SUPPLEMENT

Additional Council Report Comments
Powder Comments from CIR SSC

Ingredients

   Alkonium Clays
   HDI Polymers
   Helianthus annuus
   Nonoxynols
   Polymerized Tetramethylycyclotetrasiloxanes

CIR EXPERT PANEL MEETING
DECEMBER 14-15, 2015
Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
       Wilbur Johnson, Jr., Senior Scientific Analyst
Date: December 4, 2015
Subject: Wave 2 - September 2015 Comments from PCPC

During the preparation of the December 2015 Panel materials, comments received from the Personal Care Products Council prior to the September 2015 were inadvertently left out of some of the final report packages. The comments have been addressed by CIR staff. The comments included in this Wave 2 submission are:

- Citrus Fruit-Derived Ingredients
- Apple-Derived Ingredients
- Nonoxynols
- Silk Protein Ingredients
Memorandum

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

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

DATE: September 15, 2015


Constituents/Composition - Please delete “(non-cosmetic grade)” as there is no group that develops standards for “cosmetic grade”

In the description of the new epidemiology study, please indicate whether or not the investigators controlled for sun exposure. It is possible that people that live where citrus is grown eat more citrus and have more sun exposure.
Memorandum

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

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

DATE: September 15, 2015

         Meeting: Safety Assessment of Nonoxynols as Used in Cosmetics

Key Issues
Abstract, Discussion - In the abstract, rather than stating that the limits in Europe are not relevant, the
    CIR Expert Panel could acknowledge that because of concerns regarding environmental effects,
    the use of these ingredients is regulated or prohibited in many jurisdictions. Rather than saying
    that the endocrine effects driving the environmental concerns are not relevant, the Discussion
    should note that the CIR procedures limits the purview of the CIR Expert Panel to assessing the
    safety of cosmetic products as they are used, and the CIR review does not concern potential
    environmental exposure and effects.

    The Cosmetic Use section cites reference 11 which is the EU Cosmetic Directive (76/768/EEC). The
    Cosmetic Directive has been replaced by the Cosmetic Regulation (EC No. 1223/2009) (reference 14).
    Reference 11 needs to be deleted from the report.

    It should be noted that the “other personal cleanliness product” containing 2.5% Nonoxynol-9 is
    actually a hand cleanser.

Additional Considerations
Percutaneous Absorption - It is not clear what is meant by “skin species”.
Reference 24 - The Health Canada report is a 2001 report - it is not clear why it says “last updated” as
    it is not a report that is updated.
Memorandum

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

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

DATE: September 15, 2015


Key Issues
Introduction, Summary - Although cosmetics industry may have pointed out that there several genus species names used for apple, the Introduction should just state the multiple names and provide citations to botanical references. Industry should not have to inform CIR of multiple genus species names that may be used for a plant. It should be standard practice for CIR staff to consult botanical references for synonyms and old names for all plant-derived ingredients. Without information in the report about the sensitization potential of apples, the following general statement in the conclusion is not helpful. “The Panel is encouraging industry to be selective of the apple cultivars from which cosmetic ingredients are derived, to ensure that the finished product is non-sensitizing.” The original boilerplate statement cautioning formulators to be aware of constituents of concern is sufficient.

The report contains no information about the sensitization potential of apples and which cultivars may have less sensitizing potential. A search for apple and sensitization reveals that the proteins Mal d 1 and Mal d 3 (nonspecific lipid transfer protein) results in food allergy issues in some individuals. It is not necessary to be selective of apple cultivars to limit sensitization potential. For apple-derived ingredients, limiting protein levels in the cosmetic ingredients would be another approach. The following publications (abstracts attached) may be helpful.


Appendix - It is not correct to state that apple polyphenol extract is not a cosmetic ingredient. The Shoji et al. (2004) paper uses a trade name of Applephenon for their apple polyphenol extract. Searching the Dictionary database indicates that the trade name Applephenon has been assigned the INCI name Pyrus Malus (Apple) Fruit Extract. The information on apple polyphenol extract should be presented within the report rather than in an appendix.

Reference 49 (Shoji et al. 2004) includes specific information about the method of manufacture and composition of the apple polyphenol extract which may have use as a cosmetic ingredient. The information about method of manufacture and composition needs to be added to the report.

Additional Considerations

Although the FDA VCRP may use “(apple)” in the names with Malus Domestica, all the Dictionary names with Malus Domestica do not have “(apple)”.

The memo with the apple report reviewed at the June meeting stated that industry was completing a concentration of use survey for a number of ingredients added to the report (Callus Extract, Fruit Cell Culture Extract and ingredients listed in the VCRP but not in the Dictionary). Unfortunately, the Council did not know the ingredients had been added to the report until the June memo was available. The additional ingredients have been included in a survey that was sent out July 20, 2015. As stated at the June meeting, the complete results of the July survey will not be available for the September CIR meeting. It would have been helpful if the ongoing survey was mentioned in the memo to the September draft of the report.

Introduction - Pyrus malus should not be called a “common name”.

Definition and Structure - As information on composition of some ingredients is included in the composition/impurities section, the following should be deleted from the report. “The ingredients in this report are related by source, as each is a derivative of apple. 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 identities and concentrations cannot be known for these exclusively industry specific ingredients until such information is provided as outlined in the industry’s botanical framework. Differences in those components do not necessitate the regrouping of such ingredients, but instead warrant a comparison/contrast effort as to how those differences affect safety. Those differences are likely to be informative.”

Composition/Impurities, Pyrus Malus (Apple) Fruit Extract - As long as it is stated in the Introduction that Malus sylvestris is another name for apple, it is not necessary to restate it in this section.

Cosmetic Use, Summary - Noting the ongoing concentration of use survey in these sections would have been helpful.

Irritation and Sensitization, Non-Human, Pyrus Malus (Apple) Fruit Extract - It is not clear what is
meant by "OECD TP" - usually it is presented as OECD TG (test guideline).
Appendix - The list of plant parts containing polyphenols in the Appendix should match the list
provided in the Summary of the report, e.g., leaves also contain polyphenols.
Appendix, Subcutaneous - Please delete "Study details will be incorporated after the primary reference
is received." - as it appears that more details of the study have been added to the Appendix.
Appendix, Genotoxicity - Please provide a reference(s) for the genotoxicity assays.
Appendix, Summary - If there is going to be a Summary of the Appendix, it should include the study
on the polyphenol extract in addition to the study on procyanidin B2.
Table 8 - Where is the information on Pyrus Malus (Apple) Seed Oil? It was included in the Council
concentration of use survey (reference 3) and two uses were reported (face powder, makeup
base).
Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods.


Abstract

BACKGROUND: Allergy to a plant food can either result from direct sensitization to that food or from primary sensitization to pollen, latex, or another food.

OBJECTIVE: We sought to investigate the primary sensitizers in apple allergy across Europe, the individual allergens involved, and whether these differences determine the clinical presentation.

METHODS: Patients (n = 389) with positive case histories and skin prick test responses to fresh apple were selected in the Netherlands, Austria, Italy, and Spain. Skin prick tests and RASTs to a panel of pollens and plant foods were performed, as well as RASTs to Bet v 1 and the apple allergens Mal d 1, 2, 3, and 4.

RESULTS: In the Netherlands, Austria, and Italy apple allergy is mild (>90% isolated oral symptoms) and related to birch pollenosis and sensitization to Bet v 1 and its apple homologue, Mal d 1, which has an odds ratio of local reactions of 2.85 (95% CI, 1.47-5.55). In Spain apple allergy is severe (>35% systemic reactions) and related to peach allergy and sensitization to Mal d 3 (nonspecific lipid transfer protein), which has an odds ratio of systemic reactions of 7.76 (95% CI, 3.87-15.56).

CONCLUSION: The analysis of individual apple allergens in a clinical context has provided insight into the sensitization pathway and into the intrinsic risk an allergen bears to induce mild or severe food allergy.

CLINICAL IMPLICATIONS: Information on the sensitization pathway is essential to develop preventive strategies in food allergy. The application of individual food allergens with a known intrinsic risk will improve the prognostic value of diagnostic tests.
Abstract

BACKGROUND: Component-resolved diagnosis (CRD) using microarray technology has recently been introduced into the field of clinical allergology.

OBJECTIVE: To further validate the use of CRD by microarray technology in allergy diagnosis.

METHODS: Thirty-seven patients allergic to birch pollen were included. The discriminative value of apple-specific IgE (sIgE), recombinant Mal d 1 (rMal d 1) sIgE, apple skin prick test and rMal d 1 on the microarray was assessed between patients with a birch-related oral allergy syndrome to apple (OAS(+), n=20) and healthy control individuals (HC, n=8) without a history of inhalant allergies or apple-induced OAS. An additional comparative analysis was carried out with individuals allergic to birch pollen allergy without OAS (OAS (-); n=17).

RESULTS: rMal d 1 coupled to the microarray constitutes a discriminative marker between OAS(+) and HC with a sensitivity 95% and a specificity of 100%. However, in parallel with the traditional sIgE assay, 15 out of 17 OAS(-) individuals (88%) also displayed IgE reactivity to rMal d 1 coupled to the microarray. OAS(-) individuals are more frequently sensitized to mite (about three to four times), cat and dog dander (about two to three times) and grass pollen (about 1.5 times) as compared with OAS(+) patients.

CONCLUSION: At first glance, CRD by microarray seems to be a reliable instrument in the diagnosis of apple-mediated OAS in birch pollen allergy. However, for discriminating between sensitization and a real allergy, micro-arrayed rMal d 1 offers no advantage over conventional quantification of rMal d 1 sIgE. Most interestingly, within a single run, birch pollen-allergic patients without OAS to apple were shown to display a broader
Sensitization profiles in birch pollen-allergic patients with and without oral allerg... Page 2 of 2

sensitization to classical inhalant allergens than birch pollen-allergic patients with an apple-related OAS.

Comment in
Application of multiplexed immunoglobulin E determination on a chip in component-resolved diagnostics in allergy. [Clin Exp Allergy. 2010]

PMID: 19709127 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources

PubMed Commons

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8/25/2015
Additional indications for the low allergenic properties of the apple cultivars Santana and Elise.


Author information

Abstract
Patients with Oral Allergy Syndrome (OAS) to fresh apple may tolerate low allergenic apple cultivars. We aimed to investigate if the low allergenic properties of Elise and Santana, as previously identified in a Dutch population, could be generalised within North West Europe within the birch pollen region with regard to both the prevalence and degree of sensitization. Prick-to-prick tests (PTP) were performed in eighty-five adult patients with OAS to fresh apple in Great Britain, Switzerland and Northern Italy, before the birch pollen season, using the putatively low allergenic apple cultivars Elise, Santana, Granny Smith, Modi and McIntosh, as well as the putatively high allergenic apple cultivars Golden Delicious and Kanzi. No significant differences in percentages of negative responses of PTPs were found between the three countries. Negative responses did not differ from negative responses to the different apple cultivars we previously found in 2006/2007 in the Netherlands. The size of the PTPs of all apple cultivars tested were correlated to the size of the skin prick tests with birch pollen. These results add to the indications for the low allergenic properties of the low allergenic apple cultivars Santana and Elise, as the number of negative responses were reproducible in three countries within the birch pollen region and were similar to previous results in the Netherlands. These results justify oral challenge studies with Elise and Santana within the birch pollen region, to establish the low allergenic properties for the benefit for apple allergic consumers for definite conclusions.

PMID: 24036616 [PubMed - indexed for MEDLINE]
Memorandum

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

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

DATE: September 16, 2015


Key Issues
To be consistent with other CIR reports that mention CIR conclusions of ingredient components previously reviewed, the Introduction should mention the CIR review of Ethanolamine and Ethanolamine Salts (final report 2012). The Ethanolamine report has a conclusion of safe in rinse-off products when formulated to be non-irritating.

Additional Considerations
Introduction - The information about spiders should be removed from the Introduction.
Toxicology, Single Dose Exposure, Hydrolyzed Silk - Reference 34 (eye irritation study) is not the correct reference for the acute oral exposure study. There is another Toxicol Laboratories Limited study in the 7/3/2012 submission that concerns acute oral exposure. It is not correct to state that further details about the Hydrolyzed Silk tested were unavailable. The submission needs to be considered with the memo and related reports. The Hydrolyzed Silk tested in this acute oral study had a molecular weight of 300 Da.
Repeated Dose Exposure - The following statement is not correct: “Details relating to the composition of the test material or method of preparation were not included.” (reference 39). The submission memo and other references submitted also need to be considered. Hydrolyzed Silk Protein-2 has an average molecular weight of 650 Da and it was tested as a 6.5% water solution.
Allergenicity - In the description to reference 46, please also state the size of the silk proteins to which the subjects developed antibodies.
Discussion - “apple” needs to be deleted from the paragraph on potential inhalation exposure.
Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer, PhD, DABT
       Senior Toxicologist
Date: December 4, 2015
Subject: Wave 2: Cosmetic Powder Exposure

Enclosed is a memo, titled “Cosmetic Powder Exposure” (powder122015data1), which the CIR Science and Support Committee (CIR SSC) submitted in response to the CIR Expert Panel’s request for information on this topic at the September 2015 meeting. The memo presents estimated inhalation exposures to respirable particles from the use of loose talc-based cosmetic powders. In addition, the CIR SSC submitted copies of two published papers (powder122015data2 and powder122015data2) that reported airborne concentrations of respirable particles measured during routine use of talc-based cosmetic powders. The CIR SSC used the average concentrations reported in these papers to calculate the inhalation exposure estimates.

The estimates are conservative because, unlike loose powder products, cosmetic powder products are often fairly well compacted, may be moist or oily, and are, thus, not necessarily prone to release respirable particles to the air. As noted in the current CIR Aerosols Precedents document (http://www.cir-safety.org/cir-findings, 9/2012):

“...industry can minimize airborne particles from cosmetic powder products by controlling the milling of the ingredients and adding binding materials, such as oils, waxes or hygroscopic ingredients in formulations. The binding materials foster agglomeration of the ingredients and substantially increase their cohesivity. These measures increase the size of the particles in the product.”

The published papers reported estimates of the concentrations of respirable particles in the breathing zone, ranging from 0.48 mg/m³ for a loose face powder product to 2.03 mg/m³ for a body dusting powder, and exposure durations (per application) of 0.3 minutes to 1.23 minutes, respectively. These papers also reported average concentrations up to 0.21 mg/m³ respirable particles in the breathing zone of a baby during use of baby powder on the diaper area, and corresponding average exposure durations up to about 0.5 minutes.

As noted in CIR SSC’s memo, the estimated exposures are much less than regulatory and guidance limits established for respirable talc particles and nuisance dusts in the workplace. The American Conference of Governmental and Industrial Hygienists (ACGIH) TLV-TWA (threshold limit value – time-weighted average) for respirable talc particles is 2 mg/m³ for 8 hours. The U.S. Occupational Safety and Health Administration (OSHA) 8-hour TWA permissible exposure limit (PEL) for nuisance dusts is 5 mg/m³ for the respirable fraction in the workplace. By comparison, the 8-hour TWA exposure associated with one 1.23 minute application of a cosmetic talc-based product in which the respirable airborne fraction in the breathing zone is 2.03 mg/m³ would be 0.0052 mg/m³ (2.03 mg/m³ x 1.23 min = 2.5 mg-min/m³, and 2.5 mg-min/m³/[60 min/hr x 8 hr] = 0.0052 mg/m³ 8-hr TWA). This value (0.0052 mg/m³) is about 0.3% of the ACGHI TLV-TWA and 0.1% of the OSHA PEL.
A related topic that was mentioned during the September 2015 Panel meeting is the level of exposure to inert respirable particles that could cause adverse effects through pulmonary overloading. On this issue, the current CIR Aerosols Precedents document (http://www.cir-safety.org/cir-findings, 9/2012) states:

“Pulmonary overload is a condition in which the accumulation of any inert, poorly soluble particulate material in the lungs overwhelms the capacity of the alveolar macrophages to clear the material from the lungs. Chronic pulmonary overload can cause persistent inflammatory responses, fibrosis and tumors, although the mechanism(s) of overload-induced tumor formation is not completely understood. The European Union’s current threshold for protecting workers from pulmonary overload during occupational exposure to respirable dust particles is 1.5 mg/m³ 8-hour time-weighted average. In comparison, inhalation exposures to aerosols from cosmetic sprays will be much lower than this threshold, primarily because of the much shorter exposure duration associated with cosmetic spray use (i.e., only a few minutes).”

The data submitted by the CIR SSC may help to inform the safety assessments of ingredients in cosmetic powders. Please consider the submitted data, as well as the relevant passages quoted above from the current CIR Aerosols Precedents document, and determine whether the data warrant changes to the discussion sections of safety assessment reports or revision of the Aerosols Precedents document.
Memorandum

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

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: November 3, 2015

SUBJECT: Cosmetic Powder Exposure

At the September 2015 CIR Expert Panel meeting, the Panel requested information on the potential for inhalation exposure following the use of personal care products in powder form. This memo provides an example of exposure estimation for powder products.

The CIR SSC based its exposure calculations on loose talc-based powder products, representing a worse case scenario for exposure to powder products.

Aylott et al. (1979) measured respirable talc and reported a mean atmospheric concentration of 0.48 mg/m³ during normal use of a loose face powder (average 17.5 seconds talcing time), and 1.13 mg/m³ during use of adult dusting powder (average 39 seconds talcing time). In a second study by Russell et al. (1979), average respirable talc air concentrations of 2.03 mg/m³ were measured during routine application of talcum powder (average exposure 1.23 minutes).

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1This memo does not address the toxicology of inhaled particles. The toxicology of poorly soluble particles is well studied and additional information may be found in the report by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 122 Poorly soluble particles/Lung overload. Available from http://www.ecetoc.org/publications.


Using a breathing rate of 0.01 m³/minute⁴ the following exposures per application are calculated:

Loose face powder: \(0.48 \text{ mg/m}^3 \times 0.01 \text{ m}^3/\text{min} \times 0.3 \text{ min} = 0.00144 \text{ mg/application}\)

Adult dusting powder: \(1.13 \text{ mg/m}^3 \times 0.01 \text{ m}^3/\text{min} \times 0.65 \text{ min} = 0.0074 \text{ mg/application}\)
\(2.03 \text{ mg/m}^3 \times 0.01 \text{ m}^3/\text{min} \times 1.23 \text{ min} = 0.025 \text{ mg/application}\)

For comparison, exposure to the 2 mg/m³ ACGIH talc TLVs (ACGIH 2014) for one working day (female breathing rate light activity 9.12 m³/day⁶) would result in an exposure of 18.2 mg. Powder products consisting of primarily inert particles may be compared to OSHA Permissible Exposure Limits (PEL) values for nuisance dust, which are 5 mg/m³ for the respirable fraction and 15 mg/m³ for total dust.

Based on the low exposure, the CIR SSC believes that inhalation is not a significant route of exposure for personal care products in powder forms.

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⁴Breathing rate used in the CIR Aerosol document found at http://www.cir-safety.org/sites/default/files/aeroso092012rep_0.pdf

⁵The concentration to which a worker can be exposed day after day for a working lifetime without adverse health effects.

The following copyrighted material has been removed:


MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: December 4, 2015

Subject: Additional Data for Alkonium Clays As Used In Cosmetics

Attached is an updated concentration of use survey from the Council. [alkcly122015Data1,2] This survey confirms that the face product containing quaternium-90 bentonite at 0.88% is a lotion and is not a powder. While there are two possible powders listed in the VCRP for quaternium-90 bentonite, the Panel agreed that confirmation that this ingredient is not used in a powder would remove any need for inhalation data.

Also attached is an assay measuring the amount of free quaternary ammonium chloride produced when alkonium clays with varying amounts of dimethyl dihydrogenated tallow quaternary ammonium chloride are placed in water. [alkcly122015Data3,4] Quaternary ammonium chloride was present in the water at 10-20 ppm with a detection limit of 0.5 ppm. This addresses the data need for the amount of alkonium cation releasable/exchangeable in solution.
Memorandum

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

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

DATE: December 3, 2015

SUBJECT: Updated Concentration of Use by FDA Product Category: Alkonium Clays

The reported face and neck product containing 0.88% Quaternium-90 Bentonite is a lotion, not a powder product.
Concentration of Use by FDA Product Category – Alkonium Clays*

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Product Category</th>
<th>Maximum Concentration of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stearalkonium Bentonite</td>
<td>Eyeliner</td>
<td>0.19%</td>
</tr>
<tr>
<td>Stearalkonium Bentonite</td>
<td>Eye shadow</td>
<td>2.5%</td>
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<tr>
<td>Stearalkonium Bentonite</td>
<td>Foundation</td>
<td>0.47-1.1%</td>
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<tr>
<td>Stearalkonium Bentonite</td>
<td>Lipstick</td>
<td>0.5-2.4%</td>
</tr>
<tr>
<td>Stearalkonium Bentonite</td>
<td>Basecoats and undercoats (manicuring preparations)</td>
<td>1-1.3%</td>
</tr>
<tr>
<td>Stearalkonium Bentonite</td>
<td>Nail extenders</td>
<td>3.5%</td>
</tr>
<tr>
<td>Stearalkonium Bentonite</td>
<td>Nail polish and enamel</td>
<td>1.2-6.5%</td>
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<tr>
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<td>Other manicuring preparations</td>
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</table>

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

Information collected in 2014; Table prepared January 5, 2015
Updated August 1, 2015: removed Quaternium-90 Bentonite face powder – it is not a powder, it is a cream foundation formulation

Updated December 1, 2015: The face product containing 0.88% Quaternium-90 Bentonite is a lotion, not a powder
Memorandum

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

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

DATE: December 4, 2015

SUBJECT: Alkonium Clays

Elementis Specialties, Inc. 2015. Alkonium clays - free quaternary ammonium chloride.
ALKONIUM CLAYS – FREE QUATERNARY AMMONIUM CHLORIDE

Summary

An investigation was conducted to assess whether quaternary ammonium ions can become unbound from alkonium clays under equilibrium conditions. The results of the study show that the clay - quaternary ammonium - chloride interaction results in a strong, stable organo clay complex.

Description of the Formation of Alkonium Clays

An alkonium clay (i.e. bentonite based organo clay) is formed when a bentonite clay is treated with quaternary ammonium ions (quat) in an ion exchange reaction. Any quaternary ammonium chloride (quat chloride) salt supplied in excess of the bentonite cation exchange capacity partitions to the organo clay phase and becomes part of the organo clay complex. Free quat chloride therefore cannot be identified as clay, quat and chloride are said to be in a dynamic equilibrium in this organo clay complex.

Determination of Free Quaternary Ammonium Chloride in Alkonium Clay

Three alkonium clays were selected for stability studies. These organoclays are all derived from bentonite clay but contain varying amounts of dimethyl dihydrogenated tallow quaternary ammonium chloride.

The organoclays were dispersed in water to make up 5 weight percent dispersions, which were then equilibrated by shaking for 24 hours before analyzing the water phase for quaternary ammonium chloride content by HPLC. The results of the study showed that 10 – 20 ppm of quaternary ammonium chloride was present in the water phase. The method detection limit is approximately 0.5 ppm.

Dimethyl dihydrogenated tallow quaternary ammonium chloride has a water solubility of about 1500 to 2000 ppm, as determined by the same HPLC method.

Although all three alkonium clays tested have enough dimethyl dihydrogenated tallow quaternary ammonium chloride available to potentially saturate the water phase, this does not happen. The quaternary ammonium chloride has a very strong preference for the organo clay phase and this affinity becomes stronger as the organic loading on the clay increases.

Conclusion:

The clay – quaternary ammonium - chloride interaction results in a strong, stable organo clay complex, and quaternary ammonium ions do not significantly become unbound from alkonium clays under equilibrium conditions.

Christ Kanoles
Senior Product Stewardship Manager
December 1, 2015
MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: December 4, 2015

Subject: Additional Data for HDI Polymers

Attached please find additional data submitted by the Council for the Panel’s consideration addressing the Insufficient Data Announcement from September, 2015. Specifically, the data include method of manufacture, end capping materials, residual diisocyanates analysis, and stability data. This data includes:

1) Steareth-100/PEG-136/HDI copolymer and bis-lauryl cocaminiopropylamine/HDI/PEG-100 copolymer (and butylene glycol) – Method of manufacture, residual monomer, and stability. A high boiling aliphatic alcohol or surfactant molecule are used to consume the unreacted isocyanate groups at the ends of the polymer chains and act as an end capping agent. Residual diisocyanate is below the limit of detection (0.017%). There was no free HDI detected for both of these ingredients at temperatures up to 150˚C. [HDIply122015Data1]

2) HDI/di-C12-14 alkyl tartrate hydrogenated dilinoleyl alcohol copolymer – Stability and sensitization. This ingredient is stable at temperatures up to 50˚C for 16 weeks; no isocyanates were detected (HDI <0.5 ppm). This ingredient is expected to not be sensitizing because of high molecular weight, no fractions <1000 Da, and the absence of residual HDI monomer. [HDIply122015Data2]

3) HDI trimethylol hexyllactone crosspolymer (and silica) and HDI/PPG/polycaprolactone crosspolymer (and silica) - Method of manufacture, impurity data, and physical, chemical properties, and history. Alkylation agents and end capping agents are not used in these two ingredients. Residual HDI was <100 ppm for both ingredients; ε-caprolactone 66-73 and 240 ppm, respectively; and trimethylolpropane 4-12 and < 2 ppm, respectively. The average particle size range from 12~19 µm. These ingredients have been used since 1995 and1998, respectively, with no adverse event reports from consumers. [HDIply122015Data3-5]
Memorandum

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

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

DATE: November 23, 2015

SUBJECT: Information on HDI/Di-C12-14 Alkyl Tartrate Hydrogenated Dilinoleyl Alcohol Copolymer

Please see the memo and attachment provided by the Council on August 5, 2015 for additional information on this polymer. The information previously provided indicates that the polymerization is terminated by the addition of ethyl alcohol.

The supplier has provided the following additional information on HDI/Di-C12-14 Alkyl Tartrate Hydrogenated Dilinoleyl Alcohol Copolymer:

HDI/Di-C12-14 Alkyl Tartrate Hydrogenated Dilinoleyl Alcohol Copolymer is stable over time at different temperatures (5, 25, 50 °C for 16 weeks - storage conditions). Release of isocyanates does not occur, as demonstrated by HPLC-MS ANALYSIS (HDI < 0.5 ppm at different check times).

HDI/Di-C12-14 Alkyl Tartrate Hydrogenated Dilinoleyl Alcohol Copolymer is a high molecular weight substance which is very unlikely to penetrate through the skin, therefore, no interaction with the immunologically important dendritic cells is likely. The absence of the sensitizing monomer HDI has been shown analytically. No low molecular weight fractions (<1000 D) were detected by SEC-MAL. No reactive groups exist that would interact with biological molecules in the skin. Thus, based on these considerations no skin sensitization potential is expected.
Memorandum

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

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

DATE: November 5, 2015

SUBJECT: Information on Method of Manufacture and Stability: Steareth-100/PEG-136/HDI Copolymer and Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer

Elementis Specialties. 2015. HDI polymer manufacturing process.

Elementis Specialties. 2015. HDI polymer stability at hair dryer temperatures.
HDI POLYMER MANUFACTURING PROCESS

Product: RHEOLUMEX® 811
INCI Name: Steareth-100/PEG-136/HDI Copolymer

Product: RHEOLUMEX® 812
INCI Name: Bis-Lauryl Cocamidopropylamine/HDI/PEG-100 Copolymer (and) Butylene Glycol

Process Description of the Manufacturing Process for RHEOLUMEX® 811 and 812

Pre-dried polyethylene glycol is charged to a reaction vessel. The diisocyanate is charged to the reaction vessel followed by a catalyst. The reaction is allowed to proceed for the prescribed time period and at the prescribed temperature in order to consume all of the free diisocyanate. A high boiling aliphatic alcohol or surfactant molecule is then charged to the reactor to consume the unreacted isocyanate groups at the polymer chain ends and act as the capping agent.

Residual Raw Materials in the Final Product

The stoichiometry of the reactions is set such that there will be no unreacted diisocyanate starting material at the end of the process. GC analysis of the final products provided non-detectable results. The limit of detection is 0.017%.

The capping agent for RHEOLUMEX® 811 is a surfactant molecule, Steareth-100, which is commonly used in cosmetics formulas. The amount present in the final product is expected to be minimal based on the stoichiometry of the reaction. Steareth-100 was included in the CIR safety assessment of Alkyl PEG Ethers that was published in 2012. It concluded that alkyl PEG ethers were safe as used when formulated to be non-irritating. The report referenced Steareth-100 use levels of 0.02 – 6%.

The capping agents for RHEOLUMEX® 812 are high boiling aliphatic alcohols. They were not detected by GC analysis. The analysis has a limit of detection below 0.05 wt% for each alcohol.

Christ Kanoles
Senior Product Stewardship Manager
November 4, 2015

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All chemicals should be handled only by competent personnel, within a controlled environment. It is the buyer's/user's responsibility to ensure that his activities comply with all applicable federal, state, provincial and local laws, and to determine the conditions necessary for the safe use of this product. ELEMENTIS urges each customer or recipient of this document to study it carefully and consult appropriate expertise, as necessary or appropriate, to become aware of and understand the data contained in this document and how it relates to the product.

Elementis GmbH
Elementis Specialties
Stolberger Str. 370
50933 Köln
Germany
Telephone: ++49 (0) 221 2923 2000

Elementis Specialties, Inc.
469 Old Trenton Road
East Windsor, New Jersey
08512 USA
Telephone: 609/443-2000

www.elementis-specialties.com
HDI POLYMER STABILITY AT HAIR DRYER TEMPERATURES

Product: RHEOLUXE® 811
INCI Name: Steareth-100/PEG-136/HDI Copolymer

Product: RHEOLUXE® 812
INCI Name: Bis-Lauryl Cocominopropylamine/HDI/PEG-100 Copolymer (and) Butylene Glycol

RHEOLUXE® 811 AND RHEOLUXE® 812 both consist of HDI (1,6-hexanedisocyanate) copolymers. In order to assess the stability of these HDI copolymers, they were tested for free HDI using Gas Chromatography (GC). The temperature of the injection port was varied as part of the study.

The following injector port temperatures were used for the study. The presence of free HDI (indicative of polymer degradation) is provided in the table. The HDI Limit of Detection (LOD) is 0.017%.

<table>
<thead>
<tr>
<th>Injector Port Temperature (°C)</th>
<th>Injector Port Temperature (°F)</th>
<th>Free HDI Detected?</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>167</td>
<td>No</td>
</tr>
<tr>
<td>100</td>
<td>212</td>
<td>No</td>
</tr>
<tr>
<td>150</td>
<td>302</td>
<td>No</td>
</tr>
</tbody>
</table>

Free HDI was not detected at injection port temperatures up to 150 °C (302 °F). This shows that the polymer is stable and heat resistant to temperatures that would be expected to occur during both product formulation and end-use. Typical hair blow-dryers operate at 100 °F (38 °C), and have heat sensor controls to prevent temperatures above 140 °F (60 °C).

The data generated in this study indicate that free HDI formation due to polymer degradation does not occur at the temperatures typically encountered during the formulation and use of these HDI copolymers.

Christ Kanoles
Senior Product Stewardship Manager
November 5, 2015

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All chemicals should be handled only by competent personnel, within a controlled environment. It is the buyer/user's responsibility to ensure that his activities comply with all applicable federal, state, provincial and local laws, and to determine the conditions necessary for the safe use of this product. ELEMENTIS urges each customer or recipient of this document to study it carefully and consult appropriate expertise, as necessary or appropriate, to become aware of and understand the data contained in this document and how it relates to the product.
Memorandum

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

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

DATE: November 30, 2015

SUBJECT: Information HDI/Trimethylol Hexyllactone Crosspolymer and HDI/PPG/Polycaprolactone Crosspolymer

Toshiki Pigment Co., Ltd. 2015. HDI Polymer CIR Requirement: HDI/Trimethylol Hexyllactone Crosspolymer.

Toshiki Pigment Co., Ltd. 2015. HDI Polymer CIR Requirement: HDI?PPG/Polycaprolactone Crosspolymer.
HDI Polymer
CIR requirement

2015.11.20
Toshiki Pigment Co., Ltd.
### Toshiki’s Products

<table>
<thead>
<tr>
<th>Product name</th>
<th>Average particle size (μm)</th>
<th>Specific gravity (g/cm³)</th>
<th>Specific gravity (g/ml)</th>
<th>Oil absorbency (ml/100g)</th>
<th>non-volatile substance (%)</th>
<th>refractive index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plastic Powder D-400</td>
<td>12～18</td>
<td>1.1～1.2</td>
<td>0.6</td>
<td>60</td>
<td>&gt;98.5</td>
<td>1.50</td>
</tr>
</tbody>
</table>

- **INCI NAME: HDI/TRIMETHYLOL HEXYLLACTONE CROSSPOLYMER and Silica**
Production Manufacturing Process
Plastic Powder D-400

starting materials
↓
mixing
↓
synthesis composition
↓
washing (Water)
↓
compounding → Silica
↓
drying → Continuous drying → Outlet temperature 95°C
↓
classification
↓
sterilization
↓
packaging

* Isocyanate prepolymer: (HDI/Trimethylolpropane/ε-Caprolactone)
* Solvent
* HDI: Hexamethylene Diisocyanate

Aqueous suspension polymerization
· Reaction temperature 30°C〜100°C “solvent removal”
· Reaction time 1〜6 hours

Alkylation agent is not used in the production process.
End capping agent is not used in the production process.
Residual Monomer Analysis

ε-caprolactone and Trimethylolpropane

• Quantitative method and equipment conditions of ε-caprolactone and Trimethylolpropane
• Solvent extraction - Gas chromatography-Mass spectrometry (GC-MS method)
• This method involves using ethyl acetate to extract, and then analyzing and quantifying the ε-caprolactone and trimethylol propane contained in a sample. The operation carried out in this case is as follows.

A test sample was introduced into glass vessels and weighed, then extracted through ultrasound extraction by adding a solvent. After extraction in this way, the solution was left standing for 1 hour, a supernatant was filtered with a 0.45μm PTFE filter and a part of the obtained solution was introduced into a gas chromatograph mass spectrometer.

A standard solution was prepared by using ethyl acetate to dilute two kinds of reference standards (quantitative items) in steps, and the concentration of each compound in the samples was calculated using a calibration curve that was measured and created with that same method.

The equipment and conditions are as follows.

Equipment: GC-MS (model: JMS-Q1050GC, manufacturer: JEOL)
MS conditions: Ionization method ... EI
Ionization voltage ... 70 eV
Ion source temperature ... 200° C
GC conditions: Column ... InertCap Pure-WAX: 30 m x 0.25 mm
Column temperature ... 80 to 250° C
Sample introduction: Splitless injection

Solvent extraction: Results of measurement using the GC-MS method. The minimum determination limit for this method was 20 ppm.
Solvent extraction: Results of measurement using the GC-MS method. The minimum determination limit for this method was 4 ppm.
Residual Monomer Analysis

Residual HDI
Standard and Testing Method
Precisely measure 1.0g of sample into capped test tube. Add 10.0mL ethyl acetate and expose to ultrasonic waves. Separate in centrifuge and filtrate upper layer of clear liquid using 0.45μm membrane filter. This is the test solution.
Separately, precisely measure 0.1g HEXAMETHYLENE DIISOCYANATE into a 100mL measuring flask and fill up with ethyl acetate. Take 1mL of this liquid into another 100mL measuring flask and fill up with ethyl acetate. Filtrate the resulting liquid using 0.45μm membrane filter. This is the standard solution.
Both the sample solution and the standard solution are then subjected to the gas chromatography test. The peak area shown of HEXAMETHYLENE DIISOCYANATE in both solutions is measured and the amount is expressed using the following calculation.
Standard HEXAMETHYLENE DIISOCYANATE has a purity of over 99.5%.

\[
\text{Residual hexamethylene diisocyanate (\%) = } \frac{m}{100} \times \frac{A_2}{A_1} \times 10 \text{ ppm}
\]
A1: Peak area value of hexamethylene diisocyanate of the standard solution
A2: Peak area value of hexamethylene diisocyanate of the sample solution
m: Exact quantity of hexamethylene diisocyanate for standard preparation
M: Exact quantity of the sample

Instrumental Conditions
Detector: Hydrogen Flame Ionization Detector (FID)
Column: HITACHI Metallic Capillary Column ULTRA ALLOY (8H)1
Length 30m, Inside Diameter 0.8mm
Temperature
Detector: 200°C
Conditions: Injection: 150°C
Column: 120°C, 3min
↓ 15°C/min
150°C, 5min
↓ 30°C/min
180°C
Carrier Gas: Helium, 30kPa
Detector Gas: Hydrogen, 40mL/min
Air, 350mL/min
Injection Volume: 1.0μL

Detection limit 100 ppm
## Result

<table>
<thead>
<tr>
<th>Sample name</th>
<th>Measurement items</th>
<th>Reported value (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLASTIC POWDER D-400 (Lot. 053315)</td>
<td>$\varepsilon$-caprolactone</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Trimethylolpropane</td>
<td>less than 4</td>
</tr>
<tr>
<td></td>
<td>HDI</td>
<td>$&lt;$100</td>
</tr>
<tr>
<td>PLASTIC POWDER D-400 (Lot. 051225)</td>
<td>$\varepsilon$-caprolactone</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Trimethylolpropane</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>HDI</td>
<td>$&lt;$100</td>
</tr>
<tr>
<td>PLASTIC POWDER D-400 (Lot. 051425)</td>
<td>$\varepsilon$-caprolactone</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Trimethylolpropane</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>HDI</td>
<td>$&lt;$100</td>
</tr>
</tbody>
</table>
Action plan

Stability of HDI polymer in formula

• Sample: Emulsion (5%) 1 year old
• Analysis: HPLC (Control: Unreacted isocyanate monomer)
• Target of Analysis: HDI

Remarks:

Cosmetics containing Plastic powder D-400 is
• Launched in 1995
• No complaint from consumer for skin problem
HDI Polymer
CIR requirement

2015.11.20
Toshiki Pigment Co., Ltd.
Toshiki’s Products

<table>
<thead>
<tr>
<th>Product name</th>
<th>Average particle size (µm)</th>
<th>Specific gravity (g/cm³)</th>
<th>Specific gravity (g/ml)</th>
<th>Oil absorbency (ml/100g)</th>
<th>non-volatile substance (%)</th>
<th>refractive index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plastic Powder CS-400</td>
<td>12~18</td>
<td>1.1~1.2</td>
<td>0.6</td>
<td>55</td>
<td>&gt;98.5</td>
<td>1.50</td>
</tr>
</tbody>
</table>

- **INCI NAME: HDI/PPG/POLYCAPROLACTONE CROSSPOLYMER and Silica**
Production Manufacturing Process  
Plastic Powder CS-400

starting materials
- Isocyanate prepolymer: (HDI/Trimethylolpropane/ε-Caprolactone/Propylene Oxide/D-Glucitol)
- Solvent

down
mixing

down
synthesis composition

- Reaction temperature 30°C~100°C
- Reaction time 1~6 hours

Aqueous suspension polymerization

“solvent removal”

(Water)

compounding ← Silica

down
drying ← Continuous drying
- Outlet temperature 95°C

classification
down
sterilization
down
packaging

Alkylation agent is not used in the production process.
End capping agent is not used in the production process.
Residual Monomer Analysis

ε-caprolactone and Trimethylolpropane

• Quantitative method and equipment conditions of ε-caprolactone and Trimethylolpropane
• Solvent extraction - Gas chromatography-Mass spectrometry (GC-MS method)
• This method involves using ethyl acetate to extract, and then analyzing and quantifying the ε-caprolactone and trimethylol propane contained in a sample. The operation carried out in this case is as follows.

A test sample was introduced into glass vessels and weighed, then extracted through ultrasound extraction by adding a solvent. After extraction in this way, the solution was left standing for 1 hour, a supernatant was filtered with a 0.45μm PTFE filter and a part of the obtained solution was introduced into a gas chromatograph mass spectrometer.

A standard solution was prepared by using ethyl acetate to dilute two kinds of reference standards (quantitative items) in steps, and the concentration of each compound in the samples was calculated using a calibration curve that was measured and created with that same method.

The equipment and conditions are as follows.

Equipment: GC-MS (model: JMS-Q1050GC, manufacturer: JEOL)
MS conditions: Ionization method ... EI
Ionization voltage ... 70 eV
Ion source temperature ... 200°C
GC conditions: Column ... InertCap Pure-WAX: 30 m x 0.25 mm
Column temperature ... 80 to 250°C
Sample introduction: Splitless injection

Solvent extraction: Results of measurement using the GC-MS method. The minimum determination limit for this method was 25 ppm.
Solvent extraction: Results of measurement using the GC-MS method. The minimum determination limit for this method was 2 ppm.
Residual Monomer Analysis

Residual HDI

Standard and Testing Method
Precisely measure 1.0g of sample into capped test tube. Add 10.0mL ethyl acetate and expose to ultrasonic waves. Separate in centrifuge and filtrate upper layer of clear liquid using 0.45μm membrane filter. This is the test solution.
Separately, precisely measure 0.1g HEXAMETHYLENE DIISOCYANATE into a 100mL measuring flask and fill up with ethyl acetate. Take 1mL of this liquid into another 100mL measuring flask and fill up with ethyl acetate. Filtrate the resulting liquid using 0.45μm membrane filter. This is the standard solution.
Both the sample solution and the standard solution are then subjected to the gas chromatography test. The peak area shown of HEXAMETHYLENE DIISOCYANATE in both solutions is measured and the amount is expressed using the following calculation.

Standard HEXAMETHYLENE DIISOCYANATE has a purity of over 99.5%.

Residual hexamethylene diisocyanate (%) = \frac{m}{100} \times \frac{A_2}{A_1} \times \frac{10}{M}

A1: Peak area value of hexamethylene diisocyanate of the standard solution
A2: Peak area value of hexamethylene diisocyanate of the sample solution
m: Exact quantity of hexamethylene diisocyanate for standard preparation
M: Exact quantity of the sample

Instrumental Conditions
Detector: Hydrogen Flame Ionization Detector (FID)
Column: HITACHI Metallic Capillary Column ULTRA ALLOY (8H)1
Length 30m, Inside Diameter 0.8mm
Temperature
Detector: 200°C
Conditions: Injection: 150°C
Column: 120°C, 3min
↓ 15°C/min
150°C, 5min
↓ 30°C/min
180°C
Carrier Gas: Helium, 30kPa
Detector Gas: Hydrogen, 40mL/min
Air, 350mL/min
Injection Volume: 1.0μL

Detection limit 100 ppm
<table>
<thead>
<tr>
<th>Sample name</th>
<th>Measurement items</th>
<th>Reported value (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLASTIC POWDER CS-400 (Lot. 151723)</td>
<td>ε-caprolactone</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>Trimethylolpropane</td>
<td>Not detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Detection limit &lt; 2 ppm)</td>
</tr>
<tr>
<td></td>
<td>HDI</td>
<td>&lt; 100</td>
</tr>
<tr>
<td></td>
<td>Propylene oxide</td>
<td>Not detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Detection limit &lt; 1ppm)</td>
</tr>
<tr>
<td></td>
<td>D-Glucitol</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Action plan

Stability of HDI polymer in formula

• Sample: Emulsion (2.4%) 1 year old
• Analysis: HPLC (Control: Unreacted isocyanate monomer)
• Target of analysis: HDI

Remarks:
Cosmetics containing Plastic powder CS-400 is
• Launched in 1998
• No complaint from consumer for skin problem
MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: December 4, 2015

Subject: Helianthus annuus (Sunflower)-Derived Ingredients as Used in Cosmetics - Wave 2

Unpublished data were submitted for Helianthus annuus (sunflower)-derived ingredients. This data consist of HRIPTs of products containing Helianthus annuus-derived ingredients. The table below is a summary of this data. [Helian122015Data1-7]. The raw data is available upon request.

Table 1. Results of HRIPTs of products containing Helianthus annuus (sunflower)-derived ingredients.

<table>
<thead>
<tr>
<th>Ingredient; concentration (%)</th>
<th>Product</th>
<th>n</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helianthus annuus (sunflower) extract; 0.05</td>
<td>body oil;</td>
<td>70</td>
<td>Not sensitizing</td>
</tr>
<tr>
<td>Helianthus annuus (sunflower) seedcake; 0.405</td>
<td>Eye lotion/cream</td>
<td>638</td>
<td>Not irritating or sensitizing</td>
</tr>
<tr>
<td>Helianthus annuus (sunflower) seedcake; 0.405</td>
<td>Hand cream</td>
<td>106</td>
<td>Not irritating or sensitizing</td>
</tr>
<tr>
<td>Helianthus annuus (sunflower) seedcake; 0.405</td>
<td>Facial mask</td>
<td>211</td>
<td>Not irritating or sensitizing</td>
</tr>
<tr>
<td>Helianthus annuus (sunflower) seedcake; 0.405</td>
<td>Facial mask</td>
<td>212</td>
<td>Not irritating or sensitizing</td>
</tr>
<tr>
<td>Helianthus annuus (sunflower) seed wax; 3.5</td>
<td>Mascara</td>
<td>209</td>
<td>Not irritating or sensitizing</td>
</tr>
<tr>
<td>Helianthus annuus (sunflower) seed wax; 3.26</td>
<td>Lipliner</td>
<td>208</td>
<td>Not irritating or sensitizing</td>
</tr>
</tbody>
</table>

A study on ozonized Helianthus annuus oil was found. The Helianthus annuus oil was treated with bubbling ozone gas in a water bath at room temperature until solidified. Ozonization effected the fatty acid composition of the oil; in two different samples, the mean oleic acid content reduced from 29.2% to 28.5% and 26.3%, respectively and the mean linoleic acid content reduced from 58.3% to 42.8% and 6.8%, respectively.
Memorandum

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

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

DATE: November 2, 2015

SUBJECT: HRIPT of a Body Oil Containing Helianthus Annuus (Sunflower) Extract

Anonymous. 2015. Summary of a repeated insult patch test of a body oil containing 0.05% Helianthus Annuus (Sunflower) Extract.
CLINICAL, SINGLE-BLIND, CONTROLLED STUDY OF THE SKIN IRRITATION AND SENSITIZATION POTENTIAL OF A PRODUCT TO BE APPLIED TO THE SKIN

SUMMARY

Product Name: Body Oil
Product Code: 051598-04 that contains Helianthus Annuus (Sunflower) Extract at 0.05%.
Study Code: The dose was 0.025 mg/cm².
Report Code: 

STUDY OBJECTIVE

To prove the absence of primary and accumulated skin irritation and sensitization potential of a product to be applied to the skin under maximized conditions, with controlled product amount and application site, supervised by a dermatologist.

METHODOLOGY

Both the test product and control were applied to patch test filter paper discs and then applied to the right or left back (scapular area) of the study subjects. The applications were performed on Mondays, Wednesdays and Fridays, during 3 consecutive weeks. Forty-eight hours (48h) after the application, the patch test was removed by expert technicians and, approximately 30 minutes after removal, the site was assessed in order to check the presence of clinical signs.

After this period (induction) there was a, minimum, 10 day-period when no patch was applied to the study subjects' back (rest period). Then, the challenge period started. A single application of the patch test was performed, followed by readings after 48h and 72h.

The study subjects were assessed by a dermatologist at the start and at the end of the study and supervised all along the study.

PRINCIPAL INVESTIGATOR

STUDY LENGTH 6 weeks
FREQUENCY OF APPLICATION 9 applications on the 3 first weeks (induction period).
1 application on the last week (challenge period).
APPLICATION SITE Back (Scapular area).
NUMBER OF SUBJECTS 70 study subjects.
POPULATION DESCRIPTION Female and male subjects, aged from 18 to 69 years old, phototype II to IV (Fitzpatrick).

ETHICS This study was conducted in conformance with the Declaration of Helsinki principles, the applicable regulatory requirements, and in spirit of the Good Clinical Practice (ICH E6: Good Clinical Practice).

RESULTS During the study, no subjects presented skin clinical signs related to the product.

CONCLUSION The product did not induce primary and accumulated skin irritation and sensitization process in the study group.

The product was considered to be safe under the study conditions.
Memorandum

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

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

DATE: November 5, 2015

SUBJECT: Information on Products Containing Helianthus Annuus (Sunflower) Seedcake or Helianthus Annuus (Sunflower) Seed Wax (SLR posted October 5, 2015)


c. Product Investigations, Inc. 2014. Determination of the irritating and sensitizing propensities of a facial mask containing 0.405% Helianthus Annuus (Sunflower) Seedcake on human skin.

d. Clinical Research Laboratories, Inc. 2014. Repeated insult patch test of a facial mask containing 0.405% Helianthus Annuus (Sunflower) Seedcake.

e. Product Investigations, Inc. 2012. Determination of the irritating and sensitizing propensities of a mascara containing 3.5% Helianthus Annuus (Sunflower) Seed Wax.

CRL59312 = 0.405% Helianthus Annuus (Sunflower) Seedcake in an eye lotion

Clinical Research Laboratories, Inc.

Final Report
Repeated Insult Patch Test

CLIENT:

ATTENTION:

TEST MATERIAL:

CRL STUDY NUMBER: CRL59312 (N=600)

AUTHORIZED SIGNATURES:

Bruce E. Kanegis, M.D.
President/Medical Director

Michael J. Museutiello, Ph.D.
Executive Vice President/COO

Anita Lee Cham, M.D.
Dermatologist

REPORT DATE: August 24, 2012

371 Hoes Lane, Suite 100 • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520
Clinical Study Number: CRL59312 (N=600)
Start Date: May 14, 2012
Completion Date: August 3, 2012

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted, as indicated below.

Signature of QA Auditor

Date
**Clinical Research Laboratories, Inc.**

**FINAL REPORT**

**REPEATED INSULT PATCH TEST**

**PURPOSE**

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

**INVESTIGATIVE SITE**

Clinical Research Laboratories, Inc.
371 Hoes Lane Suite 100
Piscataway, New Jersey 08854
732-981-1616

**TEST MATERIAL**

The following test material was provided by received by Clinical Research Laboratories, Inc. on May 14th, 2012:

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Test Condition</th>
<th>Patch Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test as received.</td>
<td>Occlusive*</td>
</tr>
</tbody>
</table>

The test material was coded with the following CRI identification number:

CRL59312 (N-600)

**STUDY DATES**

This study was initiated on May 14, 2012 and was completed on August 3, 2012.

* Occlusive Strip with Integra® (Integra Medical, Mountain View, CA)
PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix 1). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

Inclusion Criteria

a. Male and female subjects between the ages of 18 and 70 years;
b. Subjects who do not exhibit any skin diseases which might be confused with a skin reaction from the test material;
c. Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;
e. Subjects who have completed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164;
f. Subjects in generally good health who have a current Subject Profile/Medical History on file;
g. Subjects who are dependable and able to follow directions as outlined in the protocol.

Exclusion Criteria

a. Female subjects who are pregnant or nursing;
b. Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;
c. Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.
Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

**Dermal Scoring Scale**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visible skin reaction</td>
</tr>
<tr>
<td>1</td>
<td>Barely perceptible erythema</td>
</tr>
<tr>
<td>1+</td>
<td>Mild erythema</td>
</tr>
<tr>
<td>2</td>
<td>Well defined erythema</td>
</tr>
<tr>
<td>3+</td>
<td>Erythema and edema</td>
</tr>
<tr>
<td>4+</td>
<td>Erythema and edema with vesiculation</td>
</tr>
</tbody>
</table>

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.
RESULTS

This study was initiated with 672 subjects. Thirty-four subjects discontinued study participation for reasons unrelated to the test material. A total of 638 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 638 subjects and under the conditions of this study, the test material identified as [redacted] Eye Cream did not demonstrate a clinically significant potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRI Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.
DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF [OBSCURED] ON HUMAN SKIN

PREPARED FOR

9 October 2009
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<th>Title</th>
<th>Page</th>
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<td></td>
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<tr>
<td>3.00</td>
<td>Sponsor</td>
<td></td>
</tr>
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<td>Study Product</td>
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<tr>
<td>12.00</td>
<td>Study Regimen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week #1 Regimen</td>
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<td>Week #2 Regimen</td>
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<td></td>
<td>Week #3 Regimen</td>
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<tr>
<td></td>
<td>Week #4 Regimen</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Week #5 Regimen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weeks #6 and #7 Regimen</td>
<td></td>
</tr>
<tr>
<td>13.00</td>
<td>Procedure Deviations</td>
<td></td>
</tr>
<tr>
<td>14.00</td>
<td>Compliance</td>
<td></td>
</tr>
<tr>
<td>15.00</td>
<td>Incidence of Responses</td>
<td>6</td>
</tr>
<tr>
<td>16.00</td>
<td>Significance of the Responses</td>
<td></td>
</tr>
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<td>17.00</td>
<td>Conclusions</td>
<td></td>
</tr>
<tr>
<td>18.00</td>
<td>Compliance with Good QA Standards</td>
<td></td>
</tr>
</tbody>
</table>
DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF [REDACTED] ON HUMAN SKIN

1.00 OBJECTIVES:

.01 To identify and characterize the skin-damaging propensities that [REDACTED] can be induced to exercise under the conditions of this modified patch test procedure.

.02 To adjudice whether the exercise of such propensities under the test conditions contraindicates the kind of skin contact that would be occasioned during the appropriate use of the product.

2.00 DESIGN:

.01 A modified version of the Repeated Insult Patch Test [REDACTED] was conducted under double-blind conditions on a panel composed of more than one hundred subjects at the outset.

.02 The regimen comprised nine sequential 24-hour induction applications and two concurrently conducted 24-hour challenge applications, one on the initial induction site and one on a naive site.

.03 During the initial phase, the skin of the contact sites was graded and the grades recorded on Wednesdays, Fridays (i.e., twenty-four hours after patches had been removed), and Mondays (i.e., forty-eight hours after patches had been removed). See Deviations in Procedure.

.04 During the challenge phase, the skin of the contact sites was graded within moments after the patches had been removed (24 hours post-application) and again twenty-four hours later. Follow-up examinations were conducted thereafter only if adverse effects were present.

.05 This study was conducted in compliance with the standards of good clinical practices generally applicable for the protection of the privileges and well-being of individuals who participate in patch test procedures.

3.00 SPONSOR:

Project Director:
Authorization:
Purchase Order:

4.00 STUDY PRODUCT:

Type of Product: Facial Cream
Sponsor Identification: [REDACTED]
Date received: 8/27/09
Quantity rec'd: >684 g. gross wt.
Form used in study: Volatilized

5.00 SITE OF STUDY:

Product Investigations, Inc.
142 North Ninth Street
Suite 16
Modesto, CA 95350

Study Personnel:

Medical Director: Morris V. Shelanski, MDCM
Dir. Derm. Services: Joseph E. Nicholson III
Dermatologist: Clinton F. Prescott Jr., MD
Technicians: Lisa Cortez, Henry Cortez
Quality Assurance: Samuel J. Charles III

6.00 DATES OF STUDY:

Started: 31 August 2009
Completed: 2 October 2009
7.00 **SELECTION OF SUBJECTS:**

.01 **RECRUITING:**
Prospective subjects were recruited from surrounding localities via phone, posters and personal contact.

.02 **INFORMED CONSENT:**
All individuals who expressed interest in participating were given an informed consent document to read. This document, which each candidate had to read and sign before being entered into the study, presented the following information:

- a. How many subjects were to be enrolled in the study;
- b. The intended use of the product;
- c. Why the product was being tested;
- d. How the test was to be performed;
- e. That the regimen was not intended to benefit a subject's health, well being, or quality of life.
- f. The different ways that participation may be detrimental to a subject's health, well being, or quality of life.
- g. That not all detrimental effects could be foreseen and made known at the time the informed consent was presented for the prospective subject's signature.
- h. What commitments a subject had to make to be in compliance; and
- i. What considerations a subject was entitled to receive and the conditions for receiving them.

.03 **DETERMINATION OF ELIGIBILITY:**
Information concerning a prospective subject's qualifications was obtained from the answers the subject gave in filling out a medical history form and in responding to specific questions. Those who did not meet the following criteria were rejected.

- a. **Inclusion Criteria:** Satisfaction of all the following items was obligatory:
  - i. The candidate was at least eighteen years old, and
  - ii. agreed to comply fully with the scheduled study regimen, and
  - iii. expressed awareness that a participant would incur risks that would affect her/his well-being, and
  - iv. denied that the amount of the stipend had induced her/him to participate against her/his better judgment, and
  - v. had read the informed consent agreement, and
  - vi. had assured the interviewer that she/he had no questions about the informed consent's contents that had not been answered to her/his satisfaction, and
  - vii. had signed the consent form willingly and without reservation.

- b. **Exclusion Criteria:** Any one of the following items was cause for rejection:
  - i. The candidate had an illness that contraindicated participation; or
  - ii. a condition that rendered the skin unsuitable for use in this study; or
  - iii. was using dosages of medications that could alter the skin's tolerance; or
  - iv. had a documented history of intolerance to the category of products submitted for study; or
  - v. was a female who was pregnant or was breast feeding an infant.

.04 **PANEL INFORMATION:**

- a. 

- b. **Demographics:**

<table>
<thead>
<tr>
<th>SEX</th>
<th>Number</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>73</td>
<td>19 - 72</td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>18 - 60</td>
</tr>
</tbody>
</table>

c. **Dedication:** This was a shared panel, i.e. the subjects were engaged in the evaluation of materials submitted by sponsors other than Estee Lauder Companies.

8.00 **SITE INFORMATION:**

.01 **LOCATION:**
was assigned Band #1 on the right side of the back of each subject.

.02 **IDENTIFICATION OF A CONTACT SITE:**
At each visit the skin around the contact site was marked to facilitate examinations after the device was removed and positioning of subsequently-applied devices as precisely as was feasible on the same site.
9.00 PATCHING DEVICES:

.01 TYPE OF DEVICE:

Partially-occlusive patching devices consisting of a 2 cm x 2 cm absorbent pad centered on the adhesive-coated surface of a 2 cm x 4 cm plastic film were used to convey and maintain the product on the skin.

.02 PREPARATION OF A PATCHING DEVICE:

The web pad of a patching device was infused with 200μl of the test material. Prepared devices were exposed to ambient air for at least 30 minutes prior to application.

.03 POSITIONING AND REMOVING A PATCHING DEVICE:

a. A prepared device was positioned on its designated site on each subject with the product-treated surface of the pad in contact with the skin.

b. Firm pressure was applied to the backing of the device to effect intimate contact of the pad with the skin and to bond the flanges of the device securely to the skin.

c. When the time came for removing the device, the device was peeled off the skin as gently as was feasible under the circumstances.

10.00 DATA ACQUISITION:

.01 GRADING PROCEDURE:

a. Examinations of the contact sites to grade the effects elicited by the product were conducted on Mondays, Wednesday and Fridays. When a subject came in on a scheduled examination day, the technician examined the skin of the contact site.

i. If no adverse effect was detected, a "0" was recorded in the subject's Case Report Form.

ii. If an adverse effect was detected, the technician entered a grade indicating her assessment of the response's intensity.

b. The subject was then sent into the patching room where the site was examined again by a second technician to ascertain independently whether or not the site should be used again. If she disagreed with the first technician's assessment, the application was held in abeyance until the issue could be resolved with the help of the supervisor and/or the investigator.

c. The supervisor or the investigator was called in only when a disagreement had to be resolved, but also to validate substantial sudden changes, e.g. when a response is deemed to merit a grade ≥3 or when a response has been judged to have decreased by two or more points from the previous day's status.

.02 CRITERIA FOR GRADING RESPONSE INTENSITY:

The following scale was used in this procedure to designate the intensities of those gross skin changes that may be occasioned by exposing the surface of the skin to a product.

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Visible Change</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical Stage</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular Dilation:</td>
<td>Faint redness with poorly defined margins</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Redness with well-defined margins</td>
<td>2</td>
</tr>
<tr>
<td>Infiltration:</td>
<td>Redness plus well-defined edema</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Redness plus papules, or vesicles or ulceration</td>
<td>4</td>
</tr>
</tbody>
</table>

.04 SITE CHANGES:

a. Switch to a Naive Site:

i. If the product had elicited a Grade 2 response on a subject, application of the product would have been switched immediately to a naive site on the subject.

b. Discontinuation of Applications:

i. If the product had elicited a second Grade 2 on a subject, application of the product would have been discontinued immediately for the remainder of the initial phase on the affected subject.

ii. If the product had elicited a Grade 3 response on a subject, application of the product would have been discontinued immediately for the remainder of the initial phase on the affected subject.
11.00 **OVERVIEW OF STUDY REGIMEN:**

<table>
<thead>
<tr>
<th></th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week #1</td>
<td>Apply</td>
<td>Remove</td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>(Removed)</td>
<td>–</td>
</tr>
<tr>
<td>Week #2</td>
<td>–</td>
<td>Grade/App</td>
<td>Remove/App</td>
<td>Grade/App</td>
<td>Grade/App</td>
<td>(Removed)</td>
<td>–</td>
</tr>
<tr>
<td>Week #3</td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>(Removed)</td>
<td>–</td>
</tr>
<tr>
<td>Week #4</td>
<td>Grade</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Week #5</td>
<td>Apply</td>
<td>Remove/Grade</td>
<td>Grade</td>
<td>Grade*</td>
<td>Grade*</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*If necessary

12.00 **STUDY REGIMEN:**

.01 **INITIAL/INDUCTION PHASE:**

**Week #1:**

**Monday:**

1. As each subject presented herself/himself at the clinic, the skin of the contact site assigned to the product submitted for study was examined and ascertained to be suitable before applications were begun.
2. A freshly-prepared patching device was applied on its assigned site.
3. The skin around the device was marked and the subject was instructed to return on Tuesday.

**Tuesday:**

1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the subject was instructed to return on Wednesday.

**Wednesday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced and the subject was instructed to return on Thursday.

**Thursday:**

1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the subject was instructed to return on Friday.

**Friday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced.
4. The subject was dismissed with instructions to remove the patching device at home on Saturday, to record the time of removal, and to return to the clinic on the following Tuesday for resumption of the regimen.

**Week #2:**

**Tuesday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. The time at which the patch was removed on Saturday was recorded.
3. A freshly-prepared patching device was applied on the same site.
4. The site-identifying marks were reinforced and the subject was instructed to return on Wednesday.

**Wednesday:**

1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and skin of the contact site was graded. The grade was recorded.
3. A freshly-prepared patching device was applied on the same site and the subject was instructed to return on Thursday.

**Thursday:**

1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the skin of the contact site was graded. The grade was recorded and the subject was instructed to return on Friday.

**Friday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced.
4. The subject was dismissed with instructions to remove the patching device at home on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

**Week #3:**

**Monday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. The time at which the patch was removed on Saturday was recorded.
3. A freshly-prepared patching device was applied on the same site.
4. The site-identifying marks were reinforced and the subject was instructed to return on Tuesday.
Tuesday, Wednesday, Thursday
The procedures followed were the same as those followed on corresponding days during Week 1.

Friday:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. A freshly-prepared patching device was applied on the same site.
iii. The site-identifying marks were reinforced.
iv. The subject was dismissed with instructions to remove the patching device at home on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

Week #4:
Monday:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The time at which the patch was removed on Saturday was recorded.

a) If the subject had undergone all nine induction applications, she/he was dismissed after being instructed as follows:
   i) to report back to the clinic on the following Monday to receive the challenge applications, and
   ii) to notify the investigator without delay should any significant changes occur in the skin of the contact site before Monday of the challenge week.

b) If the subject had not received the required number of induction applications and was deficient without valid reason, applications were continued. As many as two missed applications could be made up during this week. When the subject had undergone the required number of make up applications, she/he was dismissed after being instructed as in section a) ii, above.

.02 HIATUS/MAKE UP PHASE-
Week #4:
After the examination on Monday of Week 4, no procedures other than make-up cycles were scheduled during this period.

.03 CHALLENGE PHASE-
Week #5:
Monday:
i. As each subject returned, the skin of the initial induction site was examined and ascertained to be free of any conditions that would have rendered it unfit for undergoing the challenge applications.
ii. A prepared device was applied on the initial induction site.
iii. A second prepared device was applied on a naive site.
iv. The skin around both devices was marked and the subject was instructed to return on Tuesday.

Tuesday: (Note: If a subject was absent on Monday, she/he was patched on Tuesday.)
i. As each subject returned, the site-identifying marks around both contact sites were reinforced.
ii. Both patching devices were removed by a technician.
iii. The skin of both contact sites was graded; the grades were recorded.
iv. The subject was instructed to return on Wednesday.

Wednesday:
i. As each subject returned, the skin of both contact sites was graded; the grades were recorded.
ii. If follow-up was indicated, the subject was instructed to return on Thursday, otherwise the subject was dismissed from the study of this material.

.04 FOLLOW-UP PHASE:
Week #6 and Week #7:
During the two weeks following the exit examination, the subjects were given the opportunity to relay any information concerning effects that were relevant to the characterization of the product as well as to communicate the need for treatment of persistent or newly-occurring responses.

13.00 PROCEDURE DEVIATIONS:
The lab was closed on Monday of Week #2 due to the Labor Day holiday. To comply with the required number of applications, subjects were patched on Tuesday of Week #2 as noted above.

14.00 COMPLIANCE

<table>
<thead>
<tr>
<th>PHASE</th>
<th>No. Of AEC's</th>
<th>COMPLIANT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Required</td>
<td>EXCUSED</td>
</tr>
<tr>
<td>Induction</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Challenge</td>
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<td>0</td>
</tr>
</tbody>
</table>

107 of the 112 Subjects were in compliance with the number of required application/examination cycles during induction.
106 of the 112 Subjects were in compliance with the number of required application/examination cycles during challenge.
### 15.00 INCIDENCE OF RESPONSES:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of Response</th>
<th>Induction Phase</th>
<th>Challenge Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Visible Change</td>
<td>112 Subjects</td>
<td>106 Subjects</td>
</tr>
<tr>
<td>1</td>
<td>Faint Redness, Undefined Border</td>
<td>0 &quot;</td>
<td>0 &quot;</td>
</tr>
<tr>
<td>2</td>
<td>Intense Redness, Defined Border</td>
<td>0 &quot;</td>
<td>0 &quot;</td>
</tr>
<tr>
<td>3</td>
<td>Redness + Definite Edema</td>
<td>0 &quot;</td>
<td>0 &quot;</td>
</tr>
<tr>
<td>4</td>
<td>Redness + Papules, or Vesicles, etc.</td>
<td>0 &quot;</td>
<td>0 &quot;</td>
</tr>
<tr>
<td>No. of Responders</td>
<td>0 Subjects</td>
<td>0 Subjects</td>
<td>0 Subjects</td>
</tr>
<tr>
<td>No Data Acquired</td>
<td>0 Subjects</td>
<td>6 Subjects</td>
<td>6 Subjects</td>
</tr>
</tbody>
</table>

### 16.00 SIGNIFICANCE OF THE RESPONSES:

#### .01 Initial/Induction Phase:

No responses were noted on any of the 112 subjects who underwent at least one post-application examination. The absence of responses characterizes the product as one which is devoid of clinically significant skin-irritating propensities.

#### .02 Challenge Phase:

- **a. Original Contact Sites:**
  
  No responses were noted on any of the 106 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.

- **b. Naive Contact Sites:**
  
  No responses were noted on any of the 106 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.

### 17.00 CONCLUSIONS:

#### .01 MT#2369544 was found to be neither a clinically significant skin irritant nor a skin sensitizer under the conditions of this study.

#### .02 MT#2369544 is not contraindicated for usages entailing repeated applications on human skin under conditions appropriate for such products.

**PRODUCT INVESTIGATIONS, INC.**

### 18.00 COMPLIANCE WITH GOOD QUALITY ASSURANCE STANDARDS:

I have audited the results presented in this report and believe that, to the best of my knowledge, they accurately reflect the raw data acquired during the course of this study.

**Samuel J. Charles III**

Director, Quality Assurance
Test material = 0.405% HELIANTHUS ANNUIUS (SUNFLOWER) SEEDCAKE in a facial mask

PRODUCT INVESTIGATIONS, INC.
151 East Tenth Avenue
Conshohocken, PA 19428
610-825-5855 • fax 610-825-788

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF HELIANTHUS ANNUIUS SEEDCAKE ON HUMAN SKIN

PREPARED FOR
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DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES
OF [REDACTED] ON HUMAN SKIN

1.00 OBJECTIVES:
.01 To identify and characterize the skin-damaging propensities that [REDACTED] can be induced to exercise under the conditions of this modified patch test procedure.
.02 To adjudge whether the exercise of such propensities under the test conditions contraindicates the kind of skin contact that would be occasioned during the appropriate use of the product.

2.00 DESIGN:
.01 A modified version of the Repeated Insult Patch Test [REDACTED] was conducted on two panels whose combined total was greater than two hundred subjects at the outset.
.02 The regimen comprised nine sequential 24-hour induction applications and two concurrently conducted 24-hour challenge applications, one on the initial induction site and one on a naïve site.
.03 During the initial phase, the skin of the contact sites was graded and the grades recorded on Wednesdays, Fridays (i.e. twenty-four hours after patches had been removed), and Mondays (i.e. forty-eight hours after patches had been removed).
.04 During the challenge phase, the skin of the contact sites was graded within moments after the patches had been removed (24 hours post application) and again twenty-four hours later. Follow-up examinations were conducted thereafter only if adverse effects were present.
.05 This study was conducted in compliance with the standards of good clinical practices generally applicable for the protection of the privileges and well-being of individuals who participate in patch test procedures.

3.00 SPONSOR:

Project Director:

Authorization:

Purchase Order:

4.00 STUDY PRODUCT:
Type of Product: Facial Mask
Sponsor Identification: [REDACTED]
Date received: 11/25/13
Quantity rec’d: >665 g. gross wt.
Form used in study: As Supplied

5.00 SITE OF STUDY:
Product Investigations, Inc.
1010 Carver Road
Modesto, CA 95350

Study Personnel:
Medical Director: Morris V. Shelanski, M.D.C.M
CA Physician: Clinton E. Prescott Jr., M.D
Dir. Derm. Services: Joseph E. Nicholson III
Technicians: Lisa A. Cortez, Henry Cortez
Quality Assurance: Samuel J. Charles III

6.00 DATES OF STUDY:
Started: 2 December 2013
Completed: 10 January 2014
7.00 **SELECTION OF SUBJECTS:**

.01 **RECRUITING:**
Prospective subjects were recruited from surrounding localities via phone, posters and personal contact.

.02 **INFORMED CONSENT:**
All individuals who expressed interest in participating were given an informed consent document to read. This document, which each candidate had to read and sign before being entered into the study, presented the following information:

a. How many subjects were to be enrolled in the study;
b. The intended use of the product;
c. Why the product was being tested;
d. How the test was to be performed;
e. That the regimen was not intended to benefit a subject’s health, well being, or quality of life.
f. The different ways that participation may be detrimental to a subject’s health, well being, or quality of life.
g. That not all detrimental effects could be foreseen and made known at the time the informed consent was presented for the prospective subject’s signature.
h. What commitments a subject had to make to be in compliance; and
i. What considerations a subject was entitled to receive and the conditions for receiving them.

.03 **DETERMINATION OF ELIGIBILITY:**
Information concerning a prospective subject’s qualifications was obtained from the answers the subject gave in filling out a medical history form and in responding to specific questions. Those who did not meet the following criteria were rejected.

a. **Inclusion Criteria:** Satisfaction of all the following items was obligatory:
   i. The candidate was at least eighteen years old, and
   ii. agreed to comply fully with the scheduled study regimen, and
   iii. expressed awareness that a participant would incur risks that would affect her/his well-being, and
   iv. denied that the amount of the stipend had induced her/him to participate against her/his better judgment, and
   v. had read the informed consent agreement, and
   vi. had assured the interviewer that she/he had no questions about the informed consent’s contents that had not been answered to her/his satisfaction, and
   vii. had signed the consent form willingly and without reservation.

b. **Exclusion Criteria:** Any one of the following items was cause for rejection:
   i. The candidate had an illness that contraindicated participation; or
   ii. a condition that rendered the skin unsuitable for use in this study; or
   iii. was using dosages of medications that could alter the skin’s tolerance; or
   iv. had a documented history of intolerance to the category of products submitted for study; or
   v. was a female who was pregnant or was breast feeding an infant.

.04 **PANEL INFORMATION:**

b. **Demographics:**

<table>
<thead>
<tr>
<th>SEX</th>
<th>Number</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>131</td>
<td>18 - 76</td>
</tr>
<tr>
<td>Male</td>
<td>89</td>
<td>18 - 78</td>
</tr>
</tbody>
</table>

c. **Dedication:** These were shared panels, i.e. the subjects were engaged in the evaluation of materials submitted by sponsors other than Estee Lauder Companies.

8.00 **SITE INFORMATION:**

.01 **LOCATION:**

was assigned Band #3 on the right side of the back of each subject.

.02 **IDENTIFICATION OF A CONTACT SITE:**

At each visit the skin around the contact site was marked to facilitate examinations after the device was removed and positioning of subsequently-applied devices as precisely as was feasible on the same site.
9.00 **PATCHING DEVICES:** Distributed for Comment Only -- Do Not Cite or Quote

.01 **TYPE OF DEVICE:**

Occlusive patching devices consisting of a 2cm x 2cm absorbent pad centered on the adhesive-coated surface of a 4cm x 4cm plastic film were used to convey and maintain the product on the skin.

.02 **PREPARATION OF A PATCHING DEVICE:**

The webral pad of a patching device was evenly coated with approximately 200 mg of the test material.

.03 **POSITIONING AND REMOVING A PATCHING DEVICE:**

a. A prepared device was positioned on its designated site on each subject with the product-treated surface of the pad in contact with the skin.

b. Firm pressure was applied to the backing of the device to affect intimate contact of the pad with the skin and to bond the flanges of the device securely to the skin.

c. When the time came for removing the device, the device was peeled off the skin as gently as was feasible under the circumstances.

10.00 **DATA ACQUISITION:**

.01 **GRADING PROCEDURE:**

a. Examinations of the contact sites to grade the effects elicited by the product were conducted on Mondays, Wednesdays, and Fridays. When a subject came in on a scheduled examination day, the technician examined the skin of the contact site.

i. If no adverse effect was detected, a “0” was recorded in the subject’s Case Report Form.

ii. If an adverse effect was detected, the technician entered a grade indicating her assessment of the response’s intensity.

b. The subject was then sent into the patching room where the site was examined again by a second technician to ascertain independently whether or not the site should be used again. If she disagreed with the first technician’s assessment, the application was held in abeyance until the issue could be resolved with the help of the supervisor and/or the investigator.

c. The supervisor or the investigator was called in not only when a disagreement had to be resolved, but also to validate substantial sudden changes, e.g. when a response is deemed to merit a grade ≥3 or when a response has been judged to have decreased by two or more points from the previous day’s status.

.02 **CRITERIA FOR GRADING RESPONSE INTENSITY:**

The following scale was used in this procedure to designate the intensities of those gross skin changes that may be occasioned by exposing the surface of the skin to a product.

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Visible Change</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical Stage</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

**Inflammation**

<table>
<thead>
<tr>
<th>Vascular Dilation:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Faint redness with poorly defined margins</em></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><em>Redness with well-defined margins</em></td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infiltration:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Redness plus well-defined edema</em></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><em>Redness plus papules, or vesicles or ulceration</em></td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

.04 **SITe CHANGES:**

a. **Switch to a Naive Site:**

i. If the product had elicited a Grade 2 response on a subject, application of the product would have been switched immediately to a naive site on the subject.

b. **Discontinuation of Applications:**

i. If the product had elicited a second Grade 2 on a subject, application of the product would have been discontinued immediately for the remainder of the initial phase on the affected subject.

ii. If the product had elicited a Grade 3 response on a subject, application of the product would have been discontinued immediately for the remainder of the initial phase on the affected subject.
11.00 **Overview of Study Regimen**

<table>
<thead>
<tr>
<th></th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week #1</td>
<td>Apply</td>
<td>Remove</td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>(Removed)</td>
<td>-</td>
</tr>
<tr>
<td>Week #2</td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>(Removed)</td>
<td>-</td>
</tr>
<tr>
<td>Week #3</td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>(Removed)</td>
<td>-</td>
</tr>
<tr>
<td>Week #4</td>
<td>Grade</td>
<td></td>
<td>Grade/App</td>
<td>Remove</td>
<td>Grade/App</td>
<td>(Removed)</td>
<td>-</td>
</tr>
<tr>
<td>Week #6</td>
<td>Apply</td>
<td>Remove/Grade</td>
<td>Grade</td>
<td>Grade*</td>
<td>Grade*</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

*If necessary

12.00 **Study Regimen:**

01 **Initial/Induction Phase**

**Week #1:**

**Monday:**

i. As each subject presented herself/himself at the clinic, the skin of the contact site assigned to the product submitted for study was examined and ascertained to be suitable before applications were begun.

ii. A freshly-prepared patching device was applied on its assigned site.

iii. The skin around the device was marked and the subject was instructed to return on Tuesday.

**Tuesday:**

i. As each subject returned, the site-identifying marks were reinforced.

ii. The patching device was removed by a technician and the subject was instructed to return on Wednesday

**Wednesday:**

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.

ii. A freshly-prepared patching device was applied on the same site.

iii. The site-identifying marks were reinforced and the subject was instructed to return on Thursday

**Thursday:**

i. As each subject returned, the site-identifying marks were reinforced.

ii. The patching device was removed by a technician and the subject was instructed to return on Friday.

**Friday:**

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.

ii. A freshly-prepared patching device was applied on the same site.

iii. The site-identifying marks were reinforced.

iv. The subject was dismissed with instructions to remove the patching device on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

**Week #2:**

**Monday:**

i. As each subject returned, the skin of the contact site was graded. The grade was recorded

ii. The time at which the patch was removed on Saturday was recorded.

iii. A freshly-prepared patching device was applied on the same site.

iv. The site-identifying marks were reinforced and the subject was instructed to return on Tuesday.

**Tuesday:**

i. As each subject returned, the site-identifying marks were reinforced.

ii. The patching device was removed by a technician and the subject was instructed to return on Wednesday

**Wednesday:**

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.

ii. A freshly-prepared patching device was applied on the same site.

iii. The site-identifying marks were reinforced and the subject was instructed to return on Thursday

**Thursday:**

i. As each subject returned, the site-identifying marks were reinforced.

ii. The patching device was removed by a technician and the subject was instructed to return on Friday.
Friday:
1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced.
4. The subject was dismissed with instructions to remove the patching device on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

Week #3:
Monday:
1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. The time at which the patch was removed on Saturday was recorded.
3. A freshly-prepared patching device was applied on the same site.
4. The site-identifying marks were reinforced and the subject was instructed to return on Tuesday.

Tuesday:
1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the subject was instructed to return on Wednesday.

Wednesday:
1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced and the subject was instructed to return on Thursday.

Thursday:
1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the subject was instructed to return on Friday.

Friday:
1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced.
4. The subject was dismissed with instructions to remove the patching device on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

Week #4:
Monday:
1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. The site-identifying marks were reinforced and the subject was instructed to:
   i) report back to the clinic on the following Monday to receive the challenge applications, and
   ii) to notify the investigator without delay should any significant changes occur in the skin of the contact site before Monday of the challenge week.

HIATUS PHASE: Week 4. Tuesday through Friday and all of week 5.

.03 CHALLENGE PHASE:
Week #6:
Monday:
1. As each subject returned, the skin of the initial induction site was examined and ascertained to be free of any conditions that would have rendered it unfit for undergoing the challenge applications.
2. A prepared device was applied on the initial induction site.
3. A second prepared device was applied on a naive site.
4. The skin around both devices was marked and the subject was instructed to return on Tuesday.

Tuesday: (Note: If a subject was absent on Monday, she/he was patched on Tuesday.)
1. As each subject returned, the site-identifying marks around both contact sites were reinforced.
2. Both patching devices were removed by a technician.
3. The skin of both contact sites was graded; the grades were recorded.
4. The subject was instructed to return on Wednesday.

Wednesday:
1. As each subject returned, the skin of both contact sites was graded; the grades were recorded.
2. If follow-up was indicated, the subject was instructed to return on Thursday. Otherwise, the subject was dismissed from the study of this material.
.04 **FOLLOW-UP PHASE:**

Week No. 7 and Week No. 8:

During the two weeks following the exit examination, the subjects were given the opportunity to relay any information concerning effects that were relevant to the characterization of the product as well as to communicate the need for treatment of persistent or newly-occurring responses.

13.00 **PROCEDURE DEVIATIONS:**

Due to the Christmas and New Years Holidays, this study used a two week hiatus

14.00 **COMPLIANCE**

<table>
<thead>
<tr>
<th>PHASE</th>
<th>No Of APC's Required</th>
<th>EXCUSED</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>8</td>
<td>0</td>
<td>212</td>
<td>8</td>
</tr>
<tr>
<td>Challenge</td>
<td>1/1</td>
<td>0</td>
<td>211</td>
<td>9</td>
</tr>
</tbody>
</table>

212 of the 220 Subjects were in compliance with the number of required application/examination cycles during induction.

211 of the 220 Subjects were in compliance with the number of required application/examination cycles during challenge.

15.00 **INCIDENCE OF RESPONSES:**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>TYPE OF RESPONSE</th>
<th>INDUCTION PHASE</th>
<th>CHALLENGE PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NO VISIBLE CHANGE</td>
<td>219 SUBJECTS</td>
<td>211 SUBJECTS</td>
</tr>
<tr>
<td>1</td>
<td>FAINT REDNESS, UNDEFINED BORDER</td>
<td>0 **</td>
<td>0 **</td>
</tr>
<tr>
<td>2</td>
<td>INTENSE REDNESS, DEFINED BORDER</td>
<td>0 **</td>
<td>0 **</td>
</tr>
<tr>
<td>3</td>
<td>REDNESS + DEFINITE EDEMA</td>
<td>0 **</td>
<td>0 **</td>
</tr>
<tr>
<td>4</td>
<td>REDNESS + PAPULES, OR VESICLES, ETC.</td>
<td>0 **</td>
<td>0 **</td>
</tr>
<tr>
<td>No. of Responders</td>
<td>0 SUBJECTS</td>
<td>0 SUBJECTS</td>
<td>0 SUBJECTS</td>
</tr>
<tr>
<td>No Data Acquired</td>
<td>1 SUBJECT</td>
<td>9 SUBJECTS</td>
<td>9 SUBJECTS</td>
</tr>
</tbody>
</table>

16.00 **SIGNIFICANCE OF THE RESPONSES:**

.01 **INITIAL/INDUCTION PHASE:**

No responses were noted on any of the 219 subjects who underwent at least one post-application examination. The absence of responses characterizes the product as one which is devoid of clinically significant skin-irritating propensities.

.02 **CHALLENGE PHASE:**

a. **Original Contact Sites:**

No responses were noted on any of the 211 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.

b. **Naive Contact Sites:**

No responses were noted on any of the 211 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.
17.00 **CONCLUSIONS:**

was found to be neither a clinically significant skin irritant nor a skin sensitizer under the conditions of this study.

was not contraindicated for usages entailing repeated applications on human skin under conditions appropriate for such products.

PRODUCT INVESTIGATIONS, INC.

2/4/14

Joseph E. Nicholson III
Director, Dermatological Studies

18.00 **COMPLIANCE WITH GOOD QUALITY ASSURANCE STANDARDS:**

I have audited the results presented in this report and believe that, to the best of my knowledge, they accurately reflect the raw data acquired during the course of this study.

Samuel Charles
Director, Quality Assurance
Clinical Research Laboratories, Inc.

Report Status: Final Report
Report Date: March 31, 2014
CRL Study Number: CRL08214-5
CRL Protocol Number: CL 1.0 2014
Study Dates: February 5, 2014 – March 21, 2014
Study Title: Repeated Insult Patch Test (RIPT) – Shelanski Method
Test Material: 
Sponsor: 
Sponsor Representative: 
Investigator: Anita Lee Cham, M.D. Dermatologist

APPROVAL SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director
Date 3/3/14

Michael J. Muscatello, Ph.D.
Executive Vice President/COO
Date 3/3/14

Anita Lee Cham, M.D.
Dermatologist
Date 3/3/14
Clinical Study Number: CRL08214-5
Start Date: February 5, 2014
Completion Date: March 21, 2014

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

Signature of QA Auditor

Date
1.0 OBJECTIVE

The objective of this study was to determine the dermal irritation and sensitization potential of a test material.

2.0 INVESTIGATOR/INVESTIGATIVE SITE

Anita Lee Cham, M.D.
Dermatologist

Clinical Research Laboratories, Inc.
371 Hoes Lane, Suite 100
Piscataway, New Jersey 08854
732-981-1616

3.0 SPONSOR REPRESENTATIVE/SPONSOR

4.0 TEST MATERIAL

The following test material was provided by [redacted] and was received by [redacted] on January 30, 2014.

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Test Condition</th>
<th>Patch Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test as received</td>
<td>Occlusive*</td>
</tr>
</tbody>
</table>

The test material was coded with the following CRL identification number:

CRL08214-5

5.0 STUDY DATES

This study was initiated on February 5, 2014 and was completed on March 21, 2014.

* Occlusive Strip with Flexcon® (Strukmyer LLC, Mesquite, TX or equivalent)
6.0 PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

6.1. INCLUSION CRITERIA

a. Subject is male or female between the ages of 18 and 70 years;
b. Subject does not exhibit any skin diseases which might be confused with a skin reaction from the test material;
c. Subject agrees to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;
d. Subject agrees to refrain from getting patches wet during the course of the study;
e. Subject has signed an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"
f. Subject has completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;
g. Subject is in generally good health and has a current Subject Profile/Medical History on file;
h. Subject is dependable and able to follow directions as outlined in the protocol.

6.2. EXCLUSION CRITERIA

a. Subject is pregnant, nursing, or planning to become pregnant;
b. Subject is currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;
c. Subject reports allergies to cosmetics, toiletries, or personal care products;
d. Subject exhibits any skin disorders, sunburn, scars, excessive tattoos, etc. in the test area;
e. Subject has scheduled, or is planning to undergo, any medical or surgical procedures during the 6 week course of the study.
7.0 TEST METHOD SUMMARY

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

<table>
<thead>
<tr>
<th>Dermal Scoring Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visible skin reaction</td>
</tr>
<tr>
<td>±</td>
<td>Barely perceptible erythema</td>
</tr>
<tr>
<td>1+</td>
<td>Mild erythema</td>
</tr>
<tr>
<td>2+</td>
<td>Well defined erythema</td>
</tr>
<tr>
<td>3+</td>
<td>Severe erythema and edema</td>
</tr>
<tr>
<td>4+</td>
<td>Erythema and edema with vesiculation</td>
</tr>
</tbody>
</table>

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject may not have been patched again during the Induction Phase but may have been challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.
8.0 RESULTS

This study was initiated with 224 subjects. Twelve subjects discontinued study participation for reasons unrelated to the test material. A total of 212 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

9.0 ADVERSE EVENTS

No adverse events were reported during the study.

10.0 CONCLUSION

Based on the test population of 212 subjects and under the conditions of this study, the test material identified as [Redacted] Facial Essence did not demonstrate a potential for eliciting dermal irritation or sensitization.

11.0 RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.
Test Material = 3.5% HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX in mascara

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF HELIANTHUS ANNUUS SEED WAX ON HUMAN SKIN

PREPARED FOR

28 November 2012
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<tr>
<td>Week #1 Regimen</td>
<td>5</td>
</tr>
<tr>
<td>Week #2 Regimen</td>
<td></td>
</tr>
<tr>
<td>Week #3 Regimen</td>
<td></td>
</tr>
<tr>
<td>Week #4 Regimen</td>
<td></td>
</tr>
<tr>
<td>Week #5 Regimen</td>
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<td></td>
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<td></td>
</tr>
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<td></td>
</tr>
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<td>17.00 Conclusions</td>
<td>7</td>
</tr>
<tr>
<td>18.00 Compliance with Good QA Standards</td>
<td></td>
</tr>
</tbody>
</table>
Determination of the Irritating and Sensitizing Propensities of [Redacted] on Human Skin

1.00 Objectives:

.01 To identify and characterize the skin-damaging propensities that can be induced to exercise under the conditions of this modified patch test procedure.

.02 To adjudicate whether the exercise of such propensities under the test conditions contraindicates the kind of skin contact that would be occasioned during the appropriate use of the product.

2.00 Design:

.01 A modified version of the Repeated Insult Patch Test was conducted on two panels whose combined total was greater than two hundred subjects at the outset.

.02 The regimen comprised nine sequential 24-hour induction applications and two concurrently conducted 24-hour challenge applications, one on the initial induction site and one on a naive site.

.03 During the initial phase, the skin of the contact sites was graded and the grades recorded on Wednesdays, Fridays (i.e., twenty-four hours after patches had been removed), and Mondays (i.e., forty-eight hours after patches had been removed).

.04 During the challenge phase, the skin of the contact sites was graded within moments after the patches had been removed (24 hours post application) and again twenty-four hours later. Follow-up examinations were conducted thereafter only if adverse effects were present.

.05 This study was conducted in compliance with the standards of good clinical practices generally applicable for the protection of the privileges and well-being of individuals who participate in patch test procedures.

3.00 Sponsor:

Project Director:
Authorization:
Purchase Order:

4.00 Study Product:

Type of Product: Mascara
Sponsor Identification:
Date received: 9/15/12
Quantity rec'd: 5665 g, gross wt
Form used in study: As Supplied

5.00 Site of Study:

Product Investigations, Inc.
1010 Carver Road
Modesto, CA 95350

Study Personnel:
Medical Director: Morris V. Shelanski, MDCM
CA Physician: Clinton E. Prescott Jr, MD
Dir. Derm. Services: Joseph L. Nicholson III
Technicians: Lisa A. Cortez, Henry Cortez
Quality Assurance: Samud J. Charles III

6.00 Dates of Study:

Started: 24 September 2012
Completed: 2 November 2012
7.00 SELECTION OF SUBJECTS:

.01 RECRUITING:
Prospective subjects were recruited from surrounding localities via phone, posters and personal contact.

.02 INFORMED CONSENT:
All individuals who expressed interest in participating were given an informed consent document to read. This document, which each candidate had to read and sign before being entered into the study, presented the following information:

a. How many subjects were to be enrolled in the study;
b. The intended use of the product;
c. Why the product was being tested;
d. How the test was to be performed;
e. That the regimen was not intended to benefit a subject's health, well being, or quality of life;
f. The different ways that participation may be detrimental to a subject's health, well being, or quality of life;
g. That not all detrimental effects could be foreseen and made known at the time the informed consent was presented for the prospective subject's signature;
h. What commitments a subject had to make to be in compliance; and
i. What considerations a subject was entitled to receive and the conditions for receiving them.

.03 DETERMINATION OF ELIGIBILITY:
Information concerning a prospective subject's qualifications was obtained from the answers the subject gave in filling out a medical history form and in responding to specific questions. Those who did not meet the following criteria were rejected.

a. Inclusion Criteria: Satisfaction of all the following items was obligatory:

i. The candidate was at least eighteen years old, and
ii. agreed to comply fully with the scheduled study regimen, and
iii. expressed awareness that a participant would incur risks that would affect her/his well-being, and
iv. denied that the amount of the stipend had induced her/him to participate against her/his better judgment, and
v. had read the informed consent agreement, and
vi. had assured the interviewer that she/he had no questions about the informed consent's contents that had not been answered to her/his satisfaction, and
vii. had signed the consent form willingly and without reservation.

b. Exclusion Criteria: Any one of the following items was cause for rejection:

i. The candidate had an illness that contraindicated participation; or
ii. a condition that rendered the skin unavailable for use in this study; or
iii. was using dosages of medications that could alter the skin's tolerance; or
iv. had a documented history of intolerance to the category of products submitted for study; or
v. was a female who was pregnant or was breast feeding an infant.

.04 PANEL INFORMATION:

b. Demographics:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number</th>
<th>Age Break</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15%</td>
<td>18-30</td>
</tr>
<tr>
<td>Female</td>
<td>85%</td>
<td>18-71</td>
</tr>
</tbody>
</table>

c. Dedication: These were shared panels, i.e. the subjects were engaged in the evaluation of materials submitted by sponsors other than Estee Lauder Companies.

8.00 SITE INFORMATION:

.01 LOCATION:

[Redacted]

was assigned Band #5 on the right side of the back of each subject.

.02 IDENTIFICATION OF A CONTACT SITE:

At each visit the skin around the contact site was marked to facilitate examinations after the device was removed and positioning of subsequently-applied devices as precisely as was feasible on the same site.
0.00 PATCHING DEVICES:

0.01 TYPE OF DEVICE:

Partially occlusive patching devices consisting of a 2cm x 2cm absorbent pad centered on the adhesive-coated surface of a 7cm x 4cm plastic film were used to convey and maintain the product on the skin.

0.02 PREPARATION OF A PATCHING DEVICE:

The velor pad of a patching device was evenly coated with approximately 200 mg of the test material.

0.03 POSITIONING AND REMOVING A PATCHING DEVICE:

a. A prepared device was positioned on its designated site on each subject with the product-treated surface of the pad in contact with the skin.
b. Firm pressure was applied to the backing of the device to affect intimate contact of the pad with the skin and to bond the flanges of the device securely to the skin.
c. When the time came for removing the device, the device was peeled off the skin as gently as was feasible under the circumstances.

10.00 DATA ACQUISITION:

0.01 GRADING PROCEDURE:

a. Examinations of the contact sites to grade the effects elicited by the product were conducted on Mondays, Wednesdays, and Fridays. When a subject came in on a scheduled examination day, the technician examined the skin of the contact site.

i. If no adverse effect was detected, a "0" was recorded in the subject's Case Report Form.

ii. If an adverse effect was detected, the technician entered a grade indicating her assessment of the response's intensity.
b. The subject was then sent into the patching room where the site was examined again by a second technician to ascertain independently whether or not the site should be used again. If she disagreed with the first technician's assessment, the application was held in abeyance until the issue could be resolved with the help of the supervisor and/or the investigator.
c. The supervisor or the investigator was called in not only when a disagreement had to be resolved, but also to validate substantial sudden changes, e.g. when a response is deemed to merit a grade ≥3 or when a response has been judged to have decreased by two or more points from the previous day's status.

0.02 CRITERIA FOR GRADING RESPONSE INTENSITY:

The following scale was used in this procedure to designate the intensities of those gross skin changes that may be occasioned by exposing the surface of the skin to a product.

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Visible Change</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical Stage</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Fruit redness with poorly defined margins</td>
<td>1</td>
</tr>
<tr>
<td>Vascular Dilation:</td>
<td>Redness with well-defined margins</td>
<td>2</td>
</tr>
<tr>
<td>Infiltration:</td>
<td>Redness plus well-defined edema</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Redness plus papules, vesicles or ulceration</td>
<td>4</td>
</tr>
</tbody>
</table>

0.04 SITE CHANGES:

a. Switch to a Naive Site:

i. If the product had elicited a Grade 2 response on a subject, application of the product would have been switched immediately to a naive site on the subject.

b. Discontinuation of Applications:

i. If the product had elicited a second Grade 2 on a subject, application of the product would have been discontinued immediately for the remainder of the initial phase on the affected subject.

ii. If the product had elicited a Grade 3 response on a subject, application of the product would have been discontinued immediately for the remainder of the initial phase on the affected subject.
## 11.00 OVERVIEW OF STUDY REGIMEN: Please note deviations in schedule

<table>
<thead>
<tr>
<th></th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week #1</td>
<td>Agent</td>
<td>Return</td>
<td>Grade, Agent</td>
<td>Remove</td>
<td>Grade, Agent</td>
<td>(Remove)</td>
<td></td>
</tr>
<tr>
<td>Week #2</td>
<td>Grade, Agent</td>
<td>Return</td>
<td>Grade, Agent</td>
<td>Remove</td>
<td>Grade, Agent</td>
<td>(Remove)</td>
<td></td>
</tr>
<tr>
<td>Week #3</td>
<td>Grade, Agent</td>
<td>Return</td>
<td>Grade, Agent</td>
<td>Remove</td>
<td>Grade, Agent</td>
<td>(Remove)</td>
<td></td>
</tr>
<tr>
<td>Week #4</td>
<td>Grade</td>
<td>Return</td>
<td>Grade, Agent</td>
<td>Remove</td>
<td>Grade, Agent</td>
<td>(Remove)</td>
<td></td>
</tr>
<tr>
<td>Week #5</td>
<td>Grade</td>
<td>Return</td>
<td>Grade, Agent</td>
<td>Remove</td>
<td>Grade, Agent</td>
<td>(Remove)</td>
<td></td>
</tr>
</tbody>
</table>

\[\text{Weeks 1-4} \]

## 42.00 STUDY REGIMEN:

### 01 INITIAL/INSPECTION PHASE:

**Week #1:**

**Monday:**

1. As each subject presented himself at the clinic, the skin of the contact site assigned to the product submitted for study was examined and ascertained to be suitable before applications were begun.
2. A freshly-prepared patching device was applied on its assigned site.
3. The skin around the device was marked and the subject was instructed to return on Tuesday.

**Tuesday:**

1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the subject was instructed to return on Wednesday.

**Wednesday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced and the subject was instructed to return on Thursday.

**Thursday:**

1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the subject was instructed to return on Friday.

**Friday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced.
4. The subject was dismissed with instructions to remove the patching device on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

**Week #2:**

**Monday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. The time at which the patch was removed on Saturday was recorded.
3. A freshly-prepared patching device was applied on the same site.
4. The site-identifying marks were reinforced and the subject was instructed to return on Tuesday.

**Tuesday:**

1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the subject was instructed to return on Wednesday.

**Wednesday:**

1. As each subject returned, the skin of the contact site was graded. The grade was recorded.
2. A freshly-prepared patching device was applied on the same site.
3. The site-identifying marks were reinforced and the subject was instructed to return on Thursday.

**Thursday:**

1. As each subject returned, the site-identifying marks were reinforced.
2. The patching device was removed by a technician and the subject was instructed to return on Friday.
Friday:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. A freshly-prepared patching device was applied on the same site.
iii. The site-identifying marks were reinforced.
iv. The subject was dismissed with instructions to remove the patching device on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

Week #3:
Monday:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The time at which the patch was removed on Saturday was recorded.
iii. A freshly-prepared patching device was applied on the same site.
iv. The site-identifying marks were reinforced and the subject was instructed to return on Tuesday.

Tuesday:
i. As each subject returned, the site-identifying marks were reinforced.
ii. The patching device was removed by a technician and the subject was instructed to return on Wednesday.

Wednesday:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. A freshly-prepared patching device was applied on the same site.
iii. The site-identifying marks were reinforced and the subject was instructed to return on Thursday.

Thursday:
i. As each subject returned, the site-identifying marks were reinforced.
ii. The patching device was removed by a technician and the subject was instructed to return on Friday.

Friday:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. A freshly-prepared patching device was applied on the same site.
iii. The site-identifying marks were reinforced.
iv. The subject was dismissed with instructions to remove the patching device on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

Week #4:
Monday:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The site-identifying marks were reinforced and the subject was instructed to report back to the clinic on the following Monday to receive the challenge applications, and
iii. To notify the investigator without delay should any significant changes occur in the skin of the contact site before Monday of the challenge week.

HOLDING PHASE: Week 4. Tuesday through Friday

.03 CHALLENGE PHASE:
Week #5:
Monday:
i. As each subject returned, the skin of the initial induction site was examined and ascertained to be free of any conditions that would have rendered it unfit for undergoing the challenge applications.
ii. A prepared device was applied on the initial induction site.
iii. A second prepared device was applied on a naive site.
iv. The skin around both devices was marked and the subject was instructed to return on Tuesday.

Tuesday: (Note: If a subject was absent on Monday, she/he was patched on Tuesday.)
i. As each subject returned, the site-identifying marks around both contact sites were reinforced.
ii. Both patching devices were removed by a technician.
iii. The skin of both contact sites was graded; the grades were recorded.
iv. The subject was instructed to return on Wednesday.

Wednesday:
i. As each subject returned, the skin of both contact sites was graded; the grades were recorded.
ii. If follow-up was indicated, the subject was instructed to return on Thursday, otherwise the subject was dismissed from the study of this material.
.01 FOLLOW-UP PHASE:

Week No. 6 and Week No. 7:
During the two weeks following the exit examination, the subjects were given the opportunity to relay any information concerning effects that were relevant to the characterization of the product as well as to communicate the need for treatment of persistent or newly-occurring responses.

13.00 PROCEDURE DEVIATIONS:

None were necessary.

14.00 COMPLIANCE

<table>
<thead>
<tr>
<th>Phase</th>
<th>No. OF Helm.</th>
<th>COMPLIANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPOSED</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

15.00 INCIDENCE OF RESPONSES:

<table>
<thead>
<tr>
<th>GRADE</th>
<th>TYPE OF RESPONSE</th>
<th>INDUCTION PHASE</th>
<th>CHALLENGE PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NO VISIBLE CHANGE</td>
<td>216 SUBJECTS</td>
<td>209 SUBJECTS</td>
</tr>
<tr>
<td>1</td>
<td>EASINESS, UNDEFINED BURN</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>INCREASED EASINESS, DEFINED BURN</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>REDNESS + DEFINED EASINESS</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>REDNESS + PAPULES, OR Vesicles, ETC</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NO. OF RESPONDERS</th>
<th>216 SUBJECTS</th>
<th>209 SUBJECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAIVE CONTACT SITE</td>
<td>209 SUBJECTS</td>
<td></td>
</tr>
</tbody>
</table>

16.00 SIGNIFICANCE OF THE RESPONSES:

.01 INITIAL/INDUCTION PHASE:

No responses were noted on any of the 216 subjects who underwent at least one post-application examination. The absence of responses characterizes the product as one which is devoid of clinically significant skin-irritating propensities.

.02 CHALLENGE PHASE:

a. Original Contact Sites:

No responses were noted on any of the 209 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.

b. Naive Contact Sites:

No responses were noted on any of the 209 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.
17.00 CONCLUSIONS:
.01 [Blacked out] was found to be neither a clinically significant skin irritant nor a skin sensitizer under the conditions of this study.
.02 [Blacked out] is not contraindicated for usage containing repeated applications on human skin under conditions appropriate for such products.

PRODUCT INVESTIGATIONS, INC.

[Signature]
Joseph E. Nicholson III
Director, Dermatological Studies

18.00 COMPLIANCE WITH GOOD QUALITY ASSURANCE STANDARDS:
I have audited the results presented in this report and believe that, to the best of my knowledge, they accurately reflect the raw data acquired during the course of this study.

[Signature]
Samuel Charles
Director, Quality Assurance
Clinical
Research
Laboratories, Inc.

Final Report
Repeated Insult Patch Test

CLIENT:

ATTENTION:

TEST MATERIAL:

CRL STUDY NUMBER: CRL44113-3

AUTHORIZED SIGNATURES:

Bruce E. Kanéngiser, M.D.
President/Medical Director

Michael J. Muscatello, Ph.D.

Anita Lee Chang, M.D.
Dermatologist

REPORT DATE: August 23, 2013

371 Hoes Lane • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520
Clinical Study Number: CRL44113-3
Start Date: June 17, 2013
Completion Date: August 2, 2013

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

[Signature]
Signature of QA/Auditor

[Date]
Date
Clinical Research Laboratories, Inc.

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material on a panel of 200 subjects.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane Suite 100
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by and was received by Clinical Research Laboratories, Inc. on June 14th, 2013:

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Test Condition</th>
<th>Patch Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Applied to the patch as received.</td>
<td>Oclusive*</td>
</tr>
</tbody>
</table>

The test material was coded with the following CRL identification number:

CRL44113-3 n=200

STUDY DATES

This study was initiated on June 17, 2013 and was completed on August 2, 2013.

* Oclusive Strip with 1x200 (Dundie Medical, Moore, MN)
PANEL SELECTION

Each subject was assigned a permanent CRI identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix 1). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

Inclusion Criteria

a. Male and female subjects between the ages of 18 and 70 years;
b. Subjects who do not exhibit any skin diseases which might be confused with a skin reaction from the test material;
c. Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;
e. Subjects who have completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;
f. Subjects in generally good health who have a current Subject Profile/Medical History on file;
g. Subjects who are dependable and able to follow directions as outlined in the protocol.

Exclusion Criteria

a. Female subjects who are pregnant or nursing;
b. Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;
c. Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.
TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

**Dermal Scoring Scale**

0  No visible skin reaction
2  Barely perceptible erythema
1+  Mild erythema
2+  Well defined erythema
3+  Erythema and edema
4+  Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.
RESULTS

This study was initiated with 224 subjects. Sixteen subjects discontinued study participation for reasons unrelated to the test material. A total of 208 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table 1.

CONCLUSION

Based on the test population of 208 subjects and under the conditions of this study, the test material identified as [BLANK] Lipstick, did not demonstrate a clinically significant potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.
Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Wilbur Johnson, Jr.  
Senior Scientific Analyst  
Date: December 4, 2015  
Subject: Wave 2 Data on Nonoxynols

The following attachments were received from Women’s Voices of the Earth (WVE) after the mail date for the December 2015 Panel meeting:

- WVE Letter to Dr. Lillian Gill (transmittal memorandum: nonoxy122015pcpc3)
- WVE Letter to the CIR Expert Panel (nonoxy122015pcpc4)
- Publication on Vaginal Irritation Models (Costin et al. 2011: nonoxy122015pub1)

The letter to the Panel reinforces WVE’s initial concern over nonoxynol-9-induced, vaginal mucous membrane irritation resulting from feminine wash product use, and extends this concern to vaginally-applied products containing octoxynol-9. WVE noted that, in the CIR final safety assessment of octoxynols, the Panel considered that octoxynols and nonoxynols are sufficiently similar in chemical structure and that safety test data on nonoxynols are applicable to octoxynols. A number of vaginally-applied products containing octoxynol-9 are mentioned in WVE’s letter to the Panel. WVE is also asking that the Panel modify their tentative conclusion, considering the absence of any proven no-effect-level for nonoxynol-9-induced vaginal irritation. In response to WVE’s statement that VCRP data indicated that products containing nonoxynols are used on mucous membranes, it should be noted that nonoxynols -4 and -10 are being used in other personal cleanliness products (unnamed) and that nonoxynol-9 is being used in bath soaps and detergents and in skin care preparations, including cleansing skin care preparations. Furthermore, the results of an industry survey indicated use of nonoxynol-9 at a concentration of 2.5% in a personal cleanliness product (identified as a hand cleanser).

Regarding a copy of the publication on vaginal irritation models that WVE is bringing to the Panel’s attention, WVE has highlighted a study summary stating that use of a spermicidal gel containing 3.5% nonoxynol-9 increased a woman’s risk of HIV infection. This finding was thought to have resulted from penetration of the HIV virus into the vaginal epithelium, possibly due to nonoxynol-9-induced vaginal irritation. Again, the issue of nonoxynol-9-induced mucous membrane irritation warrants concern.

After reviewing the additional information provided, the Panel should determine whether or not their report discussion/conclusion should be revised to more adequately address the issue of nonoxynol-9-induced mucous membrane irritation. The same issue is also relevant to the safety assessment of octoxynols, and should be addressed during the re-review consideration of this ingredient group in the future.
Hello,

Please find attached a letter of comments we would like the CIR to consider at their December 2015 meeting. The letter is a followup to our comments on nonoxynols we submitted in August. We appreciate the opportunity to provide input to the panel and hope the information provided results in a robust discussion.

Attached also is a copy of a journal article that is referenced in our letter.

I would appreciate a response indicating that our comments have been received and will be distributed to the panel.

Thanks very much,

Alexandra Scranton

Director of Science and Research

Women’s Voices for the Earth
December 3, 2015

To the CIR Expert Panel:

We were pleased to see that the panel devoted time and effort in the September meeting to discussing the potential effects of nonoxynol-9 found in a feminine wash product, as a result of our letter. In light of your discussions, we would like to bring some additional information to the panel for consideration, as unfortunately, we are unable to travel to the next CIR meeting to discuss these issues in person.

1) **Can a vaginally-applied product containing nonoxynol-9 be formulated to be non-irritating?**

   It appears the latest draft report will include language in the conclusion that states that products must be formulated to be non-irritating. Given the data available for nonoxynol-9, in which irritation occurred at every level tested, does this recommendation make practical sense? Can you direct manufacturers to formulate a product to be non-irritating in the absence of any proven no-effect level for vaginal irritation? Would the panel perhaps consider, in addition to the “formulated to be non-irritating” language to add a recommendation that products intended to have vaginal exposure should not include nonoxynols?

2) **Vaginal irritation caused by nonoxynol-9 exposure is not a mere annoyance but has been shown to significantly increase risk of HIV infection.**

   As mentioned by Dr. Sadrieh of the FDA at the September CIR meeting, irritation of the vaginal tissue is not merely an annoyance or transitory condition, but can lead to other significant health problems such as increased risk of sexually transmitted diseases such as HIV. I have attached an article entitled: “Vaginal Irritation Models: The Current Status of Available Alternative and In Vitro Tests” published in the journal *Alternatives to Animal Testing* which summarizes the key data on the very front page. The authors state:

   “when it was recently tested for microbicidal potency in a large-scale phase III trial (1), the low dose of N-9 gel (3.5%) increased a woman’s risk of HIV infection instead of reducing it, when used more than three and a half times per day. A major reason for this unexpected increase is thought to be the penetration of the virus into the vaginal epithelium resulting from vaginal irritation caused by N-9.”

   As women frequently report the use of products such as feminine wash before and after being sexually active, it appears that chemicals like nonoxynol-9 are highly inappropriate, and
potentially unsafe in these products. As mentioned before, we recommend that the CIR include language in the conclusion that states that products with vaginal exposure should not include nonoxynols.

3) **Feminine wash is an intravaginal product, not an extravaginal product.**

We understand that at the September meeting, there was discussion as to whether feminine washes are externally or internally used products. This is pertinent to whether the data available from contraceptive gels containing nonoxynol-9 is relevant to expected exposure from feminine washes containing nonoxynol-9. The common practice for feminine wash use is that there is both internal and external exposure (which distinguishes feminine wash use from use of a more generic “body wash” which may only be used externally). Specifically in the case of “Very Private pH Balanced Body Wash” it is clear from the language used in the marketing of the product that the manufacturer intends internal vaginal exposure from the product.

a) “pH balanced”.

The point of having a feminine care product that is pH balanced is so that it does not alter vaginal pH. (Altered vaginal pH has been associated with increased risk of vaginitis.) There would be no reason to pH balance an externally applied product.

b) “Extra mild, low-sudsing formula is ideal for women with sensitive skin or dryness problems, even in the intimate area.”

“Dryness problems” clearly refers to vaginal dryness, a commonly reported symptom among women. External vulvar dryness is not a common condition.

c) “Contains anti-bacterial and anti-fungal components to help provide daily protection against vaginal irritation. Especially beneficial for women suffering from repeated yeast infections.”

It is hard to comprehend how an externally applied product could protect against vaginal irritation or repeated yeast infections. Internal exposure would be required to even attempt such an effect.

We believe that the data on exposure to intravaginal contraceptive gel is relevant and comparable to the exposure from the use of feminine wash. Thus we are concerned both about the irritation caused by nonoxynol-9 as well as the potential for unintended contraceptive efficacy from this feminine wash.

4) **Octoxynol-9, a similar chemical to nonoxynol-9, is also routinely found in vaginally applied feminine care products.**

In light of the current discussions on nonoxynol-9 in vaginally applied products, we believe the same concerns regarding octoxynol-9 should be addressed by the CIR. We suggest that the CIR also include new language to indicate that products with vaginal exposure should not include octoxynols.

Specifically, in the discussion section of the CIR’s 2004 assessment of octoxynols it states:
“The CIR Expert Panel considered that octoxynols and nonoxynols are sufficiently similar in chemical structure and effects that safety test data on nonoxynols are applicable to octoxynols.”

Examples of vaginally applied products containing octoxynol-9 include:

b) **Massengill Tropical Breeze Douche**: CONTAINS: Water, Citric Acid, Disodium EDTA, Sodium Benzoate, Octoxynol 9, Fragrance. [http://www.prestigebands.com/products/hygiene/massengill.html](http://www.prestigebands.com/products/hygiene/massengill.html)
c) **Massengill Fresh Scent Douche**: CONTAINS: Water, Citric Acid, Disodium EDTA, Sodium Benzoate, Octoxynol 9, Fragrance. [http://www.prestigebands.com/products/hygiene/massengill.html](http://www.prestigebands.com/products/hygiene/massengill.html)
e) **Top Care Feminine Douche**: Purified Water, Octoxynol-9, Citric Acid, Sodium Benzoate, Disodium EDTA, and Fragrance. [http://www.gianteagle.com/36800150829.aspx](http://www.gianteagle.com/36800150829.aspx)
f) **CareOne Feminine Douche Fresh Scent**: Ingredients: Purified Water, Sodium Benzoate, Disodium EDTA, Citric Acid, Octoxynol-9, Fragrance. [http://www.directionsforme.org/item/3865939](http://www.directionsforme.org/item/3865939)
g) **CareOne Feminine Douche Romantic Mist**: Ingredients Purified Water, Sodium Benzoate, Disodium Edta, Citric Acid, Octoxynol-9, Fragrance. [http://www.directionsforme.org/item/3738220](http://www.directionsforme.org/item/3738220)
   (Note that the website for this lubricant gel indicates “GAEA Gel acts as an effective and natural lubricant as well as a form of contraception. It contains Octoxynol-9, a natural microbicide that can destroy pathogens and sperm.” This product is not registered as a contraceptive drug however. The website also includes the confusing instructions “Caution: For external use only” adjacent to a graphic illustrating proper use of the prefilled vaginal applicator.)

5) **The CIR needs to implement a consistent protocol for discussing and examining health impacts of cosmetic ingredients in vaginally applied products.**

The discussions around nonoxynol-9 has clearly demonstrated that use of cosmetic ingredients in vaginally applied cosmetics require special consideration. The same ingredients that may be tolerable and safe by external epithelial skin are not necessarily safe for mucosal vaginal tissue. Unfortunately, the CIR has not acknowledged this distinction in their deliberations. Despite the fact that the VCRP data indicated products containing nonoxynols are used on mucous membranes, no discussion about the potential for vaginal mucous membrane exposure was initiated by any member of the CIR, until our letter addressed the topic. It appears there was also no discussion of vaginally applied cosmetics during the CIR’s last review of octoxynols in 2004, despite similar data on products. The omission of these considerations is of real concern both to women’s health and to the validity of the CIR’s conclusions with respect to feminine care cosmetics. We have identified a number of chemicals of concern found in feminine care
products available on our website: http://www.womensvoices.org/feminine-care-products/chemicals-of-concern-in-feminine-care-products/. We would be interested to know if the CIR has discussed the impacts to women’s health of any of these ingredients on vaginally applied cosmetics. Going forward we recommend that the CIR implement a protocol to ensure that health impacts from vaginal applications are considered or investigated for all ingredients that the CIR assesses.

Thank you for your consideration of these comments.

Alexandra Scranton
Director of Science and Research
Women’s Voices for the Earth
http://www.veryprivate.com/online-store/#!/Very-Private%C2%AE-pH-Balanced-Body-Wash-6oz/p/34614021/category=0
The following copyrighted material has been removed:

MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: December 4, 2015

Subject: Additional Data and Industry Response to the Insufficient Data Announcement for Polymerized Tetramethylcyclotetrasiloxanes

Attached, please find:

A. Revised monographs from the Personal Care Products Council’s On-Line Dictionary with the descriptions of polysilicone-2, polysilicone-4, and polysilicone-5; and a memo from the International Nomenclature Committee (INC) [PLYCTS122015Data1]

B. An industry submission regarding the safety of glyceryl allyl ether, which is reacted with polysilicone-4 to manufacture polysilicone-5 [PLYCTS122015Data2]

C. An industry response to the Insufficient Data Announcement for polymerized tetramethylcyclotetrasiloxanes. [PLYCTS122015Data3]

A. The revisions to the entries in the On-Line Dictionary are 1) the addition of “surface modifiers” to the reported functions and 2) the note “…may be used as a coating agent polymerized in situ typically on metal oxides or other materials” has been added to all three ingredient monographs. Additionally, it is the INC’s contention that these three polysilicones would not be useful as cosmetic ingredients if not coated on particles (i.e., it is unlikely that these ingredients are used independent of a metal oxide particle).

B. An industry submission recites that the glyceryl monoallyl ether, which is reacted with polysilicone-4 to manufacture polysilicone-5, is a cosmetic ingredient (INCI name glyceryl allyl ether) that was reviewed by CIR and found to be safe as used. At the time of the review, there were no uses reported for glyceryl allyl ether but alkyl glyceryl ethers were reported to be used up to 8% in rinse-off products and 3% in leave-on products, much higher concentrations than any expected to remain in polysilicone-5 (0.2% to 1% α-monoisotearyl glyceryl ether).
C. Industry submitted additional information addressing some of the data needs from the Insufficient Data Announcement from September, 2015. Summaries of this information and comments are provided below.

**Data Insufficiencies and Comments**

1) **Clarification that these polymers are only manufactured by covalently bonding them to colorant particles (in which case the INCI Dictionary does not accurately describe these ingredients) and that they do not exist, or are used, independently; and repeated dose inhalation.**

This submission recites that the polysilicone layer formed on particles does not covalently bond with the powder particle, but the polysilicone layer does not separate or exist independently by itself from the particle in supplier’s finished products. This explanation does not confirm that these polymers are **only** used for coating metal oxide powder particles, but it does confirm that this supplier manufactures these ingredients as such (Method of Manufacture below). This means that the monographs in the *Dictionary* did not (at the time of the September, 2015 CIR Expert Panel Meeting) match all cases of what is used in cosmetic products in that the metal oxides and the polymers are **not merely mixtures** but are manufactured together to make a single entity (i.e., a permanently encapsulated particle). However, as mentioned above, the *Dictionary* monographs for these ingredients have been recently updated to recite “may be used as a coating agent polymerized in situ typically on metal oxides or other materials,” and that they may function as “surface modifiers,” and it is the INC’s contention that this is the only way these ingredients are used.

In response to the request for repeated dose inhalation, the submitter contends that these ingredients are not used in sprays and inhalation should not be a concern. However, the Council survey reports that polysilicone-2 is used in perfume at 0.00095% and face powders at 1%. No repeated dose inhalation data were provided.

2) **Method of manufacture**

The submission provides a revised method of manufacture flow chart of these ingredients as coatings on metal oxides.

3) **The amount that the polymers that are bonded to the surface of the particles; do the particles have a light or heavy load of the polymers (i.e., are the reactive sites of the particles partially or fully substituted with these siloxanes**

The information provided recites that the layer of polysilicone does not form covalent bonds to the metal oxide but that it is believed that the silicone monomer adsorbs on the particle surface and, in a proceeding step, is polymerized (i.e., covalent bonds formed between silicone monomers). In the cases of polysilicone-2 and -5, the polymerized silicone shell is further modified in another step.

However, this submission does not clarify the amount or thickness (e.g., load) of polysilicone on the metal oxide particles or how active/reactive the surface of the resulting coated particle is.
4) **Absorption/metabolism. If dermally absorbed:** reproductive toxicity, 28-day dermal toxicity, and genotoxicity

The submission recites that the molecular weight of these ingredients is >100,000. The polysilicone layer renders these particles insoluble and the coated particles are too large to be dermally absorbed.

5) **Impurity data for all three ingredients including residual allyl glycerol for polysilicone-5**

Data were submitted that residual tetramethylcyclotetrasiloxane and tetradecene were below the detection limit of 5 ppm.

Residual glyceral monoally ether was not measured. However, as noted above, residual glyceral monoallyl ether is contended to be well below the maximum 8% in rinse-off products and 3% in leave-on products concentrations determined safe in a prior CIR assessment.

6) **Physical and chemical properties, especially molecular weight ranges**

The molecular weight of these ingredients is expected to exceed 100,000. These ingredients are reported to be insoluble in chloroform.

Other physical and chemical properties were not provided.

7) **Information on whether percentages given in the concentration of use survey, are percentages of the polymers in the products or of the polymer/particle combination and how are these calculated**

According to this submission, the concentrations of use submitted to the Council in their survey are the concentrations of just the polymers (excluding the metal oxides).

However, this submission does not provide the actual use levels of the polymer-coated powders or the fraction of the polysilicones that are in the powders.
Memorandum

To: Bart Heldreth, Ph.D., CIR
From: Joanne Nikitakis, INC liaison
Date: December 3, 2015
RE: Polysilicone-2, -4, -5

At the November meeting of the INC, the composition of Polysilicone-2, -4, and -5 were reviewed in response to the Expert Panel’s request for clarification about the chemistry of these materials. This memorandum provides a summary of the discussion.

In the cosmetic industry, mineral pigments are commonly surface-treated for the preparation of make-up formulations. These mineral pigments (e.g., titanium dioxide, and iron oxides) in their unmodified state have a surface that is hydrophilic and it is advantageous to render the surface hydrophobic to increase the ability of oils (including silicone oils) to wet the surface of the pigment particles. Pigment particles coated with a hydrophobic substance compress better, impart smoother skin feel, and help make various products more waterproof on the skin.

The chemistry involved with the formation of Polysilicone-2, -4 and -5 is typically performed on a substrate for the purpose of forming a coating that will change the surface properties of the substrate. Silicon hydrides (Si-H groups) are highly reactive when combined with water and are converted to Si-OH groups with hydrogen gas produced as a by-product. This reaction is carried out under nitrogen to prevent the formation of hydrogen and air mixtures that are potentially explosive. The Si-OH groups can react with each other, and also with Si-H groups. In both cases, a siloxane (Si-O-Si) bond is formed and the result is a highly crosslinked material. To completely react all of the Si-H groups, a subsequent material is added as a pendant group (e.g., tetradecene in Polysilicone-2) which covers the surface of the particle.

The surfaces of both titanium dioxide and iron oxide have hydroxyl groups, (i.e., Ti-OH or Fe-OH) that could possibly react with either Si-H or Si-OH groups to form new bonds; however the existence of such bonds has not been demonstrated to the knowledge of members on the INC. Additionally, the functionality of the material as a durable silicone coating is achieved by polymerization to encircle the particle of choice without chemical modification to its surface. If any attachment occurs between the silicone shell and the particle surface, it would be incidental and only occur at the interface between the silicone coating and the particle, leaving the vast bulk of the particle unaffected.

In theory, the chemistry to form these polysilicones could be performed in the absence of the particle. However, the formation of a resin without the presence of the embedded particle would not be useful as an ingredient. The commercial value as a coating agent is achieved in the curing process. Although the formation of the silicone coating is in situ, the INC considers these materials to be mixtures of the polysilicone and encapsulated ingredient because they are distinct entities.
Polysilicone-2, -4, -5

- P -

POLYSILICONE-2

INCI Monograph ID: 6713

Definition: Polysilicone-2 is a silicone resin formed by the polymerization of Tetramethyldicyclosiloxane (q.v.) in the presence of moisture, followed by reaction with tetradecene. See Sections 20 to 22 for the Japanese, Chinese, and Korean translations of this INCI Name.

Chemical Class: Siloxanes and Silanes

Reported Functions: Antifoaming Agent; Hair Conditioning Agent; Surface Modifier

Polysilicone-2 may be used as a coating agent polymerized in situ, typically on metal oxide particles.

Ingredient Source: Synthetic

Trade Name:
EP 1 (Shiseido Company Ltd.)

POLYSILICONE-4

INCI Monograph ID: 7165

Definition: Polysilicone-4 is a silicone resin formed by the polymerization of Tetramethyldicyclosiloxane (q.v.) in the presence of moisture. See Section 21 for the Chinese translation of this INCI Name.

Chemical Classes: Siloxanes and Silanes; Synthetic Polymers

Reported Functions: Hair Conditioning Agent; Surface Modifier; Viscosity Increasing Agent - Nonaqueous

Polysilicone-4 may be used as a coating agent polymerized in situ, typically on metal oxide particles.

Ingredient Source: Synthetic

Trade Name:
EP 0 (Shiseido Company Ltd.)

POLYSILICONE-5

INCI Monograph ID: 7166

CAS No.: 848302-17-0

Definition: Polysilicone-5 is a silicone resin formed by the polymerization of Tetramethyldicyclosiloxane (q.v.) in the presence of moisture, followed by the reaction with glyceryl monoallyl ether. See Sections 21 and 22 for the Chinese and Korean translations of this INCI Name.

Chemical Class: Siloxanes and Silanes

Reported Functions: Hair Conditioning Agent; Surface Modifier; Viscosity Increasing Agent - Nonaqueous

Polysilicone-5 may be used as a coating agent polymerized in situ, typically on metal oxide particles.

Ingredient Source: Synthetic

Trade Name:
EP 2 (Shiseido Company Ltd.)
Memorandum

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

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

DATE: November 23, 2015

SUBJECT: Information on Polysilicone-5

Glyceryl monoallyl ether that is reacted with Polysilicone-4 to make Polysilicone-5 is the same as the INCI named material Glyceryl Allyl Ether (technical name glyceryl-α-monoallylether; CAS 123-34-2). Glyceryl Allyl Ether was reviewed by CIR as part of the Alkyl Glyceryl Ether report and has a conclusion of “safe in the present practices of use and concentration.” At the time of the CIR review, Glyceryl Allyl Ether had no uses reported to either the VCRP or Council concentration of use survey. The maximum use concentrations for ingredients in the Alkyl Glyceryl Ether report were 8% Ethylhexylglycerin in rinse-off products and 3% Batyl Alcohol in leave-on products.
Memorandum

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

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

DATE: November 18, 2015

SUBJECT: Information on Polysilicone-2, -4 and -5

Anonymous. 2015. Polysilicone-2, -4, and -5 (additional information) with addendum (response to the insufficient data announcement).
Polysilicone-2, -4, and -5 (additional information)

(1) Clarification that these polymers are only manufactured by covalently bonding them to colorant particles (in which case the INCI Dictionary does not accurately describe these ingredients) and that they do not exist, or are used, independently. Repeated dose inhalation

In accordance to the X-ray Photoluminescence Spectroscopy (XPS) and the Fourier Transform - Infrared Spectroscopy (FT-IR) data (in the previous submission), the polysilicones layer does not covalently bond with the powder. Instead, it can be said that the polysilicone layer does not separate into or exist independently by itself in components of the finished products - such as oils - because of: (a) the network-like structure of the polysilicones which encases the powder, and (b) the strong adsorption of the polysilicones layer on the powder, and the insolubility acquired by its high molecular weight (MW). Therefore, neither the powder particles nor the polysilicones layer dermally absorb, causing no toxicological concern. Moreover, inhalation of the polysilicones should not be a concern due to non-usage in spray-type dosage forms, where exposure by inhalation could be of concern.

(2) Method of manufacture

Method of manufacture in a flow chart

(1,3,5,7-Tetramethylcyclotetrasiloxane(TS·4))

Chemical Vapor Deposition

Hydrosilylation

Filtration and Washing (in Ethanol) or reduced pressure drying

Pulverization

Drying

Sieving (100 mesh)

(surface-treated powder)
Glyceryl monoallyl ether is used for polysilicone-5 in lieu of 1-tetradecene. Polysilicone-4 is obtained at the end of the gaseous phase (i.e., polysilicone-4 is the precursor for polysilicone-2 and -5).

(3) The amount that the polymers that are bonded to the surface of the particles; do the particles have a light or heavy load of the polymers (i.e., are the reactive sites of the particles partially or fully substituted with these siloxanes

Based on the XPS and the FT-IR data, polysilicone layer does not form a covalent bond with the powder. However, it is believed that the polysilicone layer strongly adsorbs on the powder surface, forming a spherical shell (with a network-like structure of cross-linked polysilicones).

(4) Absorption/metabolism. If dermally absorbed: reproductive toxicity, 28-day dermal toxicity, and genotoxicity

As described in (6), the MW of the polysilicone-2, -4, and -5 is expected to exceed 100,000. Again, there is a strong adsorption of the polysilicone layer on the powder surface and a network-like, spherical shell structure of the polysilicone surrounds the particle. The insolubility of polysilicone layer - acquired as the MW increases - prevents the polysilicone from being extracted into solvents or separating into components of the final product such as oils, making it impossible for polysilicone to independently exist by itself. The polysilicone itself is insoluble and the size of the powder particles (which accompanies the polysilicone) is large such that dermal penetration does not occur. Therefore, dermal absorption of polysilicone-2, -4, and -5 does not pose a concern.

(5) Impurity data for all three ingredients including residual allyl glycerol for polysilicone-5

Residual "monomers" and corresponding additives for polysilicone-2, -4, and -5

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Residual TS-4</th>
<th>Residual 1-Tetradecene</th>
<th>Residual Glyceryl monoallyl ether</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysilicone-2</td>
<td>N.D. a)</td>
<td>N.D. a)</td>
<td>N.D. a)</td>
</tr>
<tr>
<td>Polysilicone-4</td>
<td>N.D. (expected) b)</td>
<td>N.D. (expected) b)</td>
<td>N.D. (expected) b)</td>
</tr>
<tr>
<td>Polysilicone-5</td>
<td>N.D. (expected) b)</td>
<td>N.D. (expected) b)</td>
<td>N.D. c)</td>
</tr>
</tbody>
</table>

Notes:

a) N.D.: Not detected (where detection limit < 5 ppm; previously reported)
b) The gas phase chemical reaction of TS-4 (adsorption and polymerization) is a common process for polysilicone-2, -4, and -5. It is believed that the measured residual TS-4 "monomer" level (less
than the detection limit of 5 ppm) for polysilicone-2 is applicable for polysilicone-4 and -5 (though not directly measured).

c) The residual level of glycercyl monoallyl ether was not directly measured. Except for the identity of the additive used (1-tetradecene for polysilicone-2, and glycercyl monoallyl ether for polysilicone-5), the same manufacturing process is utilized. The boiling point ($T_{bp}$) of glycercyl monoallyl ether (at 142°C) is lower than that of 1-tetradecene (at 251°C) used in polysilicone-2 – for which residuals levels were measured to be less than the detection limit (or 5 ppm) - making glycercyl monoallyl ether more prone to removal. As a result, though not directly measured, the same can be expected for polysilicone-5 (below detection limit of 5 ppm).

(6) Physical and chemical properties, especially molecular weight ranges

Each of polysilicone-2,-4, and -5 is formed by the polymerization of TS-4 in a mesh-like structure on either iron oxides or titanium dioxide, not extractable to organic solvents such as chloroform. This makes direct measurements impossible (MW is normally measured using substances extracted in solvents for measurements by Gel Permeation Chromatography (GPC)).

On the other hand, polysilicone-4 acquired by the TS-4 surface treatment of kaolin surfaces polymerizes linearly and was extractable to chloroform; the MW was measured to exceed 100,000. Therefore, the MW of the polysilicone-4 polymerizing in a mesh-like manner on either titanium dioxide or iron oxides is expected to exceed 100,000 (*Specifically, the MW of polysilicone-2 or -5 is believed to be larger than polysilicone-4 due to the addition of 1-tetradecene or glycercyl monoallyl ether). Mesh-like structure is indicated by the pyrolysis Gas Chromatography – Mass Spectroscopy (GC-MS).¹).

(7) Information on whether percentages given in the concentration of use survey, are percentages of the polymers in the products or of the polymer/particle combination and how are these calculated

The maximum use concentrations in products (reported previously) are of the concentrations of polysilicone-2, -4, and -5. The calculation for the concentration is as follows.

Polysilicone levels in products (%) = Use levels of powders in products (%) × Fraction of polysilicone(s) in powders

Calculation of the amount of polysilicone in powders (e.g. polysilicone-2)

Amount of polysilicone-4 deposited can be calculated based on an atomic analysis data, which measures the Carbon % of polysilicone-4 obtained at the end of the gaseous phase chemical reaction.

The difference between the Carbon % measured on polysilicone-2 (obtained at the end of the process) and the Carbon % measured on the polysilicone-4 was used to calculate the amount of the Carbon % due to the additive (1-tetradecene). Take one-to-one molar ratio between the amounts of 1-tetradecene (replacing the Hydrogen atom on Si-H) to that of polysilicone-2.
Addendum to Polysilicone-2, -4, and -5 (additional information)

(1) Clarification that these polymers are only manufactured by covalently bonding them to colorant particles (in which case the INCI Dictionary does not accurately describe these ingredients) and that they do not exist, or are used, independently. Repeated dose inhalation

![Figure 1: XPS spectra of Titanium dioxide (a) and Polysilicone-4-coated Titanium dioxide (b).](image)

(7) Information on whether percentages given in the concentration of use survey are percentages of the polymers in the products or of the polymer/particle combination and how are these calculated

**Detailed calculation**

- C% (measured on polysilicone-4)

\[
\text{C\% (measured on Polysilicone-4)} = \frac{\text{MW TS4 molecule} (240)}{\text{Wt Carbon in one TS4 molecule} (48)} \times \text{C\% (Polysilicone-4)} = \text{PS4 (wt\%)};
\]

- C% (measured on polysilicone-2)

\[
\text{(Carbon\% polysilicone-2) - (Carbon\% polysilicone-4)} = \text{Carbon\% increased via tetradecene addition}
\]

\[
\left(\frac{\text{MW tetradecene}}{\text{1 mol tetradecene}}\right) \times \frac{100\%}{\text{14 mol C / 1 mol tetradecene}} \times \frac{\text{# mol Carbon added by tetradecene}}{\text{total wt.}} = \text{tetradecene added (wt\%)}
\]

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