Data Supplement

Benzophenones

Hair Dye Epi

Papaya

Phosphorylcholine Polymers

Saccharide Humectants

Sage

Silicates

Tea Tree

CIR EXPERT PANEL MEETING
March 11-12, 2021

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst/Writer, CIR

Date: March 2, 2021

Subject: Amended Safety Assessment of Benzophenones as Used in Cosmetics

The draft final amended report on benzophenones, to be reviewed at the March 2021 Panel meeting, contains the 2008 opinion on Benzophenone-3 by the Scientific Committee on Consumer Safety (SCCS). The following preliminary SCCS opinion (https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_247.pdf) on Benzophenone-3 that was issued in December of 2020 appears below, and will be included in the next version of the final amended report on benzophenones.

1. *In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Benzophenone-3, does the SCCS consider Benzophenone-3 safe when used as a UV-filter in cosmetic products up to a maximum concentration of 6% and up to 0.5% in cosmetic products to protect product formulation?*

   On the basis of safety assessment, and considering the concerns related to potential endocrine disrupting properties of benzophenone-3 (BP-3), the SCCS has concluded that:

   a. The use of BP-3 as a UV-filter up to a maximum concentration of 6% in sunscreen products, either in the form of body cream, sunscreen propellant spray or pump spray, is not safe for the consumer.
   b. The use of BP-3 as a UV-filter up to a maximum concentration of 6% in face cream, hand cream, and lipsticks is safe for the consumer.
   c. The use of BP-3 up to 0.5% in cosmetic products to protect the cosmetic formulation is safe for the consumer.

2. *Alternatively, what is according to the SCCS the maximum concentration considered safe for use of Benzophenone-3 as a UV-filter in cosmetic products?*

   In the SCCS's opinion, the use of BP-3 as a UV filter in the following sunscreen products is safe for the consumer up to a maximum concentration of:

   a. 2.2% in body creams, in propellant sprays and in pump sprays, provided that there is no additional use of BP-3 at 0.5% in the same formulation for protecting the cosmetic formulation.
   b. Where BP-3 is also used at 0.5% in the same formulation, the levels of BP-3 used as UV filter should not exceed 1.7% in body creams, in propellant sprays and in pump sprays.

3. *Does the SCCS have any further scientific concerns with regard to the use of Benzophenone-3 in cosmetic products?*

It needs to be noted that the SCCS has regarded the currently available evidence for endocrine disrupting properties of BP-3 as inconclusive, and at best equivocal. This applies to all of the available data derived from in silico modelling, in vitro tests and in vivo studies, either considered individually or taken together. The SCCS considers that, whilst there are indications from some studies to suggest that BP-3 may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment.

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist
Date: March 2, 2021
Subject: New meta-analysis on hair dye use and breast cancer risk and comments from WVE

A new meta-analysis study on hair dye and breast cancer risk has just been published in February 2021.[1] The analyzed data comprised 11 case-control studies and 3 prospective cohort studies with 210,319 subjects. The pooled results suggested a slightly increased breast cancer risk in hair dyes users (pooled odds ratio (OR) = 1.07; 95% CI: 1.01 - 1.13). Specifically, the ORs for the associated risk of breast cancer were: with permanent hair dye use OR = 1.08 (95% CI: 1.03 - 1.14), with semi-permanent hair dye use 1.09 (95% CI: 0.92 - 1.28), with rinse (temporary) hair dye use OR = 1.17 (95% CI: 1.02 - 1.35), and with straightener use OR = 1.04 (95% CI: 0.96 - 1.14).

Note that the Eberle et al. 2020 paper,[2] a large-scale study which has already been incorporated into the updated Resource document, was also included in such meta-analysis. It is worthy to point out the assigned weights of the Eberle et al. 2020 study are 41.3%, 25.97%, 29.33%, and 48.71% in the calculation of ORs for permanent hair dye use, semi-permanent hair dye use, rinse (temporary) hair dye use and straightener use, respectively.[1] This means that relatively high weights were given to the Eberle et al. 2020 study during the statistical calculations, which consequently had a significant influence on meta-analysis outcomes. While the findings of Eberle et al. 2020 suggested that compared to nonuse, use of permanent dye was associated with 45% higher breast cancer risk in black women (hazard ratio (HR) 1.45; 95% CI: 1.10 - 1.90), and 7% higher risk in white women (HR 1.07; 95% CI: 0.99 - 1.16), limitations of the study design and data analysis need to be considered before jumping to a general conclusion; e.g., i) women were recruited to Eberle et al. 2020 study because they had a sister with breast cancer (i.e., all subjects in the current study had a significant risk factor of breast cancer), so the conclusions cannot be extended to the wider population; ii) since older age is a strong risk factor for breast cancer, other researchers argued the findings of this study have not been adjusted for age;[3] iii) the study analyzed data from 46,709 women and 2794 cases of breast cancer, however, only 208 of the breast cancer patients were African American, limiting the power to draw conclusions about this group; and iv) confounding factors warrant further examination when adverse effects of endocrine disrupting chemicals (EDC) are to be investigated because exposure to EDC is largely related to environmental and nutritional factors. Social or cultural factors may also associate with patterns in both hair dye usage and breast cancer risk, especially between black and white women.[4] As the authors stated in the paper, nearly half of included studies in the meta-analysis were at high risk of selection bias.[1] In addition, limitations of each involved study, especially the one being assigned with high percentage of weight in statistical analysis, were rarely discussed in the paper.

Enclosed please also find a letter received February 24, 2021 from Ms. Alexandra Scranton, Director of Science and Research, Women's Voices for the Earth (WVE), presenting comments on Hair Dye Epidemiology Resource Document (Document): 1) recommending all studies being included in Table 1, and 2) recommending creating a more specific conclusion.

The updated Document comprises 8 meta-analyses (i.e., references 9, 15, 18, 20, 29, 30, 31 and 41 in the Document), all of which are not listed in Table 1. Meta-analysis is the statistical procedure for combining data from multiple studies. Totally, around 104 epidemiology studies were covered by the meta-analyses in the Document. While some studies may be considered twice by the meta-analyses targeting at the same type of cancer (e.g., non-Hodgkin's lymphoma), the actual number of studies that have been assigned significant weights in statistical calculations is still high. Readers are encouraged to refer to the original paper for more details on characteristics of included studies, selection criteria, risk of bias, study limitations, etc. in each analysis. All genetic polymorphisms studies (references 46-52) are not listed in Table 1 as well. These studies investigated genetic variations associated with hair dye use and risk of 3 cancer types: bladder cancer, non-Hodgkin's lymphoma and breast cancer. If the Panel requests it, more information of on these studies will be added to corresponding cancer type section in Table 1.

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A special case is for Zhang et al. 2020 paper (reference 8 in the Document). This cohort study comprehensively evaluated the associations of permanent hair dye use with risk of diverse solid cancers, including basal cell carcinoma, cutaneous squamous cell carcinoma, bladder cancer, breast cancer (stratified by hormone receptor status: estrogen receptor and progesterone receptor), brain cancer, melanoma, colorectal cancer, ovarian cancer, kidney cancer, and lung cancer. Separate analyses were also conducted for various subtypes of hematopoietic cancer, such as overall non-Hodgkin lymphoma, overall T-cell non-Hodgkin lymphoma, common histological types of B-cell non-Hodgkin lymphoma (diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia or small lymphocytic lymphoma), multiple myeloma, Hodgkin lymphoma and myeloid leukemias. Study participants included 117,200 women who were divided into multiple subgroups based on frequency of use (non-use, 1 - 99 times, 100 - 199 times, ≥ 200 times) and subtypes of permanent hair dye (any hair color use, dark hair color use, light hair color use). Thus, hundreds of HR values were calculated for the possible combinations and then presented in the current study. While the major findings have been summarized in the Document, e.g., HR = 0.98 (95% CI: 0.96 - 1.01, n = 20,805) for all solid cancers under investigation (with the exception of non-melanoma skin carcinoma owing to lack of data), HR = 1.02 (95% CI: 0.98 - 1.07, n = 9,252) for overall breast cancer incidence among women with any hair color use, HR = 1.09 (95% CI: 0.97 - 1.22, n = 1,215) for overall ovarian cancer incidence among women with any hair color use, and HR = 1.05 (95% CI: 1.02 – 1.08, n = 22,560) for overall basal cell carcinoma among women with any hair color use; as per WVE's comments, the following specific outcomes are summitted herein for the Panel's consideration.

- HR = 1.28 (95% CI: 1.08 - 1.52, n = 1,287) for breast cancer (estrogen receptor negative, progesterone receptor negative) in women with any hair color use, cumulative dose (≥ 200 times);
- HR = 1.18 (95% CI: 1.01 - 1.37, n = 1,086) for breast cancer (estrogen receptor positive, progesterone receptor negative), cumulative dose (1 - 99 times) in women with any hair color; in comparison, HR = 1.08 (95% CI: 0.89 - 1.32) and HR = 0.94 (95% CI: 0.76 - 1.16) for cumulative dose (1 - 99 times) and dose (≥ 200 times) in women with any hair color, respectively;
- HR = 1.28 (95% CI: 1.01 - 1.62, n = 441) for breast cancer (estrogen receptor positive, progesterone receptor negative), cumulative dose (1 - 99 times) in women with light hair color use; in comparison, HR = 1.20 (95% CI: 0.89 - 1.61) and HR = 1.06 (95% CI: 0.78 - 1.45) for cumulative dose (100 - 199 times) and dose (≥ 200 times) in women with light hair color use, respectively;
- HR = 1.20 (95% CI: 1.08 - 1.52, n = 1,215) for ovarian cancer, cumulative dose (100 - 199 times) in women with any hair color use; in comparison, HR = 1.00 (95% CI: 0.86 - 1.16) for cumulative dose (1 - 99 times) and HR = 1.15 (95% CI: 0.96 - 1.37) for cumulative dose (≥ 200 times) in women with any hair color use, respectively;
- HR = 1.21 (95% CI: 1.00 - 1.47, n = 449) for ovarian cancer with dark hair color use; in comparison, HR = 1.09 (95% CI: 0.97 - 1.22, n = 1,215) and HR = 1.06 (95% CI: 0.89 - 1.27, n = 509) for any hair color use and light hair color use, respectively;
- HR = 3.89 (95% CI: 1.61 – 9.40, n = 24) for Hodgkin lymphoma with dark hair color use; in comparison, HR = 1.32 (95% CI: 0.82 - 2.13, n = 70) and HR = 0.70 (95% CI: 0.33 - 1.49, n = 31) for any hair color use and light hair color use, respectively;
- HR = 1.05 (95% CI: 1.02 – 1.09, n = 22,560) for basal cell carcinoma, cumulative dose (1 - 99 times) in women with any hair color use; in comparison, HR = 1.04 (95% CI: 1.00 – 1.09) and HR = 1.05 (95% CI: 1.00 - 1.09) for cumulative dose (100 - 199 times) and dose (≥ 200 times) in women with any hair color use, respectively;
- HR = 1.06 (95% CI: 1.02 – 1.11, n = 11,334) for basal cell carcinoma in women with light hair color use; in comparison, HR = 1.01 (95% CI: 0.96 – 1.06, n = 7737) for basal cell carcinoma in women with dark hair color use.

It is worthy to note that, as summarized in Zhang et al. 2020 paper (reference 8 in the Document), evidence from previous meta-analyses is not conclusive and might have been influenced by the following factors: not discriminating between personal and occupational exposure (reference 41); not able to distinguish between use of permanent and non-permanent hair dyes (reference 41 in the Document); the design of the included studies (predominantly case control studies with relatively limited power, references 9, 15, 16 and 41 in the Document); non-examination of critical aspects of exposure history (e.g., duration, frequency, and cumulative dose of use) owing to lowest common denominator of the contained studies (references 9, 15, 16 and 41 in the Document); and diagnostic challenges (reference 16 in the Document). In addition, the following facts deserve to be taken into account before a convincing statement is made:

- Results from any single observational epidemiological study warrant wider confirmation – from other epidemiological studies in different population, and from other types of research such as animal and biological studies.[5]
- The exact ingredients in hair dyes were not investigated in these studies, and hair dye formulations change over time: in response to FDA warning, the cosmetic industry has made several changes in the composition of permanent hair dyes since the 1980s; however, some studies summarized in the Document involve case subjects who used hair dyes before 1980, and the identified positive associations between such hair dye use and cancer risk were then weighted in corresponding meta-analyses (references 15, 17, 29, 47, 49 and 51 in the Document).
- Strengths of the epidemiologic studies include evaluation of a variety of populations. Limitations of some of the included studies are lack of specificity for type of hair dyes used (oxidative vs. non-oxidative) and details on color, type, or duration of use. Hair dye formulations may also differ based on the region of the world in which they are

produced and sold. Hence the specific product used and the timing of use should be better considered. The baseline cancer risk and environmental diversity of the locations where epidemiological studies were conducted should also be considered.[6]

- Observational studies cannot answer causal questions: there may be alternative reasons why hair dye use and cancer risk are correlated while hair dye is not a causal risk factor, e.g., it may be that women who are more genetically susceptible to suffering from breast cancer are more likely to use hair dyes; it may also be that women who use hair dye more commonly generally also use more unqualified cosmetics due to their financial situation, which may contain high level of EDCs.[3,5]

…

The Panel should consider the additional data summitted herein, the limitations of contained studies as well as other relevant factors in determining whether current human evidence is sufficient to support a causal relationship between personal hair dye use and cancer in general or a specific type of cancer.

References

1. Xu S, Wang H, Liu Y, et al. Hair chemicals may increase breast cancer risk: A meta-analysis of 210319 subjects from 14 studies. *PLoS One.* 2021;16(2):e0243792.
2. Eberle CE, Sandler DP, Taylor KW, White AJ. Hair dye and chemical straightener use and breast cancer risk in a large US population of black and white women. *Int J Cancer.* 2020;147(2):383-391.
3. Alipour S. Comments on: Hair dye and chemical straightener use and breast cancer risk in a large US population of black and white women. *Int J Cancer.* 2020;146(9):2651.
4. Teteh D, Ericson M, Monice S, et al. The Black identity, hair product use, and breast cancer scale. *PLoS One.* 2019;14(12):e0225305.
5. Jones M, Burgess S, Pharoah P. Expert reaction to study looking at permanent hair dyes, chemical hair straighteners and risk of breast cancer. Science Media Centre. https://www.sciencemediacentre.org/expert-reaction-to-study-looking-at-permanent-hair-dyes-chemical-hair-straighteners-and-risk-of-breast-cancer/. Updated 12-4-2019. Accessed 08-20-2020.
6. Naldi L. Comments on the CIR Expert Panel document "Hair Dye Epidemiology" with reference to Breast Cancer Risk. Unpublished information presented at the June 2018 CIR Expert Panel Meeting. 2018. Washington, DC.

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WOMEN'S VOICES FOR THE EARTH
OUR HEALTH. OUR FUTURE. TOXIC FREE.

February 24, 2021

To the CIR,

I am writing to submit comments on the latest version of the CIR's Hair Dye Epidemiology document which will be reviewed at the March meeting. My comments are on two main topics.

- Recommendation to create a more specific conclusion with respect to different types of cancer for which there may be sufficient evidence of a causal relationship with hair dye use.
- Comments on improving the usefulness Table 1 in the document by including all of the studies detailed in the narrative.

1) Recommendation to create a more specific conclusion:

The previous conclusion of the hair dye epidemiology report is

"*The Expert Panel for Cosmetic Ingredient Safety determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer*."

This is a very broad conclusion – as the Expert Panel has not found there to be sufficient evidence that hair dye causes cancer overall. But of course, few substances (tobacco smoke might be the exception) are toxic enough (and well studied enough) to be proven to cause cancers of all kinds. Menopausal hormone therapy, for example, has been well documented to increase the risk of breast cancer. But many studies have also shown it does not increase the risk of skin cancer, colon or rectal cancer, thyroid cancer, liver cancer or a myriad of other types. If you take all of those other cancers into consideration - it could be accurate to say overall that there is no causal association between hormone therapy and "cancer". But this is of course both misleading and not helpful to public health, or to the prevention of breast cancer specifically.

Given the extent of data now available on hair dye, I think it would be useful for the Expert Panel to make their conclusion more specific, and to assess if there is sufficient evidence of a causal relationship between hair dye use and any specific types of cancer.

2) Comments on improving the table

I have read previous versions of the hair dye document, and believe there are some important edits and changes that could be made which would improve its usefulness. The document covers a lot of studies (and now includes 10 more) but I have found it is hard to get a sense of the weight of evidence from the long narrative list of descriptions of the science. The table in the document, however, is a great way of synthesizing the data in brief. It is titled "Table 1. Hair Dye Epidemiology Studies considered by the Panel." However, looking through it, I have found that the table is far from complete. Numerous studies described in the narrative section, are inexplicably missing from Table 1. This makes the table considerably less helpful in analyzing the weight of the evidence, either for specific cancers, or cancer overall.

I have gone through the document and identified the 16 studies that are mentioned in the narrative but which are not included in the table. I also identified some of the studies that are cited (and relevant) but which are not described in the narrative.

The 16 studies highlighted below should be added to Table 1 and the three studies indicated should be described in the narrative.

Specifically:

<u>Reference 8 is not in the table:</u>

Reference 8. Zhang Y, Birmann BM, Han J, et al. Personal use of permanent hair dyes and cancer risk and mortality in US women: prospective cohort study. *BMJ.* 2020;370:m2942.

And the summary of Reference 8 in the narrative is missing important, relevant conclusions:

"• Positive associations were observed for risk of basal cell carcinoma, breast cancer (estrogen receptor negative, progesterone receptor negative, hormone receptor negative), and ovarian cancer

• An increased risk of Hodgkin lymphoma was observed among women with naturally dark hair, and a higher risk of basal cell carcinoma was found among women with naturally light hair."

<u>Reference 9 – is not in the table</u>

Reference 9. Turati F, Pelucchi C, Galeone C, Decarli A, La Vecchia C. Personal hair dye use and bladder cancer: a meta- analysis. *Ann Epidemiol.* 2014;24(2):151-159.

Reference 15 – has the right author, but refers to the wrong paper. The citation should be:

Takkouche B, Regueira-Méndez C, Montes-Martínez A. Risk of cancer among hairdressers and related workers: a meta-analysis. Int J Epidemiol. 2009 Dec;38(6):1512-31.

But the incorrect reference (also by Takkouche et.al.) that was included is relevant and should be included in the analysis with a summary in the narrative and included in the table – as it did identify increased risk for hematopoietic cancers:

Takkouche B, Etminan M, Montes-Martinez A. Personal use of hair dyes and risk of cancer: a meta-analysis. *JAMA.* 2005;293(20):2516-2525.

"*The pooled relative risk for ever users of hair dyes was 1.06 (95% CI, 0.95-1.18) for breast cancer (14 studies), 1.01 (95% CI, 0.89-1.14) for bladder cancer (10 studies), and 1.15 (95% CI, 1.05-1.27) for hematopoietic cancers (40 studies).*

Reference 18 – is not in the table

Reference 18. Linet MS, Vajdic CM, Morton LM, et al. Medical history, lifestyle, family history, and occupational risk factors for follicular lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014;2014(48):26-40.

Reference 19 is not in table and there should also be a summary in the narrative.

Reference 19. Zhang Y, Sanjose SD, Bracci PM, et al. Personal use of hair dye and the risk of certain subtypes of non-Hodgkin lymphoma. Am J Epidemiol. 2008;167(11):1321-1331.

"*The increased risks of follicular lymphoma (FL) (OR = 1.4, 95% CI: 1.1, 1.9) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (OR = 1.5, 95% CI: 1.1, 2.0) were mainly observed among women who started using hair dyes before 1980. For women who began using hair dye in 1980 or afterward, increased FL risk was limited to users of dark-colored dyes (OR = 1.5, 95% CI: 1.1, 2.0).*"

Reference 20 - is not in the table

Reference 20 .Cerhan JR, Kricker A, Paltiel O, et al. Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014;2014(48):15-25.

Reference 29 - is not in the table:

Reference 29. Qin L, Deng HY, Chen SJ, Wei W. A Meta-Analysis on the Relationship Between Hair Dye and the Incidence of Non-Hodgkin's Lymphoma. Med Princ Pract. 2019;28(3):222-230.

Reference 30 is not in the table:

Reference 30. Odutola MK, Nnakelu E, Giles GG, van Leeuwen MT, Vajdic CM. Lifestyle and risk of follicular lymphoma:a systematic review and meta-analysis of observational studies. Cancer Causes Control. 2020;31(11):979-1000.

Reference 31 is not in the table:

Reference 31. Shao C, Qi ZY, Hui GZ, Wang Z. Personal hair dyes use and risk of glioma: a meta-analysis. Int J Clin Exp Med. 2013;6(9):757-765.

Reference 41 is not in the table:

Reference 41 . Gera R, Mokbel R, Igor I, Mokbel K. Does the Use of Hair Dyes Increase the Risk of Developing Breast Cancer? A Meta-analysis and Review of the Literature. Anticancer Res. 2018;38(2):707-716.

Reference 46 is not in the table and there should also be a summary in the narrative:

Reference 46. Gago-Dominguez M, Bell DA, Watson MA, et al. Permanent hair dyes and bladder cancer: risk modification by cytochrome P4501A2 and N-acetyltransferases 1 and 2. Carcinogenesis. 2003;24(3):483-489.

"*Among NAT2 slow acetylators, exclusive permanent hair dye use was associated with a 2.9-fold increased risk of bladder cancer (95% CI = 1.2-7.5).*"

References 47 – 52 are not in the table:

Reference 47. Kogevinas M, Fernandez F, Garcia-Closas M, et al. Hair dye use is not associated with risk for bladder cancer:evidence from a case-control study in Spain. Eur J Cancer. 2006;42(10):1448-1454.

Reference 48. Morton LM, Bernstein L, Wang SS, et al. Hair dye use, genetic variation in N-acetyltransferase 1 (NAT1) and2 (NAT2), and risk of non-Hodgkin lymphoma. Carcinogenesis. 2007;28(8):1759-1764.

Reference 49. Zhang Y, Holford TR, Leaderer B, et al. Hair-coloring product use and risk of non-Hodgkin's lymphoma: a population-based case-control study in Connecticut. Am J Epidemiol. 2004;159(2):148-154.

Reference 50. Zhang Y, Hughes KJ, Zahm SH, et al. Genetic variations in xenobiotic metabolic pathway genes, personal hair dye use, and risk of non-Hodgkin lymphoma. Am J Epidemiol. 2009;170(10):1222-1230.

Reference 51. Da Costa RSS, Koifman RJ, Esteves VF, Schilling MPR, Koifman S, Silva IFD. Gene-Environment Interaction between Arg72Pro SNP and Selected Environmental Exposures among Brazilian Women Diagnosed with Benign Breast Disease. Asian Pac J Cancer Prev. 2020;21(12):3477-3485.

Reference 52. Guo H, Bassig BA, Lan Q, et al. Polymorphisms in DNA repair genes, hair dye use, and the risk of non-Hodgkin lymphoma. Cancer Causes Control. 2014;25(10):1261-1270.

Thanks for your consideration of these comments.

Alexandra Scranton
Director of Science and Research
Women's Voices for the Earth

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer, CIR
Date: March 2, 2021
Subject: Wave 2 - Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics

Enclosed is a human photosensitization assay performed on 50 subjects using a face cream (no SPF) containing 0.002% Carica Papaya (Papaya) Fruit Extract, applied neat (*papaya032021wave2_data*). This was a repeat insult patch test in which test materials were administered to test sites repeatedly, for a total of 6 induction exposures, over a 3-wk period. After each induction period, patches were removed, sites were irradiated, and left open for 48 h. Sites were subjected to a challenge phase after a 10-14 day rest period. The test substance was considered to be non-photosensitizing.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 24, 2021

SUBJECT: Carica Papaya (Papaya) Fruit Extract

Anonymous. 2007. An assessment of the photosensitization potential of two topical coded test products using a human photocontact allergenicity assay (face cream [no spf] contains 0.002% Carica Papaya (Papaya) Fruit Extract).

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[redacted]

FINAL REPORT

Final Report Date: February 18, 2008

[redacted]

Title: An Assessment of the Photosensitization Potential of Two Topical Coded Test Products Using a Human Photocontact Allergenicity Assay

face cream (no spf) contains 0.002% Carica Papaya (Papaya) Fruit Extract

Sponsor: [redacted]

Sponsor Study: Authorization Letter dated: December 18, 2007

Principal Investigator: [redacted] (Board Certified Dermatologist)

Testing Facility: [redacted]

February 18, 2008
Date

[redacted]
Principal Investigator

[redacted]

F I N A L R E P O R T

TITLE:

An Assessment of the Photosensitization Potential of Two Topical Test Products Using a Human Photocontact Allergenicity Assay.

[redacted]**PROTOCOL**:

[redacted]

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) ([21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with [redacted] Standard Operating Procedures (SOP's).

OBJECTIVE:

The objective of this study was to determine the photosensitization (photocontact allergenicity) potential of two topical cosmetic products to determine if these materials have a detectable photocontact allergenic potential when topically applied to human skin (see references #1 and #2).

DESIGN RATIONALE:

This was a repeat insult patch test wherein the test materials and ultraviolet radiation (solar simulated radiation) were administered to the same designated test sites over the mid or lower back area repeatedly for a total of six (6) induction exposures over a 3 week period followed by a challenge phase after a rest period of 10 to 14 days. The evaluator was blinded as to the identity of the test products.

CONDUCTION DATES:

This study was conducted from January 7, 2008 through February 8, 2008

PRINCIPAL INVESTIGATOR:

[redacted] (Board Certified Dermatologist)

Medical Director, [redacted]

E-mail address: [redacted]

KGL ADMINISTRATIVE STRUCTURE:

[redacted] (Receptionist/Panel Recruitment/Initial Screening)

[redacted] (Technician/Patch Applications and Removals/UV Irradiation)

[redacted] (Laboratory Supervisor/Expert Grader)

[redacted] (Sr. Associate Director/Quality Assurance)

TESTING FACILITY:

[redacted]

SPONSOR:

[redacted]

SPONSOR STUDY:

Authorization Letter dated: December 18, 2007

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to sign a consent form prior to enrollment. A copy of the study schedule of events, visits and dates was then given to the volunteer.

TEST MATERIALS:

The test samples used in this study were supplied by the sponsor. The products consisted of containers labeled [redacted] (7 jars) and Face Cream IV coded [redacted] (7 jars). For each test sample coded [redacted] and 1010288-037, a fresh jar was used for each patching day for both the induction phase and the challenge phase of the study. The product coded [redacted] contained volatile ingredients so it was allowed to air-dry for 15 minutes prior to occlusion. Both test products were then tested in accordance with the study protocol.

TEST DRUG ACCOUNTABILITY:

The test sample was received in good condition by our Quality Assurance Department. The test material was checked for (1) amount (2) product number or code (3) material container etc. The material was individually listed on a special sheet signed by the receiver, the laboratory supervisor and the investigator (physician). The test material was stored at ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test materials will be disposed of in accordance with established procedures after the final written report has been issued to the Sponsor.

PANEL COMPOSITION:

Healthy, Caucasian, adult volunteers with no excess hair or other marks on their back that would obscure grading of the test sites were recruited for this study. These were fair skin individuals with skin types I, II, or III defined as follows (Federal Register 43: 38260, 1978):

Type I - Always burns easily; never tans
Type II - Always burns easily; tans minimally
Type III - Burns moderately; tans gradually

None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics.

The criteria for inclusion included the following:

1 - Healthy adult male and female volunteers between the ages of 18 and 65 years with Skin Types I, II or III
2 - All were willing to attend the study visits as required and voluntarily gave their informed consent
3 - All subjects were in good general health.

Exclusion Criteria:

1 - History of sun hypersensitivity and photosensitive dermatoses
2 - All subjects with a significant history of past or ongoing internal disease, e.g., renal, hepatic, pulmonary, neurologic etc..
3 - History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema
4 - Pregnancy or mothers who were breastfeeding or planning a pregnancy
5 - Subjects receiving systemic or topical drugs or medications of any kind which could interfere with delayed immunologic responses e.g., corticosteroids, retinoids, non-steroidal anti-inflammatories and immunosuppresants
6 – Subjects receiving potentially photosensitizing medications e.g., thiazides, tetracyclines, sulfonamides, etc.
7 – Subjects with recurrent or chronic urticaria

8 - Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. All scores were recorded on the Case Report Forms. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

TEST SITE:

The test site was the mid or lower back. The test site was inspected prior to test product application to ensure that the skin was normal in appearance and free of irritation or other blemishes.

METHOD[1,2]:

Test patches were applied to the lower back of each subject. The entire test was composed of three distinct phases: (1) Pre-testing phase (2) Induction phase and (3) Challenge phase.

(1) PRE-TESTING PHASE:

After signing an informed consent form (on Day 1), the Minimal Erythema Dose (MED) of each subject was determined by exposing one side of the midback to a series of exposures (1cm diameter circular areas) in 25% increments from the xenon arc solar simulator, the details of which are listed below. The subject's MED is the shortest exposure time that produces a minimally visible faint erythema 20 to 24 hours later.

(2) INDUCTION PHASE:

Approximately 40mgs. of each test material was applied to 2x2cm square skin sites over the lower back and covered with 2x2cm squares of non-woven cotton cloth (Webril, Curity). The patches were then fastened to the skin with occlusive tape (Blenderm, 3M). The patches were left in place for twenty-four (24) hours. At the end of that period, the patches were then removed and the sites wiped off with dry gauze and exposed to three minimal erythema doses (MED's) from the xenon arc solar simulator. The sites were then left open for a forty-eight (48) hour period, after which the subjects returned to the testing facility and the patches were again reapplied to the same designated test sites under an occlusive dressing as previously outlined. Twenty-four (24) hours later, the patches were removed and the sites re-exposed to 3 MED's of solar simulated radiation. This sequence was repeated to the same test sites twice weekly for a total of three weeks (total of 6 exposures).

(3) CHALLENGE:

Eleven (11) days following the last induction dose, the subjects returned to the testing facility for a single challenge exposure. The test materials were applied as previously specified (40mgs) in **duplicate** to new designated skin sites each measuring 2x2cm on the opposite side of the lower back, under an occlusive dressing for a period of approximately 24 hours. One set of patches was then removed and any excess test material wiped off with dry gauze. The sites were then irradiated with 1/2 an MED of solar simulated radiation (SSR) plus 4J/cm^2 of

UVA which was obtained by filtering the beam from the solar simulator to eliminate short (UVB) wavelengths (see Light Source). The duplicate set of patches remained unirradiated and served as control treated sites.

EVALUATION OF SKIN REACTIONS:

All test sites were examined for reactions at 48 and 72 hours following exposure of the sites to UV radiation. Each subject reported back to the testing facility at the two time points to have the responses appraised by an evaluator other than the person applying the test products, and who was unaware of the nature of the test substances.

Skin reactions were scored according to the following scale:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesicula-bullous reaction)

LIGHT SOURCE[(3)]:

This was a 150-watt compact xenon arc source equipped with UV-reflecting dichroic mirror and a 1mm thick Schott WG-320 filter to produce simulation of the solar spectrum (290nm-400nm). A 1mm thick UG5 filter was added to remove reflected heat and remaining visible radiation. Total irradiance at skin level was measured with a calibrated Eppley Thermopile. The size of the irradiated field was approximately a 1-cm diameter circle. UVA was obtained from this same source by passing the beam through a 1mm Schott WG345 filter (Schott Glass Technologies). This provided a continuous spectrum between 320 and 420nm with a peak between 360-370nm. Total irradiance at skin level was 120mW/cm$^{2.}$ The UVA intensity was 48.7mW/cm^2.

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions of any kind were observed or reported during the study.

RESULTS:

A total of 53 healthy, Caucasian subjects who qualified were enrolled into this study. There were 40 females and 13 males ranging in age from 18 to 62 years. The demography is shown in Table 1. Three subjects (#09, #13 and #30) were dropped from the study. Subjects #09 and #30 were dropped for lack of compliance, while subject #13 (J.G.) was removed from the study after reporting that she had become pregnant. The remaining 50 subjects completed this study, as specified in the protocol.

No side-effects or unexpected reactions of any kind were observed. Following the challenge phase, no reactions suggestive of photocontact allergy were seen in any of the panelists at either 48 or 72 hours post exposure. The results of the challenge are summarized in the enclosed tables (Tables 2 through 5).

CONCLUSIONS:

Under the presently described test conditions, the test materials labeled [redacted] and Face Cream IV ([redacted]) do not possess a detectable photocontact-sensitizing potential in human skin.

REFERENCES

(1) Kaidbey, KH and Kligman AM: Photomaximization test for identifying photoallergic contact sensitizers. Contact Dermatitis, 6: 161-169, 1980.

(2) Kaidbey, KH and Kligman AM: Identification of contact photosensitizers by human assay. In "Current concepts in cutaneous toxicity, edited by V.A. Drill and P. Lazar. Academic Press Inc., pp. 55-68, 1980

(3) Berger DS: Specification and design of solar ultraviolet simulators. J.Invest.Dermtol. 53: 192-199, 1969.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	D-Y	53	F	C
02	J-C	60	F	C
03	S-F	52	F	C
04	F-S	60	M	C
05	P-R	51	F	C
06	M-D	35	F	C
07	D-A	41	F	C
08	K-P	45	F	C
09	A-B	19	F	C
10	J-F	28	F	C
11	C-D	46	F	C
12	J-V	44	F	C
13	J-G	35	F	C
14	P-H	48	F	C
15	M-F	38	F	C
16	A-C	22	F	C
17	D-P	31	F	C
18	J-M	52	M	C
19	D-B	61	M	C
20	M-R	22	M	C
21	A-N	34	F	C
22	S-R	59	F	C
23	J-M	60	M	C
24	M-M	49	F	C
25	S-M	49	F	C
26	E-C	37	F	C

TABLE 1 (continued)

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
27	M-D	52	F	C
28	D-C	40	F	C
29	S-C	22	M	C
30	A-S	20	M	C
31	K-F	23	F	C
32	G-C	62	M	C
33	H-B	27	F	C
34	M-D	45	F	C
35	M-R	37	F	C
36	S-H	41	M	C
37	J-A	46	F	C
38	K-B	61	F	C
39	P-B	62	M	C
40	E-C	18	F	C
41	V-K	18	F	C
42	D-C	53	F	C
43	B-N	31	F	C
44	C-C	43	F	C
45	L-S	44	F	C
46	J-D	23	F	C
47	R-M	60	F	C
48	M-C	40	F	C
49	B-Y	30	M	C
50	G-R	47	F	C
51	E-H	26	F	C
52	J-M	28	M	C
53	P-H	29	M	C

TABLE 2

RESULTS OF PHOTOMAXIMIZATION TESTING (48 Hour Grading)

Sample: [redacted]

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	0	0
003	0	0
004	0	0
005	0	0
006	0	0
007	0	0
008	0	0
009	Dropped from the study	
010	0	0
011	0	0
012	0	0
013	Dropped from the study	
014	0	0
015	0	0
016	0	0
017	0	0
018	0	0
019	0	0
020	0	0
021	0	0
022	0	0
023	0	0
024	0	0
025	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 2 (continued)

RESULTS OF PHOTOMAXIMIZATION TESTING (48 Hour Grading)

Sample: [redacted]

Subject Number:	Unirradiated Control	UV Irradiated
026	0	0
027	0	0
028	0	0
029	0	0
030	Dropped from the study	
031	0	0
032	0	0
033	0	0
034	0	0
035	0	0
036	0	0
037	0	0
038	0	0
039	0	0
040	0	0
041	0	0
042	0	0
043	0	0
044	0	0
045	0	0
046	0	0
047	0	0
048	0	0
049	0	0
050	0	0
051	0	0
052	0	0
053	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 3

RESULTS OF PHOTOMAXIMIZATION TESTING (72 Hour Grading)

Sample: [redacted]

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	0	0
003	0	0
004	0	0
005	0	0
006	0	0
007	0	0
008	0	0
009	Dropped from the study	
010	0	0
011	0	0
012	0	0
013	Dropped from the study	
014	0	0
015	0	0
016	0	0
017	0	0
018	0	0
019	0	0
020	0	0
021	0	0
022	0	0
023	0	0
024	0	0
025	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 3 (continued)

RESULTS OF PHOTOMAXIMIZATION TESTING (72 Hour Grading)

Sample: [redacted]

Subject Number:	Unirradiated Control	UV Irradiated
026	0	0
027	0	0
028	0	0
029	0	0
030	Dropped from the study	
031	0	0
032	0	0
033	0	0
034	0	0
035	0	0
036	0	0
037	0	0
038	0	0
039	0	0
040	0	0
041	0	0
042	0	0
043	0	0
044	0	0
045	0	0
046	0	0
047	0	0
048	0	0
049	0	0
050	0	0
051	0	0
052	0	0
053	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 4

RESULTS OF PHOTOMAXIMIZATION TESTING (48 Hour Grading)

Sample: Face Cream IV coded [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	0	0
003	0	0
004	0	0
005	0	0
006	0	0
007	0	0
008	0	0
009	Dropped from the study	
010	0	0
011	0	0
012	0	0
013	Dropped from the study	
014	0	0
015	0	0
016	0	0
017	0	0
018	0	0
019	0	0
020	0	0
021	0	0
022	0	0
023	0	0
024	0	0
025	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 4 (continued)

RESULTS OF PHOTOMAXIMIZATION TESTING (48 Hour Grading)

Sample: Face Cream IV coded [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
026	0	0
027	0	0
028	0	0
029	0	0
030	Dropped from the study	
031	0	0
032	0	0
033	0	0
034	0	0
035	0	0
036	0	0
037	0	0
038	0	0
039	0	0
040	0	0
041	0	0
042	0	0
043	0	0
044	0	0
045	0	0
046	0	0
047	0	0
048	0	0
049	0	0
050	0	0
051	0	0
052	0	0
053	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 5

RESULTS OF PHOTOMAXIMIZATION TESTING (72 Hour Grading)

Sample: Face Cream IV coded [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	0	0
003	0	0
004	0	0
005	0	0
006	0	0
007	0	0
008	0	0
009	Dropped from the study	
010	0	0
011	0	0
012	0	0
013	Dropped from the study	
014	0	0
015	0	0
016	0	0
017	0	0
018	0	0
019	0	0
020	0	0
021	0	0
022	0	0
023	0	0
024	0	0
025	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 5 (continued)

RESULTS OF PHOTOMAXIMIZATION TESTING (72 Hour Grading)

Sample: Face Cream IV coded [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
026	0	0
027	0	0
028	0	0
029	0	0
030	Dropped from the study	
031	0	0
032	0	0
033	0	0
034	0	0
035	0	0
036	0	0
037	0	0
038	0	0
039	0	0
040	0	0
041	0	0
042	0	0
043	0	0
044	0	0
045	0	0
046	0	0
047	0	0
048	0	0
049	0	0
050	0	0
051	0	0
052	0	0
053	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst/Writer, CIR

Date: March 2, 2021

Subject: Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics

A study on the sensitization potential of a foundation containing 0.08125% Polyquaternium-51 (*acrylo032021wave2_data*) was received from the Council. The maximization test (using sodium lauryl sulfate) involved 25 subjects. During induction, 48-h occlusive patch applications of the undiluted foundation (0.1 ml) were made to the forearm or back. The challenge phase was initiated after a 10-day non-treatment period. A single 48-h occlusive challenge patch application of the undiluted foundation (0.1 ml) was made to a new site on the forearm or back. Results were classified as negative, and this study is enclosed for the Panel's consideration.

Distributed for Comment Only -- Do Not Cite or Quote

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 24, 2021

SUBJECT: Polyquaternium-51

Anonymous. 2002. An evaluation of the contact sensitization potential of a topical coded product in human skin by means of the maximization assay (foundation contains 0.08125% Polyquaternium-51).

Distributed for Comment Only -- Do Not Cite or Quote

[redacted]

FINAL REPORT April 12, 2002

[redacted]

Sample: Foundation coded [redacted]

[redacted]

[redacted]

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

Sponsor: [redacted] product contains 0.08125% Polyquaternium-51

Principal Investigator: [redacted] (Board Certified Dermatologist)

Testing Facility: [redacted]

Protocol: [redacted]

Final Report Date: **April 12, 2002**

[redacted]

Principal Investigator

April 12, 2002
Date

[redacted]

F I N A L R E P O R T

PROTOCOL:

[redacted]

SPONSOR:

[redacted]

[redacted]

SPONSOR STUDY:

Authorization Letter Dated: February 26, 2002

TITLE:

Evaluation of the contact-sensitizing potential of a test agent.

OBJECTIVE:

The objective of this study is to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

TEST MATERIAL:

The test sample, supplied by the sponsor, was a product labeled Foundation coded [redacted] and tested as supplied viz., neat.

TEST PRODUCT ACCOUNTABILITY:

All test samples and materials were received in good condition by our Quality Assurance Department. The test materials and quantities were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). All test materials were stored under ambient conditions in an inaccessible location under the supervision of the investigator.

PRINCIPAL INVESTIGATOR:

[redacted] (Board Certified Dermatologist)

Medical Director, [redacted]

[redacted] **TECHNICIANS**:

[redacted] (Patcher)

[redacted] (Expert Grader)

STUDY LOCATION:

[redacted]

[redacted]

[redacted]

CONDUCTION DATES:

This study was conducted from March 4, 2002 through April 4, 2002

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics. The criteria for exclusion were:

1 - History of sun hypersensitivity and photosensitive dermatoses

2 - History of drug hypersensitivity or recurrent dermatological diseases

3 - Pregnancy or mothers who are breastfeeding

4 - Scars, moles or other blemishes over the test site which can interfere with the study

5 - Recent sunburn

6 - Subjects receiving systemic or topical drugs or medications, including potential sensitizers within the previous 4 weeks

7 - Other medical conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

INFORMED CONSENT:

After the protocol, reasons for the study, possible associated risks and potential benefits or risks of the treatment had been completely explained, signed, informed subject consent was obtained from each volunteer prior to the start of the study.

Copies of all consent forms are on file at [redacted] Each subject was assigned a permanent identification number and completed a Medical History Form. These forms are also on file at [redacted].

METHOD:

Patches were applied to the upper outer arm, volar forearm or the back of each subject. The entire test was composed of two distinct phases: (1) an Induction phase and (2) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.1ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.1ml of the test material coded [redacted] (Foundation) was applied to the same site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Challenge Phase**:

After a ten day rest period which follows the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.1ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded one hour later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	**GRADES:**	**CLASSIFICATION**:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

RESULTS:

A total of twenty-five (25) healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 13 females and 12 males. Their ages ranged from 19 to 57 years. All 25 subjects completed this investigation as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Foundation and coded [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	KEJ	37	F	B
02	RLW	40	M	B
03	DJW	45	M	B
04	MMK	34	F	C
05	MMM	36	M	C
06	JDJ	43	M	B
07	EVR	57	M	B
08	LBS	52	M	B
09	JRH	23	M	C
10	M-A	22	F	C
11	G-M	44	F	B
12	CMD	20	F	C
13	I-C	52	F	C
14	PKD	25	F	A
15	WMC	38	M	B
16	TAA	52	F	B
17	EJN	51	F	C
18	KMP	46	F	C
19	NSM	21	M	B
20	MJS	34	M	C
21	CDT	42	M	B
22	FAR	19	M	C
23	HAM	50	F	C
24	DMK	19	F	C
25	MJM	52	F	C

A = Asian
B = Black
C = Caucasian

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Foundation coded [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0

Challenge Readings:

48-Hour Reading – April 4, 2002
72-Hour Reading – April 5, 2002

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst/Writer, CIR

Date: March 2, 2021

Subject: Safety Assessment of Saccharide Humectants as Used in Cosmetics

A comment on the Saccharide Humectants report is enclosed (*saccha032021wave2_SEPPIC comments*). The comment provides the basis for a company's opinion that Anhydroxylitol is not part of the Saccharide Isomerate class, and deserves the Panel's consideration.

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Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: January 27, 2021

SUBJECT: Anhydroxylitol

SEPPIC. 2021. SEPPIC position on Anhydroxylitol - CIR report on Saccharide Isomerate.

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To the attention of PCPC

Castres, January 15th, 2021

SEPPIC position on Anhydroxylitol - CIR Report on Saccharide Isomerate

1) Method of manufacture, impurities and composition on all ingredients/ingredient mixtures

We would like to emphasize in the first place that we do not prepare anhydroxylitol as such and that we neither isolate nor purify it from the reaction mixture in which it occurs as a secondary product. The anhydroxylitol is in fact one of the reaction products observed during the manufacture of our cosmetic active ingredient named Aquaxyl™. This ingredient is targeted through a chemical reaction in which Glucose and Xylitol are firstly involved as reactants. This reaction is supported by a common mineral acid catalyst that is neutralised during the work-up of the reaction medium.
To the best of our knowledge and aside from the main chemical product that appears -Xylityl glucoside-, the by-products are unreacted raw materials (xylitol and residual traces of glucose) as well as the above mentioned anhydroxylitol which results from the deshydratation of xylitol under acidic conditions (fructose, arabinose, psicose or other sugars excepted glucose have never been identified as by-products in the reaction medium). After a neutralization step, the reaction products are finally diluted with water. The average final composition is described below:

Detailed composition:

Components	% (Concentration range)
Xylitylglucoside	35 - 50
Anhydroxylitol	24 - 34
Xylitol	5 - 15
Water	15 - 17
Glucose	0 - 5

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2) Relationship between Saccharide Isomerates class and Anhydroxylitol

The INCI name saccharide isomerate is well defined by PCPC as “a carbohydrate complex formed from a base catalyzed rearrangement of a mixture of saccharides.” This type of compounds can be viewed as a part of the very large chemical class of Carbohydrates to which anhydroxylitol belongs to, but this picture needs to be specified. Xylitol and anhydroxylitol are too broadly and vaguely described as saccharides. They are more well defined as some representative chemicals of the more restricted family of sugar alcohols or polyols. They no longer possess the key carbonyl function which determines their reactivity (they are no more prone to support simple oxidation or reduction, that is the reason why they are named non reducing sugars compared to reducing sugars, as glucose for instance) as well as their ability to easily isomerize. Aside from that consideration referring to definitions, some major differences still exist from our perspective between Saccharide isomerate and anhydroxylitol. They are described hereinafter:

Firstly, the aforementioned operating procedure “base catalyzed rearrangement of a mixture of saccharides" does not correspond to the appropriate manufacturing process to produce Aquaxyl™ and anhydroxylitol as a part of it. The formation of anhydroxylitol exclusively needs acidic conditions, as well as thermal activation, to occur. Such reaction conditions lead to an internal deshydratation of Xylitol, the non reducing sugar involved in that case as a reagent. If basic conditions were applied to a reaction mixture containing xylitol, we would never have been able to observe the formation of anhydroxylitol.

Secondly, the list of brand names that are currently covered by such a designation can be related to two significantly different chemical classes: Either the ExoPolySaccharide (EPS) chemical class or saccharides isomerate itself. More precisely in this last case and refering to open information available, the disclosed composition would be based on glucose and fructose: “Saccharide Isomerate is formed by isomerisation of plant derived D-Glucose (...) The 2 main components of the saccharide isomerate are glucose and fructose [1]”.
On one hand, Exopolysaccharides refer to high molecular weight polymers (that can exceed one million Dalton) produced by microorganisms. They are characterized by sugar-based repeating units involving mainly reducing sugars such as Glucose or mannose. Some of these units can be naturally modified by chemical functions as pyruvate, succinate, acetate or phosphate. Anhydroxylitol ($C_5H_{10}O_4$; Molecular weight 134 g/mol) which is a small, well defined molecule has nothing to do with this class of EPS that are high molecular weight polymers partially functionalized.
On the other hand, if we refer to saccharides isomerates defined as isomers of D-glucose or mixtures of glucose and fructose, we can hardly consider that anhydroxylitol is accurately defined by this wording.
It is in fact well known that some base catalyzed smooth rearrangements can occur dealing with reducing sugars as glucose for instance. In such conditions, D-glucose can isomerize in an other reducing sugar such as D-mannose. This type of conversion corresponding to the transformation of a given sugar into another sugar with another stereochemistry is well-known as epimerization. It is worthy to note that non reducing sugars as xylitol (and even more anhydroxylitol) cannot straightforwardly isomerise in another sugar. Furthermore,

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Anhydroxylitol is no more an isomer of xylitol because its molecular formula ($C_5H_{10}O_4$) is no more identical to xylitol one's ($C_5H_{12}O_5$).

To conclude, whatever the chemical composition we are comparing anhydroxylitol (as well as other constituents of Aquaxyl) to, it appears from our perspective that this chemical substance is not part of the saccharide isomerate class, following the given definition as well as considering the chemical compositions currently quoted as "saccharide isomerates".

[1] Product information Data Sheet Pentavitin® vers07 (2015)

We remain at your disposal for further information.

Yours faithfully

Herve ROLLAND, Ph.D.
Head of Sectoral Regulatory Affairs
Air Liquid group international expert in surfactant chemistry

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi Raj
Senior Scientific Writer/Analyst, CIR
Date: March 2, 2021
Subject: Wave 2 – Safety Assessment of Salvia Officinalis (Sage) – derived Ingredients as Used in Cosmetics

Enclosed, please find descriptions of two human repeated insult patch test (HRIPT) summaries, the first of a product containing 0.01% Salvia Officinalis (Sage) Leaf Extract and the second of a product containing 0.015% Salvia Officinalis (Sage) Oil), which were received after the initial mailing of the Draft Report for these ingredients (*saloff032021wave2_data*). The reported maximum use concentrations of these ingredients in leave-on formulations are 0.38% Salvia Officinalis (Sage) Leaf Extract in other skin care preparations and 0.22% Salvia Officinalis (Sage) Oil in face and neck products.

A mask formulation containing 0.01% Salvia Officinalis (Sage) Leaf Extract was tested in an HRIPT in 110 subjects.[1] The test material was applied occlusively for 24 to 48 h; 9 applications were made over a 3-wk induction period. After a 2-wk rest period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24, 48, 72, and 96 h after application. One subject exhibited low-level, mild erythema reactions (0 - 1 score, on a 0 - 4 scale) during induction; no other responses were noted during induction, or during challenge. The researchers concluded that the test material did not induce dermal sensitization.

A mask formulation containing 0.015% Salvia Officinalis (Sage) Oil was tested in an occlusive, modified Draize HRIPT, using 105 subjects.[2] The undiluted test material was applied for 47 to 71 h ; 9 applications were made over a 3-wk induction period. After a 2-wk rest period, a 48-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 1h and 48 h after patch removal. Faint, mild erythematous reactions were observed in in some subjects during induction; no adverse reactions were observed during challenge. The researchers concluded that the test material demonstrated a low potential for dermal irritation and sensitization.

1. Anonymous. 2015. Repeated insult patch test of a mask containing 0.01% Salvia Officinalis (Sage) Leaf Extract. (Unpublished data submitted by Personal Care Products Council on February 17, 2021.)

2. Anonymous. 2020. A modified Draize repeat insult patch test in a shared panel of 100 healthy volunteers, to invesigate the irritation and sensitization potential of 2 test articles following repeated cuatneous patch application (article 2 face mask contains 0.015% Salvia Officinalis (Sage) Oil). (Unpublished data submitted by Personal Care Products Council on February 17, 2021.)

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 17, 2021

SUBJECT: Salvia Officinalis (Sage) Leaf Extract and Salvia Officinalis (Sage) Oil

Anonymous. 2015. Repeated insult patch test of a mask containing 0.01% Salvia Officinalis (Sage) Leaf Extract.

Anonymous. 2020. A modified Draize repeat insult patch test in a shared panel of 100 healthy volunteers, to investigate the irritation and sensitization potential of 2 test articles following repeated cutaneous patch application (article 2 face mask contains 0.015% Salvia Officinalis (Sage) Oil).

[redacted] [redacted]

[redacted]
[redacted] **Panel #15-118** contains 0.01% Salvia Officinalis (Sage) Leaf Extract
Test Material #9: Deep Mask: Code# [redacted]

PURPOSE:	To evaluate the potential of the Test Material, as a result of repeated applications, to induce dermal sensitization in human subjects.
IRB APPROVAL:	Both the [redacted] Standard Protocol #100 and the Informed Consent were approved by the Clarus Institutional Review Board (CIRB) on January 24, 2015. A Sponsor-signed Protocol is retained in [redacted] files.
SPONSOR:	[redacted]
SPONSOR AUTHORIZATION:	September 2, 2015
SAFETY ASSURANCE:	September 3, 2015
PRINCIPAL INVESTIGATOR:	[redacted]
CO-INVESTIGATORS:	
TEST FACILITY:	[redacted]
TEST MATERIAL:	Test Material Deep Mask: Code# [redacted], a beige cream, was received on September 4, 2015, with the following instructions: Test as received; patch occlusively.
SUBJECTS:	A total of 120 subjects were enrolled; 110 subjects completed the test. One subject, #040 ([redacted]), was discontinued due to an Adverse Event. Nine subjects discontinued due to personal reasons. No subject discontinued due to test material reaction.

- continued -

[redacted]

[redacted]

[redacted]

[redacted] **Panel #15-118**

Test Material #9: Deep Mask: Code# [redacted]

METHOD:	This test was conducted according to [redacted] Standard Protocol #100 and [redacted] Standard Operating Procedures (including any Sponsor alterations).
TEST DATES:	September 9, 2015 through October 16, 2015.
SCORING SYSTEM:	See Tables I-II.
RESULTS:	See Tables I-II. During the Induction Phase, one subject exhibited a low-level (±) reaction. During the Challenge, no reactions were exhibited.
CONCLUSION:	In this Repeated Insult Patch Test, Test Material Deep Mask: Code# [redacted], did not induce dermal sensitization in human subjects.
QUALITY ASSURANCE (QA):	The QA Unit performed an in-phase audit of this study.

[redacted]

Co-Investigator (Dermatologist) Project Manager Principal Investigator

Date: 10/20/15

[redacted]

[redacted] **Panel #15-118**

Test Material #9: Deep Mask: Code# [redacted]

SUBJECTS: Each potential subject completed an [redacted] Subject History Form ([redacted] Form:SHF), including relevant medical history. (An updated Subject History Form is secured approximately every two years.) Each accepted subject was assigned a permanent [redacted] Identification Number. No subject was used if he or she exhibited any dermatological or other medical or physical condition that would preclude topical application of the Test Material. Upon enrollment, no subject reported using any medication that would interfere with the sensitization results. No known pregnant nor nursing women were used on this RIPT. No minor subjects were used on this RIPT.

An appropriate clearance period had elapsed since a subject was patched on a Repeated Insult Patch Test (RIPT) or a Photoallergy Test (PA) before being used in this RIPT.

Legally valid written IRB-approved Informed Consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

METHOD: Induction Phase: A webril/adhesive patch (Kendall Healthcare Products Company Patch #4022), or equivalent, was used occlusively. Approximately 0.2 gm of the Test Material was applied to each patch. As per [redacted] Standard Operating Procedures (SOP) ([redacted] Form:SOP/RIPT), the left side of the back was usually the test area for the Induction Phase. The subject's skin was marked with gentian violet surgical marker at the left side of the test site. The test site was recorded on the anatomical diagram of each subject's individual Data Form. In addition, at that time, the prospective placement of the Challenge test site was also recorded on the anatomical diagram.

Each subject was instructed that the patch was to remain in place and kept dry for approximately 24 hours, at which time the patch was to be removed by the subject. An approximately 24-hour period, during which no test material was applied, followed the weekday patch removals; an approximately 48-hour period followed the weekend patch removals.

Each subject returned to [redacted] on the appropriate day. The test site was observed by the [redacted] technician, and the reaction scored and recorded (see **SCORING SYSTEM**, below). The identical test site was then repatched until nine (9) Induction patchings were completed.

In accordance with [redacted] SOP, if a subject was unable to make up a missed patching during the same week, the subject was either patched four days the following week or was patched at the end of the Induction Phase. Any absences and make-up days are noted by the dates on the individual Data Form.

A series of nine (9) Induction patchings was completed over a period of approximately three weeks.

[redacted]

[redacted]

[redacted] **Panel #15-118**

Test Material #9: Deep Mask: Code# [redacted]

METHOD: (continued)

Rest Period: A Rest Period of approximately two weeks followed the last Induction patching; no test material was applied during the Rest Period. Subjects were instructed to notify [redacted] if they experienced any reaction during the Rest Period.

Challenge Phase: At the Challenge Phase, the original Induction test site was observed and each subject queried as to whether any reaction was experienced during the Rest Period. A webril/adhesive patch (Kendall Healthcare Products Company Patch #4022), or equivalent, was used occlusively. Approximately 0.2 gm of the Test Material was applied to each patch. As per [redacted] RIPT SOP, the right side of the back was usually the virgin test site for the Challenge Phase.

As per [redacted] RIPT SOP, the Challenge patch was applied to the virgin site only. Each subject was again instructed to keep the patch on and dry.

Each subject reported to [redacted] approximately 24 hours later (Challenge Reading 1), at which time the patch was removed and the Challenge site scored and recorded by the [redacted] technician. The original test site was also observed. (See **RESULTS**, below.)

Each subject reported to [redacted] at approximately 48 hours (Challenge Reading 2), approximately 72 hours (Challenge Reading 3) and approximately 96 hours (Challenge Reading 4) post-patching for additional observations; reactions were scored and recorded.

SCORING SYSTEM: See Tables I-II. The test sites were scored using the modified scoring scale of the International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27.

RESULTS: See Tables I-II. No serious adverse events related to the Test Material occurred during this test. Erythema, edema, dryness, staining, peeling and hyperpigmentation / hypopigmentation are possible, expected endpoints and not considered Adverse Reactions. This test was conducted under the supervision of a Board-Certified Dermatologist, a Co-Investigator. At Challenge Reading 3, the Dermatologist participated in the scoring of the subjects. A total of 110 subjects completed the test; 38 male and 72 female. The subjects range in age from 19 to 73.

RETENTION: All original Data Forms will be retained at [redacted] for a period of three years, or such other time as may be required by law. A laboratory retainer bottle of the Test Material shall be retained, in ambient conditions, for at least two years, or as required by law. Return or disposal of unused Test Material shall be as per the Sponsor's instructions—to be communicated within 30 days of receipt of this Final Report. [redacted] shall appropriately dispose of any Test Material after six months if no Sponsor instructions have been communicated.

[redacted]

[redacted]

[redacted] Panel #15-118

Test Material #9: Deep Mask: Code# [redacted]

TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS ENROLLED: 120
TOTAL NUMBER OF SUBJECTS COMPLETED: 110

Reaction	Induction Reading									Challenge Reading			
Grade	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**1**	**2**	**3**	**4**
0	117	114	114	113	112	113	113	112	112	111	111	110	110
±	1	1	1	1	1								
1													
1E													
2													
2E													
3E													
4E													
-													
N9R													
Total	118	115	115	114	113	113	113	112	112	111	111	110	110

SCORING SYSTEM:

0 = No visible reaction
± = Faint, minimal erythema
1 = Erythema
2 = Intense erythema, induration
3 = Intense erythema, induration, vesicles
4 = Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E = Edema
- = No reading
N9R = No 9th reading

[redacted]

[redacted]

[redacted] Panel #15-118

Test Material #9: Deep Mask: Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading									Challenge Reading			
					1	2	3	4	5	6	7	8	9	1	2	3	4
1	20301	PG	F	68	0	0	0	0	0	0	0	0	0	0	0	0	0
2	44743	GB	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0
3	43569	NB	F	35	0	0	0	0	0	0	0	0	0	0	0	0	0
4	23640	ND	M	69	0	0	0	0	0	0	0	0	0	0	0	0	0
5	36775	CA	F	54	0	0	0	0	0	0	0	0	0	0	0	0	0
6	29512	DC	F	59	0	0	0	0	0	0	0	0	0	0	0	0	0
7	37261	LC	F	65	0	0	0	0	0	0	0	0	0	0	0	0	0
8	35383	VR	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0
9	43509	LS	F	20	0	0	0	0	0	0	0	0	0	0	0	0	0
10	42114	MM	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0
11	32426	CG	F	40	0	0	0	0	X	X	X	X	X	X	X	X	X
12	35023	VC	M	66	0	0	0	0	0	0	0	0	0	0	0	0	0
13	23899	DS	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0
14	44104	AR	F	50	0	0	0	0	0	0	0	0	0	0	0	0	0
15	31777	YB	F	35	0	0	0	0	0	0	0	0	0	0	0	0	0
16	42744	JB	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0
17	37905	LM	F	26	0	0	0	0	0	0	0	0	0	0	0	0	0
18	43371	SL	F	34	0	0	0	0	0	0	0	0	0	0	0	0	0
19	44744	VD	M	51	0	0	0	0	0	0	0	0	0	0	0	0	0
20	37017	JS	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
21	44501	GJ	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
22	42478	PG	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0
23	43876	KT	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0
24	43368	TD	F	46	0	0	0	0	0	0	0	0	0	0	0	0	0
25	41665	RJ	F	69	0	0	0	0	0	0	0	0	0	0	0	0	0

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[redacted]

[redacted]

[redacted] Panel #15-118

Test Material #9: Deep Mask: Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading									Challenge Reading			
					1	2	3	4	5	6	7	8	9	1	2	3	4
26	44721	AB	M	26	X	X	X	X	X	X	X	X	X	X	X	X	X
27	08301	JD	M	44	0	0	0	0	0	0	0	0	0	0	0	0	0
28	42525	SB	M	54	X	X	X	X	X	X	X	X	X	X	X	X	X
29	39807	WM	M	59	0	0	0	0	0	0	0	0	0	0	0	0	0
30	19907	LM	F	54	0	0	0	0	0	0	0	0	0	0	0	0	0
31	25209	LF	F	46	0	0	0	0	0	0	0	0	0	0	0	0	0
32	40831	BH	M	46	0	0	0	0	0	0	0	0	0	0	0	0	0
33	24372	CJ	F	61	0	0	0	0	0	0	0	0	0	0	0	0	0
34	42448	MB	F	72	0	0	0	0	0	0	0	0	0	0	0	0	0
35	30270	WB	M	58	0	0	0	0	0	0	0	0	0	0	0	0	0
36	35182	GU	F	34	0	0	0	0	0	0	0	0	0	0	0	0	0
37	36176	AU	M	32	0	0	0	0	0	0	0	0	0	0	0	0	0
38	43261	MC	M	48	0	0	0	0	0	0	0	0	0	0	0	0	0
39	38818	EM	M	66	0	0	0	0	0	0	0	0	0	0	0	0	0
40	21666	EP	F	60	0	0	0	0	0	0	0	0	0	0	0	X	X
41	42035	DZ	M	42	0	0	0	0	0	0	0	X	X	X	X	X	X
42	08557	DH	F	50	0	0	0	0	0	0	0	0	0	0	0	0	0
43	43914	KV	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0
44	44738	DP	F	46	0	0	0	0	0	0	0	0	0	0	0	0	0
45	35471	TG	F	44	0	0	0	0	0	0	0	0	0	0	0	0	0
46	40027	TG	F	50	0	0	0	0	0	0	0	0	0	0	0	0	0
47	42274	MZ	F	60	0	0	0	0	0	0	0	0	0	0	0	0	0
48	42695	JJ	M	56	0	0	0	0	0	0	0	0	0	0	0	0	0
49	23278	KW	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0
50	37926	BK	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0

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[redacted]

[redacted]

[redacted] Panel #15-118

Test Material #9: Deep Mask: Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading									Challenge Reading			
					1	2	3	4	5	6	7	8	9	1	2	3	4
51	40970	AS	F	23	0	0	0	0	0	0	0	0	0	0	0	0	0
52	39672	FC	M	56	0	0	0	0	0	0	0	0	0	0	0	0	0
53	19757	BP	F	61	0	0	0	0	0	0	0	0	0	0	0	0	0
54	43029	KB	M	30	0	0	0	0	0	0	0	0	0	0	0	0	0
55	36337	CV	F	64	0	0	0	0	0	0	0	0	0	0	0	0	0
56	10683	DH	F	38	0	0	0	0	0	0	0	0	0	0	0	0	0
57	35559	LD	F	25	0	X	X	X	X	X	X	X	X	X	X	X	X
58	44717	TC	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
59	43834	NM	M	58	0	0	0	0	0	0	0	0	0	0	0	0	0
60	43826	RM	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0
61	39457	CD	F	43	0	0	0	0	0	0	0	0	0	0	0	0	0
62	39709	AF	M	55	0	0	0	0	0	0	0	0	0	0	0	0	0
63	42931	PI	M	46	0	0	0	0	0	0	0	0	0	0	0	0	0
64	29828	SS	F	66	0	0	0	0	0	0	0	0	0	0	0	0	0
65	29602	JP	F	46	0	0	0	0	0	0	0	0	0	0	0	0	0
66	30255	LU	M	31	0	0	0	0	0	0	0	0	0	0	0	0	0
67	41039	RF	M	61	0	0	0	0	0	0	0	0	0	0	0	0	0
68	32442	AD	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
69	40939	BB	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0
70	43902	HC	M	50	0	0	0	0	0	0	0	0	0	0	0	0	0
71	35304	CH	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
72	40444	SD	F	63	0	0	0	0	0	0	0	0	0	0	0	0	0
73	43517	VS	M	65	0	0	0	0	0	0	0	0	0	0	0	0	0
74	41433	MR	F	23	0	0	0	0	0	0	0	0	0	0	0	0	0
75	41390	RF	M	58	0	0	0	0	0	0	0	0	0	0	0	0	0

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[redacted]

[redacted]

[redacted] Panel #15-118

Test Material #9: Deep Mask: Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading									Challenge Reading			
					1	2	3	4	5	6	7	8	9	1	2	3	4
76	44163	HG	M	49	0	0	0	0	0	0	0	0	0	0	0	0	0
77	44453	EG	M	45	0	0	0	0	0	0	0	0	0	0	0	0	0
78	38892	ML	F	54	0	0	0	0	0	0	0	0	0	0	0	0	0
79	34712	LL	M	56	0	0	0	0	0	0	0	0	0	0	0	0	0
80	38699	PT	F	41	0	0	0	0	0	0	0	0	0	0	0	0	0
81	43203	AC	F	65	0	0	0	0	0	0	0	0	0	0	0	0	0
82	43204	AC	M	63	0	0	0	0	0	0	0	0	0	0	0	0	0
83	44161	RF	M	50	0	0	0	0	0	0	0	0	0	0	0	0	0
84	44324	CN	F	73	0	0	0	0	0	0	0	0	0	0	0	0	0
85	37947	GC	F	58	0	0	0	0	0	0	0	0	0	0	0	0	0
86	38726	SL	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0
87	36058	FJ	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0
88	07446	CB	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0
89	39398	RW	M	37	0	0	0	0	0	0	0	0	0	0	0	0	0
90	37725	AA	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0
91	29571	SP	F	41	0	0	0	0	0	0	0	0	0	0	0	0	0
92	29572	FV	M	51	±	±	±	±	±	0	0	0	0	0	0	0	0
93	34457	MG	F	59	0	0	0	0	0	0	0	0	0	0	0	0	0
94	44207	TS	F	49	0	X	X	X	X	X	X	X	X	X	X	X	X
95	26520	PM	F	51	0	0	0	X	X	X	X	X	X	X	X	X	X
96	33376	TT	F	41	0	0	0	0	0	0	0	0	0	0	0	0	0
97	44234	RM	M	58	0	0	0	0	0	0	0	0	0	X	X	X	X
98	44746	YD	M	25	0	0	0	0	0	0	0	0	0	0	0	0	0
99	31765	PM	M	61	0	0	0	0	0	0	0	0	0	0	0	0	0
100	17025	PT	M	63	0	0	0	0	0	0	0	0	0	0	0	0	0

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[redacted]

[redacted]

[redacted] Panel #15-118

Test Material #9: Deep Mask: Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

					Induction Reading									Challenge Reading			
Sub	HRL	Ini	Sex	Age	1	2	3	4	5	6	7	8	9	1	2	3	4
101	42224	AV	F	36	0	0	0	0	0	0	0	0	0	0	0	0	0
102	44773	GC	F	39	0	0	0	0	0	0	0	0	0	0	0	0	0
103	44774	OF	M	37	0	0	0	0	0	0	0	0	0	0	0	0	0
104	36524	CA	F	25	0	0	0	0	0	0	0	0	0	0	0	0	0
105	19027	PF	F	66	0	0	0	0	0	0	0	0	0	0	0	0	0
106	43114	PT	M	27	0	0	0	0	0	0	0	0	0	0	0	0	0
107	40048	JM	F	38	0	0	0	0	0	0	0	0	0	0	0	0	0
108	35528	RG	F	30	0	0	0	0	0	0	0	0	0	0	0	0	0
109	44749	SL	F	21	0	0	0	0	0	0	0	0	0	0	0	0	0
110	44750	ML	F	19	0	0	0	0	0	0	0	0	0	0	0	0	0
111	44775	DL	M	20	0	0	0	0	0	0	0	0	0	0	0	0	0
112	43633	SS	M	57	0	0	0	0	0	0	0	0	0	0	0	0	0
113	44783	JM	M	41	0	0	0	0	0	0	0	0	0	0	0	0	0
114	37838	MC	F	38	0	0	0	0	0	0	0	0	0	0	0	0	0
115	43612	JR	M	22	0	0	0	0	0	0	0	0	0	0	0	0	0
116	44729	KW	M	27	0	X	X	X	X	X	X	X	X	X	X	X	X
117	37513	GM	M	63	0	0	0	0	0	0	0	0	0	0	0	0	0
118	44776	JO	F	43	0	0	0	0	0	0	0	0	0	0	0	0	0
119	44777	JO	F	27	0	0	0	0	0	0	0	0	0	0	0	0	0
120	29307	YR	F	59	0	0	0	0	0	0	0	0	0	0	0	0	0

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[redacted]

[redacted]

[redacted] Panel #15-118

Test Material #9: Deep Mask: Code# [redacted]

SCORING SYSTEM*:

0	=	No visible reaction
±	=	Faint, minimal erythema
1	=	Erythema
2	=	Intense erythema
3	=	Intense erythema, induration, vesicles
4	=	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	=	Edema
DR	=	Dryness
P	=	Peeling
S	=	Staining
^	=	Hyperpigmentation / Hypopigmentation
TR	=	Tape Reaction
C	=	Change of test site
N9R	=	No 9th reading
-	=	No reading
X	=	Discontinued

*International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27. (Modified)

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[redacted]

[redacted] [redacted]

[redacted]

[redacted] Panel #15-118

Test Material #9: Deep Mask: Code# [redacted]

QUALITY ASSURANCE MEMORANDUM

This Final Report was reviewed for accuracy and conformity with both [redacted] Standard Protocol #100 and [redacted] Standard Operating Procedures (including any Sponsor alterations) and any written communication from the Sponsor.

Inspections were accomplished by a random sampling approach and reported to the Project Manager and the Principal Investigator immediately following their completion.

Any known protocol deviations have been noted in the Final Report and/or Individual Data Form.

The raw data for this study are retained at [redacted]

[redacted]

Quality Assurance Manager

QUALITY ASSURANCE UNIT

Dated: 10/20/15

This report is only submitted for the use of the party to whom it is addressed, and neither it nor the name of our company or any member of our staff may be used in connection with any advertising, promotional material, or sale without our written authorization.

[redacted]

SUMMARY REPORT

A MODIFIED DRAIZE REPEAT INSULT PATCH TEST IN A SHARED PANEL OF 100 HEALTHY VOLUNTEERS, TO INVESTIGATE THE IRRITATION AND SENSITISATION POTENTIAL OF 2 TEST ARTICLES FOLLOWING REPEATED CUTANEOUS PATCH APPLICATIONS

CONDUCTED ACCORDING TO [redacted]

[redacted]. Study Number: [redacted]

TEST ARTICLES: **1.** [redacted]
2. Bubbling Face Mask - #[redacted]
product contains 0.015% Salvia Officinalis (Sage) Oil

Confidentiality Statement:
This confidential document is the property of [redacted] and [redacted]. No information contained herein may be disclosed without the prior written approval of [redacted] or [redacted]

Please Note: [redacted]

Prepared for:

[redacted]

Prepared by:

[redacted]

Draft Report: 22nd September 2020
Final Report: 6th October 2020

[redacted]

6th October 2020

A MODIFIED DRAIZE REPEAT INSULT PATCH TEST IN A SHARED PANEL OF 100 HEALTHY VOLUNTEERS, TO INVESTIGATE THE IRRITATION AND SENSITISATION POTENTIAL OF 2 TEST ARTICLES FOLLOWING REPEATED CUTANEOUS PATCH APPLICATIONS

CONDUCTED ACCORDING TO [redacted]

[redacted] Study Number: [redacted]

I declare that the following report constitutes a true and faithful account of the procedures adopted and the results obtained in the performance of this study. The aspects of the study conducted by [redacted] were performed, where relevant, in accordance with the principles of Good Clinical Research Practice.

[redacted]

[redacted]

[redacted]

QUALITY ASSURANCE STATEMENT

This report has been audited and is considered to be an accurate description of the methods used and an accurate presentation of the data obtained during the conduct [redacted]

[redacted]

(Quality Assurance)

Date 6th October 2020

PCR COPY

TABLE OF CONTENTS

PCR CORP

KEY STUDY PERSONNEL AND RESPONSIBILITIES

Key Personnel	General Responsibilities
Principal Investigator (PI) [redacted]	The Principal Investigator (PI) responsible for ensuring sufficient resources were available to conduct the study and was responsible for the study design, review of the study protocol, authorization and summary report.
Study Supervisor (SS) [redacted]	The Study Supervisor (SS) responsible for the conduct of the study on a daily basis.
Project Manager (PM) [redacted]	The Project Manager (PM) involved with the study authorization, compilation of study results and summary report.
Sponsor Contact [redacted]	

PCR CORP

INTRODUCTION AND OBJECTIVE

The objective of this study was to investigate the irritation and sensitisation potential of cosmetic test articles, in a shared panel of 100 healthy volunteers by means of repeated cutaneous occlusive patch applications based on the modified Draize method of Jordan and King (1977)[1] to support claims such as "Dermatologically Tested", "Clinically Tested", "Kind to Skin" and "Safe for Skin".

MATERIALS AND METHODS

1. STUDY DESIGN

The study was conducted single blind, at a single center according to Master Protocol: [redacted] (See Appendix 3 for Study Authorization).

The test articles were patched under occlusive conditions using Finn chambers or equivalent occlusive patches. A total of nine inductions patches worn for 47 hours or 71 hours (patching occurred Mondays, Wednesdays and Fridays) for three weeks (a make-up day was allowed to ensure subjects had all 9 induction patches). Subjects had a rest period of 14 days. Challenge patches were applied for 48 hours and readings were made 1 hour and 48 hours post removal.

2. TEST MATERIALS

2.1. TEST ARTICLES

The test articles were supplied by the Sponsor and labelled as follow:

TA#	Test Article Name/Description	ID Code (Batch/Lot #)	Dilution/special handling*
1	[redacted]	[redacted]	[redacted]
2	Bubbling Face Mask	#[redacted]	

3. STUDY ETHICS

3.1. DECLARATION OF HELSINKI

The study conformed to the requirements of the 1964 Declaration of Helsinki and its subsequent amendments (World Medical Association; 2013)[2].

3.2. INDEMNITY PROVISION

The Sponsor was responsible, without regard to legal liability, and shall indemnify [redacted], or any of their respective officers or employees in the event of claims for compensation from subjects suffering injury or other deterioration in health or well-being as a result of participation in this study, except and insofar as such claims arise as a result of any negligent act or omission on the part of [redacted] employees or any persons undertaking or involved in the study by arrangement with [redacted].

3.3. ICH GCP

The study was conducted in accordance with applicable International Council for Harmonization. 2016. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)[3] in as much as they apply to cosmetic and consumer product testing/research.

4. QUALITY ASSURANCE

The study was conducted according to the Sponsor Authorization, the master protocol, the Standard Operating Procedures of [redacted] and according to the applicable ICH Guidelines on Good Clinical Practice, and other recognised guidelines. An audit of the final report was completed, for accuracy and completeness of presentation. Additionally, the study may be subject to the following Quality Assurance procedures:

- Review of protocol and protocol amendments for completeness, clarity and adequacy.
- Inspection and/or audit of critical phases of study conduct for compliance with protocol and [redacted] procedures.

[redacted] Quality Assurance would have informed [redacted] management of any findings that may have affected the integrity of the study.

5. RETENTION OF DATA

All raw data generated by [redacted] during the course of the study, including the sponsor authorization form and final summary report, will be retained in the [redacted] Archive for a minimum period of three years from study completion as is [redacted] policy for cosmetic products. In the event of original data being transferred to the Sponsor at their request, exact copies will be so retained. At no time will archived data be destroyed without prior written approval of the Sponsor. All study data will be available at any time, by appointment, for inspection by the Sponsor or their authorized representative. The study master protocol will be archived and retained indefinitely at [redacted].

6. REFERENCES

1. Jordan W.P. and King S. E. (1977) Contact Dermatitis 3, 19-26.

2. World Medical Association (2013). "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects". JAMA 310 (20): 2191–2194. doi:10.1001/jama.2013.281053

3. ICH E6_R2, INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE, Current Step 4 version dated 9 November 2016

PCR CORP

RESULTS

1 LOCATION AND DATES OF THE STUDY

The study was performed at [redacted] located in [redacted] between w/c 3rd September 2020 and w/e 11th September 2020.

2 SUBJECTS

111 male and female subjects were enrolled into the study. 105 subjects completed the study. The age, gender and racial composition of these subjects is presented in table in Appendix 2.

3 ADVERSE EVENTS, ADVERSE REACTIONS AND SUBJECTS NOT COMPLETING THE STUDY, DEVIATIONS

No adverse events or reactions were reported.

6 subjects withdrew for personal reasons.

There were no deviations that occurred during the conduct of the study.

4 ASSESSMENTS

Individual reactions to the test articles are presented in Appendix 1.

As demonstrated by the individual skin responses to the test articles:

[redacted]

Test Article 2 – Bubbling Face Mask - [redacted] elicited faint, mild erythematous reactions during the Induction phase of the study.

There were no questionable reactions observed during the Challenge Phase (Days 38 and 40) by any of the subjects to any of the test articles. These results support the assessment that under the conditions of the study, the test articles have demonstrated a low potential for irritation and sensitization.

CONCLUSIONS

The test articles can be considered as safe for use under the conditions of the study, and claims such as, "Dermatologically Tested", "Clinically Tested", "Kind to Skin" and "Safe for Skin" are substantiated.

PCR CORP

EXAMPLE RESULTS
TEST ARTICLE 2 – Bubbling Face Mask

Number	Code	2	3	4	5	6	7	8	9	10	MU	1 hour	47 hour
1	2	0	0	0	0	0	0	0	0	0		0	0
2	2	0	0	0	0	0	0	0	0	0		0	0
3	2	0	0	0	0	0	0	0	0	0		0	0
4	2	0	0	0	0	0	0	0	0	0		0	0
5	2	0	0	0	0	0	0	0	0	0		0	0
6	2	0	0	0	0	0	0	0	0	0		0	0
7	2	0	0	0	0	0 A	0 A	0 A	0 A	0 A		0	0
8	2	0	0	0	0	0	0	0	0	0		0	0
9	2	0	0	0	0	0	0	0	_	0	0	0	0
10	2	0	0	0	0	0	0	0	0	0		0	0
11	2	0	0	0	0	0	0	0	0	0		0	0
12	2	0	0	0	0	0	_	0	0	0	0	0	0
13	2	0	0	0	0	0	0	0	0	0		0	0
14	2	0	0	0	0	0	0	0	0	0		0	0
15	2	0	0	0	0	0	0	0	0	0		0	0
16	2	0	0	0	0	0	0	0 A	0 A	0 A		0	0
17	2	0	0	0	0 A	0 A	0 A	1 A	1 A	1 A		0	0
18	2	0	0	0	0	0	0	0	0	0		0	0
19	2	0	0	0	0	0	0	0	0	0		0	0
20	2	0	0	_	0	0	0	0	0	0	0	0	0
21	2	0	0	0	0	0	_	0	D/O	D/O		D/O	D/O
22	2	0	0	0	0	0	0	0	0	0		0	0
23	2	0	0	0	0	0	0	0	0	0		0	0
24	2	0	0	0	0	0	0 A	0 A	0 A	0 A		0	0
25	2	0	0	0	0	0 A	0 A	0 A	1 A	1 A		0	0
26	2	0	0	0	0	0	0	0	0	0		0	0
27	2	0	0	0	0	0	0 A	0 A	0 A	0 A		0	0
28	2	0	0	0	0	0	0	0	0	0		0	0
29	2	0	0	0	0	0	0	0	0	0		0	0
30	2	0	0	0	0	0	0	0	0	0		0	0
31	2	0	0	0	0	0	0 A	0 A	0 A	0 A		0	0
32	2	0	0	0	0	0	0	0	0	0		0	0
33	2	0	0	0	0	0	0	0	0	0		0	0
34	2	0	0	0	0	0	0	0	0	0		0	0
35	2	0	0	0	0	0	0	0	0	0		0	0
36	2	0	0	0	0	0	0	0	0	0		0	0
37	2	0	0	0	_	0	0 A	0 A	D/O	D/O		D/O	D/O
38	2	0	0	0	0	0	0	0	0	0		0	0
39	2	0	0	0	0	0	0	0	0	0		0	0
40	2	0	0	0	0	0 A	0 A	0 A	1 A	1 A		0 A	0
41	2	0	0	0	0	0	0	0	0	0		0	0
42	2	0	0	0	0	0	0	0	0	0		0	0
43	2	0	0	0	0	0	0	0	0	0		0	0
44	2	0	0	0	0	0	0	0	0	0		0	0
45	2	0	0	0	0	0	0	0 A	0 A	0 A		0	0
46	2	0	0	0	0	0	0	0	0	0		0	0
47	2	0	0	0	0	0	0	0	0	0		0	0
48	2	0	0	0	0	0	0	0	0	0		0	0
49	2	0	0	0	0	0	0	0	0	0		0	0
50	2	0	0	0	_	0	0	0	0	0	0	0	0
51	2	0	0	0	0	0	0	0	0	0		0	0
52	2	0	0	0	0	0	0	0	0	0		0	0
53	2	0	0	0	0	0 A	0 A	1 A	1 A	1 A		0	0
54	2	0	0	0	0	0	0 A	0 A	0 A	0 A		0	0
55	2	0	0	0	0	0	0	0	0 A	0 A		0	0

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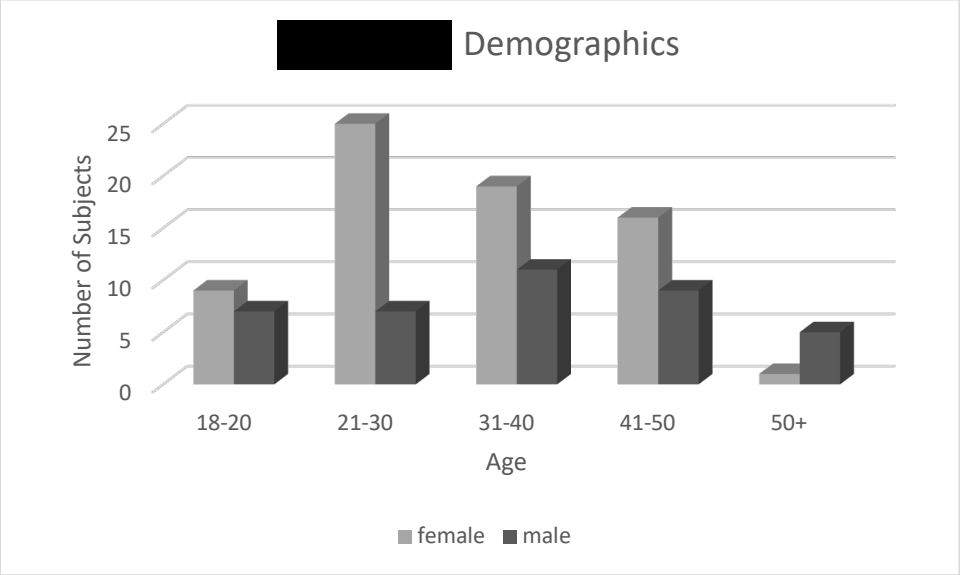
56	2	0	0	0	0		0		0		0		0		0				0	0
57	2	0	0	0	0		0		0		0		0		0				0	0
58	2	0	0	0	0		0	A	0	A	0	A	0	A	0	A			0	0
59	2	0	0	0	0		0		0		0		0		0				0	0
60	2	0	0	0	0		0		0		0		0		0				0	0
61	2	0	0	0	0		0		0	A	0	A	0	A	0	A			0	0
62	2	0	0	_	0		0		0		0		0		0		0		0	0
63	2	0	0	0	0		0		0		0		1		1				0	0
64	2	0	0	0	_		0		0		D/O		D/O		D/O				D/O	D/O
65	2	0	0	0	0		0		0		0		0		0				0	0
66	2	0	0	0	0		0		0		0		0	A	0	A			0	0
67	2	0	0	0	0		0		0		0		0		0				0	0
68	2	0	0	0	0		0		0		0		0		0				0	0
69	2	0	0	0	0		0		0		0		0		0				0	0
70	2	0	0	0	0		0		0		0		0		0				0	0
71	2	0	0	0	0		0	A	0	A	0	A	1	A	1	A			0	0
72	2	0	0	0	0	A	0	A	0	A	0	A	0	A	0	A			0	0
73	2	0	0	0	0		0		0		0		0		0				0	0
74	2	0	0	0	0		0		0		0		0		0				0	0
75	2	0	0	_	0		0		0		0		0		0		0		0	0
76	2	0	0	0	0		0		0		0		0		0				0	0
77	2	0	0	0	0		0		0		0		0		0				0	0
78	2	0	0	0	0		0		0		0		0		0				0	0
79	2	0	0	0	0		0		0		0		0		0				0	0
80	2	0	0	_	D/O		D/O		D/O		D/O		D/O		D/O				D/O	D/O
81	2	0	0	0	0		0	A	0	A	0	A	0	A	0	A			0	0
82	2	0	0	0	0		0		0		0		0		0				0	0
83	2	0	0	0	0		0		0		0		0		0				0	0
84	2	0	0	0	0		0		0		0		0		0				0	0
85	2	0	_	0	0		0		0		0		0		0		0		0	0
86	2	0	0	0	0		0		0		0	A	0	A	0	A			0	0
87	2	0	0	0	0		0		0		0		0		0				0	0
88	2	0	0	0	0	A	0	A	0	A	0	A	0	A	0	A			0	0
89	2	0	0	0	0		0		0		0		0		0				0	0
90	2	0	0	0	0		0		0		0		0		0				0	0
91	2	0	0	0	0		0		0		0		0		0				0	0
92	2	0	0	0	0		0		0		0		0		0				0	0
93	2	0	0	0	0		0		0		0		0		0				0	0
94	2	0	0	0	0		0		0	A	0	A	0	A	0	A			0	0
95	2	0	0	0	0		0		0		0		0		0				0	0
96	2	0	_	D/O	D/O		D/O		D/O		D/O		D/O		D/O				D/O	D/O
97	2	0	0	0	0		_		0		0		0		0		0		0	0
98	2	0	0	0	0		0		0		0		0		0				0	0
99	2	0	0	0	0		0		0		0		0		0				0	0
100	2	0	0	0	0		0		0		0		0		0				0	0
101	2	0	_	0	0	A	0	A	0	A	0	A	0	A	0	A	0	A	0	0
102	2	0	0	0	0		0		0		0		0		0				0	0
103	2	0	0	0	0		0		0		0		0		0				0	0
104	2	0	0	0	0		0		0	A	0	A	0	A	0	A			0	0
105	2	0	0	0	_		0		0		0		0		0		0		0	0
106	2	0	0	0	0		0		0		0		0		0				0	0
107	2	0	0	0	0		0		_		0		D/O		D/O				D/O	D/O
108	2	0	0	0	0		0		0		0		0		0				0	0
109	2	0	0	0	0		0		0		0		0		0				0	0
110	2	0	0	0	0	A	0	A	0	A	0	A	0	A	0	A			0	0
111	2	0	0	0	0		0		0		0		0		0				0	0
MEAN		0.00	0.00	0.00	0.00		0.00		0.00		0.02		0.06		0.06		0.00		0.00	0.00
STDEV		0.00	0.00	0.00	0.00		0.00		0.00		0.14		0.23		0.23		0.00		0.00	0.00

APPENDIX 2: SUBJECT DEMOGRAPHICS



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Analyst/Writer, CIR
Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist
Date: March 2, 2021
Subject: Comments from Women's Voice for the Earth on Silicates as Used in Airbrush Cosmetics

Enclosed are two letters received January 21 and February 24, 2021 from Ms. Alexandra Scranton, Director of Science and Research, Women's Voices for the Earth (WVE), presenting concerns on consumer use of airbrush makeup, as well as comments on Silicates as used in airbrush cosmetics.

According to 2021 US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) data, the use of Magnesium Aluminum Silicate in foundation makeup bases has been reported (see the Cosmic Use section of the amended Silicates report). It has now come to the attention of the Panel that Magnesium Aluminum Silicate is reported to be listed on formulation packaging as an ingredient being used in consumer products which can be applied via airbrush technology. However, information specific to the use of foundations, or any other product type, via the use of airbrush technology was not reported to the Panel in response to the industry survey, and would not be evident in the VCRP; therefore, details of this type of use (e.g., classification as a cosmetic, drug, device, etc.) are unknown.

In addition, scientific data searching efforts have largely failed in identifying spray characteristics of airbrush devices. As airbrush technology has become increasingly popular for cosmetic use, unfortunately, little guidance was developed by regulatory authorities in America, or the European Union (EU), to address safety concerns relating to potential exposure of the consumer via the inhalation route. The FDA only classifies the airbrush as a medical device, which is applied in dental restorations by using air-driven particles to roughen the tooth surface.[1] In another case involving similar application of a spray gun, the FDA recommends people use protection over the eyes, nose and lips to prevent contact with tanning mist:[2,3] use of small eye shields and nostril filters is suggested, as is covering the lips with lip balm or petroleum jelly. Unfortunately, the FDA does not provide an opinion on cosmetic airbrush usage, and it is not clear whether similar protective accessories (e.g., airbrush nose filter designed for fine particles filtration) are marketed and used by consumers for applying airbrush makeup products. As WVE pointed out in comments, duration of airbrush makeup application is considerably longer than application of other cosmetic aerosol products, and as such, consumers may take protective measures to reduce chemical exposure to body areas covered by mucous membranes, including the lips, nose, and areas in and around the eye. If so, protective measures should be considered as an additional factor determining the inhalation exposure under diverse airbrush in-use conditions.

The Panel has been informed that there are nano-enabled liquid powder cosmetics available on the market, which are thinner than most liquid cosmetics and are specially designed to be dispersed through low pressure aerosol technologies such as airbrush system. A robust understanding of the special characteristics of aerosolized liquid powder cosmetics is key to conducting inhalation risk assessment. The Panel considered two toxicological simulation studies that have demonstrated that a fraction of airborne particles/agglomerates resulting from airbrush delivery are respirable (i.e., aerodynamic equivalent diameter < 10 µm).[4,5] However, the Panel noted a lack of information on aerosol particle size distributions when these ingredients are used with cosmetic airbrush devices. Furthermore, the Panel noted particle characteristics such as size, morphology, and surface chemistry are unique to each aerosol and can affect their deposition in the respiratory tract and their interactions with biological organisms.

In the letter dated January 21, 2021, WVE provided some background information regarding the airbrush makeup formulation types and various applications on face, eyeshadow or lips, which were summarized from diverse manufacture webpages or commercial video websites. However, none of these information sources provide specific scientific parameters for performing a robust inhalation risk assessment. Further, the reliability of facts submitted by WVE with respect to airbrush ingredients warrants additional validation from the scientific perspective. For instance, WVE stated in comments: "There are two main formula types of airbrush makeup, one is silicone-based and the other is water based…Both types of airbrush makeup **commonly include** talc,

mica, titanium dioxide (TiO_2) and other colorants." Even assuming it is the case that airbrush formulations have always contained TiO_2, talc, mica and other colorants, more complexity is created in characterizing the toxicity profiles of the inhaled particles (with an aerodynamic diameter of < 10 μm), which comprise a composite mixture of substances. Note that the nano form of TiO_2 is classified as a "Carcinogen Category 2 (inhalation)" by the European Commission and is restricted to be used in applications that may lead to exposure of the end-user's lungs by inhalation.[6] In the newly updated Scientific Committee on Consumer Safety (SCCS) Opinion on TiO_2 used in cosmetic products (2020), the lung exposure to nano content of TiO_2 has been measured in various consumer products, such as hair styling aerosol sprays and loose powders for face makeup; however, TiO_2-containing airbrush cosmetics were not covered therein.[6] Being considered as aerosolized nano-enabled consumer products, airbrush devices can cause nanoparticle inhalation exposures and thus pose serious public health concerns.[4,5] In this regard, safety application of airbrush technology in cosmetics warrants more extensive investigation, which is outside the purview of the CIR review process.

Although the Panel is now aware, through alternative sources, that some ingredients (e.g., Magnesium Aluminum Silicate, Dimethicone, and Methicone) are used in consumer products which are applied via airbrush devices, there seems to be more unknown than known. There are no use data, whether frequency of use from the VCRP or use data from the industry, specific to these airbrush uses, as airbrush use is not even a category of use data that CIR receives. Furthermore, risk assessments for other use types that result in incidental inhalation exposure have some standardized, ordinary, consumer use practices basis. Consumer use practices data for these airbrush uses have yet to be forthcoming.

In a similar situation, regarding the use of dihydroxyacetone (DHA) in commercial spray "tanning" booths, it has been stated that [3]

> …the use of DHA in "tanning" booths as an all-over spray has not been approved by the FDA, *since safety data to support this use has not been submitted* to the Agency for review and evaluation. When using DHA-containing products as an all-over spray or mist in a commercial spray "tanning" booth, it may be difficult to avoid exposure in a manner for which DHA is not approved, including the area of the eyes, lips, or mucous membrane, or even internally.
>
> Consequently, FDA advises asking the following questions when considering commercial facilities where DHA is applied by spraying or misting:
>
> - Are consumers protected from exposure in the entire area of the eyes, in addition to the eyes themselves?
> - Are consumers protected from exposure on the lips and all parts of the body covered by mucous membrane?
> - *Are consumers protected from internal exposure caused by inhaling or ingesting the product?*
>
> If the answer to any of these questions is "no," the consumer is not protected from the unapproved use of this color additive. *Consumers should request measures* to protect their eyes and mucous membranes and *prevent inhalation*.

Since the safety data (frequency of use data, concentration of use data, device parameters inclusive of particle size exposures, etc.) to support *airbrush use* have not been submitted, should the Panel deem such use as "use not supported" (i.e. an insufficient data conclusion now, followed by "use not supported" when the data submission clock runs out in 2 yr)?

References

1. U.S. Food and Drug Administration (FDA). Product Classification-Airbrush. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=1324. Updated 03/01/2021. Accessed 03-02-2021.
2. U.S. Food and Drug Administration (FDA). Tanning Products. https://www.fda.gov/radiation-emitting-products/tanning/tanning-products. Updated 04/26/2019. Accessed 02-26-2021.
3. U.S. Food and Drug Administration (FDA). Sunless Tanners & Bronzers. https://www.fda.gov/cosmetics/cosmetic-products/sunless-tanners-bronzers. Updated 08/24/2020. Accessed 02-25-2021.
4. Pearce K, Gray N, Gaur P, et al. Toxicological analysis of aerosols derived from three electronic nicotine delivery systems using normal human bronchial epithelial cells. *Toxicol In Vitro.* 2020;69:104997.
5. Pearce KM, Okon I, Watson-Wright C. Induction of Oxidative DNA Damage and Epithelial Mesenchymal Transitions in Small Airway Epithelial Cells Exposed to Cosmetic Aerosols. *Toxicol Sci.* 2020;177(1):248-262.
6. Scientific Committee on Consumer Safety (SCCS). Opinion on Titanium dioxide (TiO_2) used in cosmetic products that lead to exposure by inhalation. 2020. SCCS/1617/20.

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WOMEN'S VOICES FOR THE EARTH
OUR HEALTH. OUR FUTURE. TOXIC FREE.

February 16, 2021

To the CIR:

On January 21, 2021, I submitted comments further explaining my concerns about the inhalation potential of airbrush cosmetics. These comments included information that airbrush cosmetic products include silicates that are being evaluated at the March 2021 meeting. Yet the comments do not appear to have been included with the Silicates materials posted on the CIR website, and information about airbrush cosmetics has not been incorporated into the draft discussion.

To clarify the relevance of those comments:

Specifically, two ingredients included in the Silicates assessment, **magnesium aluminum silicate** and **kaolin** are commonly found in airbrush cosmetics. In one case, magnesium aluminum silicate was listed as the second ingredient in the product (after water), indicating it is a significant component of the product.

> **Art of Air Airbrush makeup**
>
> **HD Makeup Foundation -** *Water (Aqua), Magnesium Aluminum Silicate, Cellulose Gum, Propylene Glycol, Triethanolamine, Diazolidinyl Urea. May Contain: Titanium Dioxide (CI 77891), Ultramarines (CI 77007), Iron Oxides, Disodium Distyrylbiphenyl Disulphonate, Mica (CI 77019), Luminescent Zinc Sulfide, Talc.*
>
> *Source: https://www.artofair.com/pages/ingredients*

The use of the silicate ingredients, magnesium aluminum silicate and **kaolin in airbrush cosmetics should be mentioned in the Use (Cosmetic) section of the Silicates safety assessment**.

Similarly, my airbrush cosmetic comments addressed my concern that the CIR uses boilerplate language indicating that most cosmetic sprays have particle sizes that are unlikely to be inhaled deeply into the lungs. The Pearce et.al. study[1] found to the contrary, that airbrush cosmetic sprays emit a majority of particles that are smaller than 10 microns, and thus are potentially inhalable deep into the lungs. The Silicates draft still contains the boilerplate language on inhalation which states:

[1] Pearce K, Goldsmith WT, Greenwald R, Yang C, Mainelis G, Wright C. Characterization of an aerosol generation system to assess inhalation risks of aerosolized nano-enabled consumer products. Inhal Toxicol. 2019;31(9-10):357-367. doi:10.1080/08958378.2019.1685613

> "*Concerning final consumer product formulations (typically a mixture of ingredients), the Panel has noted that in practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump spray. Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.*"

This statement is not accurate for airbrush cosmetics (which are "cosmetic sprays") and should be removed from the Silicates document.

It was clear from the discussion of Methicones at the December 2020 meeting, that the Expert Panel members were interested in having more information about airbrush cosmetics, as they were unable to determine the safety of methicones as used in airbrush cosmetics. The panel also mentioned that a larger discussion was needed around the CIR's respiratory exposures boilerplate language. While I see that Methicones are not on the agenda for the March meeting, it appears the discussion around airbrush concerns is still needed given that these same issues are relevant and concerns have been raised for the Silicates ingredients which are on the agenda.

I would like to resubmit my comments from January 21st on airbrush concerns specifically to be addressed with the Silicates safety assessment at the March meeting.

Thanks for your consideration of these comments.

Alexandra Scranton
Director of Science and Research
Women's Voices for the Earth

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WOMEN'S VOICES FOR THE EARTH
OUR HEALTH. OUR FUTURE. TOXIC FREE.

January 21, 2021

To the CIR:

At the December 2020 CIR Expert Panel meeting, the topic of airbrush makeup was brought up during the discussion of Methicones. It appeared from the discussion, that there was insufficient information available to and minimal familiarity among the Expert Panel members about airbrush makeup products, uses and exposures. I am sending these comments to help better inform the Expert Panel on airbrush makeup.

Why are we concerned about airbrush makeup?

Airbrush makeup can be inhaled deeply into the lungs:

A significant health concern with airbrush makeup (specifically addressed in the Pearce et.al. study[i1]) is that these products could have significant potential for inhalation of very small particles deep into the lungs.

This data from this study contradicts a long-held assumption of the Expert Panel that

> *"in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount."*

Similarly, the Expert Panel uses boilerplate language about the duration of exposure such as

> *"Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredient is used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects."*

This language also does not apply to airbrush makeup application in which the exposure in the breathing zone could not be considered small or incidental.

An additional potential health concern is eye irritation, as airbrush eye makeup application can involve long durations of spraying around the eyes and eyelashes.

[1] Pearce K, Goldsmith WT, Greenwald R, Yang C, Mainelis G, Wright C. Characterization of an aerosol generation system to assess inhalation risks of aerosolized nano-enabled consumer products. Inhal Toxicol. 2019;31(9-10):357-367. doi:10.1080/08958378.2019.1685613

It is important for the safety and health of airbrush makeup users, that the Expert Panel understand and address this category of cosmetics specifically, as it is a category with a vastly different exposure profile that other types of cosmetics usually considered by the Expert Panel. Currently, safety consideration of airbrush makeup is a significant gap in the Expert Panel's expertise, which represents a potential hazard for consumers.

The Basics of Airbrush Makeup:

Airbrush makeup is a liquid product, intended solely for use with an airbrush makeup applicator. A bottle of airbrush makeup comes in a dropper bottle that usually looks like this:

The airbrush makeup applicator (airbrush gun) is a device that sprays the airbrush makeup in a very fine mist onto the face and/or body. An airbrush applicator looks like this:

Airbrush makeup comes in various forms, which can be used daily, including:

Primer/Moisturizer
Foundation
Blush/Bronzer
Eyeshadow
Concealer
Colors (for lips and special effects makeup)
Tanning

No longer just a professional product, airbrushing is commonly done at home:

Airbrush makeup has been around for many decades – but originally was used mostly in professional makeup for photo shoots and films. In the last decade however, airbrush makeup, accessories and online tutorials have made airbrush makeup available to the average consumer doing their makeup at home. Several manufacturers have designed (and priced) their products specifically for those doing their makeup at home. And cosmetic bloggers have touted the benefits of wearing airbrush makeup daily.

Example quotes from manufacturers and cosmetic bloggers:

"It's easy to learn how to use an airbrush, and the Luminess system was specifically designed to be used daily in the comfort of your own home."

https://www.luminessair.com/howtovideos

"Tickled Pink Airbrush Cosmetics is a family owned and operated company based in Oregon with a very simple mission: to provide an affordable airbrush system that the average person can purchase and to keep the makeup prices reasonable without sacrificing quality."

https://www.tickledpinkairbrush.com/pages/airbrush-makeup-guru-independent-review.html

"*Airbrushing does take a little time to get used to, but once you get the hang of it, it's surprisingly quick and easy to apply and can offer a lot of benefits for those that use it on a day-to-day basis*."

https://easyairbrushmakeup.com/benefits-of-wearing-airbrush-makeup-everyday/

*"Airbrush makeup sounds like one of those very ~extra~, very next-level things only reserved for professional makeup artists and celebrities. And, to be honest, that used to be true. But in the last few years, airbrush makeup has become a pretty common tool for us ~*ReGuLaR*~ people too (even the newbies!), thanks to the creation of really excellent, easy-to-use airbrush makeup kits you can use at home."* Cosmopolitan Magazine, Jan 2020.

https://www.cosmopolitan.com/style-beauty/beauty/g30475236/best-airbrush-makeup-kits/

Duration of airbrush makeup application is considerably longer than application of other cosmetic aerosol products:

Unlike many other cosmetic aerosol products which might be sprayed for just a few seconds at a time, away from the face, airbrushing can involve minutes of continuous spraying directly to the face. The total duration depends on the number of products/layers of makeup applied, as well as the skill/familiarity of the applicator. (As folks become more comfortable applying airbrush makeup, it can go much more quickly.) As one example of the estimated time to apply airbrush makeup, the Pearce et.al. study measured exposures from a 20 minute airbrush application to a mannekin head.

The best way to understand airbrush makeup application is to watch it being done – as can be done in numerous online video tutorials. Below is a selection of short tutorials showing a variety of ways airbrush makeup is applied.

How does airbrushing work?: https://www.youtube.com/watch?v=09VQLZoXmIk&feature=emb_logo

How to apply airbrush foundation: https://www.youtube.com/watch?v=Ai-i5J2RAyo&feature=emb_logo

(Note: The airbrush gun used in this video is made by Luminess, the same airbrush applicator used in the Pearce et.al. study.)

Applying airbrush moisturizer: https://www.youtube.com/watch?v=OVMJtF9YEeY

Applying airbrush eyeshadow: https://www.youtube.com/watch?v=HzVpAm2g5xY
(airbrushing begins at 1:09)

Applying airbrush makeup to lips: https://www.youtube.com/watch?v=ILGJziGzqzQ
(airbrushing begins at 0:55)

It is often recommended to apply airbrush makeup in multiple sequential layers. For example, the Tickled Pink airbrush company recommends a multi-step process involving spraying on the following layers:

Moisturizer, Concealer, Foundation, Bronzer, Blush, Eye Shadow (multiple colors), and WaterProof Sealant. https://www.tickledpinkairbrush.com/pages/tickled-pink.htmlfirst-steps-tutorial-video/

Airbrush Makeup Ingredients:

There are two main formula types of airbrush makeup, one is silicone-based and the other is water-based.

Silicone-based airbrush makeup commonly includes methicones, siloxanes and silicates among other ingredients, while water-based airbrush makeup commonly includes water, propylene glycol, acrylates octylacrylamide copolymer, magnesium aluminium silicate and preservatives such as methyisothiazolinone. Both types of airbrush makeup commonly include talc, mica, titanium dioxide and other colorants.

Common airbrush makeup ingredients currently or recently assessed by the CIR:

Methicones:

Dimethicone
Methicone

Silicates:

Magnesium Aluminum Silicate
Kaolin
Silica

Acrylates/Octylacrylamide Copolymer:

Acrylates Octylacrylamide Copolymer

Methylisothiazolinone:

Methylisothiazolinone

Other common airbrush makeup ingredients with potential inhalation hazard concerns:

Talc

Titanium Dioxide

Mica

Thank you for your consideration of these comments. I have also attached ingredient lists for several popular brands of airbrush makeup, highlighting chemicals currently or recently under review by the CIR and those with potential inhalation hazards.

Sincerely,

Alexandra Scranton
Director of Science and Research
Women's Voices for the Earth

Airbrush Makeup ingredient lists:

(This list is not exhaustive of manufacturers or products, but instead a sampling of each.). This information is provided as it is assumed one would not be able to specifically identify airbrush makeup products from VCRP data.

Silicone-based Airbrush makeup:

Brand: MAC Cosmetics

MAC PRO Performance HD Airbrush Makeup

Ingredients: Isododecane, Trisiloxane, Water\Aqua\Eau, Dimethicone, Polysilicone-6, Silica, Octyldodecyl/ Ppg-3 Myristyl Ether Dimer Dilinoleate, Dimethicone Silylate, Butylene Glycol, Peg-10 Dimethicone, Tocopheryl Acetate, Ascorbyl Palmitate, Retinyl Palmitate, Caprylyl Glycol, Hexylene Glycol, Cetyl Peg/Ppg-10/1 Dimethicone, Diethylhexyl Malate, Methicone, Polyglyceryl-4 Isostearate, Polysilicone-11, Hexyl Laurate, Triethoxycaprylylsilane, Trimethylsiloxysilicate, Sodium Chloride, Phenoxyethanol, [+/- Mica, Iron Oxides (Ci 77491, Ci 77492, Ci 77499), Titanium Dioxide (Ci 77891), Bismuth Oxychloride (Ci 77163), Blue 1 Lake (Ci 42090), Carmine (Ci 75470), Chromium Oxide Greens (Ci 77288), Chromium Hydroxide Green (Ci 77289), Red 6 (Ci 15850), Red 6 Lake (Ci 15850), Red 7 Lake (Ci 15850), Red 21 (Ci 45380), Red 22 Lake (Ci 45380), Red 28 Lake (Ci 45410), Red 30 Lake (Ci 73360), Red 33 Lake (Ci 17200), Ultramarines (Ci 77007), Yellow 5 Lake (Ci 19140), Yellow 6 Lake (Ci 15985)]

https://www.maccosmetics.com/product/7407/921/pro/proproduct-grid/pro-performance-hd-airbrush-makeup

Brand: TEMPTU

Perfect Canvas Airbrush Blush

AQUA, CYCLOPENTASILOXANE, ETHYL TRISILOXANE, COCONUT ALKANES, TRIMETHYLSILOXYSILICATE, POLYMETHYLSILSESQUIOXANE, METHYL TRIMETHICONE, POLYETHYLENE, POLYSILICONE-11, DIMETHICONE, SILICA, BUTYLENE GLYCOL; CYCLOMETHICONE, DIMETHICONE/PEG-10/15 CROSSPOLYMER, DIMETHICONOL, DIPROPYLENE GLYCOL, DISTEARDIMONIUM HECTORITE, ISOPROPYL ALCOHOL, PEG/PPG-18/18 DIMETHICONE, PEG/PPG-20/15 DIMETHICONE, POTASSIUM SORBATE, PROPYLENE CARBONATE, SODIUM BENZOATE, SODIUM CHLORIDE, SODIUM CITRATE, SORBITAN SESQUIOLEATE, TOCOPHEROL, TOCOPHERYL ACETATE, TRIETHOXYCAPRYLYLSILANE, [+/-:CI 15850, CI 77163, CI 77491, CI 77492, CI 77499, CI 77891]

https://www.nigelbeauty.com/p-32925-perfect-canvas-airbrush-blush-1oz.aspx

Water-based airbrush makeup:

Brand: Luminess

Luminess Silk Foundation 4 In 1 Enhanced

Ingredients: Purified Water (Aqua), Butylene Glycol, Glycerin, Propylene Glycol, Azadirachta Indica (Neem) Extract, Potassium Olivoyl PCA, Stearic Acid, Hydrolyzed Silk, Triethanolamine, Calendula Officinalis Flower Extract, Glycyrrhiza Glabra (Licorice) Root Extract, Cucumis Sativus (Cucumber) Fruit Extract, Hamamelis Virginiana (Witch Hazel) Leaf Extract, Spirulina Platensis Extract, Glyceryl Stearate, PEG-100 Stearate, Acrylates Octylacrylamide Copolymer, Magnesium Aluminium Silicate, Alpha-Bisabolol, Allantoin, Potassium Sorbate, Disodium EDTA, Lecithin, Kaolin, Xanthan Gum, Phenoxyethanol, Diazolidinyl Urea, Iodopropynyl Butylcarbamate

May Contain (+/-): Mica (CI 77019), Titanium Dioxide (CI 77891), Iron Oxides (CI 77491, 77492, 77499)

https://www.luminessbeauty.com/products/airbrush-foundations/silk-4-in-1-enhanced

Brand: Aeroblend

AEROBLEND Airbrush Ingredients

WATER/AQUA, PROPYLENE GLYCOL, GLYCERIN, TALC , PERSEA GRATISSIMA (AVOCADO) OIL, SIMMONDSIA CHINENSIS (JOJOBA) SEED OIL, POLYURETHANE-34, KAOLIN, CETYL HYDROXYETHYLCELLULOSE, TETRASODIUM EDTA, BHT, TRIETHANOLAMINE, LAVANDULA OFFICINALIS (LAVENDER) OIL, CAMELLIA SINENSIS (WHITE TEA) EXTRACT, PHENOXYETHANOL, CAPRYLYL GLYCOL, POTASSIUM SORBATE, HEXYLENE GLYCOL.
MAY CONTAIN: TITANIUM DIOXIDE 13463-67-7, IRON OXIDES 1309-37-1, 20344-49-4, 1309-37-1, SILICA 7631-86-9, ULTRAMARINE BLUE, ULTRAMARINE PINK, ALUMINA, MICA

https://aeroblend.com/blogs/how-to/what-are-the-ingredients-used-in-aeroblend-airbrush-makeup

Brand: Dinair

Dinair Airbrush Makeup Foundation

Ingredients

Aqua (Water/Eau), Glycerin, Acrylates/Octylacrylamide, Copolymer, Propylene Glycol, Xanthan Gum, Phenoxyethanol, Magnesium Aluminum Silicate, Triethanolamine. MAY CONTAIN: Iron Oxides (CI 77499, CI 77492, CI 77491), Titanium Dioxide (CI 77891), Ultramarines (CI 77007)

https://www.amazon.com/Dinair-Airbrush-Makeup-Foundation-GLAMOUR/dp/B00Q3JG33K

Brand: Art of Air

Art of Air Airbrush makeup

HD Makeup Foundation - Water (Aqua), Magnesium Aluminum Silicate, Cellulose Gum, Propylene Glycol, Triethanolamine, Diazolidinyl Urea. May Contain: Titanium Dioxide (CI 77891), Ultramarines (CI 77007), Iron Oxides, Disodium Distyrylbiphenyl Disulphonate, Mica (CI 77019), Luminescent Zinc Sulfide, Talc.

https://www.artofair.com/pages/ingredients

Art of Air “Pearl Shimmer”

COMPOSITION: Water (Aqua), Propylene Glycol, Acrylates Copolymer, Acrylates/Octylacrylamide Copolymer, Triethanolamine, Glycerin, Magnesium Aluminum Silicate, Cellulose Gum, Panthenol, Aloe Barbadensis Leaf Extract, Cymbopogon Schoenanthus (Lemongrass) Extract, Cucumis Sativus (Cucumber) Fruit Extract, Panax Ginseng Root Extract, Chamomilla Recutita (Chamomile) Flower Extract, Symphytum Officinale Rhizome/Root (Comfrey) Extract, Tocopheryl Acetate (Vitamin E), Camellia Oleifera (Japanese Green Tea) Leaf Extract, Trisodium EDTA, Glyceryl Caprylate, Methylisothiazolinone, Silica, Polyester-3, Fragrance (parfum), Coumarin, Limonene. May Contain: Titanium Dioxide (CI 77891), Ultramarines (CI 77007), Iron Oxides (CI 77489), D&C Yellow 5 Lake (CI 19140), D&C Yellow 10 Lake (CI 47005), FD&C Blue 1 Lake (CI 42090), D&C Red 7 Lake (CI 15850), D&C Red 6 Lake (CI 15850), D&C Orange 5 Lake (CI 45370), Chromium Oxide Green (CI 77288), D&C Red 21 (CI 45380), D&C Red 28 (CI 45410), D&C Yellow 7 (CI 45350), Disodium Distyrylbiphenyl Disulphonate, Mica (CI 77019).

https://www.artofair.com/collections/blushes-and-bronzers/products/white-shimmer

Brand: Kett Cosmetics

Kett Hydro Metal Eyeshadow

INGREDIENTS:
PURIFIED WATER, GLYCERIN, PROPYLENE GLYCOL, MAGNESIUM ALUMINUM SILICATE, TRIETHANOLAMINE, CELLULOSE GUM, SILICA, METHYLISTHAZOLINONE, DECYLENE GLYCOL. MAY CONTAIN (+/-): TITANIUM DIOXIDE, IRON OXIDES, ULTRAMARINE BLUE, CHROMIUM GREEN OXIDE, D&C RED #6 BARIUM LAKE, D&C RED #7 CALCIUM LAKE, FD&C YELLOW #5, MICA.

https://musebeauty.pro/kett-hydro-metal/

Kett Hydro Foundation

INGREDIENTS: PURIFIED WATER, GLYCERIN, PROPYLENE GLYCOL, MAGNESIUM ALUMINUM SILICATE, TRIETHANOLAMINE, CELLULOSE GUM, SILICA, METHYLISTHAZOLINONE, DECYLENE GLYCOL. MAY CONTAIN (+/-) TITANIUM DIOXIDE, IRON OXIDES, ULTRAMARINE BLUE, CHROMIUM GREEN OXIDE, D&C RED #6 BARIUM LAKE, D&C RED #7 CALCIUM LAKE, FD&C YELLOW #5.

https://musebeauty.pro/kett-hydro-foundation-6ml/

Brand: Photo Finish

Photo Finish Airbrush Foundation

Ingredients: Purified Water, Propylene Glycol, Acrylates Octylacrylamide Copolymer, Glycerin, Triethanolamine, Magnesium, Aluminum Silicate, Phenoxyethanol, Sodium Benzoate, Titanium Dioxide, Iron Oxides, Kaolin Clay. May Contain: Xanthan Gum, Silica, Butylene Glycol, Lecithin, Mica, Cetearyl Alcohol, Polysorbate 60
https://advancedskincarestore.com/makeup/airbrush-makeup/airbrush-foundation/

Photo Finish Airbrush Primer

https://www.photofinishairbrushmakeup.com/product-page/primer

Purified Water, Propylene Glycol, Acrylates Octylacrylamide Copolymer, Glycerin, Triethanolamine, Xanthan Gum, Magnesium, Aluminum Silicate, Phenoxyethanol, Cyclomethicone, Sodium Benzoate May Contain: (Pigments) Titanium Dioxide, Iron Oxides

https://www.photofinishairbrushmakeup.com/product-page/primer

Brand: Tickled Pink

Waterproof Makeup Sealant

Ingredients: Aqua, Denatured Ethanol, Acrylic Polymers, Phenoxyethanol, Dimethlaminoethanol(DMAE Bitartrate), Tetrasodium EDTA

https://www.tickledpinkairbrush.com/water-proof-sealant/

Water-based Airbrush Foundation

Ingredients: Aqua (Purified Water), Glycerine, Silica, Coco-Glucasides/Coconut Alcohol, Cetyl Esters, Potassium Cetyl Phosphate, Kaolin, Cetyl Alcohol, PEG-40 Apricot Oil, Alchemilla Vulgaris (Lady's Mantle) Extract, Silybum Marianum Fruit (Milk Thistle) Extract, Ginko Biloba Leaf (Gingko) Extract, Equisetum, Arvense Leaf (Horsetail) Extract, Hypericum Perforatum (St. Johns Wart) Extract, Helianthus Annus (Sunflower) Seed Oil, Caprylyl Glycol, Natural Fragrance, Magnesium Aluminum Silicate, Carboxymethylcellulose, Citric Acit, Disodium EDTA. Setting Spray Ingredients: Aqua (Purified Water), Acrylates Copolymer, Propylene Glycol, Soya Protein Phthalate, Polysorbate-20, Natrual Fragrance, Disodium EDTA.

https://www.tickledpinkairbrush.com/products/waterbased-foundations.html#description

Brand: Rock Candy

NOFILTER 4K Foundation:

Matte Finish: Water, Glycerin, Hydrolyzed Rice Protein, Propanediol, Hydrolyzed Jojoba Esters, Palmitoyl Tripeptide-5, Benzyl Alcohol, Microcrystalline Cellulose, Acrylates/Octylcrylamide Copolymer, Prunus Amygdalus Dulcis (Sweet Almond) Seed Extract, Jojoba Esters, Tetrasodium Glutamate Diacetate, Tromethamine, Salicylic Acid, Xanthan Gum, Cellulose Gum, Avena Sativa (Oat) Bran Extract, Sorbic Acid, Sodium Benzoate, Potassium Sorbate, Camellia Sinensis Callus Extract, Panax Ginseng Callus Culture Extract, Phyllostachys Pubescens Meristem Cell Lysate , Titanium Dioxide (CI 77891), Iron Oxides (CI 77492), Iron Oxides (CI 77491), Iron Oxides (CI 77499).

Satin Finish: Water, Propanediol, Glycerin, Hydrolyzed Rice Protein, Brassica Napus Seed Oil, Hydrolyzed Jojoba Esters, Glyceryl Citrate/Lactate/Lineolate/Oleoate, Palmitoyl Tripeptide-5, Acrylates/Octylcrylamide Copolymer, Benzyl Alcohol, Mica, Glyceryl Caprylate, Polyglyceryl-3 Caprate, Polyglyceryl-4 Cocoate, Prunus Amygdalus Dulcis (Sweet Almond) Seed Extract, Jojoba Esters, Tromethamine, Tetrasodium Glutamate Diacetate, Salicylic Acid, Microcrystalline Cellulose, Avena Sativa (Oat) Bran Extract, Sorbic Acid, Sodium Benzoate, Potassium Sorbate, Cellulose Gum, Xanthan Gum, Camellia Sinensis Callus Extract, Panax Ginseng Callus Culture Extract, Phyllostachys Pubescens Meristem Cell Lysate, Titanium Dioxide (CI 77891), Iron Oxides (CI 77492), Iron Oxides (CI 77491), Iron Oxides (CI 77499).

https://rockcandybeauty.com/products/nofilter-4k

4K BRONZER

Water/Aqua, Aloe Barbadensis (Aloe Vera) Extract, Titanium Dioxide, Brassica Campestris Oil or Canola Oil, Hydrolyzed Rice Protein, Glyceryl Citrate/Lactate/Linoleate/Oleate, Hydrolyzed Jojoba Esters, Polyglyceryl-3 Caprate, Glyceryl Caprylate, Palmitoyl Tripeptide-5, Panax Ginseng Callus Extract, Phyllostachys Pubescens Callus Culture Extract, Camellia Sinensis Callus Culture Extract, Microcrystalline Cellulose, Lonicera Caprifolium Extract, Benzyl Alcohol, Distarch Phosphate, Jojoba Esters, Sorbic Acid, Lonicera Japonica Extract, Isopentyldiol, Xanthan Gum, Glycerin, Trifolium Pratense (Clover) Flower Extract, Avena Sativa (Oat) Bran Extract, Tetrasodium Glutamate Diacetate, Salicylic Acid, Sodium Benzoate, Potassium Sorbate, Prunus Amygdalus Dulcis (Sweet Almond) Seed Extract, Propanediol.

https://rockcandybeauty.com/products/bronzers

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice M. Fiume MMF
Senior Director, CIR
Date: March 2, 2021
Subject: Wave 2 - Safety Assessment of *Melaleuca alternifolia* (Tea Tree)-Derived Ingredients as Used in Cosmetics

Enclosed, please find two sensitization studies that were received after the initial mailing of the draft Tentative Report (*melalt032021wave2_data*). In the first study, a formulation containing 0.001% Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract was evaluated in a maximization test (25 subjects), and in the second study, a formulation containing 0.0078% Melaleuca Alternifolia (Tea Tree) Leaf Extract was evaluated in a modified Draize human repeated insult patch test (105 subjects). Neither test article was a sensitizer. (Reported maximum use concentrations of these ingredients in leave-on formulations are 0.01% Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract and 0.0001% Melaleuca Alternifolia (Tea Tree) Leaf Extract, both as used in "other skin care preparations.")

Additionally, please find enclosed comments that were received, via email, from the Australian Tea Tree Industry Association (ATTIA; *melalt032021wave2_ATTIA comments*). These comments were submitted in response to the deliberations that took place at the December 2020 meeting.

1620 L Street, NW, Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(email) cirinfo@cir-safety.org (website) https://cir-safety.org

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 24, 2021

SUBJECT: Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract and Melaleuca Alternifolia (Tea Tree) Leaf Extract

Anonymous. 2005. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (product contains 0.001% Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract.

Anonymous. 2020. A modified Draize repeat insult patch test in a shared panel of 100 healthy volunteers, to investigate the irritation and sensitization potential of 2 test articles following repeated cutaneous patch applications. (product contains 0.0078% Melaleuca Alternifolia (Tea Tree) Leaf Extract).

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[redacted]

FINAL REPORT September 13, 2005

[redacted]

Sample: Spot Treatment coded [redacted]

[redacted]

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

contains 0.001% Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract

Sponsor: [redacted]

Principal Investigator: [redacted] (Board Certified Dermatologist)

Testing Facility: [redacted]

Protocol: [redacted]

Final Report Date: September 13, 2005

[redacted]

Principal Investigator

September 13, 2005
Date

[redacted]

FINAL REPORT

[redacted] PROTOCOL:

[redacted]

SPONSOR:

[redacted]

[redacted]

SPONSOR STUDY:

Authorization Letter Dated: July 26, 2005

STUDY TITLE:

Evaluation of the contact-sensitizing potential of a coded topically-applied test agent.

STUDY OBJECTIVE:

The objective of this study is to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

TEST MATERIAL:

The test sample, supplied by the sponsor, was a product labeled Spot Treatment and coded [redacted] and tested as supplied.

TEST PRODUCT ACCOUNTABILITY:

All test samples and materials were received in good condition by our Quality Assurance Department. The test materials and quantities were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). All test materials were stored under ambient conditions in an inaccessible location under the supervision of the investigator.

PRINCIPAL INVESTIGATOR:

[redacted] (Board Certified Dermatologist)

[redacted]

[redacted]

[redacted]

[redacted]**ADMINISTRATIVE STRUCTURE:**

[redacted]l (Screening, Patch Applications/Removals, Recognize AE's)

[redacted] (Expert Grader)

[redacted]Panel Recruitment/Receptionist)

TESTING FACILITY:

[redacted]

[redacted]y

[redacted]

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CONDUCTION DATES:

This study was conducted from August 1, 2005 through September 1, 2005

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics. The criteria for exclusion were:

1 - History of sun hypersensitivity and photosensitive dermatoses

2 - History of drug hypersensitivity or recurrent dermatological diseases

3 - Pregnancy or mothers who are breastfeeding

4 – History of recurrent urticaria or hives

5 - Scars, moles or other blemishes over the test site which can interfere with the study

6 - Subjects receiving systemic or topical drugs or medications, including potential sensitizers within the previous 4 weeks

7 - Other medical conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

INFORMED CONSENT:

After the protocol, reasons for the study, possible associated risks and potential benefits or risks of the treatment had been completely explained, signed, informed subject consent was obtained from each volunteer prior to the start of the study. Copies of all consent forms are on file at [redacted]

METHOD:

Patches were applied to the upper outer arm, volar forearm or the back of each subject. The entire test was composed of two distinct phases: (1) an Induction phase and (2) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (induction patch). Since the test material coded [redacted] (Spot Treatment) contained volatile ingredients, it was allowed to air-dry for ~30 minutes prior to application to the test site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Challenge Phase**:

After a ten day rest period which follows the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded 15-30 minutes later and again 24 hours later for any reaction.

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SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

RESULTS:

A total of twenty-five (25) healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 21 females and 4 males. Their ages ranged from 18 to 64 years. All 25 subjects completed this investigation as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Spot Treatment and coded [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	R-I	53	M	C
02	M-R	41	F	C
03	T-U	48	M	C
04	JSM	53	F	C
05	L-M	48	F	C
06	R-M	23	F	C
07	N-B	24	F	C
08	JPM	46	M	C
09	SRK	49	F	C
10	M-G	51	F	C
11	JDC	34	F	C
12	S-B	51	F	C
13	K-R	48	F	C
14	B-C	26	M	C
15	A-S	51	F	C
16	T-R	38	F	C
17	D-A	36	F	C
18	ALM	18	F	A
19	K-T	18	F	C
20	M-M	62	F	C
21	C-M	64	F	C
22	T-C	37	F	B
23	L-C	21	F	C
24	M-D	18	F	A
25	DMT	18	F	C

C = Caucasian
A = Asian
B = Black

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Spot Treatment coded [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0

Challenge Readings:

48-Hour Reading – August 31, 2005
72-Hour Reading – September 1, 2005

[redacted]

SUMMARY REPORT

A MODIFIED DRAIZE REPEAT INSULT PATCH TEST IN A SHARED PANEL OF 100 HEALTHY VOLUNTEERS, TO INVESTIGATE THE IRRITATION AND SENSITISATION POTENTIAL OF 2 TEST ARTICLES FOLLOWING REPEATED CUTANEOUS PATCH APPLICATIONS

CONDUCTED ACCORDING TO [redacted] MASTER PROTOCOL: [redacted] (14APR2020)

[redacted]. Study Number: [redacted]

TEST ARTICLES:

1. [redacted]
2. **Bubbling Face Mask - #** [redacted]

product contains 0.0078% Melaleuca Alternifolia (Tea Tree Leaf Extract

[redacted]

Please Note: [redacted]

Prepared for:

[redacted]

Prepared by:

[redacted]

Draft Report: 22nd September 2020
Final Report: 6th October 2020

[redacted] 6th October 2020

A MODIFIED DRAIZE REPEAT INSULT PATCH TEST IN A SHARED PANEL OF 100 HEALTHY VOLUNTEERS, TO INVESTIGATE THE IRRITATION AND SENSITISATION POTENTIAL OF 2 TEST ARTICLES FOLLOWING REPEATED CUTANEOUS PATCH APPLICATIONS

CONDUCTED ACCORDING TO [redacted] MASTER PROTOCOL: [redacted] (14APR2020)

[redacted]

I declare that the following report constitutes a true and faithful account of the procedures adopted and the results obtained in the performance of this study. The aspects of the study conducted by PCR Corp were performed, where relevant, in accordance with the principles of Good Clinical Research Practice.

[redacted]
(Principal Investigator)

.....[redacted].....

Date 6th October 2020

[redacted]
(Project Manager)

.....[redacted].....

Date 6th October 2020

QUALITY ASSURANCE STATEMENT

This report has been audited and is considered to be an accurate description of the methods used and an accurate presentation of the data obtained during the conduct of the study.

[redacted]
(Quality Assurance)

..[redacted]....

Date 6th October 2020

PCR CORP

TABLE OF CONTENTS

PCR CORP

KEY STUDY PERSONNEL AND RESPONSIBILITIES

Key Personnel	General Responsibilities
Principal Investigator (PI) [redacted]	The Principal Investigator (PI) responsible for ensuring sufficient resources were available to conduct the study and was responsible for the study design, review of the study protocol, authorization and summary report.
Study Supervisor (SS) [redacted]	The Study Supervisor (SS) responsible for the conduct of the study on a daily basis.
Project Manager (PM) [redacted]	The Project Manager (PM) involved with the study authorization, compilation of study results and summary report.
Sponsor Contact [redacted]	

PCR CORP

INTRODUCTION AND OBJECTIVE

The objective of this study was to investigate the irritation and sensitisation potential of cosmetic test articles, in a shared panel of 100 healthy volunteers by means of repeated cutaneous occlusive patch applications based on the modified Draize method of Jordan and King (1977)[1] to support claims such as "Dermatologically Tested", "Clinically Tested", "Kind to Skin" and "Safe for Skin".

MATERIALS AND METHODS

1. STUDY DESIGN

The study was conducted single blind, at a single center according to Master Protocol: [redacted] (See Appendix 3 for Study Authorization).

The test articles were patched under occlusive conditions using Finn chambers or equivalent occlusive patches. A total of nine inductions patches worn for 47 hours or 71 hours (patching occurred Mondays, Wednesdays and Fridays) for three weeks (a make-up day was allowed to ensure subjects had all 9 induction patches). Subjects had a rest period of 14 days. Challenge patches were applied for 48 hours and readings were made 1 hour and 48 hours post removal.

2. TEST MATERIALS

2.1. TEST ARTICLES

The test articles were supplied by the Sponsor and labelled as follow:

TA#	Test Article Name/Description	ID Code (Batch/Lot #)	Dilution/special handling*
1	[redacted]	[redacted]	[redacted]
2	Bubbling Face Mask	#[redacted]	

3. STUDY ETHICS

3.1. DECLARATION OF HELSINKI

The study conformed to the requirements of the 1964 Declaration of Helsinki and its subsequent amendments (World Medical Association; 2013)[2].

3.2. INDEMNITY PROVISION

The Sponsor was responsible, without regard to legal liability, and shall indemnify [redacted], or any of their respective officers or employees in the event of claims for compensation from subjects suffering injury or other deterioration in health or well-being as a result of participation in this study, except and insofar as such claims arise as a result of any negligent act or omission on the part of [redacted] employees or any persons undertaking or involved in the study by arrangement with [redacted]

3.3. ICH GCP

The study was conducted in accordance with applicable International Council for Harmonization. 2016. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)[3] in as much as they apply to cosmetic and consumer product testing/research.

4. QUALITY ASSURANCE

The study was conducted according to the Sponsor Authorization, the master protocol, the Standard Operating Procedures of [redacted] and according to the applicable ICH Guidelines on Good Clinical Practice, and other recognised guidelines. An audit of the final report was completed, for accuracy and completeness of presentation. Additionally, the study may be subject to the following Quality Assurance procedures:

- Review of protocol and protocol amendments for completeness, clarity and adequacy.
- Inspection and/or audit of critical phases of study conduct for compliance with protocol and [redacted] procedures.

[redacted] Quality Assurance would have informed [redacted] management of any findings that may have affected the integrity of the study.

5. RETENTION OF DATA

All raw data generated by [redacted] during the course of the study, including the sponsor authorization form and final summary report, will be retained in the [redacted] Archive for a minimum period of three years from study completion as is [redacted] policy for cosmetic products. In the event of original data being transferred to the Sponsor at their request, exact copies will be so retained. At no time will archived data be destroyed without prior written approval of the Sponsor. All study data will be available at any time, by appointment, for inspection by the Sponsor or their authorized representative. The study master protocol will be archived and retained indefinitely at [redacted].

6. REFERENCES

1. Jordan W.P. and King S. E. (1977) Contact Dermatitis 3, 19-26.

2. World Medical Association (2013). "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects". JAMA 310 (20): 2191–2194. doi:10.1001/jama.2013.281053

3. ICH E6_R2, INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE, Current Step 4 version dated 9 November 2016

PCR CORP

RESULTS

1 LOCATION AND DATES OF THE STUDY

The study was performed at [redacted] between w/c 3rd September 2020 and w/e 11th September 2020.

2 SUBJECTS

111 male and female subjects were enrolled into the study. 105 subjects completed the study. The age, gender and racial composition of these subjects is presented in table in Appendix 2.

3 ADVERSE EVENTS, ADVERSE REACTIONS AND SUBJECTS NOT COMPLETING THE STUDY, DEVIATIONS

No adverse events or reactions were reported.

6 subjects withdrew for personal reasons.

There were no deviations that occurred during the conduct of the study.

4 ASSESSMENTS

Individual reactions to the test articles are presented in Appendix 1.

As demonstrated by the individual skin responses to the test articles:

Test Article 1 [redacted]

Test Article 2 – Bubbling Face Mask - # [redacted] elicited faint, mild erythematous reactions during the Induction phase of the study.

There were no questionable reactions observed during the Challenge Phase (Days 38 and 40) by any of the subjects to any of the test articles. These results support the assessment that under the conditions of the study, the test articles have demonstrated a low potential for irritation and sensitization.

CONCLUSIONS

The test articles can be considered as safe for use under the conditions of the study, and claims such as, "Dermatologically Tested", "Clinically Tested", "Kind to Skin" and "Safe for Skin" are substantiated.

PCR CORP

EXAMPLE RESULTS
TEST ARTICLE 2 – Bubbling Face Mask

Number	Code	2	3	4	5	6	7	8	9	10	MU	1 hour	47 hour
1	2	0	0	0	0	0	0	0	0	0		0	0
2	2	0	0	0	0	0	0	0	0	0		0	0
3	2	0	0	0	0	0	0	0	0	0		0	0
4	2	0	0	0	0	0	0	0	0	0		0	0
5	2	0	0	0	0	0	0	0	0	0		0	0
6	2	0	0	0	0	0	0	0	0	0		0	0
7	2	0	0	0	0	0 A	0 A	0 A	0 A	0 A		0	0
8	2	0	0	0	0	0	0	0	0	0		0	0
9	2	0	0	0	0	0	0	0	_	0	0	0	0
10	2	0	0	0	0	0	0	0	0	0		0	0
11	2	0	0	0	0	0	0	0	0	0		0	0
12	2	0	0	0	0	0	_	0	0	0	0	0	0
13	2	0	0	0	0	0	0	0	0	0		0	0
14	2	0	0	0	0	0	0	0	0	0		0	0
15	2	0	0	0	0	0	0	0	0	0		0	0
16	2	0	0	0	0	0	0	0 A	0 A	0 A		0	0
17	2	0	0	0	0 A	0 A	0 A	1 A	1 A	1 A		0	0
18	2	0	0	0	0	0	0	0	0	0		0	0
19	2	0	0	0	0	0	0	0	0	0		0	0
20	2	0	0	_	0	0	0	0	0	0	0	0	0
21	2	0	0	0	0	0	_	0	D/O	D/O		D/O	D/O
22	2	0	0	0	0	0	0	0	0	0		0	0
23	2	0	0	0	0	0	0	0	0	0		0	0
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27	2	0	0	0	0	0	0 A	0 A	0 A	0 A		0	0
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53	2	0	0	0	0	0 A	0 A	1 A	1 A	1 A		0	0
54	2	0	0	0	0	0	0 A	0 A	0 A	0 A		0	0
55	2	0	0	0	0	0	0	0	0 A	0 A		0	0

PCR COPY

56	2	0	0	0	0		0		0		0		0		0				0	0
57	2	0	0	0	0		0		0		0		0		0				0	0
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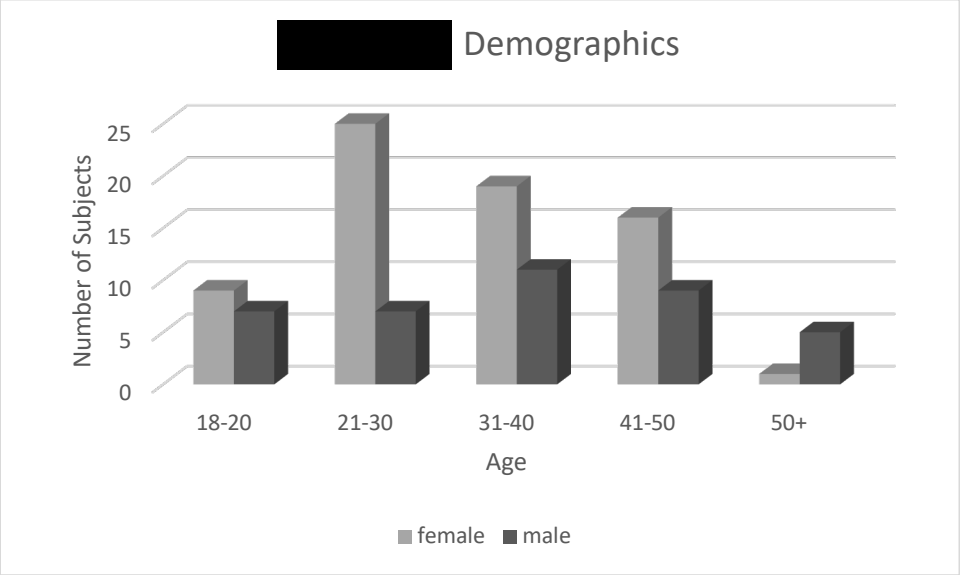
111	2	0	0	0	0		0		0		0		0		0				0	0
MEAN		0.00	0.00	0.00	0.00		0.00		0.00		0.02		0.06		0.06		0.00		0.00	0.00
STDEV		0.00	0.00	0.00	0.00		0.00		0.00		0.14		0.23		0.23		0.00		0.00	0.00

APPENDIX 2: SUBJECT DEMOGRAPHICS



PCR CORP

From: Tony Larkman
To: Bart Heldreth; Monice Fiume
Subject: CIR - draft TTO review
Date: Wednesday, February 17, 2021 12:23:37 AM
Attachments: Potential Cosmetic Functions for TTO Apr 14.pdf

Dear Bart & Monice,
I am very grateful to you and the panel for the work that has been done on the draft to date, particularly in the area of skin irritation (oxidisation).
I have removed the disclaimer from the bottom of this email to allow its inclusion in any papers or proceedings relevant to the CIR.

I have now seen the transcript of the meeting I missed (apologies once again) and I will ensure I am available in the March 2021 sessions.
I have now been through the draft for the first time, there are appear to be a couple of areas where the panel needs guidance, the points below are an attempt to address these and so better inform the panel:

The '8 Melaleuca alternifolia (tea tree)-derived ingredients as used in cosmetic formulations':

1. Melaleuca Alternifolia (Tea Tree) Extract
2. Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract
3. Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Oil
4. Melaleuca Alternifolia (Tea Tree) Leaf
5. Melaleuca Alternifolia (Tea Tree) Leaf Extract
6. Melaleuca Alternifolia (Tea Tree) Leaf Oil
7. Melaleuca Alternifolia (Tea Tree) Leaf Powder
8. Melaleuca Alternifolia (Tea Tree) Leaf Water

From the list of 8 shown above:

- ✓ Items 1, 2, 3 and 6 are all identical – they describe in various ways the essential oil that is steam distilled from the plant.
- ✓ Item 4 and 7 both appear to describe the dried leaf, the second (item 7) is probably correctly descriptive.
- ✓ Item 8 is unique and correctly descriptive of the product Australians known as 'hydrosol'; this is sometimes known as 'flower water' which suits for rose hydrosol but is not a good fit for Melaleuca Alternifolia (Tea Tree) Leaf Water.
- ✓ It is possible that someone, somewhere is extracting a product by an unknown method using the whole of the aerial portion to include both the water-soluble and water-insoluble portions; it is feasible that this could be referred to as Melaleuca Alternifolia (Tea Tree) Leaf Extract (item 5) but I have never come across this as a commercial product though something is mentioned the draft along these lines.

Thus and in my opinion there are therefore only three, rather than eight, tea tree derived ingredients suited for cosmetic formulations (although there could be a 4th – see above):

1. **Melaleuca Alternifolia (Tea Tree) Leaf Oil:** this is the essential oil (TTO) that is steam distilled from the entire aerial portion of the plant.

2. **Melaleuca Alternifolia (Tea Tree) Leaf Powder:** this is the dried powdered leaf of *Melaleuca alternifolia*.
3. **Melaleuca Alternifolia (Tea Tree) Leaf Water:** this is the collapsed steam (water) portion from which the Melaleuca Alternifolia (Tea Tree) Leaf Oil is separated.

This may be a unique opportunity to request INCI to reform the list and reduce it from eight to three (or four if a 'leaf extract' is a real product); I have asked the PCPC if they would consider championing this simplification for products from *Melaleuca alternifolia*, any assistance from the CIR would also be appreciated.

'Flower':
In the transcript the panel discussed the presence/use of the flower as a portion of TTO or hydrosol. I believe this confusion is due to the use of the term 'Flower Water' when the collapsed steam portion is marketed (we call this hydrosol); this makes sense in the concept of rose water, lavender water etc but not for tea tree. The simple fact is *Melaleuca alternifolia* plants do not commonly flower when in plantations (more than 99% of all TTO is from plantation settings and any wild derived TTO will not include any flower or portion of flower) as the entire aerial portion is harvested at ground level and is harvested on an annual cycle so flowering is not seen in plantations (except in the most unusual of seasons and then only extremely rarely) as the plants are not mature enough in this 12-month harvest cycle to produce inflorescences.

Cosmetic Functions:
The panel again struggled with this and they are right, there has been little to nothing done to formalise this for TTO or products derived from *M. alternifolia*. The SCCP, in their 2008 Opinion on TTO, stated "*The cosmetic function of Tea Tree Oil needs to be indicated, as no clear cosmetic function was given by the applicant and several non-cosmetic applications are known.*" In an attempt to address this I have attached a copy of a paper I prepared in 2014 titled 'Potential Cosmetic Functions for TTO' which lists 19 functions including 4 outliers that I believe are worth considering. I expect the US has a different set of guidelines and perhaps nomenclature for cosmetic functions but this is a good start.

Adulteration:
Despite my best efforts the panel appear not to have addressed this despite including a reference (Schmidt & de Groot, 2016) in the draft where up to 220 compounds are listed despite the authors acknowledging (in a series of footnotes in Chapter 6) that the provenance of many of the samples is questionable, they even acknowledge that one (Chinese) sample is adulterated and that many have been deliberately oxidised yet they include these data in a single table titled "Constituents identified in tea tree oils"…I find this approach baffling.
I have tried to explain that adulteration is a key and ongoing problem (50% of North American samples, 70% of EU samples in 2013/14; now down to around 35% in all jurisdictions globally in 2019/20). Significantly a number of compounds are detected in these some of which are known and potent endocrine disruptors /carcinogens/toxins in varying quantities. This is therefore a key safety question that I believe must be mentioned and if possible addressed by the panel. Data can be provided on request.
The panel describe natural variation and Dr Belsito noted "*…large variation in composition*

depending upon sources like Australia, Vietnam, China." I respectfully dispute this and believe that much of the variation is driven by overwhelming adulteration, particularly in Chinese material noting that I have never seen a commercial sample of Chinese origin (12 years of work) that is not adulterated. **Note:** a lab distilled sample of leaf/twig taken direct from a Chinese plantation and distilled in the USA conformed to all requirements of the ISO Standard (per comm. Robert Pappas). The product (Melaleuca Alternifolia (Tea Tree) Leaf Oil steam distilled from *M. alternifolia*), conditional on correct chemotype selection, produces an essential oil that is 1) invariably compliant with all particulars of the ISO 4730: 2017 Standard (ranges are provided for seasonal variation in this and other Standards) in all instances. I have seen data from South Africa, Zimbabwe, China, Kenya, New Zealand, Italy (*a hot house grown experimental sample*) and of course Australia and all conform without exception. This is because all germplasm used both in Australia and overseas all comes from the same approx. 200 families of the terpinen-4-ol chemotype of *Melaleuca alternifolia* that is native to the east coast littoral of Australia. The same is true for *M. linariifolia* though I have only seen data on this species from Australia.

I trust that this will help better inform the panel.
Regards,

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Potential Cosmetic Functions for TTO

14 April 2014

The list of 19 functions compiled below is drawn principally from Commission Decision 2006/257/EC published 9 Feb 2006 to replace the annexes in Council Directive 96/335/EC of 14 June 1993, the so-called "sixth amendment" to the Cosmetics Directive establishing an inventory and a common nomenclature of ingredients employed in cosmetic products.

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Regulation (EC) No 1223-2009 of the European Parliament and of the Council, the so-called “Cosmetic Regulation” that came into force in the EU in July 2013 was also utilised as was the EC Commission’s Health & Consumer database “CosING” (http://ec.europa.eu/consumers/cosmetics/cosing/) with ‘*Melaleuca alternifolia*’ in the search field.

ATTIA’s shortlist of cosmetic functions and the observations and references below are intended only to provide assistance; further references can be listed if required.

1. **Antimicrobial**: This function is already listed in 2006/257/EC. The function is defined in 2006/257/EC as ‘Helps control the growth of micro-organisms on the skin’. There are many studies to demonstrate this; one of the latest papers is Blackwood et al: 2013 [1]. . In CosING *M. alternifolia* leaf water (CAS: 85085-48-9) is listed with Antimicrobial as a function.

2. **Antidandruff**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as ‘Helps control dandruff’. TTO is commonly offered in commercial shampoo formulations (>600,000 hits on Google) and is likely to be accepted as such. Satchell et al: 2002 [2] demonstrated the use of a 5% shampoo resulted in a 41% improvement in the quadrant-area-severity score compared with 11% in the placebo group (P <.001) while the 5% treatment was well tolerated.

3. **Antioxidant**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as ‘Inhibits reactions promoted by oxygen, thus avoiding oxidation and rancidity’. There are many literature references available including Kim et al: 2004 [3] who describe the antioxidant capacity of TTO in two separate assays. In CosING *M. alternifolia* leaf oil (CAS: 85085-48-9 / 8022-72-8 / 68647-73-4) is listed with Antioxidant as a function.

4. **Antiplaque**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as ‘Helps protect against plaque’. Reports by Lauten et al: 2005 [4] and Soukoulis et al: 2004 [5] while inconclusive both indicate antiplaque activity nay occur in TTO.

5. **Antiseborrheic**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as ‘Helps control sebum production’. Only a single literature reference is available: Fritch: 2001 [6] stated ‘*The in vitro susceptibility of Malassezia compared with antifungal Antiseborrheic drugs and receives clinical relevance when it comes to the various local and systemic treatment options for these Skin disease is*’ which may assist in determining the suitability of attributing this function to TTO. ATTIA considers this function to be an outlier but worth consideration. In CosING *M. alternifolia* leaf water (CAS: 85085-48-9) is listed with Antiseborrheic as a function.

6. **Astringent**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as ‘Contracts the skin’. No known references can be identified for this function. Based on the composition of TTO this is likely to be an acceptable function and could be tested as such if deemed necessary. ATTIA considers this function to be an outlier but worth consideration. In CosING *M. alternifolia* leaf water (CAS: 85085-48-9) is listed with Astringent as a function.

7. **Cleansing**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as ‘Helps to keep the body surface clean’ A report by Messager et al: 2005 [7]

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concluded that TTO in Tween 80 and in formulations met the European EN 1499 in-vivo method requirements.

8. **Deodorant**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as 'Reduces or masks unpleasant body odours'. No known references are available. TTO is commonly offered in commercial deodorant formulations (>2 million hits on Google) and is likely to be accepted as such.

9. **Keratolytic**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as 'Helps eliminate the dead cells of the stratum corneum'. No known references are available. Claims of this function are common on the internet (198,000 hits on Google). More common keratolytic agents are acid (eg salicylic acid). ATTIA considers this function to be an outlier but worth consideration.

10. **Masking**: This function is not listed for TTO in 2006/257/EC and no known references are available. The function is defined in 2006/257/EC as 'Reduces or inhibits the basic odour or taste of the product'. TTO is considered odorous and may itself need masking however there is little doubt that it could function in this capacity if considered desirable.

11. **Nail conditioning**: This function is not listed for TTO in 2006/257/EC and there are several references to onychomycosis, the latest being Flores et al: 2013 [8]. The function is defined in 2006/257/EC as 'Improves the cosmetic characteristics of the nail'. Claims of this function are common on the internet (>1.2 million hits on Google) and is likely to be accepted as such.

12. **Oral care**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as 'Provides cosmetic effects to the oral cavity, e.g. cleansing, deodorising, protecting'. There are many references available including Lahijani: 2006 [9]. Claims on the internet are prolific (>3 million hits on Google) and its function in oral care is well known.

13. **Perfuming**: This function is not listed for TTO in 2006/257/EC. The function **is not** defined in 2006/257/EC. In CosING *M. alternifolia* leaf oil (CAS: 85085-48-9 / 8022-72-8 / 68647-73-4) is listed with Perfuming as a function. See Masking [10] for further detail.

14. **Preservative**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as 'Inhibits primarily the development of micro-organisms in cosmetics'. Kunicka-Styczynska et al: 2009 & 2011 [10,11] conclude that '*…all combinations of essential oils with the synthetic preservative, a synergistic effect of the preservative system components was observed, which made it possible to reduce the usable level of the synthetic preservative up to 8.5 times*'.

15. **Skin protecting**: This function is not listed in 2006/257/EC. The function is defined in 2006/257/EC as 'Helps to avoid harmful effects to the skin from external factors'. The cleansing [7] and antimicrobial [1] functions of TTO may support this function.

16. **Solvent**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as 'Dissolves other substances'. While no references are available TTO is well known as a solvent. ATTIA considers this function an outlier that is unlikely to be included in any final list.

17. **Soothing**: This function is not listed in 2006/257/EC. The function is defined in 2006/257/EC as 'Helps lightening discomfort of the skin or of the scalp'. Claims of this function are prolific on the internet (>6 million hits on Google) and its function as an anti-inflammatory agent is well known with Meyler's Side Effects of Drugs [12] stating '*…it is said to have antifungal, antiviral, anti-inflammatory, and analgesic properties, and has been increasingly incorporated into cosmetics for aromatherapy*'.

18. **Stabilising**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as 'Improves ingredients or formulation stability and shelf-life'. Refer to the preservative function [14] of TTO above.

19. **Tonic**: This function is not listed for TTO in 2006/257/EC. The function is defined in 2006/257/EC as 'Produces a feeling of well-being on skin and hair'. While no references are available claims on the internet exceed 100,000 hits on Google and its function in the relief of itching on the scalp as

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well as for tinea sufferers is well documented. In CosING *M. alternifolia* leaf water (CAS: 85085-48-9) is listed with Tonic as a function.

Notes:
a) **Antimicrobial** is likely to be linked to **Preservative** as well as to **Antioxidant** and possibly to **Stabilising**. The function antimicrobial has implications as it is therapeutic in nature and may be a 'borderline' function with spill over into both therapeutic and biocidal regulations.
b) **Antiplaque** and **Oral care** also have potential therapeutic function depending on the concentration of TTO used and may be considered 'borderline'.

References

1. Blackwood B, Thompson G, McMullan R et al. *Tea tree oil (5%) body wash versus standard care (Johnson's Baby Softwash) to prevent colonization with methicillin-resistant Staphylococcus aureus in critically ill adults: a randomized controlled trial*. J Antimicrob Chemother. 2013; 68(5):1193-9
2. Satchell AC, Saurajen A, Bell C, Barnetson RS, *Treatment of dandruff with 5% tea tree oil shampoo*. J Am Acad Dermatol 2002; 47:852-855 Lauten JD, Boyd L, Blair Hanson M, Lillie D et al. *A Clinical Study: Melaleuca, Manuka, Calendula and Green Tea Mouth Rinse*. Phytother Res. 2005; 19(11):951-7
3. Kim HJ, Chen F, Wu C, Wang X, et al. *Evaluation of antioxidant activity of Australian tea tree (Melaleuca alternifolia) oil and its components*. J Agric Food Chem. 2004; 2(10):2849-54
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6. Fritsch P, Vanscheidt W. *The Yeast Malassezia: pathogen, pathogenesis and therapy* [German]. Hautarzt. 2001; 52(1):73-86
7. Messager S, Hammer KA, Carson CF, Riley TV. *Effectiveness of hand-cleansing formulations containing tea tree oil assessed ex vivo on human skin and in vivo with volunteers using European standard EN 1499*. J Hosp Infect. 2005; 59(3):220-8
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