. PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether 16. PPG-26/HDI Copolymer 17. Steareth-100/PEG-136/HDI Copolymer 18. Stearyl HDI/PEG-50 Copolymer (19)

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
Acryloyldimethyltaurate Polymers • **AMMONIUM ACRYLOYLDIMETHYLTAURATE/VP COPOLYMER** • **HYDROXYETHYL ACRYLATE/SODIUM ACRYLOYLDIMETHYL TAURATE COPOLYMER**	383 383	This group is comprised of copolymers, the monomers of which are partially comprised of acryloyldiemthyltaurate monomers.  acryloyldimethyltaurate	1. Acrylamide/Sodium Acryloyldimethyltaurate/ Acrylic Acid Copolymer 2. Acrylamide/Sodium Acryloyldimethyltaurate Copolymer 3. Ammonium Acryloyldimethyltaurate/ Beheneth-25 Methacrylate Crosspolymer 4. Ammonium Acryloyldimethyltaurate/ Carboxyethyl Acrylate Crosspolymer 5. Ammonium Acryloyldimethyltaurate/ Laureth-7 Methacrylate Copolymer 6. Ammonium Acryloyldimethyltaurate/ Steareth-8 Methacrylate Copolymer 7. Ammonium Acryloyldimethyltaurate/ Steareth-25 Methacrylate Crosspolymer 8. Ammonium Acryloyldimethyltaurate/ Vinyl Formamide Copolymer 9. Ammonium

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Polyacryloyldimethyl Taurate 10. Dimethylacrylamide/Sodium Acryloyldimethyltaurate Crosspolymer 11. Polyacryloyldimethyltaurate Polyoxymethylene Melamine 12. Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer 13. Sodium Acrylate/Sodium Acryloyldimethyl Taurate/Acrylamide Copolymer 14. Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer 15. Sodium Acryloyldimethyl Taurate/Acrylamide/VP Copolymer 16. Sodium Acryloyldimethyltaurate/Methacrylamidolauric Acid Copolymer 17. Sodium Acryloyl Dimethyl Taurate/PEG-8 Diacrylate Crosspolymer 18. Sodium Acryloyldimethyltaurate/VP Crosspolymer

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			19. Sodium Polyacryloyldimethyl Taurate (21)
Ether, esters, and salts of Panthenol and Pantothenic Acid • **PANTHENYL ETHYL ETHER**	375	These ingredients are closely related to the recently reviewed ingredients, Panthenol and Pantothenic Acid (CIR: [R] IJT-25(SUPPL. 2)2006).  panthenol  pantothenic acid	1. Panthenyl Ethyl Ether Acetate 2. Panthenyl Triacetate 3. Calcium Pantothenate 4. Sodium Pantothenate (5)
Trimellitic Anhydride Copolymers • **ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER**	367	This group is comprised of copolymers, the monomers of which are partially comprised of trimellitic anhydride monomers. 	1. Adipic Acid/CHDM/MA/ Neopentyl Glycol/ Trimellitic Anhydride Copolymer 2. Isostearoyl Trimellitic Anhydride/ Trimethylolpropane Copolymer 3. Phthalic Anhydride/ Trimellitic Anhydride/ Glycols Copolymer 4. TDI/Trimellitic Anhydride

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Copolymer 5. Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer (6)
Ethers of Ascorbate • **TETRAHEXYLDECYL ASCORBATE**		The ingredients in this report are all ethers of ascorbic acid. These ingredients are related to Ascorbyl Dipalmitate, Ascorbyl Palmitate, and Ascorbyl Stearate which will appear in a 2014 re-review (CIR: [S] IJT-18(SUPPL. 3)1999)).	1. Ascorbyl Isostearate 2. Ascorbyl Linoleate 3. Ascorbyl Tetraisopalmitate (4)
Polyglyceryl-x Fatty Acid Esters • **POLYGLYCERYL-3 DIISOSTEARATE**	358	The ingredients in this report are all glycerin polymers, end-capped with one or more fatty acid esters.	1. Acacia Decurrens/Jojoba/ Sunflower Seed Wax Polyglyceryl-3 Esters 2. Adansonia Digitata Seed Oil Polyglyceryl-6 Esters 3. Almond Oil/ Polyglyceryl-10 Esters 4. Apricot Kernel Oil Polyglyceryl-3 Esters 5. Apricot Kernel Oil Polyglyceryl-4 Esters 6. Apricot Kernel Oil Polyglyceryl-5 Esters 7. Apricot Kernel Oil Polyglyceryl-6 Esters 8. Apricot Kernel Oil Polyglyceryl-10 Esters 9. Argan Oil Polyglyceryl-6 Esters 10. Astrocaryum Vulgare Oil Polyglyceryl-6 Esters 11. Babassu Oil Polyglyceryl-4 Esters

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			12. Babassu Oil Polyglyceryl-6 Esters 13. Bertholletia Excelsa Seed Oil Polyglyceryl-6 Esters 14. Borage Seed Oil Polyglyceryl-4 Esters 15. Borage Seed Oil Polyglyceryl-6 Esters 16. Candelilla/Jojoba/Rice Bran Polyglyceryl-3 Esters 17. Carapa Guaianensis Oil Polyglyceryl-6 Esters 18. Castor Oil Polyglyceryl-6 Esters 19. Cocoa Butter Polyglyceryl-6 Esters 20. Coconut Oil Polyglyceryl-6 Esters 21. Coffee Seed Oil Polyglyceryl-6 Esters 22. Diisostearoyl Polyglyceryl-3 Dimer Dilinoleate 23. Glyceryl/Polyglyceryl-6 Isostearate/Behenate Esters 24. Hazelnut Seed Oil Polyglyceryl-6 Esters 25. Linseed Oil Polyglyceryl-4 Esters 26. Macadamia Seed Oil Polyglyceryl-6 Esters

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			27. Macadamia Seed Oil Polyglyceryl-6 Esters Behenate 28. Mauritia Flexuosa Seed Oil Polyglyceryl-6 Esters 29. Olive Oil Polyglyceryl-3 Esters 30. Olive Oil Polyglyceryl-4 Esters 31. Olive Oil Polyglyceryl-6 Esters 32. Palm Kernel Oil Polyglyceryl-4 Esters 33. Palm Oil Polyglyceryl-3 Esters 34. Palm Oil Polyglyceryl-4 Esters 35. Palm Oil Polyglyceryl-5 Esters 36. Palm Oil Polyglyceryl-6 Esters 37. Parinari Curatellifolia Oil Polyglyceryl-6 Esters 38. PEG-4 Polyglyceryl-2 Distearate 39. PEG-10 Polyglyceryl-2 Laurate 40. PEG-4 Polyglyceryl-2 Stearate 41. PEG-150 Polyglyceryl-2 Tristearate 42. Pinus Sibirica Seed Oil Polyglyceryl-6 Esters

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			43. Polyglyceryl-6 Adansonia Digitata Seedate 44. Polyglyceryl-4 Almondate/Shea Butterate 45. Polyglyceryl-6 Apricot Kernelate 46. Polyglyceryl-10 Apricot Kernelate 47. Polyglyceryl-6 Argan Kernelate 48. Polyglyceryl-3 Beeswax 49. Polyglyceryl-3 Behenate 50. Polyglyceryl-6 Behenate 51. Polyglyceryl-10 Behenate/Eicosadioate 52. Polyglyceryl-8 C12-20 Acid Ester 53. Polyglyceryl-2 Caprate 54. Polyglyceryl-3 Caprate 55. Polyglyceryl-4 Caprate 56. Polyglyceryl-5 Caprate 57. Polyglyceryl-6 Caprate 58. Polyglyceryl-10 Caprate 59. Polyglyceryl-2 Caprylate 60. Polyglyceryl-3 Caprylate 61. Polyglyceryl-4 Caprylate 62. Polyglyceryl-6 Caprylate 63. Polyglyceryl-10 Caprylate 64. Polyglyceryl-4 Caprylate/Caprate 65. Polyglyceryl-6

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Caprylate/Caprate 66. Polyglyceryl-10 Caprylate/Caprate 67. Polyglyceryl-3 Cetyl Ether 68. Polyglyceryl-3 Cetyl Ether Stearate 69. Polyglyceryl-6 Citrullus Lanatus Seedate 70. Polyglyceryl-3 Cocoate 71. Polyglyceryl-4 Cocoate 72. Polyglyceryl-10 Cocoate 73. Polyglyceryl-8 Decabehenate/Caprate 74. Polyglyceryl-8 Decaerucate/Decaisostearate/Decaricinoleate 75. Polyglyceryl-10 Decaethylhexanoate 76. Polyglyceryl-10 Decahydroxystearate 77. Polyglyceryl-10 Decaisostearate 78. Polyglyceryl-10 Decalinoleate 79. Polyglyceryl-10 Decamacadamiate 80. Polyglyceryl-10 Decaoleate 81. Polyglyceryl-10 Decastearate 82. Polyglyceryl-3 Decyltetradecyl Ether

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			83. Polyglyceryl-3 Dicaprate 84. Polyglyceryl-6 Dicaprate 85. Polyglyceryl-5 Dicaprylate 86. Polyglyceryl-3 Dicitrate/Stearate 87. Polyglyceryl-3 Dicocoate 88. Polyglyceryl-10 Dicocoate 89. Polyglyceryl-10 Didecanoate 90. Polyglyceryl-2 Diisostearate 91. Polyglyceryl-3 Diisostearate 92. Polyglyceryl-6 Diisostearate 93. Polyglyceryl-10 Diisostearate 94. Polyglyceryl-15 Diisostearate 95. Polyglyceryl-4 Dilaurate 96. Polyglyceryl-5 Dilaurate 97. Polyglyceryl-10 Dilaurate 98. Polyglyceryl-10 Dimyristate 99. Polyglyceryl-2 Dioleate 100. Polyglyceryl-3 Dioleate 101. Polyglyceryl-5 Dioleate 102. Polyglyceryl-6 Dioleate

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			103. Polyglyceryl-10 Dioleate 104. Polyglyceryl-6 Dipalmitate 105. Polyglyceryl-10 Dipalmitate 106. Polyglyceryl-2 Distearate 107. Polyglyceryl-4 Distearate 108. Polyglyceryl-6 Distearate 109. Polyglyceryl-10 Distearate 110. Polyglyceryl-20 Docosabehenate/Isostearate 111. Polyglyceryl-20 Docosabehenate/Laurate 112. Polyglyceryl-20 Docosabehenate/Oleate 113. Polyglyceryl-10 Dodecabehenate 114. Polyglyceryl-10 Dodecacaprate 115. Polyglyceryl-10 Dodecacaprylate 116. Polyglyceryl-10 Dodeca-Caprylate/Caprate 117. Polyglyceryl-10 Eicosanedioate/Tetradec

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			anedioate 118. Polyglyceryl-4 Hazelnutseedate 119. Polyglyceryl-10 Hepta(Behenate/Stearate) 120. Polyglyceryl-6 Heptacaprylate 121. Polyglyceryl-20 Heptacaprylate 122. Polyglyceryl-20 Heptadecabehenate/Laurate 123. Polyglyceryl-10 Heptaoleate 124. Polyglyceryl-10 Heptastearate 125. Polyglyceryl-20 Hexacaprylate 126. Polyglyceryl-10 Hexaerucate 127. Polyglyceryl-10 Hexaisostearate 128. Polyglyceryl-6 Hexaoleate 129. Polyglyceryl-10 Hexaoleate 130. Polyglyceryl-5 Hexastearate 131. Polyglyceryl-6 Hexastearate 132. Polyglyceryl-2 Isononanoate/Dimer

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Dilinoleate Copolymer 133. Polyglyceryl-2 Isopalmitate 134. Polyglyceryl-2 Isopalmitate/Sebacate 135. Polyglyceryl-2 Isostearate 136. Polyglyceryl-3 Isostearate 137. Polyglyceryl-4 Isostearate 138. Polyglyceryl-5 Isostearate 139. Polyglyceryl-6 Isostearate 140. Polyglyceryl-10 Isostearate 141. Polyglyceryl-2 Isostearate/Dimer Dilinoleate Copolymer 142. Polyglyceryl-4 Isostearate/Laurate 143. Polyglyceryl-2 Laurate 144. Polyglyceryl-3 Laurate 145. Polyglyceryl-4 Laurate 146. Polyglyceryl-5 Laurate 147. Polyglyceryl-6 Laurate 148. Polyglyceryl-10

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Laurate 149. Polyglyceryl-2 Lauryl Ether 150. Polyglyceryl-4 Lauryl Ether 151. Polyglyceryl-10 Lauryl Ether 152. Polyglyceryl-10 Linoleate 153. Polyglyceryl-10 Mono/Dioleate 154. Polyglyceryl-2 Myristate 155. Polyglyceryl-3 Myristate 156. Polyglyceryl-5 Myristate 157. Polyglyceryl-6 Myristate 158. Polyglyceryl-10 Myristate 159. Polyglyceryl-10 Nonaerucate 160. Polyglyceryl-10 Nonaisostearate 161. Polyglyceryl-6 Octacaprylate 162. Polyglyceryl-20 Octadecabehenate/Laurate 163. Polyglyceryl-20 Octaisononanoate 164. Polyglyceryl-6

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Octastearate 165. Polyglyceryl-2 Oleate 166. Polyglyceryl-3 Oleate 167. Polyglyceryl-4 Oleate 168. Polyglyceryl-5 Oleate 169. Polyglyceryl-6 Oleate 170. Polyglyceryl-8 Oleate 171. Polyglyceryl-10 Oleate 172. Polyglyceryl-10 Palmate 173. Polyglyceryl-2 Palmitate 174. Polyglyceryl-3 Palmitate 175. Polyglyceryl-6 Palmitate 176. Polyglyceryl-10 Palmitate 177. Polyglyceryl-6 Palmitate/Succinate 178. Polyglyceryl-6 Pentacaprylate 179. Polyglyceryl-10 Pentacaprylate 180. Polyglyceryl-3 Pentacaprylate/Caprate 181. Polyglyceryl-10 Pentaisostearate 182. Polyglyceryl-10 Pentalaurate 183. Polyglyceryl-10 Pentalinoleate

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			184. Polyglyceryl-5 Pentamyristate 185. Polyglyceryl-4 Pentaoleate 186. Polyglyceryl-6 Pentaoleate 187. Polyglyceryl-10 Pentaoleate 188. Polyglyceryl-3 Pentaolivate 189. Polyglyceryl-4 Pentapalmitate/Stearate 190. Polyglyceryl-3 Pentaricinoleate 191. Polyglyceryl-6 Pentaricinoleate 192. Polyglyceryl-10 Pentaricinoleate 193. Polyglyceryl-4 Pentastearate 194. Polyglyceryl-6 Pentastearate 195. Polyglyceryl-10 Pentastearate 196. Polyglyceryl-3 Polyricinoleate 197. Polyglyceryl-4 Polyricinoleate 198. Polyglyceryl-5 Polyricinoleate 199. Polyglyceryl-6 Polyricinoleate 200. Polyglyceryl-10

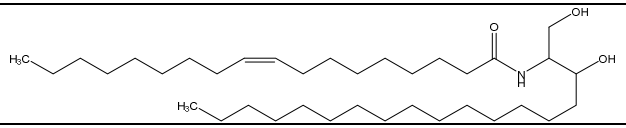
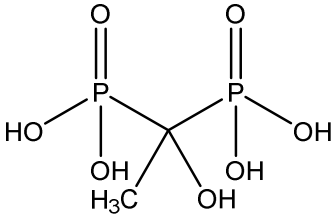
Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Polyricinoleate 201. Polyglyceryl-4 Punicate 202. Polyglyceryl-3 Rice Branate 203. Polyglyceryl-3 Ricinoleate 204. Polyglyceryl-6 Ricinoleate 205. Polyglyceryl-6 Schinziophyton Rautanenii Kernelate 206. Polyglyceryl-6 Sclerocarya Birrea Seedate 207. Polyglyceryl-2 Sesquicaprylate 208. Polyglyceryl-6 Sesquicaprylate 209. Polyglyceryl-2 Sesquiisostearate 210. Polyglyceryl-6 Sesquiisostearate 211. Polyglyceryl-2 Sesquioleate 212. Polyglyceryl-2 Sesquistearate 213. Polyglyceryl-6 Sesquistearate 214. Polyglyceryl-10 Sesquistearate 215. Polyglyceryl-2 Sorbitan

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Tetraethylhexanoate 216. Polyglyceryl-3 Sorbityl Linseedate 217. Polyglyceryl-3 Soyate/Shea Butterate 218. Polyglyceryl-2 Stearate 219. Polyglyceryl-3 Stearate 220. Polyglyceryl-4 Stearate 221. Polyglyceryl-5 Stearate 222. Polyglyceryl-6 Stearate 223. Polyglyceryl-8 Stearate 224. Polyglyceryl-10 Stearate 225. Polyglyceryl-3 Stearate SE 226. Polyglyceryl-4 Sweet Almondate 227. Polyglyceryl-6 Tetrabehenate 228. Polyglyceryl-2 Tetrabehenate/Macadamiate/Sebacate 229. Polyglyceryl-6 Tetracaprylate 230. Polyglyceryl-10 Tetradecanedioate 231. Polyglyceryl-2

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Tetraisostearate 232. Polyglyceryl-10 Tetralaurate 233. Polyglyceryl-2 Tetraoleate 234. Polyglyceryl-6 Tetraoleate 235. Polyglyceryl-10 Tetraoleate 236. Polyglyceryl-2 Tetrastearate 237. Polyglyceryl-5 Tribehenate 238. Polyglyceryl-6 Tricaprylate 239. Polyglyceryl-6 Trichilia Emetica Seedate 240. Polyglyceryl-10 Tricocoate 241. Polyglyceryl-10 Tridecanoate 242. Polyglyceryl-10 Trierucate 243. Polyglyceryl-2 Triisostearate 244. Polyglyceryl-3 Triisostearate 245. Polyglyceryl-5 Triisostearate 246. Polyglyceryl-10 Triisostearate 247. Polyglyceryl-10 Trilaurate

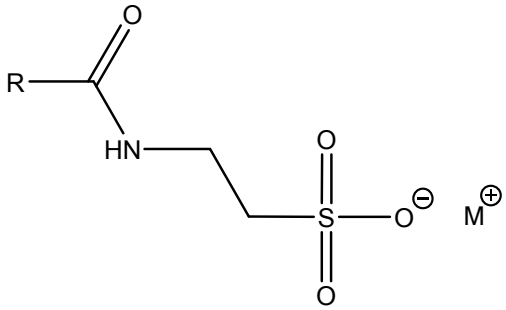
Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			248. Polyglyceryl-5 Trimyristate 249. Polyglyceryl-5 Trioleate 250. Polyglyceryl-10 Trioleate 251. Polyglyceryl-3 Triolivate 252. Polyglyceryl-4 Tristearate 253. Polyglyceryl-5 Tristearate 254. Polyglyceryl-6 Tristearate 255. Polyglyceryl-10 Tristearate 256. Polyglyceryl-6 Undecylenate 257. Polyglyceryl-10 Undecylenate 258. Polyglyceryl-6 Ximenia Americana Seedate 259. Rice Bran Oil Polyglyceryl-3 Esters 260. Rosa Rubiginosa Seed Oil Polyglyceryl-6 Esters 261. Safflower Seed Oil Polyglyceryl-6 Esters 262. Schinziophyton Rautanenii Kernel Oil Polyglyceryl-6 Esters

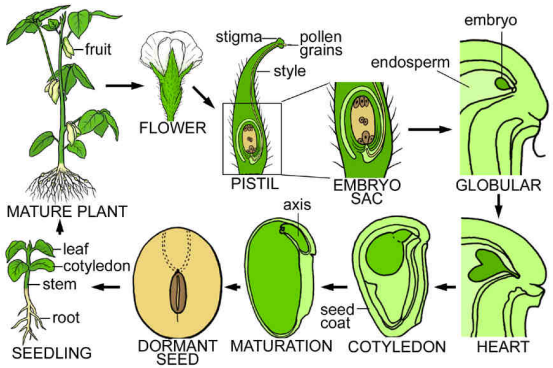
Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			263. Sclerocarya Birrea Seed Oil Polyglyceryl-6 Esters 264. Sclerocarya Birrea Seed Oil Polyglyceryl-10 Esters 265. Sesame Oil Polyglyceryl-6 Esters 266. Shea Butter Polyglyceryl-3 Esters 267. Shea Butter Polyglyceryl-6 Esters 268. Soybean Oil Polyglyceryl-6 Esters 269. Sunflower Seed Oil Polyglyceryl-3 Esters 270. Sunflower Seed Oil Polyglyceryl-4 Esters 271. Sunflower Seed Oil Polyglyceryl-5 Esters 272. Sunflower Seed Oil Polyglyceryl-6 Esters 273. Sunflower Seed Oil Polyglyceryl-10 Esters 274. Sweet Almond Oil Polyglyceryl-4 Esters 275. Sweet Almond Oil Polyglyceryl-6 Esters 276. Theobroma Grandiflorum Seed Butter Polyglyceryl-6 Esters 277. Trichilia Emetica

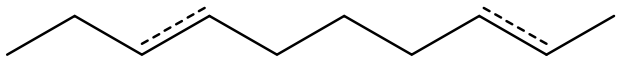
Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Seed Oil Polyglyceryl-6 Esters 278. Triisostearoyl Polyglyceryl-3 Dimer Dilinoleate 279. Watermelon Seed Oil Polyglyceryl-6 Esters 280. Watermelon Seed Oil Polyglyceryl-10 Esters 281. Ximenia Americana Seed Oil Polyglyceryl-6 Esters (282)
2-OLEAMIDO-1,3-OCTADECANEDIOL	352		**N/A** (1)
ETIDRONIC ACID	345		**N/A** (1)
Sunflower • **HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT**	344	The ingredients in this report are all derived from sunflower. While the identity and concentrations of ingredient components may vary from plant part to plant part and from extract method to extract method, those component idenities and concentrations cannot be known for these exclusively industry speciific ingredients until such information is provided as outlined in the industry's botanical framework. Differences in those components do not neccessitate the regrouping of such ingredients, but instead	1. Helianthus Annuus (Sunflower) Extract 2. Helianthus Annuus (Sunflower) Flower Extract 3. Helianthus Annuus (Sunflower) Seed 4. Helianthus Annuus (Sunflower) Seed Butter 5. Helianthus Annuus (Sunflower) Seedcake

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
		warrant a comparison/contrast effort as to how those differences effect safety. Those differences are likely to be informative. Helianthus Annuus (Sunflower) Seed Oil, Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables, and Hydrogenated Sunflower Seed Oil are three related ingredients that were recently reviewed (Final report 03/04/2011). 	6. Helianthus Annuus (Sunflower) Seed Extract 7. Helianthus Annuus (Sunflower) Seed Flour 8. Helianthus Annuus (Sunflower) Seed Wax 9. Helianthus Annuus (Sunflower) Sprout Extract 10. Hydrogenated Sunflower Seed Extract 11. Hydrolyzed Sunflower Seed Wax 12. Ozonized Sunflower Seed Oil (13)

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
Rosa canina • **ROSA CANINA FRUIT EXTRACT**	343	The ingredients from this group are all derived from *Rosa* canina (dog rose). While the identity and concentrations of ingredient components may vary from plant part to plant part and from extract method to extract method, those component idenities and concentrations cannot be known for these exclusively industry speciific ingredients until such information is provided as outlined in the industry's botanical framework. Differences in those components do not neccessitate the regrouping of such ingredients, but instead warrant a comparison/contrast effort as to how those differences effect safety. Those differences are likely to be informative. Hydrogenated Rosa Canina Fruit Oil and Rosa Canina Flower Oil are two related ingredients that were recently reviewed (Final report 03/04/2011).  	1. Rosa Canina Bud Extract 2. Rosa Canina Flower 3. Rosa Canina Flower Extract 4. Rosa Canina Flower Powder 5. Rosa Canina Fruit 6. Rosa Canina Fruit Juice 7. Rosa Canina Leaf Extract 8. Rosa Canina Seed 9. Rosa Canina Seed Extract 10. Rosa Canina Seed Powder (11)

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
Alkyl Taurate Amides and Taurate Salts • **SODIUM METHYL COCOYL TAURATE**	335	The ingredients in this report are the amides and salts of taurine.  	1. Calcium Lauroyl Taurate 2. Magnesium Methyl Cocoyl Taurate 3. Potassium Cocoyl Taurate 4. Potassium Methyl Cocoyl Taurate 5. Potassium Taurate 6. Sodium Caproyl Methyltaurate 7. Sodium Cocoyl Taurate 8. Sodium N-Isostearoyl Methyltaurate 9. Sodium Lauroyl Taurate 10. Sodium Methyl Lauroyl Taurate 11. Sodium Methyl Myristoyl Taurate 12. Sodium Methyl Oleoyl Taurate 13. Sodium Methyl Palmitoyl Taurate 14. Sodium Methyl Stearoyl Taurate 15. Sodium Methyltaurate 16. Sodium Methyltaurate Isopalmitamide 17. Sodium Methyltaurine Cocoyl Methyltaurate 18. Sodium Taurate 19. Sodium Taurine Cocoyl Methyltaurate (20)

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
Soy • **GLYCINE SOJA (SOYBEAN) PROTEIN (as "Glycine Max (Soybean) Protein")**	329	The ingredients in this report are all derived from soy. While the identity and concentrations of ingredient components may vary from plant part to plant and from extract method to extract method, those component idenities and concentrations cannot be known for these exclusively industry speciific ingredients until such information is provided as outlined in the industry's botanical framework. Differences in those components do not neccessitate the regrouping of such ingredients, but instead warrant a comparison/contrast effort as to how those differences effect safety. Those differences are likely to be informative. Glycine Soja (Soybean) Oil and Glycine Soja (Soybean) Oil Unsaponifiables Oil are two related ingredients that were recently reviewed (Final report 03/04/2011).  	1. Glycine Max (Soybean) Fiber 2. Glycine Max (Soybean) Flower/Leaf/Stem Juice 3. Glycine Max (Soybean) Leaf Cell Extract 4. Glycine Max (Soybean) Phytoplacenta Extract 5. Glycine Max (Soybean) Polypeptide 6. Glycine Max (Soybean) Pulp 7. Glycine Max (Soybean) Seedcoat Extract 8. Glycine Max (Soybean) Seed Extract 9. Glycine Max (Soybean) Seed Powder 10. Glycine Max (Soybean) Sprout Extract 11. Glycine Max (Soybean) Symbiosome Extract 12. Glycine Soja (Soybean) Extract 13. Glycine Soja (Soybean) Fiber 14. Glycine Soja (Soybean) Flour 15. Glycine Soja (Soybean) Germ Extract 16. Glycine Soja (Soybean) Hull 17. Glycine Soja (Soybean)

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Lipids 18. Glycine Soja (Soybean) Peptide 19. Glycine Soja (Soybean) Phytoplacenta Extract 20. Glycine Soja (Soybean) Protein 21. Glycine Soja (Soybean) Seed 22. Glycine Soja (Soybean) Seedcake Extract 23. Glycine Soja (Soybean) Seed Extract 24. Glycine Soja (Soybean) Seed Powder 25. Glycine Soja (Soybean) Seed Water 26. Glycine Soja (Soybean) Sprout Extract (27)
Olefins • **TETRADECENE**		The ingredients in this report are all alkenes (olefins), with various chain lengths and degrees of saturation. 	1. C18-26 Olefin 2. C20-24 Olefin 3. C24-28 Olefin 4. C24-30 Olefin 5. C26-54 Olefin 6. C28-36 Olefin 7. C30-45 Olefin 8. Decene 9. Dodecene 10. Hexadecene 11. Hexene 12. Hydrogenated Didodecene 13. Hydrogenated

Group/INGREDIENT NAME	Uses 2014	Structure/Formula/Description/Rationale	Ingredient Group Potential Add-ons (Total # in Ingredient Group)
			Tetradecenyl/Methylpentadecene 14. Hydrogenated Tridodecene 15. Octadecene 16. Octene (17)

(Potential # of Ingredients: 519)

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Scientific Analyst/Writer
Date: March 7, 2014
Subject: Wave 2 - Re-Review of Tocopherols and Tocotrienols as Used in Cosmetics

Enclosed are the Wave 2 data for the Draft Final Amended Report on the Safety Assessment of Tocopherols and Tocotrienols as Used in Cosmetics. An updated data profile is provided.

The following were received since the draft final amended report was prepared for the March meeting, and are included with this submission:

1. Personal Care Products Council. 1-31-2014. Concentration of use by FDA Product Category: Ascorbyl Tocopheryl Maleate.
    a. Ascorbyl tocopheryl maleate is used at concentrations of 0.0025-0.1% in leave-on products and 0.000055-0.005% in rinse-off products. (The updated table is provided.)
2. Comments on the CIR tentative amended report on vitamin E.
    a. This submission included an unpublished skin sensitization study in the guinea pig. (Quintiles England Ltd. 1996.)
        i. The researchers concluded dl-α-Tocopherol had moderate sensitizing potential in this study.
    b. Published papers were also included with this submission. Information from two of the three submitted papers is included in the report. Kosari et al. (2010) was not referenced because it primarily summarizes case studies that were presented in the 2002 report, or studies already included in the re-review document. Because these are published papers, they are not included with this submission; however, if you would like to see them, please contact me.

In addition to the published papers referred to above, other published studies have been obtained since the report was prepared for the Panel meeting, and the data have been added to the report. These are primarily irritation and/or sensitization studies on tocopherol and tocotrienols, as well as contact dermatitis case reports. As a result, the updated "Dermal Irritation and Sensitization" section is included for your review; the new text is indicated by vertical lines. Also included for your review are Table 7 – Case Studies, the updated Summary section, and updated Discussion section. (In the Discussion, the updated wording is denoted by underlined text.)

Please let me know if you have any questions about this submission.

Tocopherols/Tocotrienols* – Mar 2014 (Wave 2) – Monice Fiume

	Reported Use	Method of Mfg	Toxicokinetics	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhal	Repro/Dev Tox	Genotox	Carciniogenicity	Photocard	Dermal Irr/Sens	Phototoxicity	Ocular Irritation
ORIGINAL REPORT																	
Tocopherol	X	X	X	X		X			X		X	X	X	X	X		X
Tocopheryl Acetate	X	X	X		X	X			X		X	X	X	X	X	X	X
Tocopheryl Linoleate	X	X													X		
Tocopheryl Linoleate/Oleate	X																
Tocopheryl Nicotinate	X	X				X	X								X		X
Tocopheryl Succinate	X	X				X						X		X			
Dioleyl Tocopheryl Methylsilanol	X	X				X						X			X		X
Potassium Ascorbyl Tocopheryl Phosphate	X	X															
Tocophersolan	X	X				X			X		X				X		X
RE-REVIEW																	
Tocopherol	X		X	X								X	X	X	X		
Tocopheryl Acetate	X		X	X	X	X			X			X			X	X	X
Tocopheryl Linoleate	X																
Tocopheryl Linoleate/Oleate	X																
Tocopheryl Nicotinate	X																
Tocopheryl Succinate	X											X	X				
Dioleyl Tocopheryl Methylsilanol	X																
Potassium Ascorbyl Tocopheryl Phosphate	X																
Tocophersolan	X								X								
Tocotrienols	X	X	X	X					X				X		X		
Ascorbyl Tocopheryl Acetate																	
Ascorbyl Tocopheryl Maleate	X																
Tocopheryl Phosphate			X		X	X			X			X			X		X
Sodium Tocopheryl Phosphate	X																

*"X" indicates that data were available in a category for the ingredient

DERMAL EFFECTS

Dermal Irritation and Sensitization

Non-Human

From the original report on Tocopherols

Tocopherol, 1%, was a weak primary skin irritant in rabbits in one study, and it was a weak cumulative irritant in guinea pigs in another study. Cosmetic formulations containing 2% dl-tocopherol, 12% vitamin E in wheat germ, and 32% mixed tocopherols in a wheat germ and vegetable oil base had mean cumulative irritation scores of 31, 7, and 12 (maximum possible score of 64), respectively, in rabbits. Tocopheryl acetate and tocopheryl nicotinate were generally not irritating to rabbit skin. A single dose of a mixture of dioleyl tocopheryl methylsilanol and oleic acid was not irritating to rabbits, but slight erythema was observed following multiple applications. The same was observed with 75% tocophersolan in guinea pigs.[1]

A mixture containing <0.1% tocopherol was not a sensitizer in an open epicutaneous test, whereas "higher concentrations" of tocopheryl acetate can cause sensitization in this test. However, tocopheryl acetate was not sensitizing in a guinea pig maximization test. Tocophersolan was not a sensitizer in a Buehler test.[1]

Tocopherol

dl-α-Tocopherol was a moderate sensitizer in a guinea pig maximization test in 20 test and 10 control female albino Dunkin Hartley guinea pigs.{Quintiles England Ltd, 1996 5616 /id} Intradermal induction was conducted with 0.2% dl-α-tocopherol in light liquid paraffin or as an emulsion with Freund's Complete Adjuvant (FCA); epicutaneous induction was conducted with an occlusive patch of 25% tocopherol in ethanol. An occlusive 24-h challenge patch of the highest non-irritating concentration of tocopherol in ethanol was applied 2 wks after epicutaneous induction; based on a range-finding test, this concentration was determined to be 12.5%. Reactions were evaluated 24 and 48 h after patch removal. Three test animals had an erythema score of 1 at 24 h after patch removal. At 48-h after patch removal, an erythema score of 1 was reported for four animals, and a score of 2 was reported for three animals; all three of the animals that had a reaction at 24 h still had a reaction at 48 h, and for one of those animals the erythema score had increased to 2. None of the vehicle control animals reacted to tocopherol at challenge.

dl-α-Tocopherol was classified as having moderate sensitization potential in a local lymph node assay (LLNA).[62] Twenty-five µl tocopherol in 3:1 ethanol:diethyl phthalate was applied to the dorsum of the ears of CBA female mice for 3 days. The EC_3 was 7.4.

Tocopheryl Acetate

According to robust summary data submitted to ECHA, tocopheryl acetate is not irritating to rabbit skin. A 2.5 cm^2 semi-occlusive patch containing 0.5 ml undiluted tocopheryl acetate was applied to a shaved area on the back or the flank of two male and one female Vienna White rabbits, and no erythema or edema was observed. The test sites were scored 30-60 min after patch removal and at 24, 48, and 72 h after application. In a similar study using six New Zealand white rabbits, application of an occlusive patch containing 0.5 ml tocopheryl acetate to intact and abraded skin did not result in erythema or edema, and the PII was 0.

Tocopheryl Phosphate

MTP was not a dermal irritant in New Zealand rabbits.[49] A dose of 0.5 g/site of an aq. gel containing 88-101 mg/kg bw MTP (38.4 71-82 mg/kg bw α-tocopherol equivalents) was applied to a 10 cm^2 area of clipped dorsal skin of one male and two female rabbits. The semi-occlusive patch was removed after 4 h, and the test site was scored for irritation at 1, 24, 48, and 72 h after patch removal. The only observation was a barely perceptible erythema observed in the male at 60 min.

An LLNA was performed to evaluate the sensitization potential of MTP, and no evidence of sensitization was observed.[49] Groups of five female CBA/J mice were dosed with 25 µl of 5, 10, or 25% MTP in reverse osmosis water (corresponding to 1.13, 2.26, or 5.65 mg MTP, respectively); the test article was applied to the dorsal aspect of the ear daily for 3 consecutive days. On day 6, the animals were given a single intravenous injection of [H^3]thymidine, and then killed 5 h after the injection. Several negative controls and a positive control (25% hexylcinnamaldehyde in acetone/olive oil) were used.

Tocotrienols

Undiluted palm tocotrienol-rich fraction (TRF; composed of 50% tocotrienol/tocopherol complex, with 20% d-γ-tocotrienol, 5% d-δ-tocotrienol, 13% d-α-tocotrienol, and 12% d-α-tocopherol) was practically non-irritating to rabbit skin.[63] Undiluted TRF, 0.5 g, was applied to abraded and intact skin of six New Zealand albino rabbits for 24 h using an occlusive wrap; the test sites were then scored for irritation immediately and 48 h after removal of the test material. Sodium lauryl sulfate (SLS) was used as the positive control; an untreated control was also used. TRF induced slight to a well-defined erythema. The average primary irritation index (PII) for TRF was 1.0; the individual PIIs ranged from 0.8-1.2.

Human

From the original report on Tocopherols

Tocopherol and tocopheryl acetate were not irritants or sensitizers in clinical studies. Patients patch-tested by the North American Contact Dermatitis Group rarely reacted to tocopherol. A cosmetic line containing tocopheryl acetate introduced in Switzerland in 1992 resulted in a large number of outbreaks; positive patch tests with tocopheryl linoleate were seen. However,

the outbreaks were thought to be due to a metabolite or contamination of the product. Tocopheryl nicotinate was not an irritant or a sensitizer.

Tocopherol

The Mayo Clinic, Arizona, compared its positive patch-test reaction rate to tocopherol between June 1987-December 1997 to that observed during 1998-2007.[64] From 1987-1999, various concentrations of α-tocopherol in petrolatum were tested; these concentrations were not specified. In 2000-2005, patients were patch-tested with 10% α-tocopherol acetate in petrolatum; from 2005 on, undiluted α-tocopherol was used. During the period June 1987–December 1997, 1136 patients were patch-tested with tocopherol; six patients (0.53%) had a positive patch-test reaction to tocopherol. A total of 1814 patients were patch-tested in 1998-2007; 11 patients had a positive reaction to α-tocopherol in petrolatum, and one reacted to undiluted tocopherol, for a positive reaction rate of 0.66%. The difference in positive reactions was not statistically significant.

The North American Contact Dermatitis Group (NACDG) patch-tested 4454 patients in 2005-2006.[65] Finn Chambers were applied for 48 h, and the test sites were read 48-72 h and 72-186 h after patching. The frequency rate of positive patch-test reactions to undiluted dl-α-tocopherol was 0.7%; this rate was significantly lower than it was in the 2003-2004 test period (1.1% in 5139 patients; p-value 0.036; risk ratio 0.63 (0.041-0.097)), as well as during the 1994-2004 time period (p-value 0.0245; risk ratio 0.64 (0.43-0.94)). However, the frequency of reactions was greater in 2005-2006 than it was in 2001-2002; in 2001-2002, 0.5% of the 4874 patients had positive reactions to tocopherol.

The reaction rate to undiluted DL-α-tocopherol was determined in 124 patients tested by the NACDG who had allergic reactions to at least one NACDG screening allergen that was associated with a sunscreen source; these 124 patients represented 0.52% of all patients patch-tested by the NACDG from 2001-2010.[66] DL-α-Tocopherol was the most frequent inactive ingredient allergen associated with a sunscreen source; six patients (4.8%) had a reaction to tocopherol.

Tocopheryl Acetate

A cuticle softener containing 36% tocopheryl acetate was essentially non-irritating in clinical testing.[67] A 24-h single-insult occlusive patch test was conducted in 19 subjects. One subject had a + reaction, and the PII was 0.03.

According to robust summary data submitted to ECHA, dl-α-tocopheryl acetate is not a sensitizer in humans.[44] In this study, 203 subjects were exposed to undiluted tocopheryl acetate during induction; 10 applications were made over a 2-wk period. The challenge was performed after a 2-wk non-treatment period, and the test substance was applied once daily for 3 days. The mean PII after induction was 0.076/subject; none of the subjects showed a higher irritation grade than 1. No positive reactions were reported after challenge.

Tocotrienols

At concentrations ≤5%, TRF was not an irritant in a patch test or a sensitizer in human repeated insult patch test (HRIPT); irritant reactions were observed at higher concentrations.[63] The patch test was performed by applying Finn chambers containing 0%, 1%, 2.5%, 5%, 7.5%, 10%, and 20% TRF in petrolatum to the backs of 30 subjects for 48 h. The test sites were evaluated 48 h and 96 h after application of the test material using the methods of the International Contact Dermatitis Research Group (ICDRG). No irritation reactions were observed with 1, 2.5, or 5% TRF at 48 or 96 h. However, reactions were observed upon patch removal with higher concentrations, ranging from doubtful erythema with 7.5% TRF to moderate-to-well-defined erythema (total skin reaction score of 9) with 20% TRF. These reactions subsided by the 96 h reading. SLS was highly irritating, with total skin reaction scores of 44 and 32 at the 48-h and 96-h readings, respectively.

An occlusive HRIPT of 2.5% and 5% TRF in petrolatum was conducted in 25 subjects. SLS was used as a positive control, and an untreated site as a negative control. The induction patches were applied for 24 h; the test site was evaluated 30 min after patch removal, and the site was then re-patched. A 2-wk non-treatment period followed the 21-day induction period, and then a 48-h challenge patch was applied to a previously unexposed site. Challenge readings were made 48 and 96 h after patch removal. Both 2.5% and 5% TRF had cumulative irritation scores that were lower than the negative control (4 and 7 for 2.5% and 5% TRF, respectively, compared to 14 for the negative control). After challenge, two subjects had transient reactions at the 48 h reading; no reactions were observed after 96 h.

Contact Allergy – Case Reports

Numerous case reports were presented in the original CIR report on tocopherol-containing products, and additional reports have been published since the original CIR report was issued (Table 7).[68-72]

SUMMARY

This re-review addresses the safety of tocopherols and tocotrienols as used in cosmetics. In 2002, the Panel published a review on tocopherol, concluding these ingredients are safe as used in cosmetics. Tocopherol is the component most commonly associated with vitamin E. However, tocotrienols is also a component of vitamin E, so it is appropriate to develop a report that includes all of these ingredients. This summary includes only information that has become available since the CIR safety assessment was issued on tocopherols, and all information on the tocotrienols and the tocopherols that have been added to this report.

Most of the tocopherols are reported to function in cosmetics as antioxidants or skin conditioning agents; tocotrienols is not reported to function as an antioxidant, instead it is listed as functioning as a light stabilizer, oral care agent, or skin conditioning agent. VCRP data obtained from the FDA in 2013 report that the frequency of use increased considerably for both tocopherol and tocopheryl acetate. The reported use of tocopherol increased from 1072 (1998 data) to 6175 uses (2013 data), and the reported use of tocopheryl acetate increased from 1322 (1998 data) to 8960 uses (2013 data). The use concentration of tocopherol, but not of tocopheryl acetate, has increased since the original assessment. According to the survey conducted by the Council in 2013, the concentration of use of tocopherol in leave-on products increased from 2% in 1999 to 5.4% in 2013. Tocotrienols is used in 433 formulations, with a reported maximum leave-on concentration reported of 0.12%.

Tocopherols and tocotrienols are distributed throughout the body, and the distribution and metabolism varies among the tissues. Tocopherol is the predominant form of vitamin E in human and animal tissues, and it has the highest bioavailability; natural vitamin E has approximately twice the systemic availability of synthetic tocopherol. The distribution and intracellular trafficking of vitamin E may be modulated by tocopherol regulatory proteins, but only one of the proteins, tocopherol transfer protein, has been shown to influence plasma and tissue α-tocopherol concentrations.

The structural differences between tocopherol and tocotrienols result in a difference in the penetration of these compounds into tissues. The presence of three unsaturated bonds in the carbon side chain allows tocotrienols to penetrate tissues with saturated fatty layers, such as the brain and the liver, more readily than tocopherol, which has a saturated carbon side chain. However, the tocotrienols are not as prevalent in the body as the tocopherols, and oral absorption of the tocotrienols has been reported to be incomplete. Orally administered tocopherols and tocotrienols are distributed in the skin and adipose tissue. Dermally applied tocopheryl acetate is hydrolyzed to tocopherol upon exposure to UV. Dermally-applied tocopherols do penetrate the skin.

Toxicity of dermally-applied (single-dose) tocopheryl acetate and tocopheryl phosphate and orally-administered tocophersolan (repeated dose) or tocopheryl phosphate (single and repeated-dose) is not remarkable. In rats fed a diet containing ≤3% tocotrienols for 13 wks, a statistically significant decrease in platelets in males, but not females, in a dose-dependent manner was thought to be a physiological response.

Undiluted tocopheryl acetate was not irritating to rabbit eyes in one study, but it produced weak to moderate conjunctival irritation in another study. Undiluted mixed tocopheryl phosphates (MTP) was not irritating to rabbit eyes.

Numerous genotoxicity studies were conducted with tocopherol, tocopheryl acetate, MTP, and tocopheryl succinate. The only remarkable result was a weak positive result for tocopheryl succinate in a sister chromatid exchange assay in the presence of metabolic activation.

Topical treatment of Skh-1 mice with 5 mg d-α-tocopherol for 15 wks, following 10 wks of UVB irradiation, resulted in a trend toward increased tumor multiplicity in females compared to those mice exposed to vehicle only. A non-statistically significant increase in tumor burden was observed following treatment with tocopherol compared to controls. However, fewer tumors were malignant in animals dosed with tocopherol than in the controls. Mixed results were observed in a tumor promotion study; higher doses of tocopherol increased tumor multiplicity, and greater increases were seen after 98 days than after 153 days. In oral studies, tocopheryl acetate and tocopheryl succinate tended to decrease tumors in rodents. Tocotrienols delayed the onset of the appearance of tumors.

dl-α-Tocopherol was a moderate sensitizer in a guinea pig maximization test, and was classified as having moderate sensitization potential in an LLNA. In clinical patch-tests conducted by the Mayo Clinic in 1814 patients in the years 1998-2007, 11 patients had a positive reaction to α-tocopherol in petrolatum (concentrations of 10% or not specified), and one reacted to undiluted tocopherol, for a positive reaction rate of 0.66%. In testing conducted by the NACDG in 4454 patients between 2005-2006, the frequency rate of positive patch-test reactions to undiluted dl-α-tocopherol was 0.7%. In patients tested by the NACDG who had allergic reactions to at least one NACDG screening allergen that was associated with a sunscreen source (0.52% all patients patch-tested by the NACDG from 2001-2010), DL-α-tocopherol was the most frequent inactive ingredient allergen associated with a sunscreen source, with 6/124 patients (4.8%) reacting to tocopherol. Several case reports of contact dermatitis to tocopherol-containing products have been described.

Undiluted tocopheryl acetate was not irritating to rabbit skin, and tocopheryl acetate did not have photoallergenic effects in guinea pigs. A cuticle softener containing 36% tocopheryl acetate was essentially non-irritating in a single-insult occlusive patch test in 19 subjects, and undiluted tocopheryl acetate is not a sensitizer in humans.

An aq. gel containing 88-101 mg/kg bw MTP was not irritating to rabbit skin, nor was undiluted palm TRF. No evidence of sensitization was observed in an LLNA with MTP. In clinical testing, TRF was not an irritant in human subjects at concentrations up to 5%; however, reactions were observed at higher concentrations, ranging from doubtful erythema with 7.5% TRF to moderate-to-well-defined erythema (total skin reaction score of 9) with 20% TRF. TRF, 2.5 and 5%, was not a cumulative irritant or a sensitizer in an HRIPT in 25 subjects.

Tocopherol, tocopheryl acetate, and tocopheryl phosphate had some photoprotective effects in mice, and tocopherol and tocopheryl acetate were shown to have a photoprotective effect in humans. Tocopheryl acetate inhibited contact dermatitis in rats and reduced erythema, and tocotrienols reduced allergic dermatitis in mice.

The CIR recognizes that many articles on the effects of vitamin E supplementation can be found in the published literature; however, these articles are not included in this safety assessment because they are not relevant to the cosmetic use of the tocopherols.

DISCUSSION

The Expert Panel determined that the 2002 safety assessment on tocopherols should be expanded to include tocotrienols (a 2013 priority), as well as a few additional tocopherols. Although data were not available on all of the ingredients, the Panel found the existing data on the tocopherols are sufficient to support the safety of this entire family of ingredients.

The Panel noted that the current reported maximum use concentration of tocopherol (i.e., 5.4%) is higher than what was reported in the original assessment (i.e., 2%), and that irritation and sensitization data at these higher concentrations are not available for tocopherol. The Panel discussed the issues of irritation and sensitization during both the original and current review of tocopherols, and in both instances, determined that the irritation and sensitization potentials of the ingredients included in this review were not of concern. In the 2002 safety assessment, the Panel was initially concerned with possible irritation and sensitization because of a large number of outbreaks reported in Switzerland with the release of a new line of cosmetics that contained tocopheryl linoleate; however, the researchers thought the outbreaks were due to either a contaminant or a metabolite. Other safety data in the 2002 report indicated that tocopherol was not an irritant or a sensitizer. Irritation and sensitization data that are available since the 2002 review was issued indicate that tocopheryl acetate is not an irritant or a sensitizer, and tocopheryl phosphate is not a sensitizer. Additionally, the Panel commented that although moderate sensitization potential was reported in a guinea pig maximization test, dermal reactions to tocopherol in humans are rare, and as such, the North American Contact Dermatitis Group deleted this ingredient from its standard testing because of the extremely low incidence of reactions.

During the original review of tocopherols, the Panel did carefully consider that the tumor promoting ability of tocopherol, tocopheryl acetate, and tocopheryl succinate had been extensively studied. In most studies, tocopherol is reported to inhibit tumor promotion, and studies published since the original tocopherol report seem to support this conclusion. The general experience of the Panel is that tocopherol is not a tumor promoter. Additionally, photocarcinogenicity testing with tocopherol did not raise any concerns for the Panel.

The Panel also noted that they are aware of epidemiology studies that have been conducted with vitamin E, and results of these studies are inconclusive; positive and negative effects have been observed with the use of vitamin E supplements. After acknowledging the availability of vitamin E supplement studies with mixed results, the Panel stated that the systemic exposure of vitamin E supplementation is much higher than that expected during cosmetic use; therefore, any negative conclusions made during these studies did not cause concern for the cosmetic use of these ingredients.

Natural tocopherols and tocotrienols are plant-derived ingredients. However, these ingredients are specific, purified, highly-enriched lipid compounds, and often the tocopherols are produced synthetically. For these reasons, the usual concerns expressed during the discussion of botanical ingredients did not apply to the ingredients in this report.

Finally, the Panel discussed the issue of incidental inhalation exposure to tocopherols. The Panel stated that although there were no inhalation data available, the tocopherols are used at relatively low concentrations in products that could incidentally be inhaled, e.g., tocopheryl acetate is used at up to 5% in foot powders and sprays and up to 0.2% in aerosol hair spray formulations, and tocopherol is used at up to 1% in pump hair spray formulations. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Table 5. Frequency and concentration of use according to duration and type of exposure – new ingredients

	# of Uses[14]	*Max Conc of Use (%)*[15]	*# of Uses*[14]	*Max Conc of Use (%)*[16]	*# of Uses*[14]	*Max Conc of Use (%)*[15]
	Tocotrienols		**Ascorbyl Tocopheryl Maleate**		**Sodium Tocopheryl Phosphate**	
Totals*	**433**	**0.0015-0.12**	**38**	**0.000055-0.1**	**10**	**NR**
Duration of Use						
Leave-On	*182*	*0.015-0.12*	*36*	*0.0025-0.1*	*7*	*NR*
Rinse-Off	*240*	*0.0015*	*2*	*0.000055-0.005*	*3*	*NR*
Diluted for (Bath) Use	*11*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	6	0.019-0.039	9	0.02	2	NR
Incidental Ingestion	61	0.016-0.019	1	0.0025	NR	NR
Incidental Inhalation-Spray	74[a,c]	NR	24[a,b]	NR	4[a,c]	NR
Incidental Inhalation-Powder	26[b,c]	NR	NR	NR	NR	NR
Dermal Contact	360	0.0015-0.12	37	0.005-0.1	10	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	0.015	NR	0.000055-0.0003	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	3	NR	NR	NR	NR	NR
Mucous Membrane	297	0.0015-0.019	1	0.0025-0.005	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

*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.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.
[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, there fore the information is captured in both categories
NR – no reported use

Table 7. Case reports

Product	Case Report	Reference
moisturizing cream containing α--tocopherol	patient developed worsening of rosacea with pruritus and desquamation after use of cream; positive patch test results were observed with the moisturizing cream (++ at 48 h, 96 h, and 7 days); patch testing with the individual cream components resulted in a positive reaction to 0.5% α-tocopherol in pet.; a ROAT with the cream resulted in a positive result after 96 h; patch testing with 0.5% α-tocopherol in pet was negative in 10 controls	68
skin lotion containing 0.002% *D*- γ -tocopherol; ointment containing 5% *DL*-α-tocopherol acetate in pet.	patient developed itchy erythema after 7 mos using a lotion; rash spread after using the ointment; positive patch test to the lotion, the ointment, 5% *DL*-α-tocopherol acetate (all were ++ on days 2, 3, and 7), and to 2% pet. and 0.2% glycyrrhetinic acid (also ingredients in the ointment; + on day 2, ++ on days 3 and 7); patient did not react to 0.5% *DL*-α-tocopherol acetate; 5 controls did not react to *DL*-α-tocopherol acetate (or glycyrrhetinic acid)	69
vitamin E oil	eczematous dermatitis occurred on the eyelids and neck of a subject with xerotic skin after 4 wks of use; patch testing with an Italian baseline series and the oil resulted in a positive reaction to the oil only; a ++ reaction was observed on day 2 and +++ on day 3; a strong positive reaction was observed on day 3 in a ROAT on the volar forearm using the subject's own product; negative results were obtained in follow-up testing 1 mo. later; various concentrations and brands of tocopheryl acetate were used; negative results were obtained in a ROAT using a new sample of neat vitamin E oil.	70
vitamin E acetate lipogel	a patient developed eyelid and periocular dermatitis after using the lipogel; patch testing with the baseline series and the product resulted in positive results with the product only (+ on day 2 and ++ on day 3); ROATs on the volar forearm with the subject's product gave a positive result on day 4; however, additional patch tests performed with the active ingredient and excipients in the lipogel and various concentrations and brands of tocopheryl acetate produced negative result; negative results were also observed 1 month later in patch tests and ROATs performed using the vitamin E acetate lipogel	70
vitamin E lipogel (with cyclopentasiloxane)	a patient developed itching eczematous dermatitis on the eyelid after using the lipogel for 3 mos; the patient previously had used other vitamin E acetate products on other areas of the body with adverse effects; patch-testing with a baseline series and the patient's own lipogel produced positive reaction to the lipogel only (+ on day 2 and ++ on day 3); a ROAT on the volar forearm using the lipogel gave a strong positive result after 3 days additional patch tests performed 3 wks later with all the ingredients in the lipogel and with various concentrations of tocopheryl acetate produced negative results; however, an additional ROAT of a vitamin E acetate spray that contained only tocopheryl acetate and cyclopentasiloxane produced a positive reaction after 3 days, while a ROAT with pure tocopherol acetate oil did not; he researches concluded the reaction to the lipogel was the result of a compound allergy induced by the gel	71
cream containing DL- α -tocopheryl nicotinate	a patient developed itchy eruptions and well-defined edematous erythema after using the cream; patch testing was positive to the cream, 0.1% DL- α -tocopheryl nicotinate in pet. (+), and other components of the cream; patch tests with 1% D- α -tocopherol in pet. and 1% DL- α -tocopherol in pet. were negative; patch testing with 0.1% DL- α -tocopheryl nicotinate in pet in 3 subjects was negative	72

Abbreviations: pet. – petrolatum; ROAT - repeated open application test

NEW REFERENCES IN WAVE 2 TEXT

16. Personal Care Products Council. 1-31-2014. Concentration of use by FDA Product Category: Ascorbyl Tocopheryl Maleate. Unpublished data submitted by Personal Care Products Council. 1 pages.

61. Quintiles England Ltd. 1996. Skin sensitization study in the guinea pig. Unpublished data submitted by Personal Care Products Council. 4 pages.

62. Kern PS, Gerberick GF, Ryan CA, Kimer I, Aptula A, and Basketter DA. Local lymph node data for the evaluation of skin sensitization alternatives: A second compilation. *Dermatitis*. 2010;21(1):8-32.

63. Hasan ZAA, Ismail R, and Ahmad S. Does the palm tocotrienol-rich fraction induce irritant contact dermatitis? *Journal of Oil Palm Research*. 2008;20:508-515.

64. Adams AK and Connolly SM. Allergic contact dermatitis from vitamin E: The experience at Mayo Clinic Arizona, 1987 to 2007. *Dermatitis*. 2010;21:199-202.

65. Zug KA, Warshaw EM, Folwer JF Jr, Maibach HI, Belsito DV, Pratt MD, Sasseville D, Storrs FJ, Taylor JS, Mathias CGT, DeLeo VA, and Rietschel RL. Patch-test results of the North American Contact Dermatitis Group 2005-2006. *Dermatitis*. 2009;20(3):149-160.

66. Warshaw EM, Wang MZ, Maibach HI, Belsito DV, Zug KA, Taylor JS, Mathias CGT, Sasseville D, Zirwas MJ, Fowler JF Jr., DeKoven JG, Fransway AF, DeLeo VA, Marks JG Jr., Pratt MD, and Storrs FJ. Patch Test Reactions Associated With Sunscreen Products and the Importance of Testing to an Expanded Series: Retrospective Analysis of North American Contact Dermatitis Group Data, 2001 to 2010. *Dermatitis*. 2013;24(4):176-182.

68. Santos AR, Fernandez-Redondo V, Perez PL, Concheiro CJ, and Toribio J. Contact allergy from vitamins in cosmetic products. *Dermatitis*. 2008;19(3):154-156.

69. Ohko K, Ito A, and Ito M. Allergic contact dermatitis syndrome due to tocopherol acetate, in addition to glycyrrhetinic acid. *Journal of Cosmetics, Dermatological Sciences and Applications*. 2012;2(1):38-40.

70. Corazza M, Minghetti S, Borghi A, Bianchi A, and Virgili A. Vitamin E contact allergy: a controversial subject. *Dermatitis*. 2012;23(4):167-169.

71. Corazza M, Ricci M, Minghetti S, Borghi A, Bianchi A, and Virgili A. Compound allergy to a lipophilic gel containing vitamin E acetate and cyclopentasiloxane. *Dermatitis*. 2013;24(4):198-199.

72. Oshima H, Tsuji K, Oh I, and Koda M. Allergic contact dermatitis due to DL-alpha-tocopheryl nicotinate. *Contact Dermatitis*. 2003;48(3):167-168.

Concentration of Use by FDA Product Category
Ascorbyl Tocopheryl Maleate

FDA Product Category	Maximum Concentration of Use
Eye lotion	0.02%
Hair conditioners	0.000055%
Shampoos (noncoloring)	0.0003%
Foundations	0.1%
Lipstick	0.0025%
Bath soaps and detergents	0.005%
Skin cleansing	0.005%
Face and neck products not spray	0.1%
Suntan products not spray	0.1%

Information collected in 2013-2014
Table prepared January 31, 2014

Date
February 14th, 2014

Subject: Comments on CIR tentative amended report on Vitamins E

The CIR (Cosmetic Ingredient Review) Expert Panel is currently reviewing the safety of Tocopherols & Tocotrienols. It has published the Safety Assessment of Tocopherols and Tocotrienols as used in Cosmetics on December 18, 2013 as a tentative amended report for public comment, which is open until February 14, 2014. We would like to bring to the attention of the Expert Panel further information with regard to skin sensitization of vitamin E, particularly of dl-α-tocopherol i.e. a Guinea pig maximization test with dl-α-tocopherol as well as further literature with regard to skin sensitization of vitamin E.

Skin Sensitization Study

Ref.	Skin sensitisation study in the Guinea pig. Magnusson and Kligman Maximisation Test. Study conducted at Quintiles England Ltd., Ledbury, England; Study No. AJK/42381, dated October 24, 1996 (unpublished report)
Type	Guinea pig maximization test
Guideline + deviations	OECD Guideline No. 406 (adopted July 17, 1992)
GLP	Yes
Test substance / Batch	dl-α-Tocopherol, Lot 510841.
Species / sex	Guinea pigs, albino Dunkin Hartley strain / female (young, nulliparous, non-pregnant)
Date	October 24, 1996
Result	Sensitization ratio 35%

Materials and Methods
The test material was commercial dl-α-Tocopherol. The test substance was a clear orange viscous liquid. It was stored under a nitrogen atmosphere in the refrigerator.
The positive control was mercaptobenzothiazole (MBT) applied at 10% concentration in light paraffin for intradermal application and in acetone for topical application (induction and elicitation). Positive control experiment was performed in April/May 1996.

In order to assess the skin sensitisation potential of dl-α-Tocopherol for worker safety evaluation, the Maximisation Test in accordance with OECD Guideline No. 406 was carried out in 30 (20 test and 10 control, body weight range 492 to 611 g) female albino guinea pigs.
The intradermal induction of sensitisation was carried out with 0.2% solution of the test article in light liquid paraffin or in emulsion with Freund's Complete Adjuvant. The epicutaneous induction of sensitisation was conducted with a 25% concentration of the test article in ethanol (Whatman No. 3 filter paper) under occlusion (Blenderm surgical tape). Two weeks after the epidermal induction, the challenge was completed by epicutaneous application of the test article in the highest non irritating concentration, i.e. 12.5% (as determined in the range-finding phase of the study) in ethanol under occlusive dressing for 24 hours. Skin reactions i.e. erythema and eschar as well as oedema formation were evaluated at 24 and 48 hours after removal of the dressing.

Results
Seven test animals exhibited slight to moderate erythema following challenge with 12.5% test article, at the 24 and/or 48 hour examination. None of the test animals responded positively to challenge with the vehicle at any examination.
None of the control animals reacted positively to challenge with either 12.5% test article or the vehicle, ethanol at any examination.

Group	Cage No.	Animal No.	Test article at 12.5% 24 h	Test article at 12.5% 48 h	Ethanol 24 h	Ethanol 48 h
tocopherol	3	1	1	2	0	0
		2	1	1	0	0
		3	0	0	0	0
		4	0	0	0	0
		5	0	1	0	0
	4	1	0	0	0	0
		2	0	0	0	0
		3	0	1	0	0
		4	0	0	0	0
		5	0	0	0	0
	5	1	0	0	0	0
		2	0	0	0	0
		3	0	2	0	0
		4	0	0	0	0
		5	0	2	0	0
	6	1	*	*	*	*
		2	0	0	0	0
		3	1	1	0	0
		4	0	0	0	0
		5	0	0	0	0
Control	7	1	0	0	0	0
		2	0	0	0	0
		3	0	0	0	0
		4	0	0	0	0
		5	0	0	0	0
	8	1	0	0	0	0
		2	0	0	0	0
		3	0	0	0	0
		4	0	0	0	0
		5	0	0	0	0

* Animal found dead prior to challenge

In the non-concurrent positive control experiment with Mercaptobenzothiazole (MBT) four of the 10 test animals exhibited positive responses to challenge with 10% MBT at the 24 and the 48 hour observations, resulting in a response incidence of 40%. None of the test animals responded to challenge with the vehicle at any of the observations. None of the control animals responded to challenge with either 10% MBT or the vehicle at any of the observations.

These results confirm that Mercaptobenzothiazole (MBT) is a moderate sensitizer under the conditions of this study and the test system is therefore considered to be validated.

Conclusion
Given the results of this study, it is concluded that the test article, dl-α-tocopherol, exhibited a moderate sensitising potential in the guinea pig under the conditions of this study.
According to this result and the GHS labelling requirements, dl-α-tocopherol is classified and labelled for worker safety as skin sensitizer category 1.

Discussion on the skin sensitisation potential of dl-α-tocopherol in light of its use in cosmetics

In addition to the study results provided above, dl-α-tocopherol has also been tested in the Local Lymph Node Assay (LLNA) categorizing the substance as a moderate sensitizer with an EC3 of 7.4% (Kern et al. 2010).

With regard to human data cases of allergic contact dermatitis to vitamin E have been reviewed by Kosari et al. (2010) and evaluated for their relevance for use of vitamin E in skin care products. The authors came to the conclusion: *"It appears that vitamin E–induced ACD is an uncommon phenomenon; incidence is low despite its widespread use in skin care products. Given its antioxidant and photoprotective properties, vitamin E should remain an ingredient in skin care products."*

The allergic contact dermatitis potential has also been evaluated based on the experience at Mayo Clinic Arizona between 1987 and 2007 (Adams and Connolly 2010). The authors came to the conclusion: *"Vitamin E appears to be a relatively rare contact allergen in our experience".*

Thus, although a moderate potential for skin sensitisation in animals exists the number of human cases is extremely limited and has to be regarded in view of the very broad topical use of dl-α-tocopherol for several decades as an antioxidant. At common use concentrations skin sensitisation in humans does not seem to be an issue.

Furthermore, although the cosmetic use of vitamin E increased 1998 to 2013 more than 5-fold the North American Contact Dermatitis Group deleted this ingredient from its standard testing because of the extremely low incidence of reactions (CIR Tentative Amended Report for Public Comment, 2013).

The very limited number of human cases with dl-α-tocopherol and with regards to its wide uses in cosmetics for several decades indicates that skin sensitization at the current use concentration reported in cosmetics is not an issue.

Comments on the skin sensitization potential of dl-α-tocopherol acetate

As reported in the CIR tentative amended report dl-α-tocopherol acetate was not photoallergenic in Himalayan guinea pigs, and the study also allows the conclusion that dl-α-tocopherol acetate is not allergenic without UV-irradiation. This is currently not mentioned in the CIR tentative amended report.

Additional comments to the CIR Tentative Amended Report

May we further add a few other comments to the CIR Tentative Amended Report for Public Comment in order to improve the document:

- In the legend to Figure 2 it seems there has been some mix-up on the position of the methyl groups for α- and γ-tocopherol. We suggest the legend to be:

  - wherein methyl groups A and B are present in the case of α-tocopherol, only **B** for β-tocopherol, only **A** for γ-tocopherol, and neither for δ-tocopherol

  - wherein methyl groups C and D are present in the case of α-tocotrienol, only **D** for β-tocotrienol, only **C** for γ- tocotrienol, and neither for δ- tocotrienol

- Table 1: it would be desirable to have CAS-Nos. for all compounds if available.
- Table 1: The structure of Potassium Ascorbyl Tocopheryl Phosphate should be checked (ascorbyl phosphate bridge without carbon atom)

- Table 2: The molecular weight of tocopheryl acetate cannot be the same as that of tocopherol (suggest to cancel this item as no other physico-chemical data are given for tocopheryl acetate)
- Page 6, second line should probably read 24.2 nmol/**g** (instead of nmol/**kg**)

References:

Adams, Alison K; Connolly, Suzanne M (2010) Allergic contact dermatitis from vitamin E: the experience at Mayo Clinic Arizona, 1987 to 2007. Dermatitis 21(4): 199-202.

Kern, Petra S.; Gerberick, Frank G.; Ryan, Cindy A.; Kimber, Ian; Aptula, Aynur; Basketter, David A (2010) Local Lymph Node Data for the Evaluation of Skin Sensitization Alternatives: A Second Compilation. Dermatitis 21(1): 8-32.

Kosari, Payman; Alikhan, Ali; Sockolov, Mary; Feldman, Steven R (2010) Vitamin E and allergic contact dermatitis. Dermatitis 21(3): 148-53.

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: March 7, 2014
Subject: Wave 2 Comments - Draft Report on Tripeptide-1, Hexapeptide-12, and Related Amides

Additional comments, provided by Dr. Karl Lintner, on the draft report that were not available for inclusion with the March 2014 Panel documents are attached (See tripep032014data2 pdf). In consideration of some of the comments provided, it should be noted that Dr. Lintner is questioning the maximum use concentration of 1% that is being reported by industry. He stated that the only way to achieve a 1% pal-GHK concentration in a formulation is to use the neat powder at this level, and that the Sederma Company has never sold pure peptide to any company. Furthermore, he noted that the average concentrations (estimated) of peptides in personal care products range from < 1 ppm (0.0001%) to 10 ppm (0.001%). After considering the *in vitro* effects relating to biological activity, he asserted that the peptides reviewed in the draft report are safe for cosmetic use at use concentrations between 3 ppm and 10 ppm.

It is possible that the comments provided may assist the Panel in determining the extent, if any, at which peptide-induced biological activity at use concentrations in a cosmetic formulation should be a concern.

CIR review of Palmitoyl-Tripeptide-1 and Palmitoyl-Hexapeptide-12

Contribution by Prof. Dr. Karl Lintner

1. INTRODUCTION

I have read the Draft Report of Feb. 21, 2014 and would like to submit a few comments and arguments to the Committee for consideration.
These arguments are based on my personal knowledge of the introduction, testing and commercialization of these two peptides to the cosmetic market worldwide.

As my CV (attached) indicates, I have worked for ten years as a research scientist in the field of peptide chemistry, biochemistry and biology.
As Technical Director of the Sederma company in France, in charge of developing new cosmetic ingredients in 1990 and onwards, I personally supervised the laboratory development of Palmitoyl-Gly-His-Lys (now called Palmitoyl-Tripeptide-1) and Palmitoyl-Val-Gly-Val-Ala-Pro-Gly (now called Palmitoyl-Hexapeptide-12). I also was involved in the purchase of these peptides at larger than lab scale, in the formulation of the peptides into various solutions (such as Biopeptide-CL, Biopeptide-EL, Dermaxyl, Matrixyl-3000); I instigated and/or supervised some of the *in vitro* and clinical tests of these peptides over these last 20 years. I ordered the various safety tests supporting the suitability for cosmetic use of the peptide solutions.
I have retired from this company in 2010 and work as an independent consultant. I have no conflict of interest to declare.

My testimony here will refer only to these two peptides; no generalization to other peptides (of other sequences, or of identical sequence but from other potential suppliers) is justified unless specifically indicated, as will be seen.

I ask forgiveness of those members of the Committee who are more familiar with peptides in general than others, for voicing some of the generalities that I need to expose in the following.

2. NOMENCLATURE

I share the feeling of confusion that is expressed in Mr. W. Johnson, Jr.'s draft report and the following transcription of the panel discussion with respect to "what is really being investigated and reviewed?" The Pal-Gly-His-Lys peptide was (apparently) the first synthetic peptide of specified amino acid sequence to be submitted (in 1991) to the CTFA Nomenclature committee, followed soon thereafter by the Pal-Val-Gly-Val-Ala-Pro-Gly peptide. Why on Earth the CTFA Nomenclature committee refrained from adopting the universally accepted IUPAC nomenclature for peptides (with a 1-Letter code for each Amino acid) that would have allowed consumers, dermatologists and other scientists to know exactly which peptide sequence is contained in the cosmetic formula, was and still is a mystery to me. The initial name of "Palmitoyl-oligopeptide" given to two entirely different substances made no sense; but argumentation with the committee did not succeed. As the number of synthetic peptides submitted to the committee increased, a new system was put in place, with **chronological numbering** of peptides, taking into account ONLY the length of the peptide (di-peptide-x, tri-peptide-y, etc.) and NOT revealing the sequence, but only the amino acid composition. Until the very recent retirement of the "Palmitoyl-oligopeptide" name, neither Sederma nor finished product formulating companies using those two peptides had a choice of naming either peptide with anything other then this ambiguous INCI designation. Hence the impossibility to extract reliable information on the use of these peptides from the FDA files.
Only Sederma (having had patent rights until recently on these peptides) can supply (under confidentiality conditions) reliable data on the amount (kilograms since 1991) of the two peptides under consideration used in various regions of the world, although it cannot be concluded that other suppliers (China) proposed the same peptides in countries where the patents were not filed.[1]

Although the CIR draft report (and the INCI dictionary) seems to imply that Palmitoyl-oligopeptide and Palmitoyl-Hexapeptide-12 could mean both the Pal-Val-Gly-Val-Ala-Pro-Gly AND/OR the Pal-Ala-Pro-Gly-Val-Gly-Val sequences, I am able to confirm that Sederma used the Palmitoyl-oligopeptide INCI name ONLY for either Pal-Gly-His-Lys or Pal-Val-Gly-Val-Ala-Pro-Gly sequences. To my (not 100% exhaustive) knowledge, the APGVGV sequence was never proposed by anyone on the cosmetic market, certainly not by SEDERMA.

It should be noted that contrary to a good number of other suppliers of synthetic peptides (who followed the trend), Sederma has always communicated openly about the peptide sequences proposed, allowing for a transparent basis for safety assessment by the formulating entities.

A move by the PCPC Nomenclature committee to adopt IUPAC compliant peptide naming would be highly desirable (albeit an administrative nightmare now, given the great number of peptides proposed) in view of truly informing the general and the specialized public about the peptides being used…

---

[1] This situation did not arise until a few years ago when synthetic peptides in cosmetic products became a sufficient success story to make copying of the top selling peptides an interesting proposition to these companies abroad.

3. PEPTIDE SEQUENCE

Any scientist involved in peptide chemistry, biochemistry, biophysics and biology knows from own experience and the vast literature on the topic that peptides possess properties which are very tightly connected to the following parameters:

Amino acid composition
Amino acid sequence
Length of peptide
Chemical modification of reactive groups

Yield of synthesis, solubility, binding to cell membranes, enzymatic (metabolic) stability, specificity and selectivity of bioactivity and thus safety are ALL contingent on the exact molecular structure of the peptide in question.

Three examples of my own experience shall illustrate this:

- ✓ The most potent vasoconstrictive substance in our body is an octapeptide (Angiotensin II) of the sequence Asp-Arg-Val-Tyr-Val-His-Pro-Phe. Changing the aromatic Phenylalanine side chain in the last amino acid to a cyclohexyl-alanin side chain totally abolishes the activity of the peptide. Many other very simple modifications of the peptide do the same.
- ✓ The Palmitoyl-Tripeptide-1 (Pal-Gly-**His-Lys**), as the documents in the draft report indicate, stimulates collagen synthesis in human dermal fibroblasts in monolayer cell culture. But the Palmitoyl-Gly-**Lys-His** peptide (a fragment of Parathyroid Hormone) stimulates lipolysis in adipocytes in culture. It also is much more difficult to synthesize.
- ✓ Palmitoylation of a peptide of known biological activity can have a number of effects which each have to be verified individually:
  - Somewhat improved bioavailability in the *stratum corneum* and epidermis
  - Increase in potency of the peptide
  - Decrease up to inactivation of the bioactivity.

The dipeptide Carnosine (beta-Ala-His) is a potent anti-oxidant peptide well described in the scientific literature, circulating at relatively high concentration in our blood. N-palmitoylation of this dipeptide leads to a very strong PRO-oxidant activity (own unpublished experiments).

Hence, to evaluate the safety and suitability of the two peptides of this report, it is scientifically not justified to read across from other sequences or to neglect the palmitoylation, to compare with Copper- or Magnesium- complexed peptides etc.

4. PEPTIDE SYNTHESIS

All peptides offered for sale by Sederma are made by Solid Phase Synthesis Methods, in GMP facilities, at scales of 1kg to ≈5kg per batch. They are quality controlled at arrival and formulated into the solutions and preparations commercially called Biopeptide-CL (100ppm of Pal-Gly-His-Lys), Biopeptide-EL (100 ppm of Pal-VGVAPG), Dermaxyl (200 ppm of Pal-VGVAPG), Matrixyl 3000 (100ppm of Pal-Gly-His-Lys), Maxilip (1000ppm of Pal-Gly-His-Lys). These solutions contain standard quality ingredients such as DI-water,

glycerin USP, Butylene glycol as major solvents; Dermaxyl is an exception as a non-aqueous based balm.

Peptides are delivered as dry powder, with Certificates of Analysis. Composition and peptide content are quality controlled via amino acid analysis, HPLC on a routine basis; initial checks during development and/or random checks include LC-MS.
Impurities of the non-peptide remnant (as indicated in the draft report) are residual acetate, non-reacted palmitoyl acid and moisture. Incorrect peptides (shorter or misaligned sequences) are below detection level.

These peptides have been supplied reliably since 1990 by reputable European chemical companies to Sederma.

The Memorandum by W. Johnson Jr. and the ensuing discussion (1st part of the Draft report) raises the question of impurities in the synthetic peptides and the need for their analysis and risk assessment. While this remark may be pertinent in the case of peptides, it is of course pertinent and true for ALL chemically produced substances, and probably even more for "naturally" obtained/derived substances, be they cosmetic, pharmaceutical or food ingredients.
The safety of a substance produced by one supplier – and recognized by an authority such as the CIR committee – is not necessarily guaranteed by some other supplier of superficially identical substances, be it Shea butter (cold pressed or hexane extracted), arbutin (synthetic or plant extracted) or peptides shipped from various regions of the world…

5. USE LEVELS

The two peptides (in the palmitoylated version) have been tested, as the documents cited in the draft report recall, in a number of more or less sophisticated *in vitro* experiments, by research staff at Sederma and/or outside CROs.
Based on the results of these experiments, recommended use levels for the peptides in cosmetic application were determined. Some vehicle controlled (or not) clinical studies with panelists were carried out at these use levels.

The draft report indicates that FDA voluntary reporting data show cosmetic uses of the Pal-Gly-His-Lys (=Pal-GHK) peptide range from absurdly low (0.0000001%) to absurdly high (1%) concentrations. The first value is absurdly low (in view of the fact that *in vitro* activity was not discernible below 2 ppm = 0.0002%, 2000 times higher), the product probably just claiming to contain "peptides" but not using them for any other than label claim purposes; the second value is absurdly high, given the fact that even if the BIOPEPTIDE-CL solution is sold neat (as is) to a consumer, it would only contain 0.01% (100ppm) of the peptide. The only way to achieve a 1% Pal-GHK concentration in a formula is to use the neat peptide powder at this level. Apart from formulation difficulties (and patent issues: Sederma **never** sold the peptide pure to any company), the raw material cost of such a formula would be just ridiculously high (even if bought in low-cost countries from patent infringing suppliers). It is highly probable that the reporting to FDA of such a concentration is based on error and confusion between the peptide solution and the pure peptide contained therein.

Therefore, in view of the economic considerations (B-to-B supply of Biopeptide-CL) and the clinically tested and supplier recommended use level, it can be safely assumed that cosmetic formulas around the world (essentially leave-on products with "wrinkle appearance" claims) have used and still use these two peptides (but supplied in solution) at the range of 1 to 5 ppm, very rarely at higher (10 ppm) levels, but possibly often at much lower levels for reasons of cost.

This allows us a bit of calculation, as it would be carried out in the context of Threshold of Toxicological Concern. Although I realize that the TTC approach is usually not applied to **proteins** (for debatable reasons), we are not considering high- or medium molecular weight protein fragments, but peptides of Molar masses below 1000 Daltons, even including the palmitoyl chain. For the sake of the argument, allow me to do the calculation:

5 ppm of the pure peptide in a wrinkle cream = 5 mg/kg of cream.
That becomes 5 nanograms/mg of cream.
At the generally accepted applied dose (SPF testing) of 1.5 to 2mg /cm^2, we apply 7.5 to 10 nanograms per cm^2. With a facial surface of, say 200 cm^2, that would lead to 2000ng or 2µg of peptide applied to the body, i.e. a dose of 2µg/60kg = 33 ng/kg body weight.

But where does the peptide end up? Can we find it in the blood stream? Does it get metabolized? What effects can be expected from these concentrations?

The publication (cited in the draft report) by Lintner and Peschard does indicate that palmitoylation of a dipeptide increases diffusion of the "lipopeptide" (Palmitoyl-carnosine) into the epidermal layers, compared to the unmodified carnosine. The experiment described did, alas, not allow us to separate the epidermal from the dermal layer, such that statements about reaching the dermis are not necessarily substantiated.

A radiolabeling study of the penetration of another "lipopeptide" (Pal-KTTKS= Pal-Lys-Thr-Thr-Lys-Ser) carried out on behalf of Sederma showed that of this topically applied pentapeptide (or its radiolabelled fragments) only 3% reached the dermal layer. In both studies, the **trans**-dermal penetration of the peptides (radio-label) was negligible.

Systemic absorption of the peptides under consideration can thus be considered as non-existent, even if 3 or 5 or 10% of such a palmitoylated peptide were to reach the dermis (≈1-3 ng/kg bw) without degradation by proteolytic enzymes.

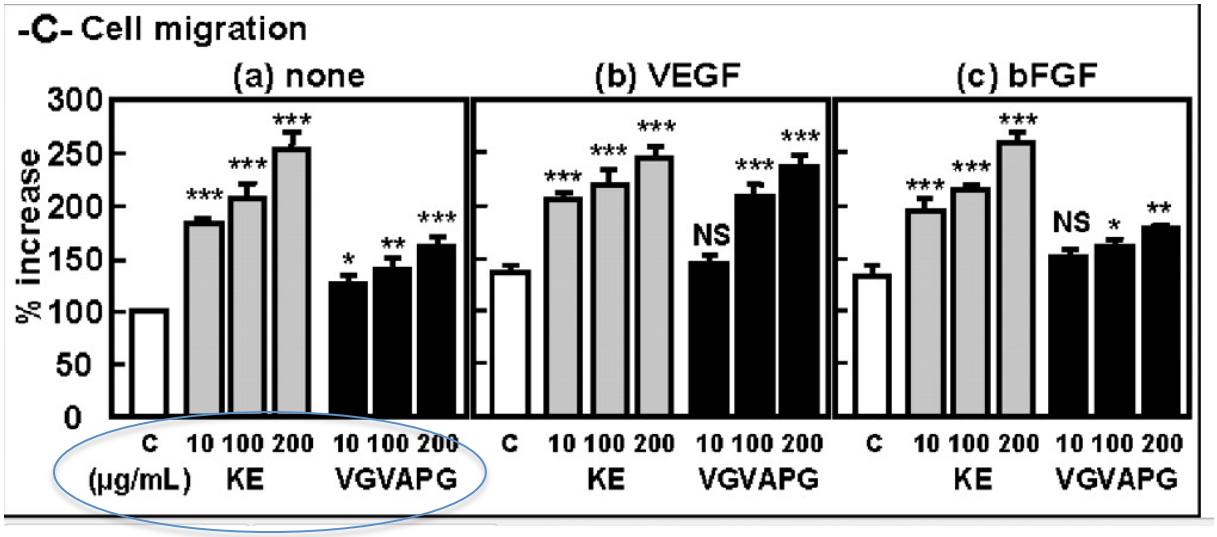
The publications by Sachs and by Dalpozzo (refs. 20 and 21) in the draft report finally indicate that the Gly-His-Lys peptide is unstable in plasma and hydrolyzed into its component amino acids within minutes. This is not an isolated case; most small peptides are metabolized in the blood within minutes, a problem the Pharma industry has found to be a major obstacle to using peptides as drugs.

The above-cited study by Lintner and Peschard on Carnosine also showed that no significant amount of radiolabel (Iodinated histidine) was found in the receptor fluid of the Franz cells. The almost identical (very low: 0.01% - 0.05% of topically applied radiolabel) level of radio signal in the receptor fluid for the two peptides (palmitoyl

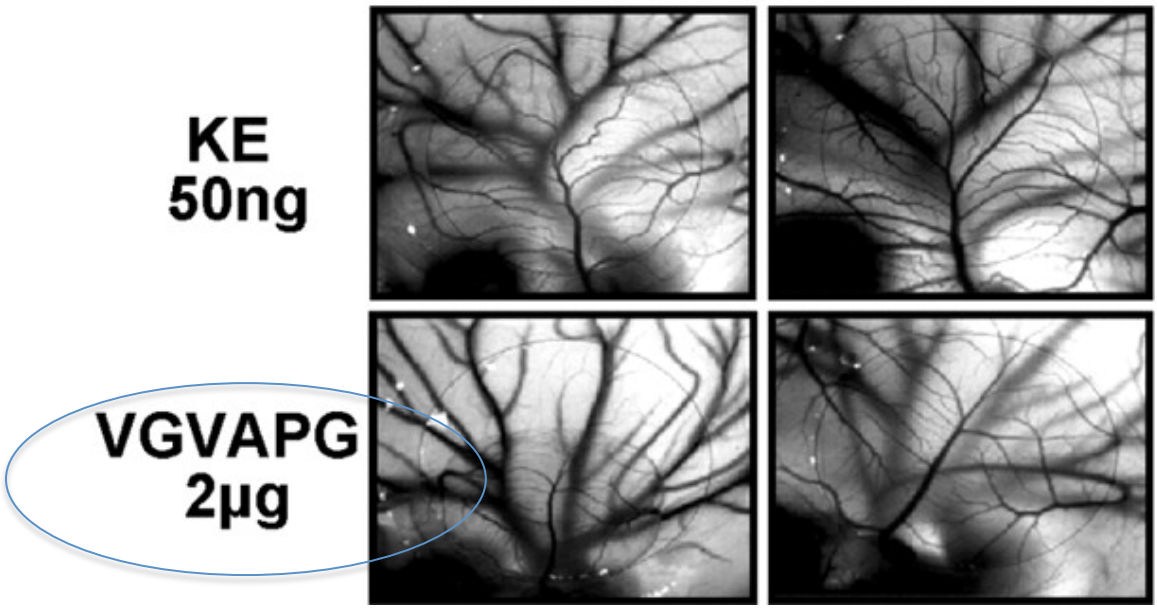
carnosine and carnosine) might allow the conclusion that the peptides had been hydrolyzed and the iodinated free histidine was the only observable entity in the receptor fluid.

6. SAFETY EVALUATION

The various studies cited in the draft report on biological effects and/or toxicological concerns of the two peptides are for the most part far removed from the domain of topical application to the skin from a cosmetic product. Either the publications cited relate experiments at much higher concentrations that those used in cosmetics (ref. 37 on immune suppression by GHK), or on *in vitro* studies on invertebrate pathology (ref 40), on non-palmitoylated copper peptides (ref 41, 43); as to the VGVAPG peptide, MMP upregulation (ref 51, 52) is found at ≈200ppm and cell adhesion modulation (ref. 11) at ≈700ppm. Chemotactic activity in lung carcinoma cells is observed significantly only at the specific concentration of $5*10^{-8}$M (3.5µg/L). Reference 38 (Hornebeck) on angiogenesis is NOT, as written in the draft report, about Pal-VGVAPG but about the non-acylated peptide; and the articles contradicts itself with respect to concentrations employed, from 200ng/mL to 2µg to 200µg/L such that it is difficult to conclude about the true quantities studied[2] (in any case not the 50ng mentioned in the Draft report).



[2]COPY&PASTE from the freely accessible article cited (ref 38): In vivo angiogenesis was performed according to an established shell-less culture technique, exposing the CAM to direct access for experimental handling (Averbar et al., 1974). At day six of embryonic development, angiogenic areas were delimited with a silicon ring (Weber Métaux, France) and PBS (as control) or κ-elastin (50 ng) or VGVAPG peptide (200 ng) in a final volume of 20 µl were placed inside the rings. The embryos were then placed in an incubator to induce spontaneous angiogenesis and were treated daily. Treated areas were photographed daily from day 6 to day 10 of embryonic development.



7. EXPOSURE

Taking into account the concentrations of the peptides in the commercial solutions sold by Sederma (100ppm, 100 ppm and 1000 ppm of Pal-Gly-His-Lys in the preparations called Biopeptide-CL, Matrixyl 3000 and Maxilip respectively) and the recommended use concentrations of these products in finished cosmetic formulas (3-5%, 1% respectively), we find 3 -10 ppm (mg/kg) of the peptides in the cosmetics.

Let us do some calculations:

- Pal-GHK 5ppm in a skin care cream
- = 5 mg/kg
- = 5 µg/g
- = 5 ng/mg
- applying 2mg/cm^2 > leads to 10 ng/cm^2 applied peptide
-

Penetration beyond epidermis: ≈3% of applied quantity

- > = 300pg/cm^2
- For a face of 200 cm$^{2:}$ 60ng
- 200 cm^2 x 0,1cm average skin thickness (s.c. to dermis) = 20cm^3 =20mL (volume):
    - Mol. Weight of Pal-GHK: ≈600
    - 60ng = 0.1nMol
    - thus: 60ng in 20mL skin= 3µg/L = **5nMol/L; way below any studied/evidence bio-activity level; this does not yet take into account that Pal-GHK is only ≈60% GHK**
    -
- 20 mL skin contain ≈20% protein, of which ≈ 80% collagen I
- => ≈3.2 mL protein volume ≈ 6.4g collagen mass (with a density ≈2) = 6.4*10^9 ng of collagen
- Hypothesis: 1% fragmented (renewal): 6.10^7 ng collagen fragments, of which GHK (MW≈300): if only repeated once within collagen sequence (MW 100.000):

300/100,000 = 3/1000 = 1/330; free GHK (1/330th of the fragmented collagen) represents $6.4*10^7$ng/330= ≈200,000 ng (in our volume of treated facial skin)

- Ratio « applied GHK» / « GHK fragments naturally present »:
- (of the 60 ng **Pal**-GHK, only a part is GHK!)
- i.e. 35 $ng^{applied}$ /200,000 $ng^{naturally\ present}$ => or 1/5700
- => the skin contains at least about 6000 times more naturally present GHK than the amount applied (generously) from a cosmetic product
-
- **WORST CASE? 100% penetration? Multiply the amount by 33, still get a ratio of "applied" over "naturally present" of 1/170.**
-

Idem Elastin:

-
- 20 mL skin contain ≈20% protein, of which ≈ 2% elastin
- => ≈0.08 mL elastin volume ≈ 160mg elastin mass (with a density ≈2) = $1.6*10^8$ ng of elastin
- Hypothesis: 1% fragmented (renewal): $1.6*10^6$ ng elastin fragments, of which VGVAPG (MW ≈500): **repeated six times**[3] within (tropo)elastin sequence (MW 72,000): 3000/72,000 ≈ 1/25; free VGVAPG (1/25th of the fragmented elastin) represents $1.6*10^6$ng/25= 64000 ng (in our volume of treated facial skin)

- Ratio « applied VGVAPG» / « VGVAPG fragments naturally present »:
- (of the 60 ng **Pal**-VGVAPG, only 70% are VGVAPG!)
- i.e. 42$ng^{applied}$ /64,000 $ng^{naturally\ present}$ or 1/1524
-
- => the skin contains at least about 1500 times more naturally present VGVAPG than the amount applied (generously) from a cosmetic product
-
- **WORST CASE? 100% penetration? Multiply the amount by 33, still get a ratio of "applied" over "naturally present" of 1/46.**

8. CONCLUSION

A number of questions are raised in and by the Draft report on Palmitoyl-Tripeptide 1 and Palmitoyl-Hexapeptide-12:

- ✓ **What does the INCI name of Palmitoyl-oligopeptide designate?**
  - It has become clear that ONLY the two peptides now called Palmitoyl-Tripeptide-1 and Palmitoyl-Hexapeptide-12 are the ones on the market under this (old) name
- ✓ **How are they obtained?**
  - In pure powder form by solid phase peptide synthesis, in reputable GMP equipped facilities with high purity and corresponding analytical data
- ✓ **How are they used in cosmetic formulations?**

[3] Charlotte Blanchevoye, Nicolas Floquet, [...], and Laurent Debelle: Interaction between the Elastin Peptide VGVAPG and Human Elastin Binding Protein. The Journal of Biological Chemistry, 288, 1317-1328

- Both peptides are presented to the market by SEDERMA (the only patent holder until recently) in various forms of pre-mixes with trade names (Biopeptide-CL, Biopeptide-EL, Maxilip, Matrixyl 3000, Dermaxyl…)

✓ **At what level are the peptides found in cosmetic consumer products?**

- Average doses (estimated) range from less than 1 ppm (0.0001%) to 10 ppm (0.001%); it is extremely unlikely that formulators use significantly higher levels of the peptides given their price, availability, recommended use levels from the supplier and clinical trials of claim substantiation

✓ **Given the *in vitro* effects observed for these palmitoylated peptides, do they need to be considered as drugs?**

- Clearly not. Almost any substance applied to skin (or tested in *in vitro* cell culture studies) will show, under a chosen protocol, some bioactivity: Vitamins, flavonoids (including isoflavones), alkaloids (caffeine, to name but one), terpenes and derivatives, hydrolyzed proteins (mixtures of generally unidentified peptides=protein fragments), even glycerin can be shown to stimulate synthesis of this effect or inhibit release of that effector; genetic and epigenetic modulations can be observed for almost any substance in these protocols.
- What makes a substance a drug is
  - the expressed INTENT (treatment and/or prevention of pathological states, changes of bodily function or structure), with which it is proposed to the public
  - and/or the measurable systemic effects on the body in places other than the local site of application to the skin.

✓ **If the peptides penetrate into the skin, do they expose the consumer to unreasonable risk?**

- Given the available toxicological data on these peptides, the fact that they are identical (except for the palmitoylation) to protein fragments already existing in the human body, that their small size (3-mer and 6-mer) precludes them from possessing allergenicity potential, the extremely low amount of **transdermal** penetration seen in two radio-label studies on related palmitoyl-peptides (Pal-Carnosine, Pal-KTTKS), and the huge excess (compared to applied quantities) of the presence of the same peptide sequences naturally occurring in the skin as a consequence of normal (and age-induced) tissue renewal, my answer would be: these peptides are safe for cosmetic use at the recommended use levels between 3-10ppm.
- As a reminder for comparison, it might be useful to recall that retinol, used at 700 -1500 ppm has an activity profile partly similar to these peptides (stimulation of collagen synthesis, thickening of the skin, gene modulation…) but possesses a toxicological profile considerably more noteworthy and pertinent (skin irritation, teratogenicity, oral toxicity…). The same could be said about a number of plant-derived substances (caffeine, quercetin, salicylic acid…and many others).

✓ **Are these conclusions useful and valid for appreciating the many other peptides offered to the cosmetic market?**

- In some parts YES, in other parts NO.
  - Peptides of small size (<15 amino acids) can be considered free of presenting allergenic risks.

- Peptides possessing a sequence that is identical to the one found in the human body ("Matrikine concept" or similar approach), acylated or not, and promoted/used in consumer products at similar use levels to the ones presented and discussed here, should be considered in a similar manner.
- Peptides containing unusual/noncoded amino acids, longer chain lengths, more exotic bioactivity… may need some extended scrutiny.

Respectfully submitted
Prof. Dr. Karl Lintner
KAL'IDEES S.A.S.
March 3, 2014