SUPPLEMENT

Eucalyptus Globulus

Ginkgo Biloba

Malic Acid

Peppermint

Polyaminopropyl Biguanide

Sultaines

Witch Hazel

Zinc Salts

CIR EXPERT PANEL MEETING
DECEMBER 4-5, 2017

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MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: November 20, 2017

Subject: Additional Data for *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients As Used In Cosmetics

Sensitization and photosensitization data on Eucalyptus Globulus Leaf Oil (0.1%) were submitted by the Council [*Eucaly122017Data*]. The studies were conducted in 1980 when the International Nomenclature of Cosmetic Ingredients (INCI) name was "Eucalyptus Oil". The 2nd edition (published in 1977) of the *Cosmetic Ingredient Dictionary* gives the same definition as the current "Eucalyptus Globulus Leaf Oil" (Eucalyptus Globulus Leaf Oil is the volatile oil obtained from the leaves of *Eucalyptus globulus* and other species of *Eucalyptus*). Eucalyptus Globulus Leaf Oil was non-irritating, non-sensitizing and there were no indications of photosensitization. The studies are summarized below:

- In a patch test (n = 101) of a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%) using open and occlusive patches, a weak, non-vesicular reaction (+) was observed in four subjects at the first reading, but not the second, and in two other subjects only at the second reading. In the open patches, there were no reactions observed at either reading.

- In a human repeated insult patch test (HRIPT; n = 52) conducted on a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%), open and occlusive patches were used. Six subjects had a weak, non-vesicular reaction (+) at a few of the induction readings; none of the subject had a reaction after the challenge patch.

- In a photosensitization patch test, a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%) was applied to the backs of subjects (n = 101) and repeated

approximately 2 weeks later. The test sites were exposed to an UV light after the administration of the second patch was administered. There were no signs of photosensitization in any subject.

- In a photosensitization patch test (n = 52), occlusive patches of a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%) were administered 3 days per week for 10 applications. The test sites were exposed to an UV light after the first, fourth, seventh, and tenth induction patches and the challenge patch were read. There were no signs of photo-sensitization in any subject at any reading.

The Research Institute for Fragrance Materials (RIFM) has replied to CIR's query about their intentions with regards to writing their own safety assessment of Eucalyptus Globulus Leaf/Twig Oil and Eucalyptus Globulus Leaf Water, which only function as fragrance ingredients. These ingredients are not scheduled for review by the Expert Panel for Fragrance Safety in the near future.

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Memorandum

TO: Bart Heldreth, P.h.D.,
Executive Director, Cosmetic Ingredient Review(CIR)

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

DATE: November 9, 2017

SUBJECT: Eucalyptus Globulus Leaf Oil

Research Testing Laboratories Incorporated. 1980. Human subject patch test study: Schwartz-Peck Prophetic Patch and Draize-Shelanski Repeat Insult test of a skin cream containing 0.1% Eucalyptus Oil.

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HUMAN SUBJECT PATCH STUDY [redacted]

conducted for

[redacted]

A skin cream was formulated with 1.466% essential oils, of which 6.8813% was eucalyptus oil (CAS 8000-48-4). Thus, the skin cream contained 0.1% eucalyptus oil.

submitted by

Samuel M. Peck, M.D., Senior Investigator

Irwin I. Kantor, M.D., Consulting Dermatologist

Joseph F. Migliarese, Ph.D., Executive Director

RESEARCH TESTING LABORATORIES INCORPORATED

November 11, 1980

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TABLE OF CONTENTS

SCHWARTZ-PECK PROPHETIC PATCH

The skin cream contains 0.10% eucalyptus oil (CAS 8000-48-4)

DRAIZE-SHELANSKI REPEAT INSULT

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[redacted]

SCHWARTZ-PECK PROPHETIC PATCH

1/5/81 9.M.9

[redacted]

7. Skin Cream [redacted]

[redacted]

[redacted]

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SKIN CREAM [redacted]

SCHWARTZ-PECK PROPHETIC PATCH PROCEDURE

In September 1980, the subjects participating in this study were patched with the above mentioned product for the purpose of determining whether the ingredients contained therein were capable of producing immediate or primary irritation of the skin, or were capable of producing any allergenic sensitization of the skin.

The patch tests were performed as open and closed patches in the following manner:

1. After the skin of the upper back was thoroughly cleansed and allowed to dry, the test product was put on the back after it had been applied to Band-Aid strips supplied by) for occlusive patching. The results were read forty-eight hours later.

2. Simultaneously an open patch was applied using the volar aspect slightly above the left wrist, and read forty-eight hours later.

3. After a rest period of approximately fourteen days, a second open and closed insult was applied and read forty-eight hours later.

In addition, in order to evaluate light sensitization, the subjects' backs were exposed to an ultra-violet light source (Hanovia Tanette Mark I Lamp) at a distance of twelve inches for one minute. This lamp has a wave length including 3600°. The skin sites where the closed patches had been applied were irradiated after the second insult had been read. The subjects returned forty-eight hours after this exposure to note whether any ultra-violet light sensitization had occurred.

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The patch test readings were interpreted according to the International Contact Dermatitis Research Group: Terminology of Contact Dermatitis, Acta Dermatovener (Stockholm) 50:287-292, 1970.

Negative	-
Weak (non-vesicular) reaction	1+
Strong (edematous or vesicular) reaction	2+
Extreme (bullous or ulcerative) reaction	3+

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SKIN CREAM [redacted]

Subj	CLOSED PATCHES 1st Insult	CLOSED PATCHES 2nd Insult	OPEN PATCHES 1st Insult	OPEN PATCHES 2nd Insult	ULTRA VIOLET LIGHT
11	1+	-	-	-	-
28	-	1+	-	-	-
51	1+	-	-	-	-
84	1+	-	-	-	-
85	1+	-	-	-	-
104	-	1+	-	-	-

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SUMMARY OF PATCH RESULTS

SKIN CREAM [redacted]

INSULT	READING			
	Neg	1+	2+	3+
Closed				
1	97	4	-	-
2	99	2	-	-
Ultra Violet				
2	101	-	-	-

Open: All subjects were negative

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SUBJECTS WHO PARTICIPATED IN SCHWARTZ-PECK PROPHETIC PATCH STUDY

Number	Subject	Sex	Age	Vocation
1	R.A.	F	35	Housewife
2	I.A.	F	61	Housewife
3	N.A.	M	62	Retired
4	V.A.	F	35	Housewife
5	S.B.	F	32	Housewife
6	I.B.	F	47	Waitress
7	J.C.	F	26	Nurse
8	N.B.	F	36	Housewife
9	N.B.	F	36	Housewife
10	J.B.	F	31	Housewife
11	P.B.	F	31	Housewife
12	K.B.	F	31	Teacher
13	K.B.	F	25	Housewife
14	M.B.	F	63	Housewife
15	R.B.	F	55	Housewife
16	M.C.	F	30	Housewife
17	F.C.	F	30	Housewife
18	J.C.	M	53	Maintenance
19	E.C.	F	39	Housewife
21	M.D.	F	33	Housewife
22	H.D.	F	49	SchoolAide
23	A.D.	F	56	Housewife
24	E.D.	F	39	Housewife
25	S.G.	F	61	Retired
26	P.D.	F	34	Housewife
27	D.E.	F	22	Student
28	R.F.	F	26	Housewife
29	C.F.	F	39	Housewife
30	M.F.	F	36	Housewife
31	L.F.	F	34	Housewife
32	B.F.	M	18	Student
33	M.F.	F	35	Housewife
34	L.F.	F	33	Housewife
35	E.G.	F	49	Housewife
36	L.G.	F	48	Housewife
37	O.G.	F	60	Housewife
38	M.G.	F	30	Housewife
39	M.G.	F	39	Housewife
40	L.G.	F	61	Clerk
41	E.G.	F	46	Housewife
42	H.G.	F	28	Housewife
43	B.H.	F	74	Housewife
44	A.H.	F	51	Housewife
45	G.H.	F	48	Housewife
46	L.H.	F	18	Student
47	J.H.	F	28	Housewife
48	B.H.	F	24	Housewife
49	L.H.	F	50	Housewife
51	D.K.	F	34	Housewife
52	L.K.	F	70	Housewife

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SUBJECTS WHO PARTICIPATED IN SCHWARTZ-PECK PROPHETIC PATCH STUDY

Number	Subject	Sex	Age	Vocation
53	I.L.	F	56	Housewife
54	V.L.	M	54	Maintenance
55	E.L.	F	53	Housewife
56	A.L.	F	32	Housewife
57	T.M.	F	52	Clerk
58	R.M.	F	34	Housewife
59	M.M.	F	42	Housewife
60	E.M.	F	39	Housewife
61	R.M.	F	42	Housewife
62	P.M.	F	40	Housewife
65	L.M.	F	59	Housewife
66	R.M.	F	41	Teacher
67	L.M.	F	27	Housewife
68	L.N.	F	41	Housewife
69	L.N.	F	39	Teacher
70	G.N.	F	47	Housewife
71	K.N.	F	35	Housewife
72	M.N.	F	44	Housewife
73	M.N.	F	36	Housewife
74	B.O.	F	36	Housewife
75	J.P.	F	39	Housewife
76	L.P.	F	64	Housewife
77	I.P.	M	67	Retired
78	A.P.	F	65	Housewife
79	M.P.	F	21	Ins.Investigator
80	K.P.	F	45	SchoolLunch
81	R.P.	M	42	Salesman
82	S.P.	F	35	Housewife
83	D.R.	F	47	Housewife
84	M.R.	F	33	Housewife
85	M.R.	F	41	Housewife
86	N.R.	F	41	Housewife
87	M.R.	F	41	Housewife
88	C.R.	F	62	Housewife
89	E.R.	F	47	Housewife
90	M.R.	F	19	Housewife
91	P.S.	F	33	Housewife
92	A.S.	F	36	Housewife
93	H.S.	M	51	Metalurgist
94	B.S.	F	40	Housewife
95	D.S.	F	36	Housewife
96	S.S.	F	38	Housewife
97	C.T.	F	63	Housewife
98	T.T.	F	49	Housewife
99	E;T,	F	66	Housewife
100	J.T.	F	39	Waitress
101	N.U.	F	33	Housewife
102	J.V.	F	65	Housewife
103	D.W.	F	36	Housewife
104	J.Z.	M	69	Retired
105	R.Z.	F	43	Housewife

The following subjects dropped from the study for personal reasons, not product related:
20, 50, 63, 64

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DRAIZE-SHELANSKI REPEAT INSULT

[redacted]

7. Skin Cream [redacted]

[redacted]

The skin cream contained 0.1% eucalyptus oil

[redacted]

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SKIN CREAM [redacted]

DRAIZE-SHELANSKI REPEAT INSULT PROCEDURE

In September 1980, the subjects participating in this study were patched with the above mentioned product for the purpose of determining whether the ingredients contained therein were capable of producing immediate or primary irritation of the skin, or were capable of producing any allergenic sensitization of the skin.

The patch tests were performed as open and closed patches in the following manner:

1. After the skin of the upper back was thoroughly cleansed and allowed to dry, the test product was put on the back after it had been applied to Band-Aid strips supplied by for occlusive patching. The results were read forty-eight hours later.

2. Simultaneously an open patch was applied using the volar aspect slightly above the left wrist, and read forty-eight hours later.

3. The open and closed insults of the test product were applied every Monday, Wednesday and Friday for three and a half weeks for ten insults.

4. After a rest period of approximately fourteen days, an eleventh open and closed insult was applied and read forty-eight hours later.

In addition, in order to evaluate light sensitization, the subjects' backs were exposed to an ultra-violet light source (Hanovia Tanette Mark I Lamp) at a distance of twelve inches for

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one minute. This lamp has a wave length including 3600 A°. The skin sites where the closed patches had been applied were irradiated after the first, fourth, seventh, tenth and eleventh insults had been read. The subjects returned forty-eight hours after these exposures to note whether any ultra-violet light sensitization had occurred.

In order to facilitate interpretation and at the same time reduce both potential fatigue and tape reactions, a quadrant approach to patching the back was undertaken. The portion of the back that was to be patched was divided into four quadrants. Three of the quadrants were used for induction patching, and one was used solely as a virgin site for the challenge. The first quadrant received the first, fourth, seventh and tenth insults, the second quadrant received the second, fifth and eighth insults, and the third quadrant received the third, sixth and ninth insults. Patches were applied to the same site within each quadrant. This method makes it possible to read delayed reactions.

The patch test readings were interpreted according to the International Contact Dermatitis Research Group: Terminology of Contact Dermatitis, Acta Dermatovener (Stockholm) 50:287-292, 1970.

Negative ..... -
Weak (non-vesicular) reaction ..... 1+
Strong (edematous or vesicular) reaction ... 2+
Extreme (bullous or ulcerative) reaction ... 3+

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SKIN CREAM [redacted]

Subj No	1st Ins	U-V	2nd Ins	3rd Ins	4th Ins	U-V	5th Ins	6th Ins	7th Ins	U-V	8th Ins	9th Ins	10th Ins	U-V	11th Ins	U-V
2	-	-	-	-	-	-	1+	-	-	-	-	-	-	-	-	-
3	1+	-	1+	-	-	-	1+	-	-	-	1+	-	-	-	-	-
14	-	-	1+	1+	-	-	-	1+	1+	-	-	1+	1+	-	-	-
21	-	-	-	-	-	-	-	-	-	-	-	1+	-	-	-	-
51	-	-	-	-	-	-	-	-	-	-	-	1+	-	-	-	-
54	-	-	-	-	-	-	-	-	-	-	-	1+	-	-	-	-

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SUMMARY OF PATCH RESULTS

SKIN CREAM [redacted]

INSULT	READINGS				Not Re-patched
	Neg	1+	2+	3+	
Closed					
1	51	1	-	-	-
2	50	2	-	-	-
3	51	1	-	-	-
4	52	-	-	-	-
5	50	2	-	-	-
6	51	1	-	-	-
7	51	1	-	-	-
8	51	1	-	-	-
9	48	4	-	-	-
10	51	1	-	-	-
11	52	-	-	-	-
Ultra Violet					
1	52	-	-	-	-
4	52	-	-	-	-
7	52	-	-	-	-
10	52	-	-	-	-
11	52	-	-	-	-

Open: All subjects were negative

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SUBJECTS WHO PARTICIPATED IN DRAIZE-SHELANSKI REPEAT INSULT STUDY

Number	Subject	Sex	Age	Vocation
1	C.A.	F	55	Housewife
2	C.A.	F	63	Housewife
3	S.B.	F	36	Housewife
4	P.B.	F	32	Housewife
5	E.B.	F	64	Housewife
6	N.C.	F	43	Housewife
7	L.C.	F	28	Housewife
8	P.C.	F	40	Housewife
9	K.C.	F	40	Housewife
10	D.D.	F	37	Housewife
11	G.D.	F	42	Housewife
12	M.D.	F	39	Housewife
13	L.E.	F	44	Housewife
14	D.F.	F	25	Housewife
15	A.F.	F	53	Housewife
16	J.F.	F	45	Housewife
17	E.F.	F	30	KeyPunch
18	M.G.	F	43	Housewife
19	D.G.	F	27	Lab.Tech.
20	L.G.	F	48	Housewife
21	M.H.	F	44	Housewife
22	H.J.	F	63	Retired
23	L.K.	F	28	Housewife
24	M.L.	F	30	Housewife
25	T.L.	F	34	Reg.Nurse
26	S.L.	F	36	Sales
27	A.L.	F	58	Housewife
28	M.L.	F	44	Housewife
29	C.L.	F	31	Housewife
30	H.M.	F	69	Housewife
31	J.M.	F	26	Housewife
32	L.M.	F	47	Housewife
34	D.O.	F	54	Housewife
35	C.O.	F	43	Housewife
37	M.P.	F	35	Reg.Nurse
38	R.P.	F	31	Housewife
39	C.P.	F	71	Retired
40	M.P.	M	66	Retired
41	M.R.	F	31	Housewife
42	K.R.	F	38	CrossingGuard
43	B.R.	F	35	Housewife
44	L.R.	F	34	Housewife
45	R.S.	F	31	Reg.Nurse
46	E.S.	F	40	Housewife
47	C.S.	F	29	Housewife
48	L.S.	F	65	Housewife
49	C.S.	F	59	Housewife
50	R.T.	F	56	Housewife
51	A.V.	F	47	Housewife
52	Y.W.	F	52	Housewife
53	E.W.	F	38	Housewife
54	C.Z.	F	31	Housewife

The following subjects dropped from the study for personal reasons, not product related: 33, 36

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[redacted]

[redacted]

PRODUCT NAME: [redacted]
FORMULA NUMBER:
PROJECT NUMBER:
REPORT NUMBER:

1. Animal Toxicity/Irritancy Tests

POSITIVE	RESULTS	NEGATIVE
	Skin Irritant	
_____	Open	_____
_____	Closed	_____
	Ocular Irritant	
_____	Undilute	_____
_____	Rinse	_____
_____	Dilute	_____
_____	Oral Toxicity	_____
_____	Percutaneous Toxicity	_____

2. Human Patch Tests

POSITIVE	RESULTS	NEGATIVE
	Prophetic Patch Test	
_____	Closed	✓ b
_____	Open	✓
_____	Photosensitization	✓
	Repeat Insult Patch Test	
_____	Closed	✓
_____	Open	✓
_____	Photoirritation	✓
_____	Photoallergenicity	✓

3. Human Usage Test

POSITIVE	RESULTS	NEGATIVE
_____	Irritation	_____
_____	Sensitization	_____

[redacted]

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[redacted] SKIN CREAM [redacted]

[redacted]

I. Schwartz-Peck Prophetic Patch

A. Closed patch; 101 subjects

1) 1st insult: 4 It

2) 2nd insult: 2 It

B. Open patch; 101 subjects

1) 1st insult: 0/101

2) 2nd insult: 0/101

C. Ultraviolet exposure (2nd insult) 0/101

II. Draize-Shelanski Repeat Insult; 52 subjects

	1	2	3	4	5	6	7	8	9	10	11
Closed	1 It	2 It	1 It	0/52	2 It	1 It	1 It	1 It	4 It	1 It	0/52
Open	0/52	—									→
U.V.	0/52			0/52			0/52			0/52	0/52

III. Other Testing

[redacted]

[redacted]

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: November 20, 2017
Subject: Wave 2 – *Ginkgo biloba*-Derived Ingredients

The Council has provided data on Ginkgo Biloba Leaf Extract (*ginkgo122017wave2_data1* and *ginkgo122017wave2_data2*). These data include information on extraction methods, composition and impurities information, and dermal irritation and sensitization data. Ginkgo Biloba Leaf Extract (100%; ethanol:water:butylene glycol extract) was not irritating in 20 subjects in a 24 h patch test and no sensitization was observed in a semi-occluded human repeated insult patch test (HRIPT) of 201 subjects with a leave-on product containing 0.1% Ginkgo Biloba Leaf Extract.

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(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

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Personal Care Products Council
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Memorandum

TO: Bart Heldreth, P.h.D
Executive Director, Cosmetic Ingredient Review (CIR)

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

DATE: November 6, 2017

SUBJECT: Ginkgo Biloba Leaf Extract

Anonymous. 2017. Summary: HRIPT of a leave-on product containing 0.1% Ginkgo Biloba Leaf Extract.

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Product Number	% Ginkgo Biloba Leaf Extract	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail
1	0.1	Leave - On	YES	SEMI OCCLUSIVE	201	NO	0	0	0	0	PASS

Product Number 1

Calculation of Amount of Ginkgo Biloba Leaf Extract in mg/cm2	
Concentration of Ginkgo Biloba Leaf Extract in Product in %	0.1
Amount of Product applied to Skin during HRIPT in ml/mg	0.2
Patch Size cm^2	4
Dose density of product applied to patched skin in mg/cm2	50
Dose Density of Ginkgo Biloba Leaf Extract applied to patch skin in mg/cm2	0.05000000
Conclusion: Amount of Ginkgo Biloba Leaf Extract applied to skin is 0.05 mg/cm^2	

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ICDRG Reading scale	
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 (may be weeping)
E	Edema
–	No reading

Details of Test methodolgy and Results	
0	panelist discontinued due to test material reactions
24 hrs	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge
24, 48, 72, 96 hrs post patching	Challenge readings

Grading Scale interpretation	
Low Level Reactions	1
High Level Reaction	2 and above

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Memorandum

TO: Bart Heldreth, P.h.D
Executive Director, Cosmetic Ingredient Review (CIR)

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

DATE: November 13, 2017

SUBJECT: Ginkgo Biloba Leaf Extract

Anonymous. 2017. Summary information Ginkgo Biloba Leaf Extract.

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November 2017

Ginkgo Biloba Leaf Extract

Questions

- Extraction methods
- Composition and impurities
- Toxicological data, specifically dermal and ocular irritation and sensitization data
- How well does the composition of the material tested by NTP represent your company's cosmetic ingredient? ;flavonol glycosides, terpene lactones (bilo-balide, ginkgolide A, ginkolide B, ginkgolide C), and ginkgolic acid"
- How much quercetin does your company's ingredient contain?

1. Extraction methods

Trade Name	Extraction method
Ginkgo Extract	extracted with ethanol-water solution
Ginkgo Extract BG	extracted with ethanol-water solution, evaporated and resolved in 50%BG

2. Composition and impurities

Trade Name	(a)Composition, (b)Impurity data
Ginkgo Extract	(a) Flavonoid, glycoside and tannin (b) Heavy metals : Not more than 10ppm Arsenic : Not more than 2ppm
Ginkgo Extract BG	(a) Flavonoid, glycoside and tannin (b) Heavy metals : Not more than 10ppm Arsenic : Not more than 2ppm

3. Toxicological data, specifically dermal and ocular irritation and sensitization data

Ginkgo Extract BG

	Human patch test
Participants	20 Japanese people
Concentration	100%
Application	24 hours
Result	Negative

4. Flavonol glycosides, terpene lactones (bilobalide, ginkgolide A, ginkolide B, ginkgolide C), and ginkgolic acid

Typical analysis data of Ginkgo Extract BG: 0.51% flavonol glycosides and 0.16% terpene lactones (0.08% bilobalide, 0.04% ginkgolide A, 0.02% ginkolide B and 0.02% ginkgolide C). Ginkgolic acid is lower than 0.1 ppm.

Typical analysis data Ginkgo Extract BG: 0.21% quercetin.

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MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: November 20, 2017

Subject: Additional Information for *Hamamelis virginiana* (Witch Hazel) As Used In Cosmetics

The Research Institute for Fragrance Materials (RIFM) has replied to CIR's query about their intentions with regards to writing their own safety assessment of Hamamelis Virginiana (Witch Hazel) Flower Water, which only functions as a fragrance ingredient. This ingredient is not scheduled for review by the Expert Panel for Fragrance Safety in the near future.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: November 20, 2017
Subject: Wave 2 – Malic Acid

Dr. Belsito has shared a relevant article on the potential cytotoxicity and apoptotic effects of Malic Acid in human skin keratinocytes.

> Yu-Ping Hsiao YP; Lai WW; Wu SB; et al. 2015. Triggering Apoptotic Death of Human Epidermal Keratinocytes by Malic Acid: Involvement of Endoplasmic Reticulum Stress- and Mitochondria-Dependent Signaling Pathways, Toxins (Basel). 7(1): 81–96.

This reference may be accessed for free at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303815/

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: November 20, 2017
Subject: Wave 2 Data on *Mentha piperita* (Peppermint)-Derived Ingredients

The data listed below (in *pepper122017data1* and *pepper122017data2* files) on Mentha Piperita (Peppermint) Extract were received from the Council and are being submitted as attachments to this memorandum. A data summary document (*pepper122017wave2studysummaries*) is also attached for the Panel's review. The data that were received include:

pepper122017data1 file:

- Certificate of analysis of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract
- Human Repeated insult patch test (HRIPT) of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract
- *in vitro* ocular irritation test of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract
- Bacterial reverse mutation assay of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract
- Executive summary of an HRIPT of a cosmetic product containing 0.00554% Mentha Piperita (Peppermint) Extract
- Executive summary of a human maximization test of a cosmetic product containing 0.00554% Mentha Piperita (Peppermint) Extract

pepper122017data2 file:

- Composition data an aqueous solution composed of 7.5% Mentha Piperita (Peppermint) Extract
- Method of manufacture of an aqueous solution composed of 7.5% Mentha Piperita (Peppermint) Extract
- Impurities data of an aqueous solution composed of 7.5% Mentha Piperita (Peppermint) Extract
- Ocular irritation study (rabbits) of an aqueous solution composed of 7.5% Mentha Piperita (Peppermint) Extract
- Skin irritation study (rabbits) of an aqueous solution composed of 7.5% Mentha Piperita (Peppermint) Extract
- Maximization test (guinea pigs) of an aqueous solution composed of 7.5% Mentha Piperita (Peppermint) Extract

These data will be added to the safety assessment after the Panel meeting.

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Wave 2 Data on *Mentha piperita*-Derived Ingredients

CHEMISTRY

Physical and Chemical Properties

Mentha Piperita (Peppermint) Extract

The following physical properties are included in a certificate of analysis for a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract: specific gravity (1.031) and refractive index (1.4498).[1]

Method of Manufacture

Mentha Piperita (Peppermint) Extract

According to one company (anonymous), the main steps in the process of manufacturing a trade name mixture defined as an aqueous solution containing 7.5% Mentha Piperita (Peppermint) Extract are: solubilization of *Mentha piperita* in water, separation of soluble and insoluble phases, and filtration and sterilizing filtration.[2]

Composition

Mentha Piperita (Peppermint) Extract

According to one company (anonymous), Mentha Piperita (Peppermint) Extract (trade name mixture) is an aqueous solution composed of 7.5% (maximum percentage) Mentha Piperita (Peppermint) Extract, with < 40 ppm pulegone and < 50 ppm menthol.[2] The following statement relating to composition was also provided: "Our active can be divided in sugars (47%), mineral ashes (38%), proteins (13%), and polyphenols (2%)."

Impurities

Mentha Piperita (Peppermint) Extract

The following information relating to impurities is included in a certificate of analysis for a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract: lead (< 10 ppm), arsenic (< 3 ppm), mercury (< 1 ppm), and pesticide residues (meets USP specification).[1]

Impurities data on Mentha Piperita (Peppermint) Extract (trade name mixture), defined as an aqueous solution containing 7.5% Mentha Piperita (Peppermint) Extract are: alkaloids (< 0.05 g/l; assay of alkaloids performed with Dragendorff reagent), copper (0.23 ppm), iron (3.76 ppm), manganese (21 ppm), nickel (0.19 ppm), and zinc (3.14 ppm).[2] In an assay of allergens, no allergens were detected in this aqueous solution (i.e., the concentrations were less than the sensitivity of the method (< 1 ppm)). There also was no trace of pesticides in this aqueous solution.

GENOTOXICITY STUDIES

Mentha Piperita (Peppermint) Extract

The genotoxicity of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract was evaluated in the Ames test using the following *Salmonella typhimurium* strains, with and without metabolic activation: TA97a, TA98, TA100, TA102, and TA1535.[3] The trade name mixture was diluted with sterile distilled water to a concentration of 10% (effective concentration of extract = 0.25%) prior to testing each strain. Sterile deionized water served as the solvent control and positive controls (not stated) were also used. The test substance was not cytotoxic to the test system and was not genotoxic to any of the strains tested, either with or without metabolic activation. The bacterial strains tested were sensitive to the positive control mutagens and had a spontaneous reversion rate that was well within the accepted values for each strain.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

The skin irritation potential of a trade name mixture containing 7.5% Mentha Piperita (Peppermint) Extract was evaluated using 3 rabbits (strain not stated).[2] The mixture (0.5 ml) was applied, under a semi-occlusive dressing, to intact skin for 4 h. The area (cm^2) of application was not stated. No cutaneous reactions were observed, and the authors concluded that the mixture was a non-irritant.

Irritation and Sensitization

Human

Mentha Piperita (Peppermint) Extract

A human repeated insult patch test (HRIPT) on a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract was performed using 52 male and female subjects.[4] Prior to application, the mixture was prepared as a 10% dilution using distilled water (effective concentration of extract = 0.25%). A 1" x 1" semi-occlusive patch containing the diluted mixture (0.2 ml) was applied for 24 h to the upper back (between the scapulae) 3 times per week for a total of 9 applications. Following a 2-week non-treatment period, the diluted mixture (0.25% Mentha Piperita (Peppermint) Extract) was applied to a new test site that was adjacent to the original site. Reactions were scored at 24 h and 72-h post-application. There was no evidence of dermal irritation or allergic contact sensitization in any of the subjects tested. Also, no adverse events were identified during the study.

The cumulative irritation and/or allergic contact sensitization potential of cosmetic product (an off-white cream) containing 0.00554% Mentha Piperita (Peppermint) Extract was evaluated in an HRIPT involving 51 male and female subjects.[5] The cream (~ 0.23 g) was applied for 24 h to the upper back (between the scapulae; area not stated). The application procedure (induction and challenge) is identical to the one that is reported in the preceding study. Also, challenge reactions were scored at the same intervals. The product did not cause dermal irritation or allergic contact dermatitis in any of the subjects tested.

Sensitization

Animal

Mentha Piperita (Peppermint) Extract

The skin sensitization potential of a trade name material containing 7.5% Mentha Piperita (Peppermint) Extract was evaluated in the maximization test using 10 albino guinea pigs.[2] The first induction involved 2 intradermal injections of the trade name material, 2 intradermal injections of Freund's complete adjuvant (FCA), and 2 intradermal injections of a mixture of FCA and the trade name material. The second induction involved topical application of the product 24 h after brushing with 10% sodium lauryl sulfate (SLS). Following a 19-day non-treatment period, the challenge phase involved topical applications of the tradename material (undiluted and at a concentration of 50% (effective concentration of extract = 3.75%)) under an occlusive dressing for 24 h. No macroscopic cutaneous reactions attributable to allergy were associated with application of the trade name material. There also were no cutaneous intolerance reactions in animals of the negative control group (further details not provided).

Human

Mentha Piperita (Peppermint) Extract

A maximization test on a cosmetic product (off-white cream) containing 0.00554% Mentha Piperita (Peppermint) Extract was performed using 26 male and female subjects.[6] Initially, the test site (upper outer arm; area not stated) was pre-treated with 0.25% aqueous SLS, applied under an occlusive patch for 24 h. The product (0.05 ml) was then applied, under an occlusive patch, to the same site for 48 h (or for 72 h, if placed over a weekend). Product application was followed by re-application of the SLS patch for 24 h. This sequence was repeated for a total of 5 induction exposures. Following a 10-day non-treatment period, a new test site (on opposite arm) was pre-treated with SLS prior to application of the challenge patch. At challenge, the product (0.05 ml) was applied for 48 h, under an occlusive patch, to the same site. Reactions were scored at the time of patch removal and 48 h later. No instances of contact allergy were at 48 h or 72 h after application of the challenge patch. Because the product did not possess a detectable contact-sensitizing potential, the authors stated that it would not likely cause contact sensitivity reactions under normal use conditions.

OCULAR IRRITATION STUDIES

In Vitro

Mentha Piperita (Peppermint) Extract

The ocular irritation potential of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract was evaluated using an *in vitro* toxicity testing system consisting of normal, human-derived epidermal keratinocytes.[7] The cells had been cultured to form a stratified squamous epithelium that is similar to that found in the cornea. The procedure utilized a tetrazolium salt (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT)) that is reduced by succinate dehydrogenase (in viable m itochondria of viable cells) to a formazan derivative. The amount of MTT that is reduced by a culture is proportional to the number of viable cells. The trade name mixture, at a concentration of 10% in corn oil (effective concentratration of extract = 0.25%) and a volume of 100 µl, was added to cell cultures; the incubation periods were 1 h, 4 h, and 24 h. Corn oil served as the negative control. An ET_{50} (time of exposure needed for a test material to reduce the viability of treated tissues to 50% of control tissues) was calculated. Values for % viability were: 108% (at 1 h), 100% (at 4 h), and 34% (at 24 h). Results indicated that the trade name mixture at a concentration of 10% (ET_{50} = 15.5 h (non-irritating, minimal)) had an ocular irritation potential that was somewhat less that sodium dodecyl sulfate at a concentration of 0.3% (ET_{50} = 740 minutes (12.3 h)).

In Vivo

Mentha Piperita (Peppermint) Extract

A trade name mixture containing 7.5% Mentha Piperita (Peppermint) Extract was instilled (0.1 ml) into 1 eye of each of 3 New Zealand rabbits.[2] Slight conjunctival redness was observed in 2 animals and lacrimation was observed in 1 animal. The trade name mixture was classified as a slight ocular irritant.

References

1. Anonymous. Certificate of analysis of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract. Unpublished data sumitted by the Personal Care Products Council on 11-6-2017. 2017. pp.1

2. Anonymous. Safety assessment of Mentha Piperita-Derived Ingredients as used in cosmetics (information on Mentha Piperita (Peppermint) Extract. Unpublished data submitted by the Personal Care Products Council on 11-6-2017. 2017. pp.1-2.

3. Consumer Product Testing Company. Bacterial reverse mutation assay (trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract. Unpublished data submitted by the Personal Care Products Coucil on 11-6-2017. 2017. pp.1-6.

4. Consumer Product Testing Company. Repeated insult patch test of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract. Unpublished data submitted by the Personal Care Products Council on 11-6-2017. 2017. pp.1-9.

5. Consumer Product Testing Company. Executive summary of a repeated insult patch test of a cosmetic product (off-white cream containing 0.00554% Mentha Piperita (Peppermint) Extract). Unpublished data submitted by the Personal Care Products Council on 11-6-2017. 2017. pp.1-3.

6. Ivy Laboratories (KGL, Inc. Executive summary of a human maximization test of an off-white cream containing 0.00554% Mentha Piperita (Peppermint) Extract. Unpublished data submitted by the Personal Care Products Council on 11-6-2017. 2011. pp.1-4.

7. Consumer Product Testing Company. The MatTek Corporation sub-Draize mildness testing (MTT - ET50) using the Epiocular® toissue model *in vitro* toxicity testing system (trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract). Unpublished data submitted by the Personal Care Products Council on 11-6-2017. 2017. pp.1-5.

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Personal Care Products Council
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Memorandum

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

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

DATE: November 6, 2017

SUBJECT: Mentha Piperita (Peppermint) Extract

The trade name mixture tested in all of the studies associated with this memo contains 2.5% Mentha Piperita (Peppermint) Extract. This is a whole plant extract made with water and Triethyl Citrate.

Anonymous. 2017. Certificate of analysis trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract.

Consumer Product Testing Co. 2017. Repeated insult patch of a trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract.

Consumer Product Testing Co. 2017. The MatTek Corporation sub-Draize mildness testing (MTT ET-50) using the EpiOcular™ tissue model *in vitro* toxicity testing system (trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract).

Consumer Product Testing Co. 2017. Bacterial reverse mutation assay (trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract).

Consumer Product Testing Co. 2012. Executive summary of a repeated insult patch test of cosmetic product (off-white cream containing 0.00554% Mentha Piperita (Peppermint) Extract).

Ivy Laboratories (KGL, Inc.). 2011. Executive summary of a human maximization test of an off-white cream containing 0.00554% Mentha Piperita (Peppermint) Extract.

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August 2017

Certificate of Analysis
trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract

Analysis

	Specification	**Result**
Specific Gravity	1.025-1.045	1.031
Refractive Index	1.4421-1.4621	1.4498
Color	Gardener 6 Max	Gardner 1
Odor	Characteristic	Characteristic
Lead	Less than 10 ppm	Conforms
Arsenic	Less than 3 ppm	Conforms
Mercury	Less than 1 ppm	Conforms
Pesticide Residues	Meets USP <561>	Conforms

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Consumer Product Testing Co.

ISL 1975

FINAL REPORT

CLIENT:

ATTENTION:

TEST: Repeated Insult Patch Test
Protocol No.: CP-01.01S

TEST MATERIAL: Tradename mixture containing 2.5% Mentha Piperita (Peppermint) Extract

EXPERIMENT REFERENCE NUMBER: C17-0790.01

Reviewed by: Richard R. Eisenberg, M.D.
Medical Director
Board Certified Dermatologist

Approved by: Michael Caswell, Ph.D., CCRA, CCRC
Vice President, Clinical Evaluations
13 April 2017

Approved by: Joy Frank, R.N.
Executive Vice President, Clinical Evaluations
4/13/17

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Consumer Product Testing Co.

EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study Number: C17-0790.01

The Consumer Product Testing Company, Incorporated (CPTC) Quality Assurance Unit (QAU) is responsible for auditing the conduct, content and reporting of all clinical trials that are conducted at CPTC.

This trial has been conducted in accordance with the Declaration of Helsinki, the ICH Guideline E6 for *Good Clinical Practice*, the requirements of 21 CFR Parts 50 and 56, other applicable laws and regulations, CPTC Standard Operating Procedures, and the approved protocol.

The CPTC QAU has reviewed all data, records, and documents relating to this trial and also this Final Report. The following QAU representative signature certifies that all data, records, and documents relating to this trial and also this Final Report have been reviewed and are deemed to be acceptable, and that the trial conforms to all of the requirements as indicated above.

All records and documents pertaining to the conduct of this trial shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QAU to obtain custody of trial records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, trial-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

William Cavaliere
Quality Assurance Representative

4/17/2017
Date

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Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: Fifty-seven (57) qualified subjects, male and female, ranging in age from 21 to 79 years, were selected for this evaluation. Fifty-two (52) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] to 79 years.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material:

Trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extrac

Study Schedule:

Panel #	Initiation Date	Completion Date
20170070	February 22, 2017	April 6, 2017

[a]With parental or guardian consent

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Methodology:

Prior to the initiation of this study, the test material was prepared as a 10% dilution, using distilled water.

The upper back between the scapulae served as the treatment area. Approximately 0.2 ml the test material, or an amount sufficient to cover the contact surface, was applied to the 1" x 1" absorbent pad portion of a clear adhesive dressing. This was then applied to the appropriate treatment site to form a semi-occlusive patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications were discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of one day following each Tuesday and Thursday removal, and two days following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic Day 1 and Day 3 post-application.

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Methodology (continued):

Evaluation Criteria (Erythema and additional Dermal Sequelae):

0	=	No visible skin reaction	E	=	Edema
0.5	=	Barely perceptible	D	=	Dryness
1	=	Mild	S	=	Staining
2	=	Moderate	P	=	Papules
3	=	Marked	V	=	Vesicles
4	=	Severe	B	=	Bullae
			U	=	Ulceration
			Sp	=	Spreading

Erythema was scored numerically according to this key. If present, additional Dermal Sequelae were indicated by the appropriate letter code and a numerical value for severity.

Adverse Events: There were no adverse events.

Amendments: There were no amendments.

Deviations: There were no deviations.

Results: The results of each participant are appended (Table 1).

Observations remained negative throughout the test interval.

Subject demographics are presented in Table 2.

Summary: Under the conditions of this study, test material, . indicated no potential for dermal irritation or allergic contact sensitization.

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Table 1
Panel #20170070

Individual Results

Subject Number	Day1*	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site Day 1*	Day 3
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0[m]	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	DID NOT COMPLETE STUDY										
29	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal
m = Additional makeup day granted at the discretion of the clinic supervisor

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Table 1
(continued)
Panel #20170070

Individual Results

Subject Number	Induction Phase									Virgin Challenge Site	
	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	DID NOT COMPLETE STUDY						
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	DID NOT COMPLETE STUDY											
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	DID NOT COMPLETE STUDY									
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	DID NOT COMPLETE STUDY									
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal

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Table 2
Panel #20170070

Subject Demographics

Subject Number	Initials	Age	Gender
1	F-P	77	F
2	MEH	65	F
3	JIR	52	M
4	HUS	57	M
5	F-M	38	M
6	MJC	38	F
7	F-V	78	M
8	MAH	76	F
9	J-C	79	M
10	SAV	52	F
11	EMZ	72	F
12	A-S	70	F
13	SER	72	F
14	B-C	75	F
15	LJW	76	F
16	A-V	60	F
17	MAM	35	M
18	M-A	69	F
19	HLF	40	F
20	WYA	46	F
21	SJH	36	F
22	DJB	55	F
23	VJW	54	F
24	LME	52	F
25	A-A	33	F
26	TSR	29	F
27	DJL	65	F
28	RML	49	F
29	M-A	62	F

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Table 2
(continued)
Panel #20170070

Subject Demographics

Subject Number	Initials	Age	Gender
30	J-K	60	F
31	R-M	51	F
32	PAI	62	F
33	ZDS	28	F
34	LJL	56	F
35	ONG	33	F
36	DAL	21	M
37	JPL	57	F
38	KLK	30	F
39	J-B	55	M
40	G-O	79	F
41	SLK	59	F
42	PAF	56	F
43	A-B	44	F
44	G-T	56	F
45	W-S	38	M
46	RAC	42	F
47	TAF	42	F
48	DMK	70	M
49	CCL	21	F
50	SMF	28	F
51	JGT	29	F
52	J-M	71	F
53	LMK	77	F
54	BAD	73	F
55	LME	75	F
56	J-J	78	F
57	BIB	25	M

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Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT:

ATTENTION:

TEST: The MatTek Corporation Sub-Draize Mildness Testing (MTT ET-50) Using the EpiOcular™ Tissue Model *In Vitro* Toxicity Testing System

TEST ARTICLE:

Trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract

EXPERIMENT REFERENCE NO.: V17-0772

3/12/17

Steven Nitka
Vice President
Laboratory Director

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70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

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EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: V17-0772

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed under Good Laboratory Practice principles (including government regulations to the extent applicable) and in accordance with standard operating procedures and applicable standard protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date listed below. The findings of this inspection may have been reported to management and the Study Director.

Date of data inspection: 3/17/17

Quality Assurance:

3/17/17

Signature/Date

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

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Objective:

To evaluate the test article for irritancy potential utilizing the MatTek Corporation EpiOcular *in vitro* toxicity testing system. The protocol used was developed to differentiate between articles for which the standard Rabbit Eye Draize testing is insensitive.

Introduction:

"MatTek's patented EpiOcular corneal Model consists of normal, human-derived epidermal keratinocytes which have been cultured to form a stratified, squamous epithelium similar to that found in the cornea. The epidermal cells, which are cultured on specially prepared cell culture inserts using serum free medium, differentiate to form a multilayered structure which closely parallels the corneal epithelium . . . " This system " . . . provides a predictive, morphologically relevant *in vitro* means to assess ocular irritancy."[1]

EpiOcular, when used with the recommended cell metabolism assay, can quickly provide toxicological profiles. The procedure utilizes a water-soluble, yellow, tetrazolium salt (MTT {3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide}), which is reduced by succinate dehydrogenase in the mitochondria of viable cells to a purple, insoluble formazan derivative. Substances which damage this mitochondrial enzyme inhibit the reduction of the tetrazolium salt. The amount of MTT reduced by a culture is therefore proportional to the number of viable cells.

Test Article:

trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract

Experimental Interval: March 8, 2017 to March 10, 2017

Method:

The Sponsor requested the article's irritation potential at 10%. After the appropriate tissue preparation, 100 microliters of the test article, at 10% in corn oil and the negative control (corn oil) were added to the Millicells containing the EpiOcular samples. The six (6) well plates containing the dosed EpiOcular samples were then incubated at 37°C, five (5)% carbon dioxide and ≥ 90% humidity.

[1]MatTek Corporation, 200 Homer Avenue, Ashland, Massachusetts 01721

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Method (continued):

After the appropriate exposure period, each insert was individually removed from its plate and rinsed with phosphate buffered saline (PBS) to remove any residual material. Each was then rinsed a second and third time. Following the 3 rinses, each Millicell was submerged in 5 milliliters of assay media for 10 minutes, at room temperature. This final soak removed any residual, absorbed article. After the 10 minutes, excess liquid was shaken off and each EpiOcular tissue was placed into 300 microliters of MTT solution. The EpiOcular samples were then returned to the incubator.

After the three (3) hour MTT exposure, each insert was removed and gently rinsed with PBS to remove any residual MTT solution. Excess PBS was shaken from each of the inserts, which were then blotted on the bottom using paper towels. The inserts were then each placed into one (1) well of a 24 well extraction plate. Each insert was then immersed in two (2) milliliters of extraction solution, at room temperature, overnight. After the extraction procedure, the liquid within each insert was decanted back into the well from which it was taken. The remaining extractant solution was then agitated and a 200 microliter aliquot of each extract was removed for evaluation. A Molecular Devices SpectraMax M5 Microplate Reader was used to determine the absorbance of each extract at 570nm. With the absorbance of the negative control (corn oil) defined as 100%, the percent absorbencies of the articles were determined. The percentages listed below directly correlate with the cell metabolism in the EpiOcular samples.

Results:

Article (% & Exposure)	System	Percent Viability	Percent Inhibition
Lot#: 020617			
(10% - 24 hrs.)	EpiOcular	34	66
(10% - 4 hrs.)	EpiOcular	100	0
(10% - 1 hr.)	EpiOcular	108	-8

Discussion:

Based on the literature (Kay, J.H. and Calandra, J.C., "Interpretation of eye irritation tests," *J. Soc. Cosmetic Chem.*, 13, 281-289 (1962)), Draize scores below 15 are classified as minimal to non-irritating. Mildness levels below those which the Draize test can differentiate may be desired. There follows data which exhibits this protocol's ability to differentiate between virtually non-irritating concentrations of two different reference articles.

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Discussion (continued):

Benzalkonium Chloride		
In Vivo %	Draize MMAS[2]	ET-50 (min)
0.10%	0	212.7
0.03%	0	2053.0

Sodium Dodecyl Sulfate		
In Vivo %	Draize MMAS[2]	ET-50 (min)
0.30%	0	740.1
0.10%	0	1938.3

Under the conditions of this test, the 020617 test article, at 10%, elicited *in vitro* results which indicate that its ET-50 is 15.5 hours.

Conclusion:

Under the conditions of this test, the results indicate that the 0617 test article, at 10%, has an ocular irritation potential somewhat less than sodium dodecyl sulfate at 0.3%.

Record Retention:

All records and documents pertaining to the conduct of this study shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QA Department to obtain custody of study records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, study-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

Professional personnel involved:

Steven Nitka, B.S.	-	Vice President Laboratory Director (Study Director)
Lillian Vazquez, B.S.	-	Laboratory Supervisor
Christine Vomehm	-	Quality Assurance Compliance Specialist
William Cavaliere	-	Quality Assurance Group Leader

[2]Modified maximum average score

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Consumer Product Testing Co.

ESTABLISHED 1975

BACTERIAL REVERSE MUTATION ASSAY

FINAL REPORT

STUDY NUMBER: M17-0789

SPONSOR:

SPONSOR'S REPRESENTATIVE:

TESTING FACILITY: Consumer Product Testing Company, Inc.
70 New Dutch Lane
Fairfield, NJ 07004
PH: (973) 808-7111 Ext. 202
FX: (973) 244-7517
Email: kgoins@cptclabs.com

STUDY DIRECTOR: D. Keith Goins, Ph.D.
Director, Microbiology

STUDY INITIATION DATE: February 21, 2017

STUDY COMPLETION DATE: March 17, 2017

REPORT PREPARED BY: D. Keith Goins 03/17/2017
D. Keith Goins, Ph.D. — Date
Director, Microbiology

REPORT REVIEWED BY: Patricia De Lorenzo 3/17/17
Quality Assurance — Date

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1.0 STUDY PURPOSE

The purpose of this study was to evaluate if the test samples would induce a mutagenic response in five different strains of *Salmonella typhimurium*, namely TA97a, TA 98, TA 100, TA102, and TA 1535. Test samples were screened at different dose levels by plating them with the tester strains both with and without Aroclor™ 1254 induced rat liver microsomes (S9). The test sample was considered mutagenic if it caused an increase in revertant colonies above the spontaneous background (i.e. no test sample) level.

2.0 TEST SAMPLES

The test sample was received from the sponsor and assigned the test sample number indicated below. The test sample was stored as indicated by the client-supplied storage conditions until testing commenced.

Name: trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract

Lot No: 020617
Storage Conditions: Room Temperature
CPTC ID No.: M17-0789.01

3.0 TEST SYSTEM:

The test systems used for the Bacterial Reverse Mutation Assay were :

Salmonella typhimurium TA 97a
Salmonella typhimurium TA 98
Salmonella typhimurium TA100
Salmonella typhimurium TA 102
Salmonella typhimurium TA1535

4.0 TEST SYSTEM JUSTIFICATION:

The Bacterial Reverse Mutation Assay is widely used to evaluate the mutagenic properties of chemicals.The test is based on the work of Dr. Bruce Ames and his coworkers and is commonly referred to as the Ames Test. Their studies involved the development of select histidine auxotrophs of *S. typhimurium* that are normally growth arrested due to mutations in a gene needed to produce the essential amino acid Histidine. In the absence of an external histidine source, the cells cannot grow to form colonies unless a reversion of the mutation occurs which allows the production of histidine to be resumed. As might be expected, spontaneous reversions occur with each of the strains. However, chemical agents can induce a mutagenic response so that the number of revertant colonies is substantially higher than the spontaneous background reversion level. The test involves the analysis of the number of revertant colonies that are obtained with each strain in the presence and absence of the test sample. Since the mutagenic response of a formulation could vary with the concentration, test samples are routinely dosed over an appropriate concentration range. In this study, a complete set of positive and negative controls was included with each assay, and was plated routinely with all of the tester strains. Aroclor™ 1254 induced rat liver microsomes were included to mimic the *in vivo* activity of the liver enzymes in activating some pro-mutagens to mutagenic status.

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5.0 PROCEDURE:

All testing was conducted in accordance with non-GLP Protocol M17-0789 (See attachment A)

5.1 SOLUBILITY

The solubility of the test sample was tested in different solvents at the 10% concentration. Test sample M17-0789.01 was soluble in Sterile Deionized Water. This was the solvent used for testing.

5.2 BACTERIAL REVERSE MUTATION (AMES MUTAGENICITY) ASSAY

The bacterial reverse mutation assay was used to evaluate the mutagenic potential of the test sample at 1 concentration of the test sample per plate: 10%. Testing was done with the appropriate solvent control and positive cultures were plated with overnight cultures of the test systems (TA 97a, TA 98, TA 100, TA102, TA 1535) on selective minimal agar in the presence and absence of Aroclor-induced rat liver S9. All dose levels of the test sample, solvent control and positive controls were plated in triplicate. (Refer to attachment A: Protocol M17-0789 for detailed test procedure).

6.0 RESULTS

Results for the mutagenicity test for test materials M17-0789.01 are presented in the following Tables:

Table 1: Ames Mutagenicity (w/o S9 Activation) for M17-0789.01

Table 2: Ames Mutagenicity (w/ S9 Activation) for M17-0789.01

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Ames Mutagenicity Test Results
Table # 1: Number of revertants without S-9 activation

Client: **Study #** M17-0789.01
Sample: **Lot#** 020617
Concentration tested at : 10% Concentration
Solvent used = Sterile DI H_2O

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 97a	1-	37	983	30
	2-	37	1011	34
	3-	31	1055	31
Average =		35	1016	32
Std. Deviation =		3.46	36.30	2.08

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 98	1-	39	954	37
	2-	36	998	39
	3-	38	1026	43
Average =		38	993	40
Std. Deviation =		1.53	36.30	3.06

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 100	1-	42	1126	48
	2-	37	1183	49
	3-	44	1154	43
Average =		41	1154	47
Std. Deviation =		3.61	28.50	3.21

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 102	1-	271	1282	266
	2-	259	1311	270
	3-	274	1340	253
Average =		268	1311	263
Std. Deviation =		7.94	29.00	8.89

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 1535	1-	15	840	12
	2-	12	912	10
	3-	14	827	11
Average =		14	860	11
Std. Deviation =		1.53	45.79	1.00

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Ames Mutagenicity Test Results
Table # 2: Number of revertants with S-9 activation

Client: **Study #** M17-0789.01
Sample: **Lot#** 020617
Concentration tested at : 10% Concentration
Solvent used = Sterile DI H_2O

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 97a	1-	42	1126	42
	2-	48	1154	44
	3-	47	1169	41
Average =		46	1150	42
Std. Deviation =		3.21	21.83	1.53

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 98	1-	45	1140	46
	2-	44	1112	40
	3-	48	1083	41
Average =		46	1112	42
Std. Deviation =		2.08	28.50	3.21

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 100	1-	50	1254	56
	2-	54	1268	58
	3-	50	1197	53
Average =		51	1240	56
Std. Deviation =		2.31	37.61	2.52

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 102	1-	285	1425	276
	2-	288	1467	284
	3-	297	1397	281
Average =		290	1430	280
Std. Deviation =		6.24	35.23	4.04

Test Strain #		Solvent Control	Positive Control Est. #	10% sample
TA 1535	1-	19	855	21
	2-	20	955	23
	3-	20	984	14
Average =		20	931	19
Std. Deviation =		0.58	67.68	4.73

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7.0 PROTOCOL DEVIATIONS/AMENDMENTS

There were no protocol deviations or amendments for this study.

8.0 CONCLUSION/DISCUSSION

The results in Table 1 and Table 2 show that the test strains are sensitive to the positive control mutagens and had a spontaneous reversion rate well within the accepted values of each strain, indicating that under the test conditions, the strains were sensitive to the detection of potentially genotoxic agents. Test sample M17-0789.01 was not cytotoxic to the test system.

The metabolic activation using the S9 activation mixture shows an active microsomal preparation.

Using the same test conditions, there was no detectable genotoxic activity associated with the single concentration (10% concentration) of the following test sample either in the presence or absence of S9 enzyme activation:

M17-0789.01

trade name mixture containing 2.5% Mentha Piperita (Peppermint) Extract

9.0 RECORDS AND RETENTION

All records and documents pertaining to the conduct of this study shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QA Department to obtain custody of study records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, study-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

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EXECUTIVE SUMMARY

Name of Protocol:	Repeated Insult Patch Test (Humans)
Research Institution:	Consumer Product Testing Co. (CPTC) Fairfield, NJ 07004 USA
Investigating Physician:	Richard R. Eisenberg, M.D. Board Certified Dermatologist
CPTC Panel No.:	20120211
CPTC Study No.:	C12-2921.02
Experimental Start Date:	June 20, 2012 (Panel 20120211)
Requesting Company:	
Requesting Company Study No.:	
Test Material Description:	(Off-white cream) containing 0.00554% Mentha Piperita (peppermint) Extract

OBJECTIVE

This study was conducted to evaluate the potential of the off-white cream (sample no. 4321.01) to induce primary or cumulative irritation and/or allergic contact sensitization in normal, adult volunteers following repeated applications under patch test conditions.

METHODOLOGY

The study was conducted under the supervision of a board-certified dermatologist. Fifty-six (56) subjects were enrolled in the study.

Subject Inclusion Criteria

1. Fifty (50) male and female subjects, 18-70 years of age.
2. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
3. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
4. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
5. Considered reliable and capable of following directions.

Subject Exclusion Criteria

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1. Ill health or taking medication(s), other than birth control, which could influence the purpose, integrity or outcome of the study.
2. Females who are pregnant or nursing.
3. A history of adverse reactions to cosmetics or other personal care products.

The upper back between the scapulae served as the treatment area. Approximately 0.2g of the test material, or an amount sufficient to cover the contact surface, was applied to the 1" X 1" absorbent pad portion of an adhesive dressing. This was then applied to the appropriate treatment site to form a semi-occluded patch.

Induction Phase:

Patches were applied three (3) times per week for a total of nine (9) applications over a period of three weeks. Twenty-four hours after application, the patches were removed, and twenty-four to forty-eight hours after patch removal, the test sites were evaluated for irritation according to the scale below:

Evaluation Criteria (Erythema and additional Dermal Sequelae):

0	= No visible skin reaction	E	= Edema
0.5	= Barely perceptible	D	= Dryness
1	= Mild	S	= Staining
2	= Moderate	P	= Papules
3	= Marked	V	= Vesicles
4	= Severe	B	= Bullae
		U	= Ulceration
		Sp	= Spreading

Challenge Phase:

After a rest period of approximately two weeks (no patch application), the test material was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patches were removed twenty-four hours after application, and the test sites were evaluated at the clinic twenty-four and seventy-two hours post-application.

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RESULTS

Fifty-one (51) subjects completed the study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material. Observations remained negative throughout the test phase.

SUMMARY

Under the conditions of this study, test material, 4321.01, did not induce dermal irritation nor any evidence of induced allergic contact dermatitis in human subjects.

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EXECUTIVE SUMMARY

Name of Protocol:	Human Maximization Test
Research Institution:	Ivy laboratories (KGL, INC.) 505 Parkway, Broomall, PA 19008-4204
Investigating Physician:	Kays Kaidbey, M.D. Board-Certified Dermatologist
KGL Protocol No.:	7244
Experimental Start Date:	March 21, 2011
Requesting Company:	
Requesting Company Study No.:	
Test Material Description:	(Off-White Cream)

containing 0.00554% Mentha Piperita (Peppermint) Extract

OBJECTIVE

The objective of this study was to assess the skin sensitizing potential of an off-white cream (sample no. 3792.01) for topical use by means of the maximization test.

METHODOLOGY

Twenty-seven (27) healthy, normal adult volunteers of both sexes between the ages of 20 and 65 years were enrolled in the study. Panelists with no blemishes, excess hair or other marks on their volar forearms, upper arms or back that would obscure grading of the test sites served as subjects.

Inclusion Criteria:

1. Healthy adult male and female volunteers between the ages of 18 and 65 years;
2. All were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. Subjects with any significant internal diseases e.g., cardiac, pulmonary, renal, hepatic, etc.;

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2. History of allergy or hypersensitivity to cosmetics, toiletries or other dermatological products;
3. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticarial;
4. Pregnancy or mothers who were breastfeeding or planning a pregnancy;
5. Scars, moles or other blemishes over the upper arm(s) which could have interfered with the study;
6. Subjects receiving systemic or topical drugs or medications which could have interfered with delayed immunologic responses e.g., corticosteroids, non-steroidal anti-inflammatories, retinoids, immunosuppressants;
7. Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

METHOD:

The patch was applied to the upper outer arm of each subject. The entire test was composed of (1) an Induction phase (2) a Rest phase and (3) a Challenge phase.

Induction Phase:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated skin site on a 15mm disc of Webril cotton. The loaded webril disc was then fastened to the skin with occlusive tape (Blenderm, 3M) for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied under a fresh Webril disc to the same site and covered with an occlusive tape [Blenderm, 3M] (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, the 0.25% SLS patch was again reapplied to the test site for 24 hours under an occlusive dressing, followed by reapplication of a fresh induction patch with the test material to the same site under an occlusive dressing. 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.

Rest Period:

No exposure to the test material or to sodium lauryl sulfate (SLS) was made during this rest period which lasted 10 days after the last induction exposure.

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Challenge Phase:

After the rest period which followed 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 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 then covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and 0.05ml of the test material was applied to the same site, as described 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 and again 48 hours later for any reactions.

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-seven (25 females and 2 males) healthy, adult volunteers ranged from 20 to 65 years were enrolled into this study. One subject failed to maintain the scheduled study visits, and was lost to follow-up as required by the protocol. The remaining twenty-six (26) subjects completed this investigation. No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION

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Under the conditions of this test, the off-white cream (sample no. 3792.01) did not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 6, 2017

SUBJECT: Mentha Piperita (Peppermint) Extract

Anonymous. 2017. Safety assessment of Mentha Piperita Derived Ingredients as Used in Cosmetics (information on Mentha Piperita (Peppermint) Extract.

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

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Safety assessment of Mentha Piperita-Derived Ingredients as Used in Cosmetics

Date : 6th November 2017

Our product is an aqueous solution composed of 7.5% (maximum percentage) Mentha piperita (Peppermint) Extract with less than 40 ppm of pulegone and less than 50 ppm of menthol.

- Composition

Our active can be divided in sugars (47%), mineral ashes (38%), proteins (13%) and polyphenols (2%).

- Method of manufacturing

The main steps of the manufacturing are:

- solubilization of *Mentha piperita* in water,
- separation of soluble and insoluble phases,
- filtration and sterilizing filtration.

- Impurities data

Assay of alkaloids was performed with the Dragendorff reagent. The quantity of alkaloid is less than the limit of sensitivity of the method (<0,05g/l).

Assay of heavy metals (Arsenic, Copper, Iron, Manganese, Mercury, Nickel, Lead and Zinc) indicated traces of Copper (0.23 ppm), iron (3.76 ppm), Manganese (21.00 ppm), Nickel (0.19 ppm) and Zinc (3.14 ppm). These traces are safe for consumers.

There is no trace of pesticides in this ingredient.

Assay of allergens was carried out to characterize and quantify of 26 allergen compounds in order to comply with the requirements of European Regulation 1223/2009.
Allergens were not detected in this ingredient. Their concentrations are thus less than the sensitivity of the method (<1ppm).

- Safety study

1) **Assessment of irritant/corrosive effect on the eyes, OCDE 405.**

The pure product (trade name material containing 7.5% Mentha piperita (Peppermint) Extract) was instilled into the eye of three New Zealand rabbits at the dose of 0.1 ml.
The ocular reactions observed during the study remained very slight and only recorded at the conjunctivae level: redness in 2 animals only 1 hour the test product instillation and a lachrymation in the animal only on the examination time 1 hour.
In conclusion, the result obtained, enable to conclude that the test product is slightly irritant for the eye and must not be classified.

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2) Assessment of acute irritant/corrosive effect on the skin, OCDE 404.

The pure product (trade name material containing 7.5% Mentha piperita (Peppermint) Extract) was applied, as supplied, at the dose of 0.5mL, under semi-occlusive dressing during 4 hours on an undamaged skin area of 3 rabbits.

No cutaneous reactions were observed in any animal whatever the examination time. The results obtained, enabled to conclude that the product is no irritant to skin and must not be classified.

3) Assessment of sensitizing properties on albino guinea pig.

Maximisation test according to Magnusson and Kligman, OCDE 406.

After induction (intradermic injection and topical application) of 10 animals of treated group with the test product and a 19-days rest phase, the challenge phase, under occlusive dressing for 24 hours, consisted to a single topical application of the test product at 100% and diluted at 50%.

The methodology of the chronological development is :

- Induction phase :
    - 1st induction :
        - 2 intradermal injections of the product at 100% (trade name material containing 7.5% Mentha piperita (Peppermint) Extract)
        - 2 intradermal injections of Freund's Complete Adjuvant diluted at 50% in a physiological saline solution
        - 2 intradermal injections of a mixture with equal volumes – Freund's Complete Adjuvant at 50% and the product at 100%
    - 2nd induction :
        - Topical application on the same zone, with the product at 100%, 24h after brushing with 0.5ml of a solution of Sodium lauryl sulfate at 10%.
- Rest phase : 19 days
- Challenge phase : topical application under occlusive dressing at the following concentrations : 100% and 50%

No macroscopic cutaneous reactions attributable to allergy was recorded and no cutaneous intolerance reaction was recorded in animals from the negative control group.

In conclusion, the product must be not classified.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: November 20, 2017
Subject: Wave 2 Data on Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

Comments (in *polyam092017 data1* file) on the Draft Final Report on Polyaminopropyl Biguanide that were received from Women's Voices For The Earth are attached for the Panel's review. Additional information on current products containing this ingredient is presented in these comments.

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WOMEN'S VOICES FOR THE EARTH

OUR HEALTH. OUR FUTURE. TOXIC FREE.

November 16, 2017

To the CIR,

I am writing to provide you with more information on current products containing Polyaminopropyl Biguanide which are of particular concern in that they are dispensed in pump or aerosol sprays. Largely, I identified these products by conducting a simple Google search for "Polyaminopropyl Biguanide ingredients mist" and similar search terms. I believe there are categories of products which are not being discussed by the CIR which are possibly not included in the VCRP data. While it is good to know that one company, Lonza, has stated that they would not use Polyaminopropyl Biguanide in an aerosolized product, this does not appear to be the current position of numerous other brands including Pantene, Matrix, L'Oreal, Garnier and others.

Specifically, I have identified a number of hair products, not "hair sprays" precisely but hair products such as volumizers, detanglers and the like. (See attached list of products). These hair products are packaged in pump sprays and each contain Polyaminopropyl Biguanide. I do not believe this list to be an exhaustive list of these types of products.

Secondly, the other major category of products containing Polyaminopropyl Biguanide is face mists. (See attached list for names of products.) Face mists are pump spray products intended to be sprayed directly at the face, thus allowing for significant potential for inhalation. Face mists are recommended by manufacturers to be used numerous times per day such as:

- before applying moisturizer;
- again before applying primer;
- and again before applying foundation;
- to set your makeup so it lasts longer;
- to revive your makeup (reblend your foundation later in the day);
- to absorb excess face oil;
- to boost absorption of your face cream;
- spritzing your face for cooling and refreshing on a hot day;
- post-yoga class;
- whenever you hit that mid-afternoon slump at the office;
- to avoid *drying* of skin on an airplane; etc.

From: https://beautyeditor.ca/2016/08/03/are-face-mists-necessary)

One face mist manufacturer specifically recommends the following regimen:

"For optimal radiance, clarity and purification of the skin, we recommend spraying MAYAWATER 20 times per day holding the can 7 inches from the face in a circular motion.
Spray in a circular motion while inhaling to the count of 4. Retain the breath for 4 seconds. Then exhale for the count of 4. This process should be repeated 4 times."

From: https://shopmayawater.com/pages/how-to-use-mayawater

I am particularly concerned that the margin of safety calculation conducted for the September meeting would significantly underestimate inhalation exposures to a person following this recommended regimen for a face mist containing Polyaminopropyl Biguanide. (As I understand it, the margin of safety calculation the CIR conducted used an assumed use of hair spray directed at the hair (not the face) once a day, 5 days a week.)

In addition to products marketed as face mists, there are several micellar water products which contain Polyaminopropyl Biguanide. While these products are not packaged as face mist pump sprays, manufacturers frequently provide specific guidance that these products can (and should) be decanted into pump spray bottles and used as face mists. Three prominent examples of micellar waters containing Polyaminopropyl Biguanide are:

L'Oreal Cleansing Micellar Waters

Garnier SkinActive Micellar Cleansing Water

Lancome Eau Fraîche Douceur Micellar Cleansing Water

As for manufacturer recommendations on the use of these products:

The L'Oreal website states:

"*Micellar Water Hack #5: Use It as a Facial Mist*

For days when you're not wearing any makeup and you just want to freshen your skin a little bit, turn to micellar water. Pour it into a spray bottle and spritz it onto your face in the middle of the day when you feel you need a refresh."

https://www.lorealparisusa.com/beauty-magazine/skin-care/skin-care-essentials/micellar-water-hacks-to-try.aspx

Similarly the Garnier website states:

"Skin Mist

On those days that you are not wearing makeup and would like to freshen your skin, a micellar water mist is perfect. Apply while you are hiking or exercising outdoors to freshen skin and to lift off any dirt or pollution. It will help you feel fresh even if you are partaking in a heavy-duty nature activity."

http://www.garnierusa.com/articles-tips/skincare/cleansing/micellar-water-hacks-will-completely-overhaul-your-cleansing-routine.aspx

The Lancome website links to “four unexpected ways to use micellar water” including:

“If you’ve run out of facial mist and need a quick alternative, fill up a small spray bottle with micellar water. Since the formula doesn’t need to be washed away, it offers a soothing boost and can actually help skin stay clean!”

https://www.skincare.com/article/lancome-eau-fraiche-douceur-micellar-water-review
https://www.skincare.com/article/micellar-water-hack

I hope you will find this additional information useful to your deliberations. I continue to regret that the CIR appears to rely solely on the FDA’s VCRP data for information on the use of ingredients. This process limits the information the CIR sees about products that are currently on the market. For example, the transcripts of the previous meeting seem to indicate a general understanding was reached among many CIR members that Polyaminopropyl Biguanide is no longer used in pump spray hair products, which unfortunately is simply untrue. Similarly, the concern around face mists and micellar waters containing Polyaminopropyl Biguanide was never introduced (perhaps this specific product category cannot be individually picked out of VCRP data). I also noted that representatives of manufacturers of some of these products were in the room for the September meeting. Solicitation of information from these representatives could have been illuminating.

Once again, especially in light of the tragedy in Korea, I strongly encourage the CIR to use the greatest precaution in establishing the safety of this chemical, particularly for its use in any cosmetic products with the potential to be inhaled.

Thank you for your careful consideration of these comments.

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

Hair products: thickening spray, detanglers, thermal protection spray containing Polyaminopropyl Biguanide

The name of the product is followed by a URL at which you can view the list of ingredients that includes Polyaminopropyl Biguanide.

Pantene Curly Hair Heat Protection & Shine Spray (pump spray)

https://www.amazon.com/Pantene-Curly-Protection-Shine-Spray/dp/B003Q5KN3K

Matrix Biolage Colorlast Shine Shake (pump spray)

http://www.ulta.com/biolage-colorlast-shine-shake?productId=xlsImpprod6490098

Arrojo wave mist (pump spray)

http://store.arrojoproduct.com/merchant.mvc?Screen=PROD&Product_Code=AP100-69M&Store_Code=AP

R+Co Dallas Thickening Spray (pump spray)

http://shop.nordstrom.com/s/space-nk-apothecary-rco-dallas-thickening-spray/4486117

Sweet Poof™ Volumizing Spray (pump spray)

https://www.originalmoxie.com/volumizing-hair-treatment/

Original Sprout Miracle Detangler (pump spray)

https://www.originalsprout.com/natural-detangler

eSalon Get Heated Repair Thermal Protect Mist (pump spray)

https://www.esalon.com/products/v/344/get-heated-repair-thermal-protect-mist

PHYTO SPECIFIC Integral Hydrating Mist (pump spray)

http://www.ulta.com/phyto-specific-integral-hydrating-mist?productId=xlsImpprod12291959

Sebastian Texture Maker (pump spray)

https://chatters.ca/products/sebastian_texture_maker

Face and Body Mists containing Polyaminopropyl Biguanide

Colorado Aromatics Face and Body Mist

http://coloradoaromatics.com/product/face-care/tonerhydrosol/

Garden of Wisdom Yarrow Blossom Healing and Hydrating Mist

http://www.gardenofwisdom.com/catalog/item/4264762/10059124.htm

(Note that in the Garden of Wisdom product, the ingredient is specifically listed as “Cosmocil CQ Polyaminopropyl Biguanide” which is the ingredient manufactured by Lonza,.)

Skin Dressing Skin Refresher

https://www.skindressing.com/product-p/sr-whb-t.htm

Verefina Ultra Hydrating Rosewater Mist

http://www.verefina.com/ultra-hydrating-rosewater-mist-qty-24/

Verefina After Sun Mist

http://www.verefina.com/mini-after-sun-mist/

Brume De Thé Body Mist

https://www.thebeautyblazers.com/products/brume-de-the-body-mist-50ml

One Love Organic Vitamin D Moisture Mist

https://shop.thinkheyday.com/products/one-love-organics-vitamin-d-moisture-mist

Malibu C B5 Face & Body Moisture Mist

https://www.malibuc.com/products/cn/3608/B5-Face-and-Body-Moisture-Mist

Saltspring Soapworks Lavender Fennel Mist

https://www.saltspringsoapworks.com/products/lavender-fennel-mist

True Nature Botanicals Pacific Mist

http://www.norahlovesmakeup.com/2015/07/15/true-nature-botanicals-exfoliating-cleanser-pacific-mist/

(Ingredient specifically noted as Cosmoquil CQ made by Lonza.)

De La Torre Hydrating Toning Mist

https://www.delatorreskincare.com/collections/toners-and-tonics/products/hydrating-toning-mist

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: November 20, 2017
Subject: Wave 2 – Sultaines

The Council has provided method of manufacturing data on Lauryl Hydroxysultaine and human repeat insult patch tests (HRIPTs) for Lauryl Hydroxysultaine and Cocamidopropyl Hydroxysultaine (*sultan122017wave2_data1* and *sultan122017wave2_data2*). Lauryl Hydroxysultaine is produced by quaternizing lauryl dimethylamine *in situ* with sodium oxiran-2-ylmethanesulfonate. Cocamidopropyl Hydroxysultaine (4% solids) and Lauryl Hydroxysultaine (4% solids) were not irritating or sensitizing in 2 separate HRIPTs of 51 subjects under semi-occlusive patches.

These submissions from the Council also contained additional process diagrams for Cocamidopropyl Hydroxysultaine.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: November 6, 2017

SUBJECT: Cocamidopropyl Hydroxysultaine

Anonymous. 2017. Product information Cocamidopropyl Hydroxysultaine: Process diagram.

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

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November 2017

Product Information

Product Name: Cocamidopropyl hydroxysultaine

Subject: **Process Diagram**

Dimethylaminoproplyamine + Coconut oil

↓

Intermediate 1

Intermediate 1 + Bisulfite solution + Specific Chlorine containing compound (Petrochemical) + Water

↓

Cocamidopropyl hydroxysultaine **(Contained NaCl (Mineral))**

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 7, 2017

SUBJECT: Cocamidopropyl Hydroxysultaine and Lauryl Hydroxysultaine

Anonymous. 2017. Method of manufacture Colateric CBS (Cocamidopropyl Hydroxysultaine).

Consumer Product Testing Co. 2017. Repeated insult patch test ColaTeric CBS 4% solids (Cocamidopropyl Hydroxysultaine).

Anonymous. 2017. Method of manufacture Colateric LHS (Lauryl Hydroxysultaine).

Consumer Product Testing Co. 2017. Repeated insult patch test ColaTeric LHS 4% solids (Lauryl Hydroxysultaine).

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November 2017

Colateric CBS

Cocamidopropyl Hydroxysultaine

Step One

Coconut Oil is reacted with Dimethylaminopropylamine to form Cocoamidopropyl dimethylamine.

↓

Step Two

Cocoamidopropyl dimethylamine is reacted with sodium 3-chloro-2-hydroxy-1-propanesulfonate to make the final product, Cocamidopropyl hydroxysultane.

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Consumer Product Testing Co.

FINAL REPORT

CLIENT:
Colonial Chemical, Inc.
225 Colonial Drive
South Pittsburg, TN 37380
USA

ATTENTION:
Kacie Howard

TEST:
Repeated Insult Patch Test
Protocol No.: CP-01.01S

TEST MATERIAL:
ColaTeric CBS 4% Solids, Lot#: 54331L16
Cocamidopropyl Hydroxysultaine

EXPERIMENT REFERENCE NUMBER:
C17-3590.01

Reviewed by:
Richard R. Eisenberg, M.D.
Medical Director
Board Certified Dermatologist

Approved by:
Michael Caswell, Ph.D., CCRA, CCRC
Vice President, Clinical Evaluations
20 Sep 2017

Approved by:
Joy Frank, R.N.
Executive Vice President, Clinical Evaluations
9/20/17

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QUALITY ASSURANCE UNIT STATEMENT

Study Number: C17-3590.01

The Consumer Product Testing Company, Incorporated (CPTC) Quality Assurance Unit (QAU) is responsible for auditing the conduct, content and reporting of all clinical trials that are conducted at CPTC.

This trial has been conducted in accordance with the Declaration of Helsinki, the ICH Guideline E6 for *Good Clinical Practice*, the requirements of 21 CFR Parts 50 and 56, other applicable laws and regulations, CPTC Standard Operating Procedures, and the approved protocol.

The CPTC QAU has reviewed all data, records, and documents relating to this trial and also this Final Report. The following QAU representative signature certifies that all data, records, and documents relating to this trial and also this Final Report have been reviewed and are deemed to be acceptable, and that the trial conforms to all of the requirements as indicated above.

All records and documents pertaining to the conduct of this trial shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QAU to obtain custody of trial records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, trial-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

William Cavaliere
Quality Assurance Representative

9/22/2017
Date

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Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: Fifty-eight (58) qualified subjects, male and female, ranging in age from 18 to 69 years, were selected for this evaluation. Fifty-one (51) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] to 79 years.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material: ColaTeric CBS 4% Solids, Lot#: 54331L16

Study Schedule:

Panel #	Initiation Date	Completion Date
20170293	August 7, 2017	September 15, 2017

[a]With parental or guardian consent

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Methodology:

The upper back between the scapulae served as the treatment area. Approximately 0.2 ml of the test material, or an amount sufficient to cover the contact surface, was applied to the 1" x 1" absorbent pad portion of a clear adhesive dressing. This was then applied to the appropriate treatment site to form a semi-occlusive patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications were discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of one day following each Tuesday and Thursday removal, and two days following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic Day 1 and Day 3 post-application.

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Methodology (continued):

Evaluation Criteria (Erythema and additional Dermal Sequelae):

0	=	No visible skin reaction	E	=	Edema
0.5	=	Barely perceptible	D	=	Dryness
1	=	Mild	S	=	Staining
2	=	Moderate	P	=	Papules
3	=	Marked	V	=	Vesicles
4	=	Severe	B	=	Bullae
			U	=	Ulceration
			Sp	=	Spreading

Erythema was scored numerically according to this key. If present, additional Dermal Sequelae were indicated by the appropriate letter code and a numerical value for severity.

Adverse Events: There were no adverse events.

Amendments: There were no amendments.

Deviations: There were no deviations.

Results: The results of each participant are appended (Table 1).

Observations remained negative throughout the test interval.

Subject demographics are presented in Table 2.

Summary: Under the conditions of this study, test material, ColaTeric CBS 4% Solids, Lot#: 54331L16, indicated no potential for dermal irritation or allergic contact sensitization.

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Table 1
Panel #20170293

Individual Results

ColaTeric CBS 4% Solids, Lot#: 54331L16

Subject Number	Induction Phase									Virgin Challenge Site	
	Day1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	DID NOT COMPLETE STUDY											
8	DID NOT COMPLETE STUDY											
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	DID NOT COMPLETE STUDY							
12	0	0	0	0	0	0	0	0	0	0	0	DNC
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	DID NOT COMPLETE STUDY								
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal
DNC = Did not complete study

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Table 1
(continued)
Panel #20170293

Individual Results

ColaTeric CBS 4% Solids, Lot#: 54331L16

Subject Number	Induction Phase									Virgin Challenge Site	
	Day1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	----------DID NOT COMPLETE STUDY----------											
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	----------DID NOT COMPLETE STUDY----------										
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal

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Table 2
Panel #20170293

Subject Demographics

Subject Number	Initials	Age	Gender
1	BEL	24	F
2	MIC	63	F
3	IRS	47	M
4	J-P	51	F
5	MER	45	F
6	AHS	53	M
7	JMP	41	F
8	NMP	35	F
9	ILH	41	F
10	S-L	69	F
11	LMD	36	F
12	AMP	41	F
13	KAM	69	F
14	AMD	68	F
15	RJL	26	M
16	A-C	66	F
17	GAM	51	M
18	MLG	48	F
19	YAC	24	F
20	L-M	59	F
21	LJC	43	F
22	CMZ	51	F
23	BGM	65	F
24	V-M	61	M
25	TLW	54	F
26	S-S	47	F
27	ADG	37	F
28	ZLR	68	F
29	AMJ	45	F

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Table 2
(continued)
Panel #20170293

Subject Demographics

Subject Number	Initials	Age	Gender
30	S-G	44	F
31	S-N	53	F
32	PMN	60	F
33	SBK	58	M
34	REV	57	F
35	TMC	49	F
36	SDF	51	F
37	RPW	54	M
38	W-M	57	M
39	LKF	69	F
40	SDW	48	F
41	R-A	58	F
42	RMM	53	M
43	R-B	64	F
44	TLA	37	F
45	DBR	61	F
46	IMT	33	F
47	JVS	62	F
48	LAT	54	F
49	SEB	27	F
50	MDF	54	F
51	J-E	24	M
52	W-R	24	M
53	LQS	18	M
54	M-Y	38	F
55	N-G	36	F
56	EBS	65	F
57	BAP	65	F
58	D-M	53	M

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ColaTeric LHS

Lauryl dimethylamine is reacted with epichlorohydrin-sodium bisulfite intermediate to make the final product, Lauryl hydroxysultaine.

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FINAL REPORT

CLIENT:	Colonial Chemical, Inc. 225 Colonial Drive South Pittsburg, TN 37380 USA
ATTENTION:	Kacie Howard
TEST:	Repeated Insult Patch Test Protocol No.: CP-01.01S
TEST MATERIAL:	ColaTeric LHS 4% Solids, Lot#: 57009E17 Lauryl Hydroxysultaine
EXPERIMENT REFERENCE NUMBER:	C17-3590.02

Reviewed by: Richard R. Eisenberg, M.D.
Medical Director
Board Certified Dermatologist

Approved by: Michael Caswell, Ph.D., CCRA, CCRC
Vice President, Clinical Evaluations
20SEP2017

Approved by: Joy Frank, R.N.
Executive Vice President, Clinical Evaluations
9/20/17

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QUALITY ASSURANCE UNIT STATEMENT

Study Number: C17-3590.02

The Consumer Product Testing Company, Incorporated (CPTC) Quality Assurance Unit (QAU) is responsible for auditing the conduct, content and reporting of all clinical trials that are conducted at CPTC.

This trial has been conducted in accordance with the Declaration of Helsinki, the ICH Guideline E6 for *Good Clinical Practice*, the requirements of 21 CFR Parts 50 and 56, other applicable laws and regulations, CPTC Standard Operating Procedures, and the approved protocol.

The CPTC QAU has reviewed all data, records, and documents relating to this trial and also this Final Report. The following QAU representative signature certifies that all data, records, and documents relating to this trial and also this Final Report have been reviewed and are deemed to be acceptable, and that the trial conforms to all of the requirements as indicated above.

All records and documents pertaining to the conduct of this trial shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QAU to obtain custody of trial records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, trial-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

William Cavaliere
Quality Assurance Representative

9/22/2017
Date

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

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Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: Fifty-eight (58) qualified subjects, male and female, ranging in age from 18 to 69 years, were selected for this evaluation. Fifty-one (51) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] to 79 years.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material: ColaTeric LHS 4% Solids, Lot#: 57009E17

Study Schedule:

Panel #	Initiation Date	Completion Date
20170293	August 7, 2017	September 15, 2017

[a]With parental or guardian consent

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Methodology:

The upper back between the scapulae served as the treatment area. Approximately 0.2 ml of the test material, or an amount sufficient to cover the contact surface, was applied to the 1" x 1" absorbent pad portion of a clear adhesive dressing. This was then applied to the appropriate treatment site to form a semi-occlusive patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications were discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of one day following each Tuesday and Thursday removal, and two days following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic Day 1 and Day 3 post-application.

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Methodology (continued):

Evaluation Criteria (Erythema and additional Dermal Sequelae):

0	=	No visible skin reaction	E	=	Edema
0.5	=	Barely perceptible	D	=	Dryness
1	=	Mild	S	=	Staining
2	=	Moderate	P	=	Papules
3	=	Marked	V	=	Vesicles
4	=	Severe	B	=	Bullae
			U	=	Ulceration
			Sp	=	Spreading

Erythema was scored numerically according to this key. If present, additional Dermal Sequelae were indicated by the appropriate letter code and a numerical value for severity.

Adverse Events: There were no adverse events.

Amendments: There were no amendments.

Deviations: There were no deviations.

Results: The results of each participant are appended (Table 1).

Observations remained negative throughout the test interval.

Subject demographics are presented in Table 2.

Summary: Under the conditions of this study, test material, ColaTeric LHS 4% Solids, Lot#: 57009E17, indicated no potential for dermal irritation or allergic contact sensitization.

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Table 1
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Individual Results

ColaTeric LHS 4% Solids, Lot#: 57009E17

Subject Number	Induction Phase										Virgin Challenge Site	
	Day1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	----------DID NOT COMPLETE STUDY----------											
8	----------DID NOT COMPLETE STUDY----------											
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	----------DID NOT COMPLETE STUDY----------							
12	0	0	0	0	0	0	0	0	0	0	0	DNC
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	----------DID NOT COMPLETE STUDY----------								
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal
DNC = Did not complete study

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Table 1
(continued)
Panel #20170293

Individual Results

ColaTeric LHS 4% Solids, Lot#: 57009E17

Subject Number	Induction Phase									Virgin Challenge Site	
	Day1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	DID NOT COMPLETE STUDY											
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	DID NOT COMPLETE STUDY										
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal

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Table 2
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Subject Demographics

Subject Number	Initials	Age	Gender
1	BEL	24	F
2	MIC	63	F
3	IRS	47	M
4	J-P	51	F
5	MER	45	F
6	AHS	53	M
7	JMP	41	F
8	NMP	35	F
9	ILH	41	F
10	S-L	69	F
11	LMD	36	F
12	AMP	41	F
13	KAM	69	F
14	AMD	68	F
15	RJL	26	M
16	A-C	66	F
17	GAM	51	M
18	MLG	48	F
19	YAC	24	F
20	L-M	59	F
21	LJC	43	F
22	CMZ	51	F
23	BGM	65	F
24	V-M	61	M
25	TLW	54	F
26	S-S	47	F
27	ADG	37	F
28	ZLR	68	F
29	AMJ	45	F

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Table 2
(continued)
Panel #20170293

Subject Demographics

Subject Number	Initials	Age	Gender
30	S-G	44	F
31	S-N	53	F
32	PMN	60	F
33	SBK	58	M
34	REV	57	F
35	TMC	49	F
36	SDF	51	F
37	RPW	54	M
38	W-M	57	M
39	LKF	69	F
40	SDW	48	F
41	R-A	58	F
42	RMM	53	M
43	R-B	64	F
44	TLA	37	F
45	DBR	61	F
46	IMT	33	F
47	JVS	62	F
48	LAT	54	F
49	SEB	27	F
50	MDF	54	F
51	J-E	24	M
52	W-R	24	M
53	LQS	18	M
54	M-Y	38	F
55	N-G	36	F
56	EBS	65	F
57	BAP	65	F
58	D-M	53	M

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Director
Date: November 20, 2017
Subject: Wave 2 data - Safety Assessment of Zinc Salts as Used in Cosmetics

A REACH dossier for Zinc Laurate was discovered on the European Chemicals Agency website. Relevant new inhalation data are included here.

Zinc Laurate – ECHA data

The "total dustiness" (i.e., airborne fraction) of Zinc Laurate is 241.82 mg/g. The mass median aerodynamic diameter (MMAD) of total dustiness (airborne) fraction (mono-modal distribution) is 8.50 µm (distribution fitted to cascade impactor data). The geometric standard deviation (GSD) of MMAD is 4.36. The fractional deposition in human respiratory tract (multiple-path particle dosimetry (MPPD) model, based on calculated MMAD) is 60.2% head. 1.8% tracheobronchial, and 5.6% pulmonary.

Physical form/color: solid: particulate/powder; white

Inhalation LD_{50} - > 5.08 mg/L air (actual concentration) in rats

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