Safety Assessment of Brown Algae-Derived Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	March 15, 2019
Panel Meeting Date:	April 8-9, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Lillian C. Becker, former Scientific Analyst/Writer and Priya Cherian, Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Priya Cherian, Scientific Writer/Analyst
Date: March 15, 2019
Subject: Draft Final Report of the Safety Assessment on Brown Algae-Derived Ingredients

Enclosed is the Draft Final Report of the Safety Assessment of Brown Algae-Derived Ingredients as Used in Cosmetics. (It is identified as *broalg042019rep* in the pdf document).

At the December 2018 meeting, the Panel concluded that 6 of the 82 brown algae-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment. These ingredients include Alaria Esculenta Extract, Laminaria Digitata Extract, Laminaria Saccharina Extract, Macrocystis Pyrifera (Kelp) Extract, Undaria Pinnatifida Extract, and Undaria Pinnatifida Cell Culture Extract. The Panel came to this conclusion by assessing the systemic toxicity potential (either in repeated dose studies or GRAS status/use in food) and sensitization data of the ingredients. The Panel concluded that the data are insufficient to determine the safety of the remaining ingredients under the intended conditions of use in cosmetic formulations. In order to analyze the safety of these remaining ingredients, the following data are needed:

- Systemic toxicity data
- Sensitization data

Although this safety assessment includes 82 brown algae-derived ingredients, it should be noted that several of these ingredients appear to be equivalent based on the accepted scientific name, as given in the definition by the wINCI *Dictionary*. Accordingly, the total number of distinct cosmetic ingredients is 74. Table 1 in the report has been updated to include all 82 ingredients, along with their respective synonymous names.

Since the December Panel meeting, CIR has received the following data, which have been incorporated into the report and have been designated by highlighting (*broalg042019data1* through *broalg042019data15*).

- *broalg042019data 1*: summary of edible seaweeds and French regulations
- *broalg042019data2*: dermal toxicity, sensitization, solvent information, and arsenic/iodine impurities data on several brown algae-derived ingredients (summary information from UNITIS)
- *broalg042019data3*: human sensitization data on a cream containing Cystoseira Amentacea/Caespitosa/Branchycarpa Extract and a cream containing Himanthalia Elongata Extract
- *broalg042019data4*: specifications, method of manufacturing information, heavy metal impurities, ocular irritation data, and dermal irritation data for a mixture containing water, Himanthalia Elongata Extract, Fucus Vesiculosus Extract, and saccharomyces cerevisiae extract
- *broalg042019data5*: specifications, method of manufacturing information, heavy metal impurities, ocular irritation data, and dermal irritation data for a mixture containing caprylic/capric triglyceride, Laminaria Ochroleuca Extract, and tocopherol
- *broalg042019data6*: specifications, method of manufacturing information, heavy metal impurities, ocular irritation data, and dermal irritation data for a mixture containing water, Ascophyllum Nodosum Extract, and Halopteris Scoparia Extract

- *broalg042019data7*: specifications, method of manufacturing information, heavy metal impurities, ocular irritation data, and dermal irritation data for a mixture containing water and Fucus Serratus Extract
- *broalg042019data8*: specifications, method of manufacturing information, heavy metal impurities, ocular irritation data, and dermal irritation data for a mixture containing water, butylene glycol, and Lessonia Nigrescens Extract
- *broalg042019data9:* specifications, method of manufacturing information, heavy metal impurities, ocular irritation data, dermal irritation data, a bacterial reverse mutation assay, and sensitization data for a mixture containing water, Fucus Spiralis Extract, and tetraselmis chi extract
- *broalg042019data10:* specifications, method of manufacturing information, heavy metal impurities, ocular irritation data, and dermal irritation data for a mixture containing water and Sargassum Muticum Extract
- *broalg042019data11:* specifications, method of manufacturing information, heavy metal impurities, ocular irritation data, dermal irritation data, and sensitization data for a mixture containing water and Pelvetia Canaliculata Extract
- *broalg042019data12:* sensitization data of a trade name mixture containing Fucus Vesiculosus Extract
- *broalg042019data13:* composition data and sensitization data of a trade name mixture containing Sargassum Filipendula Extract
- *broalg042019data14:* updated use information for Halidrys Siliquosa Extract
- *broalg042019data15:* additional dose information on UNITIS HRIPTs

As the inclusion of this new data may help the Panel decide on a conclusion of safety for several more of these brown-algae derived ingredients, a table has been provided presenting each ingredient, as well as a notation of the presence or absence of systemic toxicity data (repeated dose studies or use in food/as a GRAS substance) and sensitization data. This table can be found in the packet as *broalg042019data16*.

Comments provided by the Council before and after the December meeting on the Tentative Report have been addressed (*broalg042019pcpc1, broalg042019pcpc2, broalg042019pcpc3, and broalg042019pcpc4)*. Comments received from the CIR SSC (*broalg042019pcpc2*) suggest that "knowing the major constituents of an ingredient should also be a route to a safe conclusion." Does the Panel agree with this suggestion? If this suggestion is accepted, then it is important to emphasize that the conclusion applies to the material as described in the CIR safety assessment.

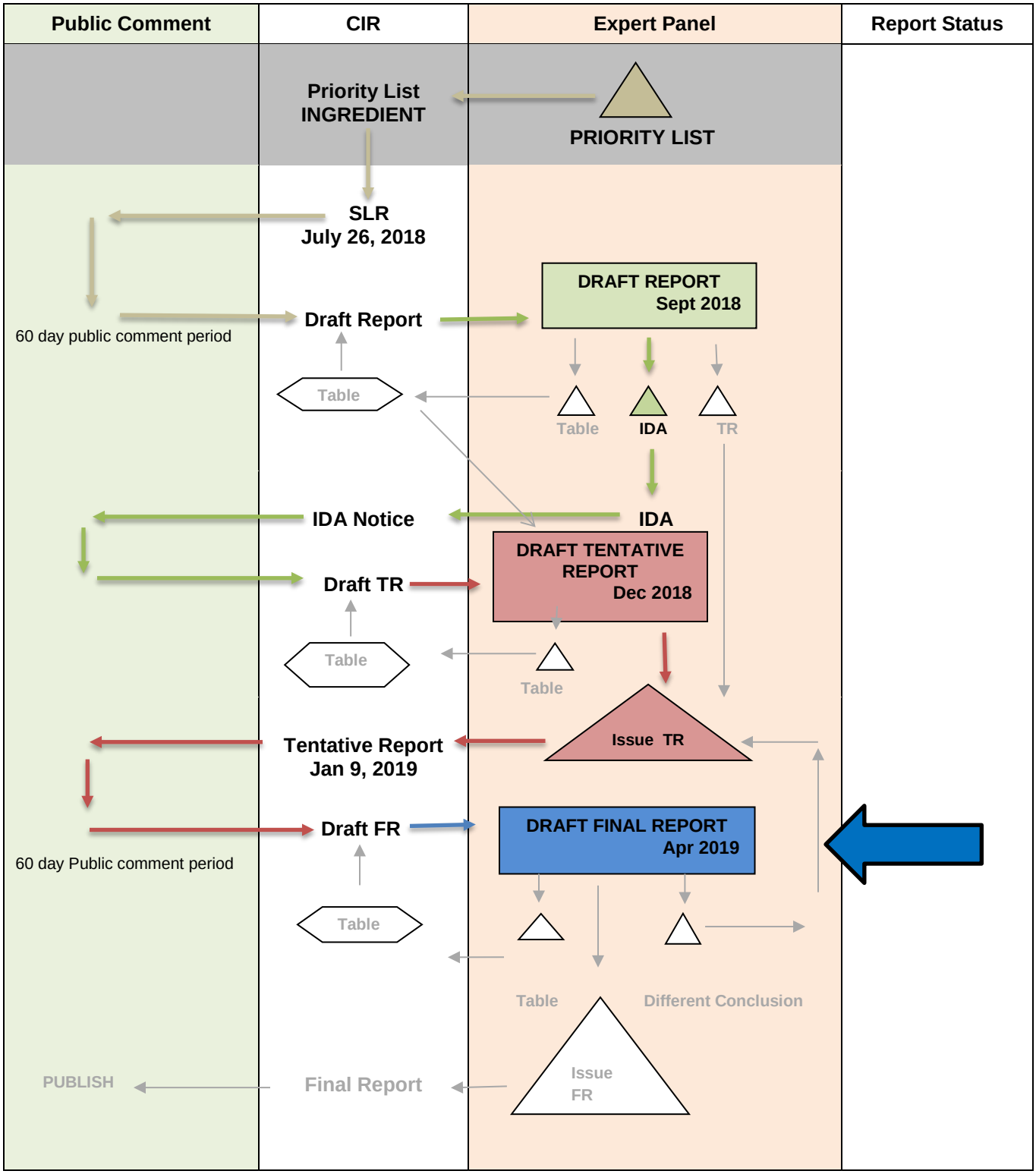
In addition, the flow chart (*broalg042019flow*), updated data profile (*broalg042019prof*), 2019 VCRP data (*broalg042019FDA*), minutes (*broalg042019min*), history (*broalg042109hist*), and search strategy (*broalg042019strat*), have been included in this packet.

The Panel should carefully consider the Abstract, Discussion, and data presented in this report. If the Panel determines that the information that was received since the Tentative Report was issued satisfies the data needs for additional ingredients, then those ingredients should be identified, and a revised Tentative Report should be issued. If the data that were received do not change the conclusion, then a Final Report with the current split conclusion should be issued.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Brown Algae-derived ingredients

MEETING April 2019



History of Brown Algae

August 2018: SLR announced for public comment

September 2018: draft report reviewed by Panel; the Panel issued an IDA; the Panel requested the following data:

- Composition and organic constituent data for each of these Brown Algae-derived cosmetic ingredients
- 28-Day dermal toxicity data for those ingredients that are not GRAS
- Sensitization data at relevant use concentrations for all ingredients (e.g., Macrocystis Pyrifera (Kelp) Extract at 36.4%)
- Genotoxicity data for those ingredients that are not GRAS

Following the September 2018 meeting, information regarding manufacturing, composition, genotoxicity, sensitization, skin irritation, and ocular irritation regarding several brown algae ingredients were received.

December 2018: the Panel reviews the draft tentative report; issues a safe as used conclusion for 6 of the 82 ingredients, and insufficient conclusion for the remaining ingredients. The Panel requested systemic toxicity data and sensitization data for these remaining ingredients

January/February 2019: Comments received from Council; Data received from Council regarding manufacturing, composition, genotoxicity, sensitization, skin irritation, and eye irritation of several brown algae ingredients

April 2019: Panel reviews the draft Final report

Brown Algae Data Profile for ***April 2019***. Writer – Priya Cherian																				
		ADME		Acute toxicity			Repeated dose toxicity			Irritation					Sensitization						
	Use	Log K_{ow}	Dermal Penetration	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Animal	Ocular In Vitro	Dermal Animal	Dermal Human	Dermal In Vitro	Animal	Human	In Vitro	Repro/Devel	Genotoxicity	Carcinogenicity	Phototoxicity
1. Agarum Cribrosum Extract	x																				
2. Alaria Esculenta Extract	x x												x			x					
3. Ascophyllum Nodosum							x														
4. Ascophyllum Nodosum Extract	x			x						x	x	x	x		x	x			x		
5. Ascophyllum Nodosum Powder	x	x																			
6. Cladosiphon Novae-Caledoniae Extract																					
7. Cladosiphon Okamuranus Extract	x																				
8. Cystoseira Amentacea/Caespitosa/ Branchycarpa Extract											x		x			x			x		
9. Cystoseira Baccata Extract													x			x					
10. Cystoseira Balearica Extract																					
11. Cystoseira Caespitosa Extract																					
12. Cystoseira Compressa Extract				x															x		
13. Cystoseira Compressa Powder																					
14. Cystoseira Tamariscifolia Extract													x			x					
15. Dictyopteris Membranacea Extract (Retired)																					
16. Dictyopteris Polypodioides Extract	x												x			x					
17. Dictyota Coriacea Extract																					
18. Durvillea Antarctica Extract	x																				
19. Ecklonia Cava Extract				x			x												x		
20. Ecklonia Cava Water							x														
21. Ecklonia Kurome Extract																					
22. Ecklonia Kurome Powder																					
23. Ecklonia/Laminaria Extract																					
24. Ecklonia Maxima Extract																					
25. Ecklonia Maxima Powder																					
26. Ecklonia Radiata Extract	x																				
27. Eisenia Arborea Extract																					
28. Fucus Serratus Extract	x										x		x								
29. Fucus Spiralis Extract											x		x	x		x			x		
30. Fucus Vesiculosus	x																				
31. Fucus Vesiculosus Extract	x x			x			x				x		x	x		x			x		
32. Fucus Vesiculosus Powder	x																				
33. Halidrys Siliquosa Extract	x										x		x			x			x		
34. Halopteris Scoparia Extract											x		x			x					
35. Himanthalia Elongata Extract	x										x		x								
36. Himanthalia Elongata Powder													x								
37. Hizikia Fusiforme Extract																				x	
38. Hizikia Fusiformis Water																					

Brown Algae Data Profile for ***April 2019***. Writer – Priya Cherian																				
		ADME		Acute toxicity			Repeated dose toxicity			Irritation					Sensitization						
	Use	Log K_{ow}	Dermal Penetration	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Animal	Ocular In Vitro	Dermal Animal	Dermal Human	Dermal In Vitro	Animal	Human	In Vitro	Repro/Devel	Genotoxicity	Carcinogenicity	Phototoxicity
39. Hizikia Fusiformis Callus Culture Extract																					
40. Hydrolyzed Ecklonia Cava Extract																					
41. Hydrolyzed Fucus Vesiculosus Extract																					
42. Hydrolyzed Fucus Vesiculosus Protein																					
43. Kappaphycus Alvarezii Extract																					
44. Laminaria Angustata Extract (Retired)																					
45. Laminaria Cloustoni Extract	x																				
46. Laminaria Diabolica Extract																					
47. Laminaria Digitata Extract	x											x	x x	x		x					
48. Laminaria Digitata Powder	x																				
49. Laminaria Hyperborea Extract	x												x			x					
50. Laminaria Japonica Extract	x						x				x		x	x							
51. Laminaria Japonica Powder							x														
52. Laminaria Longissima Extract																					
53. Laminaria Ochotensis Extract (Retired)																					
54. Laminaria Ochroleuca Extract	x										x		x								
55. Laminaria Saccharina Extract													x			x			x		
56. Lessonia Nigrescens Extract	x										x		x								
57. Lessonia Nigrescens Powder																					
58. Macrocystis Pyrifera (Kelp)	x										x					x			x		
59. Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract																					
60. Macrocystis Pyrifera (Kelp) Extract	x										x			x							
61. Macrocystis Pyrifera (Kelp) Juice																					
62. Macrocystis Pyrifera (Kelp) Protein	x																				
63. Nereocystis Luetkeana Extract											x			x							
64. Pelvetia Canaliculata Extract	x										x		x			x					
65. Pelvetia Siliquosa Extract																					
66. Phyllacantha Fibrosa Extract													x			x					
67. Saccharina Angustata Extract																				x	
68. Saccharina Japonica Extract																					
69. Saccharina Longicruris Extract																					

Brown Algae Data Profile for ***April 2019***. Writer – Priya Cherian																					
		ADME		Acute toxicity			Repeated dose toxicity			Irritation					Sensitization						
	Use	Log K_{ow}	Dermal Penetration	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Animal	Ocular In Vitro	Dermal Animal	Dermal Human	Dermal In Vitro	Animal	Human	In Vitro	Repro/Devel	Genotoxicity	Carcinogenicity	Phototoxicity
70. Sargassum Filipendula Extract	x										x			x		x	x				
71. Sargassum Fulvellum Extract				x																	
72. Sargassum Fusiforme Extract																					
73. Sargassum Glaucescens Extract													x								
74. Sargassum Horneri Extract																					
75. Sargassum Muticum Extract	x										x		x								
76. Sargassum Pallidum Extract																				x	
77. Sargassum Siliquastrum Extract																					
78. Sargassum Thunbergii Extract																					
79. Sargassum Vulgare Extract	x																				
80. Sphacelaria Scoparia Extract	x												x			x					
81. Undaria Peterseniana Extract																					
82. Undaria Pinnatifida Extract	x						x						x		x	x					
83. Undaria Pinnatifida Cell Culture Extract											x			x			x		x		
84. Undaria Pinnatifida Leaf/Stem Extract																				x	
85. Undaria Pinnatifida Powder	x						x													x	
86. Undaria Pinnatifida Root Powder																					

Brown Algae

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
1. Agarum Cribrosum Extract	-	-	X	X	X	X	X	X					N	N	N	n	n	√
2. Alaria Esculenta Extract	-	-	X	X	X	X	X	X										√
3. Ascophyllum Nodosum	-	-	√	X	√	X	X	X										√
4. Ascophyllum Nodosum Extract	84775-78-0	√	√	X	√	X	X	C										√
5. Ascophyllum Nodosum Powder	-	-	√	X	X	X	X	X										√
6. Asterionellopsis Glacialis Extract	-	-	X	X	X	X	X	X										X
7. Cladosiphon Novae-Caledoniae Extract	-	-	X	X	X	X	X	X										X
8. Cladosiphon Okamuranus Extract	-	-	X	X	X	X	X	X										
9. Cystoseira Amentacea/ Caespitosa/ Branchycarpa Extract	-	-	X	X	X	X	X	X										
10. Cystoseira Baccata Extract	-	-	X	X	X	X	X	X										
11. Cystoseira Balearica Extract	-	-	X	X	X	X	X	X										
12. Cystoseira Caespitosa Extract	-	-	X	X	X	X	X	X										
13. Cystoseira Compressa Extract	-	-	X	√	X	X	X	X										
14. Cystoseira Compressa Powder	-	-	X	X	X	X	X	X										
15. Cystoseira Tamariscifolia Extract	-	-	X	X	X	X	X	X										
16. Dictyopteris Membranacea Extract (Retired)	-	-	X	√	X	X	X	X										
17. Dictyopteris Polypodioides Extract	-	-	X	X	X	X	X	X										
18. Dictyota Coriacea Extract	-	-	X	X	X	X	X	X										
19. Durvillea Antarctica Extract	-	-	X	X	X	X	X	X										
20. Ecklonia Cava Extract	-	-	X	√	X	X	X	X										

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
21. Ecklonia Cava Water	-	-	X	X	X	X	X	X										
22. Ecklonia Kurome Extract	-	-	X	X	X	X	X	X										
23. Ecklonia Kurome Powder	-	-	X	X	X	X	X	X										
24. Ecklonia/Laminaria Extract	-	-	X	X	X	X	X	X										
25. Ecklonia Maxima Extract	-	-	X	X	X	X	X	X										
26. Ecklonia Maxima Powder	-	-	X	X	X	X	X	X										
27. Ecklonia Radiata Extract	-	-	X	X	X	X	X	X										
28. Eisenia Arborea Extract	-	-	X	X	X	X	X	X										
29. Fucus Serratus Extract	94167-02-9	-	√	√	X	X	X	X										
30. Fucus Spiralis Extract	-	-	√	X	X	X	X	X										
31. Fucus Vesiculosus	-	-	X	√	√	X	X	X										
32. Fucus Vesiculosus Extract	283-633-7	√	X	X	X	X	X	X										
33. Fucus Vesiculosus Powder	-	√	X	√	X	X	X	X										
34. Halidrys Siliquosa Extract	-	-	X	X	X	X	X	X										
35. Halopteris Scoparia Extract	-	-	X	X	X	X	X	X										
36. Himanthalia Elongata Extract	-	-	X	X	√	X	X	X										
37. Himanthalia Elongata Powder	-	-	X	X	X	X	X	X										
38. Hizikia Fusiforme Extract	-	-	X	X	√	X	X	X										
39. Hizikia Fusiformis Water	-	-	X	X	X	X	X	X										
40. Hizikia Fusiformis Callus Culture Extract	-	-	X	X	X	X	X	X										
41. Hydrolyzed Ecklonia Cava Extract	-	-	X	X	X	X	X	X										
42. Hydrolyzed Fucus Vesiculosus Extract	84696-13-9	-	√	X	X	X	X	X										
43. Hydrolyzed Fucus Vesiculosus Protein	-	-	X	X	X	X	X	X										
44. Kappaphycus Alvarezii Extract	1220882-73-4 (generic)	-	X	X	X	X	X	X										

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
45. Laminaria Angustata Extract (Retired)	-	√	X	X	X	X	X	X										
46. Laminaria Cloustoni Extract	90046-11-0 92128-82-0	-	X	X	X	X	X	X										
47. Laminaria Diabolica Extract	-	-	X	X	X	X	X	X										
48. Laminaria Digitata Extract	90046-12-1 92128-82-0	√	√	X	√	√	X	X										
49. Laminaria Digitata Powder	-	√	X	X	X	√	X	X										
50. Laminaria Hyperborea Extract	90046-13-2 92128-82-0	√	√	X	√	√	X	X										
51. Laminaria Japonica Extract	92128-82-0	√	√	√	√	√	X	X										
52. Laminaria Japonica Powder	-	-	X	X	X	X	X	X										
53. Laminaria Longissima Extract	-	-	X	X	X	X	X	X										
54. Laminaria Ochotensis Extract (Retired)	-	√	X	X	X	√	X	X										
55. Laminaria Ochroleuca Extract	92128-82-0	-	√	X	X	X	X	X										
56. Laminaria Saccharina Extract	90046-14-3 92128-82-0	√	√	X	X	√	X	X										
57. Lessonia Nigrescens Extract	-	-	X	X	X	X	X	X										
58. Lessonia Nigrescens Powder	-	-	X	X	X	X	X	X										
59. Macrocystis Pyrifera (Kelp)	-	√	√	X	X	X	X	X										
60. Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/ Stipe Juice Extract	-	-	X	X	X	X	X	X										
61. Macrocystis Pyrifera (Kelp) Extract	347174-92-9	√	√	X	X	√	X	X										
62. Macrocystis Pyrifera (Kelp) Juice	-	-	X	X	X	X	X	X										
63. Macrocystis Pyrifera (Kelp) Protein	-	-	X	X	X	X	X	X										
64. Nereocystis Luetkeana Extract	-	√	X	X	X	√	X	X										
65. Pelvetia Canaliculata Extract	223751-75-5	-	√	X	X	X	X	X										
66. Pelvetia Siliquosa Extract	-	-	X	X	X	X	X	X										

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
67. Phyllacantha Fibrosa Extract	-	-	X	X	X	X	X	X										
68. Rissoella Verruculosa Extract	-	-	X	X	X	X	X	X										
69. Saccharina Angustata Extract	-	-	X	X	X	X	X	X										
70. Saccharina Japonica Extract	-	-	X	X	X	X	X	X										
71. Saccharina Longicruris Extract	-	-	X	X	X	X	X	X										
72. Sargassum Filipendula Extract	-	-	X	X	X	X	X	X										
73. Sargassum Fulvellum Extract	-	-	X	X	X	X	X	X										
74. Sargassum Fusiforme Extract	-	-	X	X	X	X	X	X										
75. Sargassum Glaucescens Extract	-	-	X	X	X	X	X	X										
76. Sargassum Horneri Extract	-	-	X	X	X	X	X	X										
77. Sargassum Muticum Extract	-	-	X	X	√	X	X	X										
78. Sargassum Pallidum Extract	-	-	X	X	X	X	X	X										
79. Sargassum Siliquastrum Extract	-	-	X	X	√	X	X	X										
80. Sargassum Thunbergii Extract	-	-	X	X	X	X	X	X										
81. Sargassum Vulgare Extract	-	-	X	X	X	X	X	X										
82. Sahel Scenedesmus Extract	-	-	X	X	X	X	X	X										
83. Sphacelaria Scoparia Extract	-	-	X	X	X	X	X	X										
84. Undaria Peterseniana Extract	-	-	X	X	X	X	X	X										
85. Undaria Pinnatifida Extract	-	-	X	√	X	X	X	X										
86. Undaria Pinnatifida Cell Culture Extract	-	-	X	X	X	X	X	X										
87. Undaria Pinnatifida Leaf/Stem Extract	-	-	X	X	X	X	X	X										
88. Undaria Pinnatifida Powder	-	√	X	X	X	√	X	X										
89. Undaria Pinnatifida Root Powder	-	√	X	X	X	√	X	X	N	N	N							

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
1. Agarum Cribrosum Extract	-						
2. Alaria Esculenta Extract	-						
3. Ascophyllum Nodosum	-						
4. Ascophyllum Nodosum Extract	-						
5. Ascophyllum Nodosum Powder	84775-78-0						
6. Asterionellopsis Glacialis Extract	-						
7. Cladosiphon Novae-Caledoniae Extract	-						
8. Cladosiphon Okamuranus Extract	-						
9. Cystoseira Amentacea/Caespitosa/ Branchycarpa Extract	-						
10. Cystoseira Baccata Extract	-						
11. Cystoseira Balearica Extract	-						
12. Cystoseira Caespitosa Extract	-						
13. Cystoseira Compressa Extract	-						
14. Cystoseira Compressa Powder	-						
15. Cystoseira Tamariscifolia Extract	-						
16. Dictyopteris Membranacea Extract (Retired)	-						
17. Dictyopteris Polypodioides Extract	-						
18. Dictyota Coriacea Extract	-						
19. Durvillea Antarctica Extract	-						
20. Ecklonia Cava Extract	-						

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
21. Ecklonia Cava Water	-						
22. Ecklonia Kurome Extract	-						
23. Ecklonia Kurome Powder	-						
24. Ecklonia/Laminaria Extract	-						
25. Ecklonia Maxima Extract	-						
26. Ecklonia Maxima Powder	-						
27. Ecklonia Radiata Extract	-						
28. Eisenia Arborea Extract	-						
29. Fucus Serratus Extract	94167-02-9						
30. Fucus Spiralis Extract	-						
31. Fucus Vesiculosus	-						
32. Fucus Vesiculosus Extract	-						
33. Fucus Vesiculosus Powder	-						
34. Halidrys Siliquosa Extract	-						
35. Halopteris Scoparia Extract	-						
36. Himanthalia Elongata Extract	-						
37. Himanthalia Elongata Powder	-	X	X	X	X	X	X
38. Hizikia Fusiforme Extract	-						
39. Hizikia Fusiformis Water	-						
40. Hizikia Fusiformis Callus Culture Extract	-						
41. Hydrolyzed Ecklonia Cava Extract	-						
42. Hydrolyzed Fucus Vesiculosus Extract	84696-13-9						
43. Hydrolyzed Fucus Vesiculosus Protein	-						

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
44. Kappaphycus Alvarezii Extract	1220882-72-4 (generic)						
45. Laminaria Angustata Extract (Retired)	-						
46. Laminaria Cloustoni Extract	90046-11-0 92128-82-0						
47. Laminaria Diabolica Extract	-						
48. Laminaria Digitata Extract	90046-12-1 92128-82-0						
49. Laminaria Digitata Powder	-						
50. Laminaria Hyperborea Extract	90046-13-2 92128-82-0						
51. Laminaria Japonica Extract	92128-82-0						
52. Laminaria Japonica Powder	-						
53. Laminaria Longissima Extract	-						
54. Laminaria Ochotensis Extract (Retired)	-						
55. Laminaria Ochroleuca Extract	92128-82-0						
56. Laminaria Saccharina Extract	90046-14-3 92128-82-0						
57. Lessonia Nigrescens Extract	-						
58. Lessonia Nigrescens Powder	-						
59. Macrocystis Pyrifera (Kelp)	-						
60. Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract	-						
61. Macrocystis Pyrifera (Kelp) Extract	347174-92-9						
62. Macrocystis Pyrifera (Kelp) Juice	-						
63. Macrocystis Pyrifera (Kelp) Protein	-						

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
64. Nereocystis Luetkeana Extract	-						
65. Pelvetia Canaliculata Extract	223751-75-5						
66. Pelvetia Siliquosa Extract	-						
67. Phyllacantha Fibrosa Extract	-						
68. Rissoella Verruculosa Extract	-						
69. Saccharina Angustata Extract	-						
70. Saccharina Japonica Extract	-						
71. Saccharina Longicruris Extract	-						
72. Sargassum Filipendula Extract	-						
73. Sargassum Fulvellum Extract	-						
74. Sargassum Fusiforme Extract	-						
75. Sargassum Glaucescens Extract	-						
76. Sargassum Horneri Extract	-						
77. Sargassum Muticum Extract	-						
78. Sargassum Pallidum Extract	-						
79. Sargassum Siliquastrum Extract	-						
80. Sargassum Thunbergii Extract	-						
81. Sargassum Vulgare Extract	-						
82. Sahel Scenedesmus Extract	-						
83. Sphacelaria Scoparia Extract	-						
84. Undaria Peterseniana Extract	-						

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
85. Undaria Pinnatifida Extract	-						
86. Undaria Pinnatifida Cell Culture Extract	-						
87. Undaria Pinnatifida Leaf/Stem Extract	-						
88. Undaria Pinnatifida Powder	-						
89. Undaria Pinnatifida Root Powder	-						

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

SciFinder

INCI names and CAS No.

Ascophyllum Nodosum – 33 substance hits; 0 useful
Ascophyllum Nodosum Extract – 1 substance hits; 0 useful
Ascophyllum Nodosum Powder – 1 substance hit; 0 useful
Fucus Serratus Extract – 1 substance hit; 0 useful
Fucus Spiralis Extract – 1 substance hit; 0 useful
Hydrolyzed Fucus Vesiculosus Extract – 1 substance hit; 0 useful
Kappaphycus Alvarezii Extract – 1 substance hit; 0 useful
Laminaria Cloustoni Extract – 2 substance hits; 0 useful
Laminaria Digitata Extract – 2 substance hits; 0 useful
Laminaria Hyperborea Extract – 2 substance hits; 0 useful
Laminaria Japonica Extract – 1 substance hit; 0 useful
Laminaria Saccharina Extract – 2 substance hits; 0 useful
Laminaria Ochroleuca Extract – 1 substance hit; 0 useful
Macrocystis Pyrifera – 79 substance hits; 0 useful
Macrocystis Pyrifera (Kelp) Extract – 1 substance hit; 0 useful
Pelvetia Canaliculata Extract – 1 substance hit; 0 useful
Saccharina Angustata Extract – 1 substance hit; 0 useful

PubMed

((((((((((((((Agarum Cribrosum Extract) OR Alaria Esculenta Extract) OR Ascophyllum Nodosum) OR Ascophyllum Nodosum Extract) OR Ascophyllum Nodosum Powder) OR Asterionellopsis Glacialis Extract) OR Cystoseira Tamariscifolia Extract) OR Cladosiphon Novae-Caledoniae Extract) OR Cladosiphon Okamuranus Extract) OR Cystoseira Amentacea/Caespitosa/ Branchycarpa Extract) OR Cystoseira Baccata Extract) OR Cystoseira Balearica Extract) OR Cystoseira Caespitosa Extract) OR Cystoseira Compressa Extract) OR Cystoseira Compressa Powder) OR 84775-78-0 AND (tox[sb]) = 55 hits, 5 possibly useful.

((((((((((((((Cystoseira Tamariscifolia Extract) OR Dictyopteris Membranacea Extract) OR Dictyopteris Polypodioides Extract) OR Dictyota Coriacea Extract) OR Durvillea Antarctica Extract) OR Ecklonia Cava Extract) OR Ecklonia Cava Water) OR Ecklonia Kurome Extract) OR Ecklonia Kurome Powder) OR Ecklonia/Laminaria Extract) OR Ecklonia Maxima Extract) OR Ecklonia Maxima Powder) OR Ecklonia Radiata Extract) OR Eisenia Arborea Extract) OR Fucus Serratus Extract) OR **94167-02-9** AND (tox[sb]) = 41 hits, 4 possibly useful.

((((((((((((Fucus Spiralis Extract) OR Fucus Vesiculosus) OR Fucus Vesiculosus Extract) OR Fucus Vesiculosus Powder) OR Halidrys Siliquosa Extract) OR Halopteris Scoparia Extract) OR Himanthalia Elongata Extract) OR Himanthalia Elongata Powder) OR Hizikia Fusiforme Extract) OR Hizikia Fusiformis Water) OR Hizikia Fusiformis Callus Culture Extract) OR Hydrolyzed Ecklonia Cava Extract) OR Hydrolyzed Fucus Vesiculosus Extract) OR 84696-13-9) OR Hydrolyzed Fucus Vesiculosus Protein) OR Kappaphycus Alvarezii Extract OR 1220882-73-4) AND (tox[sb]) = 231 hits, 4 possibly useful.

((((((((((((Laminaria Angustata Extract) OR Laminaria Cloustoni Extract) OR 90046-11-0) OR 92128-82-0) OR Laminaria Diabolica Extract) OR Laminaria Digitata Extract) OR Laminaria Digitata Powder) OR 90046-12-1) OR 92128-82-0) OR Laminaria Hyperborea Extract) OR 90046-13-2) OR 92128-82-0) OR Laminaria Japonica Extract) OR 92128-82-0) OR Laminaria Japonica Powder) OR Laminaria Longissima Extract) OR Laminaria Ochotensis Extract) AND (tox[sb]) = 31 hits, 1 possibly useful.

((((((((((((Laminaria Ochroleuca Extract) OR Laminaria Saccharina Extract) OR Lessonia Nigrescens Extract) OR Lessonia Nigrescens Powder) OR Macrocystis Pyrifera) OR kelp) OR Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract) OR Macrocystis Pyrifera (Kelp) Extract) OR Macrocystis Pyrifera (Kelp) Juice) OR Macrocystis Pyrifera (Kelp) Protein) OR Nereocystis Luetkeana Extract) OR **92128-82-0**) OR **90046-14-3**) OR **92128-82-0**) OR **347174-92-9**) OR **223751-75-5** AND (tox[sb]) = 1 hit, not useful

((((((((((((Pelvetia Canaliculata Extract) OR **223751-75-5**) OR Pelvetia Siliquosa Extract) OR Phyllacantha Fibrosa Extract) OR Rissoella Verruculosa Extract) OR Saccharina Angustata Extract) OR Saccharina Japonica Extract) OR Saccharina Longicruris Extract) OR Sargassum Filipendula Extract) OR Sargassum Fulvellum Extract) OR Sargassum Fusiforme Extract) OR Sargassum Glaucescens Extract) OR Sargassum Horneri Extract) OR Sargassum Muticum Extract) OR Sargassum Pallidum Extract) OR Sargassum Siliquastrum Extract AND (tox[sb]) 40 hits, 5 possibly useful

((((((((((Sargassum Thunbergii Extract) OR Sargassum Vulgare Extract) OR Sahel Scenedesmus Extract) OR Sphacelaria Scoparia Extract) OR Undaria Peterseniana Extract) OR Undaria Pinnatifida Extract) OR Undaria Pinnatifida Cell Culture Extract) OR Undaria Pinnatifida Leaf/Stem Extract) OR Undaria Pinnatifida Powder) OR Undaria Pinnatifida Root Powder) AND (tox[sb]) = 21 hits, 3 possibly useful

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon https://java.epa.gov/oppt_chemical_search/
https://java.epa.gov/oppt_chemical_search/
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
the Research Institute for Fragrance Materials (RIFM) should be contacted

Brown Algae Minutes

September 2018 Meeting

Day 1 – Group 1

DR. MARKS: This is a first review of these 83 ingredients. They're complex if I interpreted Dr. Lowe's presentation, which was excellent from two years ago, I guess. On page 156, they are a functional group of plants and protozoa and unique organisms. They don't fit real nicely into one little bundle.

I think we're going to have to clarify whether all 83 in this report are seaweed kelp brown algae, or whether there's a unique brown algae in this, or there's protozoa. As with all of these botanicals -- and this even more, I think, complex chemistry and composition -- they vary in their composition levels depending on the species.

We have 83 here, no small number. How they were grown, where they're harvested, what sea they were grown in, how they were manufactured. They've been contaminated with heavy metals, specifically arsenic. We eat them, so at least some of them are grass.

And so that leads to my first question. Tom and Rons, do you like all 83? Are there ones we should eliminate, and if we do I'd like to know why. But presumably, the only reason you eliminate it is, it isn't a brown algae. I assume these are all brown algae.

DR. HELDRETH: Yes. Our understanding from the presentation that Dr. Lowe gave was we arranged those that he determined brown algae. Then we also sent a message to the INCI nomenclature committee, who has a biologist who's an expert in the taxonomy of these types of things to give us an analysis. And to our best understanding, all of the ingredients in this report are along the lines of a kelp or seaweed-type of brown algae.

DR. MARKS: I think that's really important to capture. And I will, in the introduction, indicate -- or somewhere that these are all brown algae, and they're all seaweed, basically. Okay. Tom, Ron and Ron, go back to the question, is there any reason to eliminate any one of these?

DR. HILL: I have a question. Do we have any sort of a phylogenetic tree that fits these algae? I mean, because otherwise we're looking at -- is there a group of deciduous trees, or something, which may be closely related or not very closely related. I'm not sure how much read across one can do from one species to the next, perhaps none. But if I know that two are closely related, that's a start.

DR. HELDRETH: It was Dr. Lowe's assertion that these were related.

DR. HILL: Well, I know they're all brown algae; but again, I mean, that's like saying all

flowering plants. That's about as close as that gets me, I believe.

DR. HELDRETH: From Dr. Lowe's explanation, it wasn't really just based on whether or not they were the color brown.

DR. HILL: Yeah. I know that.

DR. HELDRETH: It was a classification of a specific kelp-type of algae that excluded things like, you know, little bacteria or other things that get classified in the very vague name algae. And he suggested not only based on the similarities within the brown group, but how they're often used in things like food and stuff that these ingredients were similar enough to be group.

DR. HILL: Okay. But I still wonder if it's possible to get a phylogenetic tree.

DR. EISENMANN: She did. If you look at Table 4.

DR. HILL: Okay. That's effective, what she's got?

DR. EISENMANN: It does break it down into subclass or family. There's actually three -- or four. And this is from a website, algae database. You can tell that some are more related than others.

DR. HILL: Right. I'm a visual learner guy. Like, you know, when you get a phylogenetic tree it's very pictorially useful. But, I mean, that's a lot to ask. If there's not one commercially available, which there probably isn't, but maybe there is, that would be helpful.

DR. MARKS: I guess when -- let's see, it was Dr. Row, correct?

DR. SHANK: Lowe.

DR. MARKS: Lowe. His presentation, he says we employ four main criteria, pigmentation, obviously, that's the brown. Storage products. I assume we're going to get that from composition. And we're going to read across -- hopefully we'll get multiple compositions so that we can read across. On flagella, I don't think we're worried about that in this case.

I'm looking on page 165 is where he talks about algal divisions, Ron Hill. And then if you go right before that on page 163, I liked how that figure was labeled. Hypothetical. That doesn't help much, does it? And they have those nice little arrows going into different divisions and whatever.

DR. HILL: I have a colleague that works on algae symbionts in the context of natural products. And basically, he sends them off now to get genetic profiling at Aberdeen so that we have a better idea than just that. I do remember this slide because it's very colorful.

DR. MARKS: I think we've settled on all the ingredients are okay, unless we hear differently.

DR. SHANK: Okay to be, inserted better.

DR. MARKS: Included. I'm sorry. Included in this report.

DR. SLAGA: Yes.

DR. MARKS: Yes. Exactly. I'm sorry. I didn't get into what are the needs yet. Yeah, I have some needs too also. Okay. They are glass, but how many of these specific species are grass? Or is that just kelp that's grass?

DR. SLAGA: A lot of them are kelp.

DR. MARKS: Yeah. But if you use the word kelp, is that inclusive of all? I don't know. Ron Shank, Ron is now getting down to the meat of this.

DR. SHANK: Well, the grass ones are Laminaria and Undaria. And from the page where all these ingredients are numbered, the Laminaria are number 44 to 55. And the Undaria are numbers 81 to 86. And these are grass food additives. I'd say all we need is skin sensitization. There's also grass for Hizikia, numbers 37 to 39, but they're not currently used. If they were used, we'd have to have skin sensitization data.

Then in Wave 2 we did get some skin sensitization on some, but not many. For all the rest, I would say we need a 28 dermal toxicity study. And a skin sensitization study for all the extracts, at least. Assuming that the extracts contain the components in the other preparations, which is a huge assumption I think. I don't know if that helps, but that's where I come from.

DR. MARKS: I think it's a really good start, because it gives us some framework. You're really focusing initially on the grass --

DR. SHANK: The grass ingredients.

DR. MARKS: -- grass brown algae. And that -- again, I'll summarize this in a minute, make sure I have the right numbers. But I like that. I can tell you with the skin sensitization, you were mentioning that, Ron. I took the ones with the highest uses. Like the fucus vesiculosus extract, 6 percent.

Wave 3 had a mixture and an HRIPT, but I didn't see that the percentage of that brown algae in the mixture was mentioned. Was it? Did I overlook that? Because then I couldn't -- if I knew it was 6 percent, I'd say fine, that looks okay. The same you'd talked about the Laminaria that all we really need is the skin sensitization. In Wave 3 we got another HRIPT. That's of the extract, but it didn't tell me what the percentage was.

Is that correct?

MS. CHERIAN: That's the percentage that wasn't mentioned in there.

DR. MARKS: No. Neither one of them. I would say I'd want --

DR. EISENMANN: All the ones from BiotechMarine did give concentration in the extract. They gave it kind of as a range, the dry extract is, and they tested it neat. Most of that material was either in glycol water or caprylic/capric triglyceride. There was a few propylene glycol extract.

Their information did give -- I mean, occasionally I had to go back and ask them for it, and that's written on each thing by hand. Then there was another table from a different company, and they were reluctant to give concentration. They just said it was in the range of .5 to 10 percent for all of them on that one table, which was less than desirable.

But from all the information from BiotechMarine, they did -- and it's not in all of the summaries that are for Wave 2, but it's all --

DR. MARKS: We'll need to go back and get that.

DR. EISENMANN: Right.

DR. MARKS: Because if that's the case, and if it's up to 10 percent -- the one was 6 percent for the fucus extract. The Laminaria digitata extract, 5 percent. If they were tested up to 10 percent, then that becomes a nonissue. Because the HRIPT's were normal.

DR. EISENMANN: I don't know if they ever have that high of concentration of an extract, that company don't. I'd have to look back. But they all say how much -- they don't give exact, but they give a reasonable sized range. Not like the other summary that came in, that is for all of the extract was .5 to 10 percent. Not helpful.

DR. MARKS: We still need to be sure of what the percentage of the extract was in these HRIPTs. We can't say it's safe if I don't know the percentage. It gets back to, Ron, your question. The other was Laminaria again and other grass group. Digitata powder, that was up to 40 percent in a leave-on. We need to have sensitization on that.

And then I was picking just the ones with a high either use or concentration. Macrocystis pyrifera kelp extract is used up to 36 percent, so I want to see sensitization on that. Yeah, I had an IDA. I figured we'd get to an insufficient data announcement. Now the question is which ones.

That's the initial sensitization but, Ron, I'm going to go back on what you said because I gave specific species. But you were more general in terms of groups that we needed, which is good.

DR. SHANK: To start off, yes.

DR. MARKS: And then you had the 28-day tox also on the others. Then really, what is it, Undaria, is that what it is?

DR. SHANK: Undaria.

DR. MARKS: Undaria species. Again, you felt just the sensitization data on them. And I would think if we used the same reasoning we've done in the past, we really wanted -- most of these are extracts anyway. But if we get the extract, presumably it would be a concentrated form of the contents or ingredients. Ron Hill, yeah?

DR. HILL: Well, just with the caveat that it may depend on what -- the trouble is when you get a percentage added to a formulation and it's so much percent of the extract, is that a .1 percent extract of what you're adding at 5 percent?

DR. MARKS: That was the problem I had with these. I couldn't decide, on Wave 3, how much of the actual brown algae percentage was in that testing, because it was X percentage of a mixture.

DR. HILL: And so, lacking that information, I don't know how you --

DR. MARKS: That's one of the data we'll request. Okay. I like the way Ron divided things up, Ron Shank. Shall we start with that in terms of that's the way we would start with this large group of ingredients? And then we'll see how the approach from the other team is. And then as time goes on, we'll even be more focused.

DR. BERGFELD: Can I ask Ron a question? Ron Shank? When you have grass ingredients and people ingest all these, at what concentrations, are they 100 percent?

DR. SHANK: Usually they don't -- you know, grass usually don't give a concentration.

DR. BERGFELD: Is it the whole though? Whatever it is, the whole algae, they're just eating that?

DR. SHANK: Oh no, that's defined. But how much is used in individual products usually isn't stated as far as I remember.

DR. KATZ: They usually don't state it; although there may be some exceptions, but they usually don't. And I think it's important, as I mentioned before, when you're talking about grass, please make sure that you say grass as related to food additives, so that it's clear that it's not grass as related to a cosmetic ingredient.

DR. BERGFELD: Do you think it would be worthwhile exploring what the grass food additives have actually done? And in any way they might have talked about mixtures or full, just consumption of the actual algae. I mean, with all these vegetarians and funny eaters, I mean, they may be ingesting 100 percent of a product, of food stuff.

DR. SHANK: Very good question. In the literature search, were there FDA files that listed the grass ingredients and what data were supplied to show it was grass?

MS. CHERIAN: I'm not sure. I didn't do that part, but I can go back and check.

DR. SHANK: Okay. Because my experience with it is a lot of it is just a number of scientists, and researchers, responded to FDA and said, this has been used widespread for a long time and it's generally recognized as safe. But there isn't a huge database to confirm the safety. That's my recollection.

DR. BERGFELD: Jim, one of the audience wants to.

DR. MARKS: Oh, I'm sorry. Thank you. Come on right up to one of the microphones so we capture it. Thank you. Thanks, Wilma. I was trying to capture Ron's divisions.

DR. ZIMMERMAN: Merle Zimmerman, American Herbal Products Association. A bunch of these brown algae that are identified are in wide used as food ingredients. I know I eat at least two of the species in this list with my lunch at the sushi bar on Monday. That might also be a relevant piece of information for purposes of exposure and safety.

DR. SHANK: Yes.

DR. ZIMMERMAN: I can do some searches. If you'd like me to bring some stuff back, let me know.

DR. BERGFELD: That really would be great. Because as I'm listening to all of this, and the need for sensitization, if you could establish sort of the amount that's ingested in historical review, we might be able to come up with not such a great need for sensitization. Because we know about nickel. If you're sensitized to nickel, if you eat it, you break out, if nickel is incorporated in any of the food stuff.

DR. MARKS: I would still want to see their local lymph node assay, just to get an idea of is it a sensitizer or not. Then either getting pig max or more importantly an HRIPT. I wouldn't assume just because we eat it and we don't break out in a rash, that if we put it on topically, we would be okay. I'd like to see the skin sensitivity. As far as the 28-day tox, if you can tell Dr. Shank what you're eating of those other ones today, and if

you come back tomorrow, we you know it's probably grass. That's, of course, a joke. Ron, thank you for laughing.

Let me see if I have this right, Ron. I want to be sure. And if not, either I'll -- I was thinking about asking you to do your division, but I figured that would be it.

I'm going to second a motion tomorrow. I suspect it's going to be an insufficient data announcement. And with our discussions we took the Ron Shank approach. If you want, I can leave that out. That the grass ingredients, and they were number 37 to 29, that's the Hizikia species, the 44 to 55, the Laminaria species, and the 81 to 86, the Undaria species, we need sensitization data. For the rest of the ingredients we need 28-day tox and sensitization.

DR. SHANK: Those numbers that I used come from the table that begins on page 12 and list all 86. And each one is numbered.

DR. MARKS: Is this one that is from the -- let me see here. The table I'm using is this one here that gives you what tests have been done.

DR. SHANK: Are they numbered?

DR. MARKS: And it's numbered 1 through --

DR. SHANK: Eighty-six.

DR. MARKS: Is it 86? I said 83, I thought.

DR. EISENMANN: There's a few that have been taken off of that table because they weren't actually brown.

DR. MARKS: Okay, that's why.

DR. EISENMANN: Because I think the actual number is 82.

DR. MARKS: Oh, now it's 82.

DR. SHANK: Okay.

DR. EISENMANN: I keep trying to find the 83rd[d] ingredient and I haven't found it. If you find me an 83rd ingredient, I'll put it in.

DR. MARKS: Can we have an auctioneer here as far as how many ingredients?

DR. KATZ: Do you know which three or four should be removed?

DR. MARKS: Well, that can be clarified in the next rendition, I think.

DR. SHANK: The table on 12 goes to 89, one through 89.

DR. HILL: There's two tables and they both go to 89.

DR. MARKS: Oh yeah, there's Wave 3 again. Do you have the Wave 3 table where -- in multicolor?

DR. SHANK: No. This is in the original document.

DR. MARKS: Okay. I think I had that one here. Does that corresponds? It's the Hizikia, 37 to 39. There's Hizikia extract, water and callus culture extract. Are those the three that -- I think I heard you right, 37 to 39, Ron?

DR. SHANK: Yes. That's what I said. Actually, it looks like -- well, unfortunately it's which table you use.

DR. MARKS: Okay.

DR. SHANK: It's the Hizikias. And in the very first table we got, that would be 38 to 40. But in the other table it's 37 to 39.

DR. MARKS: Well, maybe what I should do is just put -- rather than the numbers, put --

DR. SHANK: The actual names.

DR. MARKS: Yeah. I have the names in parentheses.

DR. SHANK: Okay.

DR. MARKS: I thought this was the original one. This isn't? Again, I think we got three different tables. Because the last one was the one that had the multicolor original submission, Wave 2 and Wave 3, in red and blue. Maybe I'll use that one. Let me see what number Hizikia is there. Thirty-seven, 38, 39. It's again 37 to 39. Okay. And then the next ones are the Laminaria group. And I'll say approximately 44 through 55.

DR. SHANK: Yes.

DR. MARKS: Okay. And then the last group of the grass kelp is 81 to 86, the Undaria species. And I assume these are all species, right? I'm correct in saying species?

DR. EISENMANN: Mm-hmm.

DR. MARKS: Okay. And we need the sensitization and actually, specifically, I mentioned some other ones where we need -- because of either the frequent use or the high concentration -- individual I put down there. And then for the rest of the ingredients, we need a 28-day tox since they're not grass. And then we also need sensitization for them.

That makes it actually pretty straight forward at this point. We'll see how complex the Belsito team makes it. But does that sound good? This is actually going a little more -- thank you, Ron, for suggesting that way of approaching it.

DR. SHANK: Okay.

DR. MARKS: Any other comments? Tom?

DR. SLAGA: No.

DR. MARKS: Ron Hill? We're obviously going to see it again, particularly if it goes out as an insufficient data announcement, which is hard for me to imagine it won't. Priya, any questions?

MS. CHERIAN: No.

DR. MARKS: Any others from industry? Okay.

DR. SLAGA: It's a very nice summary.

DR. MARKS: Oh, yeah.

DR. SLAGA: That helped a lot.

DR. MARKS: Okay. Thanks, Priya. Let's go ahead and with that we will move on to hydrogen peroxide, one of our favorite disinfectants.

Day 1 – Group 2

DR. BELSITO: Oh my God.

DR. LIEBLER: Kelp.

DR. BELSITO: Wave 2. Now here -- we're getting Wave 4.

DR. LIEBLER: Wave 4 is just the greatest hits of Waves 2 and 3.

MS. CHERIAN: It's just a summarization of the sensitization and dermal to make it easier.

DR. BELSITO: Okay. Well, we definitely need to limit arsenic. We need limits on heavy metals. What about these extractions? Methanol, hexane, chloroform?

DR. LIEBLER: You know, so I thought we actually had a lot of information about the different prep methods, and they seem to me to fall into a couple of categories. Maybe two or three categories to get these ground-up powders, to get these alcohol extractions or these aqueous extracts.

And I wonder if it might not be possible to prepare a kind of a map diagram that just shows the

major ways in which brown algae is converted to cosmetic products. Maybe not so much with a high level of detail in the map, but under method of manufacture it could be right there. I would imagine maybe sort of an inverted pitchfork trident thing, you know, with three pathways. Because then you'd have a table with lots of information for the individual ingredients.

MS. CHERIAN: Okay.

DR. BELSITO: Okay. Now, we know a lot about the impurities, we know a lot about the method of manufacture, we know zilch about composition.

DR. LIEBLER: Yeah. I had a more specific question about composition, which was do we -- because of Wave 2, we now have data on the actual cosmetic ingredients, not just on some representative algae from the literature.

DR. BELSITO: Right.

DR. LIEBLER: So, that's good. And I had a question about constituents of concern with respect to sensitization for example. And we don't have data on those for any representative, at least -- I might have missed it in the blizzard of Wave 2 or Wave 3.

DR. BELSITO: Well first of all, the two biggies are Laminaria digitata and macrocystis. Those are the ones that are most frequently used, right?

MS. CHERIAN: Yes.

DR. BELSITO: And we have an HRIPT on 46 humans for laminaria, but we have no data for macrocystis.

MS. CHERIAN: We have some data for that ingredient --

DR. BELSITO: We have no sensitization data.

MS. CHERIAN: -- either in Wave 2 or 3.

DR. BELSITO: I didn't see it.

MS. CHERIAN: Okay. Let's see.

DR. BELSITO: And all of the times that these were irritant, it was always with propylene glycol. And I thought propylene glycol was the irritant there. I was okay with the irritation, but we have no sensitization data for macrocystis. And we have just an HRIPT on 46 individuals for laminaria.

And we also have no tox data for either one of them. And at most, we have 28-day tox data. And

that raises the whole issue of iodine concentration and thyroid effects.

DR. LIEBLER: You're talking about macrocystis?

DR. BELSITO: Yeah. Now the thyroid issues with ingestion of these kelps were extremely high amounts, but we don't have absorption data. And then we don't really have good genotox data. And then we have some endocrine effects. We don't have photo, we don't have composition, we don't have 28-day dermal absorption. We don't have sensitization on macrocystis, we don't have photo. The genotox, there's some report of endocrine affects.

DR. LIEBLER: Yeah. I'm trying to get some idea of how widespread food consumption is with the ones that we're using. Macrocystis, laminaria digitata, laminaria saccharina approved as food additive or direct food addition, food for human consumption as a source of iodine or as a dietary supplement. I don't know to what extent that factors into our need for dermal tox or additional tox data.

My hunch with these is that we may be treating these more the way we treat other kinds of botanicals, where our major concerns is going to be sensitization and constituents of concern. Maybe that's not accurate, but that how I first approached these.

DR. KLAASSEN: Well, they are considered food additives, especially for animals to quite a high extent, without apparent toxicity, which gives me some support.

DR. LIEBLER: In the acute oral toxicity study, it's Table 21, PDF Page 55, we have a relatively small selection of brown algae compounds that have been tested -- or brown algae that have been tested. For our report, the fucus vesiculosus, there are three different studies in Swiss mice.

But if you look at all the brown algae that have been tested there's, let's see one, two, three, four, five, six, seven, eight studies, all of which have oral LD50s in the thousands. These are sort of the profile of nontoxic substances.

As far as dermal absorption, you know, it's basically a botanical. So, it's got sort of a wide variety of chemical substances, many of which are not absorbed at all.

DR. BELSITO: But we don't even know what they are.

DR. LIEBLER: That's a concern I have is the chemical composition of these. But I would say, particularly with respect to constituents of concern relative to sensitization. And of course, I didn't realize that these tended to accumulate arsenic so much.

DR. BELSITO: Right.

DR. LIEBLER: I found that interesting and surprising. Think of all the kelp in the world. This could actually be a major reservoir of arsenic other than the earth's crust.

DR. KLAASSEN: I think that arsenic form is not so toxic. It says in here some place that they're arsenic sugars. And I know at least fish, also, concentrate arsenic and puts it in a form that's not toxic like the inorganic form is. But I'm not entirely positive about this. But yeah, that's kind of interesting.

DR. LIEBLER: Paul have comments?

DR. BELSITO: Brown algae. "Extracts to 36 percent. Powders to 40. Juices no concentration. Water no concentration. Many uses with no concentration data provided. Plant-like, seaweed, protozoa, unique kingdoms -- very diverse group, too diverse?? Impurities; phytosterols, alginic acid, heavy metals, especially, arsenic, and phthalates. No data on composition. Tox data limited, but no level of toxicity. This one is touch with such a diverse number of sources and ingredients; don't know where to begin other than composition and impurity data base on some sort of plausible grouping." And that was my problem. We're just sort of assuming these all have the same composition.

DR. LIEBLER: Well, yeah. I mean, I suppose implicitly we're assuming that they have similar enough composition to be grouped together. If we did play the mental exercise of deciding to break these up, how would we break them up?

DR. BELSITO: I don't know.

DR. LIEBLER: With what would seem to be anything other than arbitrary.

DR. BELSITO: But wouldn't it be nice if we had composition on a couple different -- like at least the two that are primarily used for laminaria and the macrocystis?

DR. LIEBLER: Right. No, I agree. That's one of the notes I had, is that we need data on composition for the representative of the major groups. Particularly, I thought constituents of concern. Maybe you're not as concerned about sensitization with these, Don?

DR. BELSITO: I don't know. I mean, that's was one of my needs. I raised to you was an HRIPT of 46 sufficient for the laminaria, but we have nothing on macrocystis, which is the other one that has a high concentration of use.

DR. LIEBLER: I think we definitely need that. And I think of these as botanical. And with

botanicals, we almost always are looking for constituents of concern. Flavonoids, terpenoids, things like that. And at least if we have representative data for the different classes, along with safety data on sensitization, then we can draw a conclusion.

We don't have genotox on major -- we have genotox on a couple of fucus vesiculosus?

DR. BELSITO: Mm-hmm.

DR. LIEBLER: But we don't have it on any of the laminaria, do we?

DR. BELSITO: Nope.

DR. LIEBLER: Or the macrocystis?

DR. BELSITO: Nope.

DR. LIEBLER: I think we need that.

DR. HELDRETH: Is there one for laminaria saccharina extract? At least according to Priya's table, it looks like there's genotox for Number 55.

DR. LIEBLER: I might have buzzed by it.

DR. BELSITO: The genotox is not on laminaria though.

DR. LIEBLER: We have laminaria digitata, prep method concentration not specified, AMES assay with and without metabolic activation. There's a reference, I didn't look at it. Is that what you're referring to, Bart?

DR. HELDRETH: In Priya's cheat sheet table here, number 55 in the table says laminaria saccharina extract.

DR. LIEBLER: Oh, sorry.

MS. CHERIAN: Oh, it's in Wave 2.

DR. HELDRETH: So, data came in Wave 2.

DR. LIEBLER: I think the other problem in reviewing this report is the data are spread out over so many reports, that I just was missing stuff.

MS. CHERIAN: And I think fucus vesiculosus was the highest number of uses and concentration. But the concentration might have gone down.

DR. LIEBLER: Okay, so the cheat sheet's only for the skin endpoints, right?

DR. KLAASSEN: Right.

DR. BELSITO: Mm-hmm.

DR. LIEBLER: Yup.

DR. HELDRETH: No. It has repro, geno.

DR. KLAASSEN: Oh, he's talking about the one she handed out 30 minutes ago.

MS. CHERIAN: That's the data profile.

DR. HELDRETH: Yeah, the data profile.

MS. CHERIAN: Yeah. So, it's not on there. The genotox data is not on there, it's in Wave 2. That's only skin sensitization and irritation.

DR. LIEBLER: Alright. I think -- it's hard to tell what we have at this point.

MS. CHERIAN: Yes. Yeah.

DR. BELSITO: But the genotox data is on laminaria saccharina and not digitata?

DR. HELDRETH: True.

DR. LIEBLER: And where are you getting that, Don?

DR. BELSITO: Wave 2.

DR. HELDRETH: So, on Page 6 of Wave 2, it says for laminaria saccharina extract, the genotox says, tradename mixture containing this ingredient in seawater and methylpropanediol AMES test, salmonella strains. It lists five of those with and without metabolic activation in dose 50 to 5000 micrograms per plate, non-mutagenic.

DR. LIEBLER: Okay. But I think we need to have representative genotox for the major classes. And it looks like we've got it for laminaria.

DR. BELSITO: But does that take care of laminaria digitata?

DR. LIEBLER: In addition to the Wave 2, there is what was in the report, Table 23, which said laminaria digitata -- this is PDF 60 in the original report. And it's an AMES assay with and without metabolic activation. But it doesn't specify concentrations.

DR. BELSITO: Right.

DR. LIEBLER: It's probably not a great study. So, it's thin and nonexistent for macrocystis.

DR. BELSITO: Right.

DR. LIEBLER: But we've got two fucus vesiculosus in the report, Table 23, with

concentrations. One is a common assay, which isn't the best; it's not very sensitive. And the other is the chromosome aberration OECD GL 487. So, we really need more on fucus vesiculosus unless that's in Wave 2.

MS. CHERIAN: There's no genotox.

DR. LIEBLER: None?

MS. CHERIAN: For that ingredient, no.

DR. LIEBLER: Okay.

DR. BELSITO: Macrocystis.

DR. LIEBLER: Fucus I was talking about. And then macrocystis. So, we're lacking genotox for both of those. We don't have any AMES for fucus.

MS. CHERIAN: No.

DR. LIEBLER: I mean, relatively to the number of ingredients is really spotty.

DR. BELSITO: Okay. So insufficient, is that fair to start with?

DR. LIEBLER: Yes. Right.

DR. BELSITO: Okay. And do we have enough on the residual impurities? Or do we just simply say restrict arsenic, heavy metals and extraction solvents?

DR. LIEBLER: I think actually we've got a lot of data on the residual metal impurities, or arsenic and metals. And we obviously should treat that in a discussion and say restrict. I'm more concerned about the lack of data on the organic constituents of concern.

DR. BELSITO: What do you mean, the extractants?

DR. LIEBLER: No.

DR. BELSITO: The solvents?

DR. LIEBLER: Like terpenoids and flavonoids. Not the impurities, the constituents of concern that could contribute to sensitization.

DR. BELSITO: Okay.

DR. LIEBLER: All the data we have so far are non-sensitizing?

MS. CHERIAN: Yes.

DR. KLAASSEN: It looks pretty clean.

DR. BELSITO: We don't have a lot of sensitization data.

DR. LIEBLER: I mean, how comfortable are you with the sensitization?

DR. BELSITO: I don't know what's in them.

DR. LIEBLER: Well, okay. If you were concerned about sensitization with these, then that increases the need for data on the constituents of concern that are associated with sensitization.

DR. BELSITO: Right.

DR. LIEBLER: If you had a very thorough list of studies that were to show non-sensitizing in humans, at use concentrations, then I wouldn't be so concerned about having data on terpenoids and flavonoids and so forth.

DR. BELSITO: So, we need composition on laminaria and macrocystis?

DR. LIEBLER: Yes.

DR. BELSITO: We need a 28-day dermal? Or are you happy with a grass status?

DR. LIEBLER: I think the grass status helps. We've got Table 22, Oral repeated dose. We hardly have any studies in which there's evidence of toxicity, either in acute or repeat dose.

DR. BELSITO: (Inaudible) dose with the extract for iodine.

DR. LIEBLER: Yeah.

DR. BELSITO: Thyroid affects.

DR. LIEBLER: Right. I mean, because it's such a big group, we don't have a comprehensive data set for toxicity with all of them. But for what we do, it's a pretty consistent message; these aren't really toxic.

DR. BELSITO: So, you don't need a 28-day dermal?

DR. LIEBLER: I don't think we need the 28-day dermal. If you take that information, plus the widespread use of these as dietary supplements or food additives.

DR. BELSITO: Okay, so we're not worried about dermal absorption because we have all of this grass status, dietary supplement, et cetera.

DR. LIEBLER: Right.

DR. BELSITO: Okay. And then we need composition on laminaria, macrocystis, sensitization and irritation and concentration of use for macrocystis. And we're okay with the 46 for laminaria?

DR. LIEBLER: If you're okay with it, I'm okay with it.

DR. BELSITO: Well, I guess we'll see what the composition looks like. Photo absorption?

DR. LIEBLER: Photo absorption?

DR. BELSITO: Yeah.

DR. LIEBLER: Oh, I'm sure they all absorb. I mean, they're complexed, you know, botanicals. They all absorb.

DR. BELSITO: So, then we need photosensitization/photo-irritation?

DR. LIEBLER: I don't think that necessarily follows. Do we have any photosensitization on any of them?

DR. BELSITO: Nope.

DR. LIEBLER: I mean, complexed organic mixtures all absorb, but not all of the absorbing materials -- I mean, most of the absorbing materials are not photo allergens or photosensitizers.

DR. BELSITO: Right. But some of them are.

DR. LIEBLER: I mean, with pure compounds, absorption tells you something.

DR. BELSITO: Right.

DR. LIEBLER: With mixtures, absorption doesn't tell you anything. So, the kind of logic use in RIFM where if it has absorption above or below the benchmark, clears it, that doesn't apply in mixtures like this.

DR. BELSITO: Right. So how do we deal with that?

DR. LIEBLER: If we had --

DR. BELSITO: Composition.

DR. LIEBLER: -- composition. Again, constituents of concern, including known photosensitizers. Flavonoid, terpenoid sensitizers. That's why I kept coming back to that point. If those are low, or minimal, or at least documented and the measured amounts are present in ingredients that have been tested, at least for sensitization, then I think we're okay.

For photo, that's really hard to predict for mixtures. For pure compounds, sure. But for mixtures, it's really hard to predict. And then I don't know that we're going to get very far by saying we want photosensitization on everything. I mean, we can ask for photosensitization on representative ingredients from the major groups.

DR. BELSITO: So, photosensitization, phototoxicity for laminaria and macrocystis, or concentration of use?

DR. LIEBLER: Yeah. And if we don't get that and they respond with data on constituents, particularly organic constituents that might be associated with photosensitization, then we can take that into consideration.

DR. BELSITO: What about genotox?

DR. LIEBLER: Based on what I've seen so far, I think the data are thin. We'd like more genotox data. Particularly for --

DR. BELSITO: For laminaria.

DR. LIEBLER: On the laminaria.

DR. BELSITO: On macrocystis.

DR. LIEBLER: Macrocystis, right. Yeah.

DR. BELSITO: Anything else? Developmental repro? No?

DR. LIEBLER: I really doubt it. I mean, I don't think we're going to need it.

DR. BELSITO: Are we clear on the genotox, on the idea that they're used as foods?

DR. LIEBLER: What do we have on carcinogenesis?

DR. BELSITO: Nothing.

DR. LIEBLER: Nothing.

DR. KLAASSEN: Well, you know, this is our first time around. I think we should ask for genotoxicity.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay. For again, laminaria and macrocystis?

DR. KLAASSEN: Right.

DR. LIEBLER: I agree with you, Curt.

DR. KLAASSEN: And regarding phototoxicity, that's -- you know, these chlorophyll-type compounds and chlorophyll degradation products are photosensitizers. So therefore, to request those there is some reason.

DR. LIEBLER: I think we agreed on that. I think we agreed we're going to ask for that.

DR. KLAASSEN: But all I'm saying is it's not just grabbing out of nothing. There's a kind of a reason for it.

DR. BELSITO: The list I have so far is we would like some information on the composition of laminaria and macrocystis. Sensitization and irritation and concentration of use for macrocystis. Phototoxicity, photosensitization at concentration of use for macrocystis and laminaria. And some genotox on laminaria and macrocystis. That it?

DR. LIEBLER: Yes.

DR. BELSITO: Anything else?

DR. KLAASSEN: That should be good enough.

DR. BELSITO: Any other comments on brown algae? Okay.

DR. LIEBLER: I think this will be easier to deal with next time when we can have it all in one document.

DR. KLAASSEN: Yeah.

DR. BELSITO: Oh, well, then we still get Wave 7 and 8. Okay.

Day 2

DR. BELSITO: Well, this is huge and I'm not going to read all of them, but the two major ones laminaria digitate and macrocystis. And we thought we could use those as our sort of, for lack of a better word, read across to brown algae.

We thought that there was a lot of data about impurities, but we don't know what these are made of. We don't know composition. So, we're asking for the composition on laminaria and macrocystis to see how similar different types of brown algae were.

We do have sensitization and irritation on the laminaria, but not the macrocystis, and we're asking for that. And we're asking for genotoxicity on the laminaria and the macrocystis extract, as insufficient data.

DR. BERGFELD: So, that's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Dr. Marks?

DR. MARKS: We second the insufficient data announcement. We, or I might say Ron Shank, had a different approach which was appealing. Ron divided these -- what is it 83 ingredients -- into two groups, the grass group and the non-grass group. And the grass group was, depending on which list -- I think we got three

different tables -- but the hizikia species, 37 to 39, at least, in the table I use, and the laminaria species 44 to 55 numbered, and then the undaria species, 81 to 86. We wanted the sensitization data on those. For the rest of the ingredients, which were not grass ingredients, we wanted a 28-day tox and sensitization. We like, obviously, the composition. I didn't feel as comfortable with the sensitization data on several of the ingredients you mentioned.

In Wave 3 we did get HRIPT, which was good for the fucus vesiculosus, and the laminaria digitata extract at 5 percent. But, in both of those, I wasn't able to determine what the concentrations of those ingredients were in that mixture. They just said the mixture was tested and the HRIPT was okay; but I didn't know what percentage of that mixture was the actual algae ingredient.

For the laminaria digitata powder, that's being used at 40 percent, and I saw no evidence as far as sensitization confirming its safety. And the macrocystis extract, that's used at 36.4 percent and there was no data on sensitization.

So, I think we can roll together what both teams need. Our team found it appealing the way Ron Shank approached it. So, a lot of the toxicity data, such as the 28-day tox wouldn't be necessary for the grass ingredients of this large group.

DR. BERGFELD: Do you want to comment, Dan?

DR. LIEBLER: It actually disturbs me to realize I had the same idea as Ron Shank. But I'm curious as to whether or not we can actually get a good inventory of the ingredients, in our report, that are associated with grass for food enhancers and flavor adjuvants and so forth. So, can we get a good listing of that, do we know?

DR. MARKS: Well, that could certainly be in the insufficient data announcement.

DR. SHANK: So, we know which are which. Because I like the idea -- I mean, I recognize as well, all kidding aside, that many of these are widely consumed. And this could be very similar to some of our other botanical ingredients where, like apple or orange or something, that, you know, they're widely consumed and we mostly focused on the skin endpoints.

So, I agree with that. And I just want to make sure that we can -- I'd like to know to the extent to which we could get a good inventory, what is grass? What could be considered that way?

DR. BERGFELD: Linda, could you respond at all?

MS. KATZ: No, not really, because I don't do grass, it's not within my jurisdiction. I'm

presuming that you can always make a FOIA request and the FDA can provide that information; but it's not something from my group. One of the other groups, the Office of Food Additive Safety is the one who handles that determination.

DR. BERGFELD: Thank you. Any other comments?

DR. MARKS: I think, as again as this moves forwards we need to really, in the introduction and discussion, really emphasis how complex this is. And the algae that their definition, at least by Dr. Lowe's presentation, is that they're functional groups and that they're mixtures. I asked yesterday whether these are all seaweeds, and it appears they are all seaweeds. They aren't protozoa, or they aren't some unique kingdom. So, I think that's important.

And then, obviously, we not only have the complexity of botanicals in terms of their chemistry composition -- which we're going to ask for the composition. But these composition levels varied depending on species, varied on growing, harvesting, method of manufacture. And then, these particularly is concerned about contamination by heavy metals and arsenic, and that all needs to be captured in the discussion.

DR. BERGFELD: I want to make one comment since there's so much data here; that I personally, as a Chair, would like the data profile updated with all the Wave information that came through.

DR. MARKS: Oh sure, we'll see that in the next rendition.

DR. BERGFELD: Okay.

DR. SLAGA: That'll be very helpful.

DR. BELSITO: Priya did a very good job of putting all of those sensitization and irritation data together for us, so good work.

MS. CHERIAN: Thank you.

DR. MARKS: Yes, and method of manufacture and impurities. Each Wave came with another two pages of tables, or three or four.

DR. LIEBLER: I had suggested a map. No, just a schematic, because it seemed like there were some recurrent themes with a lot of little individual differences of the types of preparations that are made; sort of a powder versus an alcoholic extract versus an aqueous extract, et cetera. And maybe like an upside down trident that might have examples of some of the families and how they're -- just to orient the reader into how these things are turned from kelp, you know, algae to products that are more tangible. So, that's what I suggested to Priya.

DR. MARKS: And we certainly divided the botanical as to safe and insufficient, depending on whether the final product is an extract or a powder or a juice or whatever; so, that is important.

DR. BERGFELD: All right. I think that we've had enough discussion, then, to call to question. All those in favor of the conclusion of insufficient data announcement? Thank you. Unanimous. Well, that was quick. Thank you, Don, and thank you Jim. As I thought it would be longer. Let's move on to the next ingredient, the Acrylates Copolymers, Dr. Marks.

DR. HELDRETH: Before we move on, could we just get a reiteration of the needs, so that Priya has everything she needs for the announcement.

DR. BERGFELD: Okay.

DR. BELSITO: Why don't you go ahead Jim because you added some in. I'm fine adding as many insufficiencies as we need at this point.

DR. MARKS: The first thing would be which one of these algae really are grass designated? And then the second, we basically need sensitization for everything. But from the hizikia, the laminaria and the undaria, we felt we had enough to move forward since these are grass ingredients that all we need was sensitization. The rest of the ingredients we want the 28-day tox, along with sensitization -- and genotox.

And composition. Don, you had brought out a couple of lead ingredients for composition. As far as I'm concerned, let's get as much composition as we can get for as many different species of algae. But, Don, you were specific in naming species.

DR. BELSITO: Well, most of them are very low concentration of use with the exception of the laminaria digitata, which is at 50 percent. I'm sorry I made a mistake; I had written down that sensitization was at 50 percent propylene glycol, it's 5. So, I guess we need sensitization for that as well.

And the macrocystis, which is at 33, I think, .4 percent in a leave-on. So, I just sort of saw those as the two lead products. And if we can get composition on them, and seeing that the compositions of these algae are pretty similar, we could use data from the read-across for those two that are used in very high amounts, to help clear a lot of other information.

DR. MARKS: So, I think as much composition as we can get.

DR. BELSITO: But we have a lot of sensitization and irritation, as you can see, from the table that Priya provided for us yesterday.

DR. MARKS: Yeah. Unfortunately, they weren't in the ones that are most commonly used.

DR. BELSITO: Right.

DR. MARKS: And there were some big numbers of use. And that's why you picked those out, Don, I concur.

DR. BERGFELD: Are you okay with the needs assessment and what is needed?

MS. CHERIAN: Yes.

DR. BERGFELD: All right, we'll move on then. We're going on then, again, to the Copolymers, Dr. Marks?

December 2018 Meeting

Group 1 – Day 1

DR. BELSITO: Okay, brown algae-derived ingredients. At the September meeting we issued an insufficient data announcement for the 82 ingredients. And we wanted composition and organic constituent data for each of these brown algae-derived cosmetic ingredients. Twenty-eight-day dermal toxicity for ingredients that are not GRAS, sensitization data at relevant use concentrations for all ingredients, and genotoxicity data for those ingredients that are not GRAS.

Since that time, we've gotten a bunch of data. Some of which we got in waves just before the prior meeting, and it has now been incorporated into the report. And we have comments from the council. Then we got another Wave 3, on brown algae, which looked at the Laminaria Digitata extract at 20 percent for sensitization. However, it's used at 40 percent. But it also turns out that the ones that have the highest concentration of use, the Laminaria Digitata and the Macrocystis, are also GRAS substances.

Anyway, we certainly didn't get nearly as much as the data that we asked for, since we're asking for, like, data on all of these ingredients, which we're not going to get.

I, honestly, don't quite know where to go. I mean, for me we asked for concentration of use, we got 20 percent with the Laminaria. But when you sort of look at what these things are composed of, it's not likely that they're going to be sensitizing. I think the biggest issue is the heavy arsenic and heavy metal composition for them. But I'm just curious as to what the rest of my team thinks.

DR. LIEBLER: Well, I'm about where you are, Don. My overall comment on this group, is that this is beginning to make sense. We have GRAS for several of the most used ingredients, tox data on a couple of the

non-GRAS ingredients, including the mucosa. And the overall tox and genotox profile on these are all clean.

I don't know if the body of sensitization data is sufficient for you, so that was a question mark for me. But I'm moving towards safe as used on these.

DR. BELSITO: I mean, when you look at what's in them, it's really pretty banal stuff. I'm not seeing anything coming out of them, even like you would see in a botanical. There's no fragrance-like ingredients, there are no pinings. There are none of those things, comings out of these algae, that would sensitize from, at least, the limited data that I see. And I don't really believe that there's going to be any difference, among any of these, in terms of potential sensitizers.

DR. LIEBLER: We do have a growing assembly of information on constituents. And there's still more along the lines of chemical classifications. I'm scrolling up to the tables that have them. It's better, it's still not ideal. I can't say that we have data that shows that the flavonoids in these don't include constituents of concern.

So, that's what I was looking for, or at least some kind of numbers on those. I don't see those yet. And I don't know if anything is available. But on the other hand, the safety data that we have doesn't give a whiff of sensitization. And my main question was whether or not the concentrations tested were sufficient on sensitization, Don. And you just pointed out we're a little short of maximum use concentration.

DR. BELSITO: We clearly don't have the data for Macrocystis. And for Laminaria, in the wave we got, it was at 20 percent. But, I'm not seeing anything there that would be a sensitizer. I agree, the composition data is somewhat limited. But when you look at it, I'm just not seeing anything that catches my eye as potentially causing skin sensitization. Paul and Curt, what did you --

DR. EISENMANN: I still haven't gotten the company, that's using that highest concentration, to confirm or deny those high concentrations. I'm still working on them. I was hoping by now they would have given me some kind of a response, but they haven't yet.

DR. KLAASSEN: I guess maybe the greatest confidence, in regard to toxicity, is that some of these are GRAS substances. I know that doesn't cover the external effects on the skin, but again, there's really no indication that anything's happening.

DR. SNYDER: I struggled with this group. It's large, it's complex. And every time you kind of think you have some data that you maybe could use to read across, then you realize, well, is this really reading

across. But my overall sense was that the systemic toxicity issue, for the ones that we have data on, is very, very low.

And so then I, by default, went to the sensitization. And again, it's the same thing. We have some sensitization data, it's not at the concentration we'd like to have it at, it's not with all the ingredients, but I think we have a body of it -- as you said Don -- that there's no reason to suggest that sensitization would be an issue with these. Particularly, in light of the fact, as Curt said, many of these are GRAS; or there are no constituents of concern that we have data to indicate would be of concern. Again, it's difficult, but I think we're there.

DR. LIEBLER: We have a large number of ingredients. And we have a relatively smaller percentage of those that are actually used, must less heavily used. And of those, those are where all of our GRAS ingredients are. But we have a couple of major ones in the heavily-used category. Like the fucosa that aren't GRAS, but we have tox data on those. And the tox data suggests that there's no systemic toxicity potential for these.

So, even though we don't have data on even a plurality of the ingredients we're looking at, we have sufficient information, I think, on the ones with the highest uses and exposures, to make me feel confident in moving towards a safe-as-used assessment on these.

DR. BERGFELD: How would you put that in your discussion to cover all of these ingredients?

DR. LIEBLER: It's hard. I don't remember now. I'm scrolling down past the tables, which fractions of these are not -- oh, no reported use. It's a pretty big table, Table 22. Looks like there's at least 30 in there, maybe more.

MS. FIUME: Probably about 48.

DR. LIEBLER: Okay.

DR. BELSITO: I also think that at some point we need to bring in the discussions that we had, several years back, on the division of these into brown and red and green. And I remember there was information in those presentations as to some composition that we don't have here, in terms of general content.

DR. EISENMANN: There's a table in there that gives it. But, personally, I think you should just focus on what's in brown algae and forget the other groups of algae at this point.

DR. BELSITO: No, I understand. But what I'm saying is, is the information that we have here -- the information from that presentation as to what was in brown algae? Because I thought there was more.

DR. EISENMANN: I think it is in there. I'm not sure there's that much more. I think it probably is what's in the cell wall, and alginates in the Fucoidan-type materials. I'm not sure there is --

DR. LIEBLER: This is about four years ago --

DR. EISENMANN: Something like that.

DR. LIEBLER: -- that we had this presenter. And I don't know if Priya's got those slides in that deck. If she's been through the deck, then she's got it.

MS. CHERIAN: Yeah. It was included in the last pack of information.

DR. LIEBLER: Okay. So we've got it.

MS. CHERIAN: Mm-hmm.

DR. LIEBLER: Thank you.

DR. EISENMANN: One thing that struck me, is in the introduction there's a sentence that more or less says how different these materials are. I think I would start the introduction differently and say how similar these -- what the algae have in common, instead of saying how different they are.

And yes, they have some difference; but one thing they do have in common is they're all marine. Which does make a difference compared to, like, other groups of algae where you have them growing in all different types of environments. So, these are all, at least, marine species. Plus they have cell wall materials in common.

I think if you changed the introduction -- to me, when I first read the introduction I thought, if they're all so different, why are they being reviewed together. But if you focus on the similarities, in the introduction, the tone will change and I think it will sound much better than how it's currently presented.

DR. SADRIEH: And then you also have the reason why it's appropriate to review them in that report; bottom line. That's a good idea.

DR. BELSITO: Interestingly, when you look at the sensitization data, we have an HRIPT for Halidrys Siliquosa, if that's how you pronounce it, Siliquosa, at 48 percent. It's not the Laminaria that we asked for, but it's a very high percentage. This is on PDF 55, I think. The first paragraph. The extract 48 percent water. I guess it's the concentration of test substance that's not provided.

I guess that also raises the question, is 40 percent the actual amount of Laminaria, or is it 40 percent of an extract, which contains only a percentage of Laminaria Digitata.

DR. EISENMANN: I'm still trying to get that clarified for sure. But I can only ask, I can't make

them tell me what's going on.

DR. LIEBLER: So in other words, the stuff that they used was 48 percent extract in 52 percent water. The concentration of that stuff, in the material that was applied, is unknown.

DR. EISENMANN: Um hmm.

DR. LIEBLER: Yeah, I think the concept of reading across is really not applicable, with these complex mixtures, unless we have much more extensive chemical substance characterization. So that we could say that, for example, with this extract, constituents of concern were similar to, let's say, fucosa. And then we could say, well, at least in terms of the concentrations of substance of concern, these are equivalent. But we're not in any position to do any sort of read across with these. So, we take the ones we can get and then we decide what that's telling us about the overall body.

I'm relatively impressed at the volume of data we've got already for these. Considering that half of the group isn't even used.

DR. BERGFELD: I'd like to ask a question about that. Couldn't you divide them into the GRAS and then enumerate with those? And then the non-use group and then the ones in use, what the testing --

DR. LIEBLER: Oh, that was Ron Shank's suggestion, originally, how to handle these. The problem is the ones that are listed as GRAS, are actually, numerically, a small percentage of this whole report. So, they turn out to be among the ones that are most widely and heavily used. But they don't help us with very many ingredients in this report. So then we have to turn to what we had tox data for, also things that are heavily used, but not GRAS, and where those have a uniformly favorable tox profile based on the data we have.

So, the thing that's left outstanding, is that for many of the individual ingredients in this report, we have no data. And so the question is, do we say sort of the biological similarity of these marine organisms allows us to have confidence in this assessment, overall, based on a lack of any data in the testing materials, showing significant adverse effects.

And like I said, I started out by saying I'm leaning towards safe as used. I'm waiting to see if more stuff comes in. I don't know if we still have requests out for additional data, that haven't been addressed. Do you think that this is as good a package as we're going to have or can we expect more?

DR. SADRIEH: Our feeling is this is probably as good as you're going to get.

DR. EISENMANN: I'm not aware of anymore coming in, other than maybe a few clarifications

I'm hoping for. But not that I'm aware of. And I think part of the issue of these ingredients, a lot of them are being sold as even more complex mixtures. So, they're coming in with other plants, with other algae species. And then they're testing those more complex mixtures, rather than testing the algae alone. So, it's kind of pretty complex.

DR. SNYDER: So, to Wilma's point, maybe the way to approach this report is to have a really large intro section that really clearly indicates what data we're utilizing. The GRAS/non-GRAS is obviously very important. The high-use, high-concentration ingredients. And then, parcel it that way to see where we're at. That's what I was trying to do when I reviewed it. And it was very hard. Every time I thought I had something, then it wouldn't clear something else.

And then our discussion is going to have to be very robust in why we we're leaning towards safe as use. We don't have any red flags. But then again, we don't have all the data that may give us indication of these red flags. But again, instead of saying safe as used, maybe we need to say, safe as long as they're within the composition of the ingredients you reviewed in this report.

So, maybe somewhat different how we state it. Because it is really driven by composition impurities. We have pulled out the impurities, the heavy metals, the pesticides, the phthalates, and all that kind of stuff; but we don't know if there's others because we don't have the data.

So we're going to have to be very specific, if we go safe as used, as to what we're saying. Because I think we do have some gaps that are just -- I don't think we're going to get the data. I don't even think we know what data for ask for, to be honest.

DR. BELSITO: If you sort of look at the type of data we're asking for -- so if you go to Table 8, this is general compositions of brown algae. I guess this maybe what was presented at our talk several years back. But then you go down to Table 9, and quite clearly, with the exception of fucus vesiculosus, they're not really looking at all the constituents.

So, for the ascophyllum it looks like they were just more interested in the metals. Yeah, because then they say, water not reported. I mean, you know that there's water. Carbohydrates, not reported. They're not really looking at the entire composition.

And the same thing for the Laminaria. They're not reporting lots of different factors. So I think the only one in that table, that comes even close to being complete, is the fucus vesiculosus. But I mean, these overwhelmingly are carbohydrates, fats and fiber, is what we're looking at.

DR. LIEBLER: It appears that they did not make measurements of, for example, terpenes and flavonoids.

DR. BELSITO: Right.

DR. LIEBLER: And those would be what we would be concerned about with most botanicals for sensitization. And so, we just have no data because for whatever reason it appears they didn't analyze it. But on the other hand, the data that we have suggest that there's no sensitization potential with these. So, I keep coming around in these circles with these compounds.

The only other thing I can think of is to provide maybe a little more framework and logic behind our -- I hate to use the term reading across, for lack of a better term -- read across to these is. If we considered what we have data on by possibly genus, do we have representative data on the genus subgroups. And I didn't try and look at that because it would be kind of an onerous exercise. Have you tried to look at it that way, Priya?

MS. CHERIAN: I have not.

DR. LIEBLER: Priya, use the mic please.

MS. CHERIAN: I have not.

DR. LIEBLER: Okay. I mean, right now we're kind of going by looking at the ingredients that are used and have the most uses. Those are the ones we tend to have more data for. They're either GRAS, or we have data on tox and sensitization and so forth.

And so, for the ones that are used, I'm actually quite comfortable with safe as used. It's having half the report -- it's things we have no uses for and no data. So, maybe the decision we're facing is do we say sufficient for those? Somehow the ones that are in use, for which we have data, and then for the others not?

Or do we try and group by genus, and make the assumption that within the genus we have representative data we can read across within that genus. And I'm not sure that's really valid; but I'm just throwing that out there to see if anybody else thinks that might be a reasonable approach.

DR. KLAASSEN: I think the approach is reasonable, but I don't think -- there are so many classes of compounds here, that's probably not going to help us.

MS. CHERIAN: I haven't specifically looked through every genus to see if there was data for each. But I don't think there would be enough.

DR. BELSITO: If we did it by subclass, maybe. But getting down to genus, no.

DR. LIEBLER: I mean, if we did it by family.

MS. CHERIAN: It's probably close. Yeah, it's probably close.

DR. SNYDER: The bottom line here is what we really need is more composition data, particularly organic constituents, because that's what many of the -- that's the uncomfortable. I mean, I guess we could just keep -- I mean, I don't know if we're going to get it, or if it's not available. We have some, but we certainly don't have enough to fill all the gaps. Because it's such a diverse group.

DR. BELSITO: We don't even have it for any of them. I mean, Table 8 and Table 9 are it. And it just lists terpenes, it doesn't give us percentages.

DR. SNYDER: Well, I guess that, combined with the fact that we didn't get the 28-day dermal, to know whether any of them are absorbed, I think we are obligated to go insufficient.

MS. FIUME: I was just going to say there is no -- we've done it many times where we've had split decisions. So, if you find that you can support the safety of some of them, we can go with some type of safe or safe with qualifications. For those that you don't feel comfortable that the data are there, insufficient data is always an option as part of the conclusion. We can do a mixed conclusion.

DR. LIEBLER: That would be the most conservative approach. I think that we would actually end up covering a lot of the ones that are in use. And then we would not have sufficient data -- we would be insufficient for some that are in use and everything that's not in use. And the stuff that's not in use, we're not going to get the characterization on that. I mean, it's just not going to happen.

I think I would favor that approach. I think I could justify that to somebody who is skeptical. And that's what our standard should be.

DR. BELSITO: So, then Table 23, Priya did what Ron asked for at the last meeting. And she has the GRAS substances; and then she has brown algae species used in food products. So, I just didn't understand the difference between 23 and 24. All of the ones that are GRAS are used in food products, because you've got Cladosiphon Okamuranus as being used in a food product, but not being GRAS.

MS. CHERIAN: Not all of them are listed as GRAS. But when I did research, I saw some that are used as food products, but aren't labeled as GRAS.

MR. GREMILLION: There's no requirement that a company notify FDA when they make a GRAS determination. Companies could be operating under self-determination that their product is GRAS. That's

another complication with classifying it that way.

DR. EISENMANN: But those materials are actually food. They're not used in food, they're food. And one note is -- in Table 24 -- Laminaria Angustata. Well, the INCI name for that one is Saccharina Angustata. So, if you say the food are safe, then Saccharina Angustata Extract should be safe because that's the current name. That's the difficult part of it now, too, a lot of the names are changing.

DR. BELSITO: Which one are you talking -- which Laminaria?

DR. EISENMANN: Angustata.

DR. SNYDER: Fifth one down.

DR. BELSITO: Oh, okay. So, Dan, your suggestion was to take Table 23, and 24, and say that those are safe as used; and the others are insufficient based upon dermal absorption or composition? Is that what you're saying?

DR. LIEBLER: I would start out as you started out, those in Table 23 and 24, safe as used. And then I would add, into the safe category, those for which we actually do have tox data, even if it's not dermal; and those for which we do have sensitization data. But we could use the body of sensitization data, perhaps, if the dermatologist agree, to conclude that there's no potential for sensitization amongst these.

DR. BELSITO: But sensitization data doesn't get rid of the fact that we don't have absorption, and we don't know what's in it, getting back to Paul's point.

DR. LIEBLER: So, okay, here's the -- what I'm suggesting is the first cut. The ones that we would keep in the report, potentially, as safe as used, would include those that are GRAS, those that are used in food, and those for which -- if they're not in either of those tables -- for which we do have tox data, which is like a couple of fucosas.

And then we take that group and we make a conclusion about sensitization, based on the available data. That still could be insufficient for some of those, but that's going to be your call, Don. You and Wilma and Jim, I think.

And then the others, we don't really have anything. We can't read across to anything. And we'll simply have to say that those are insufficient. That would probably leave us with, maybe, a dozen or so that clear the bar, maybe 15. And the rest are going to be insufficient.

DR. SNYDER: A 200-page report just became a 250-page report.

DR. LIEBLER: It's just bytes on your hard drive.

MS. FIUME: Can I ask a question about looking for the absorption? I often get confused with this and with botanicals. We state that because they're large complex mixtures, it's impractical to look for absorption data. So, when you're talking about not having the 28-day dermal, to see what absorbs for the systemic toxicity, is it because of concerns of specific impurities that may absorb? And that's where the concern is, not having any absorption data or 28-day dermal tox?

DR. LIEBLER: You can't do absorption study with these. Because they're heterogeneous mixtures of things that will certainly be absorbed, and things that will certainly not be absorbed. And preparation to preparation, the amounts absorbed is going to vary as well. Absorption data for these is pretty meaningless.

The only way in which it would make sense, is if there was a particular constituent of concern that we want to know if it's absorbed from typical ingredients. You know, fucosa, let's say. If Laminin were in it, is it absorbed? If Quercetin were in it, is it absorbed? But we're not talking about that. We don't even know if Quercetin is in it.

We don't even know what questions to ask in order to do the experiment. And I don't think we're going to get the data. So, I think the issue of the ability to treat these in that way, is just not before us. We really have to go with the data we have or simply say it's insufficient. And I think we probably would be better off asking for tox endpoints than analytical endpoints.

DR. BELSITO: So, then when you're looking at tox endpoints, I don't think genotox alone clears that. And all of the genotox is negative. So, then you're really looking at, I presume, oral repeat dose studies. And then where do we cut it off? Do we want at least 13 weeks? At what point do we say we have enough oral tox to make us feel comfortable?

DR. SNYDER: Typical toxicity studies you start off with acute oral. You get your doses, so you know -- once you identify your toxicity, then you can escalate longer duration of exposure to see if you have additional issues. And so, it's not set in stone, it's a systematic approach. There is a reason to how you do it. And so, longer duration gives you more confidence that you have no health concerns.

DR. BELSITO: Right. So, at what point do we want that confidence? Do we want four weeks? Do we want 13 weeks? Do we want --

DR. SNYDER: Yeah, usually a 4-week study, with very low toxicity, gives me tremendous

confidence on a very low-concentration ingredient. I don't think we need to go beyond that, and in that regard. But if there's constituents of concern, then we know that it takes longer, then -- that's what I look at when I make an evaluation. It's a lot more complicated than it may first seen.

DR. BELSITO: But we don't know the constituents.

DR. SNYDER: That's the problem. It's all about composition. You know, particularly organic constituents, we don't know.

DR. BELSITO: So, in the absence of that, is there any length of study, short of a two-year study, that you would be comfortable with? Because the longest study, I think, we have is 13 weeks.

DR. KLAASSEN: I think we could be -- I could be satisfied with a 4-week study, most likely.

DR. BELSITO: We actually have a 32 and 36 in a lifetime, but most of them are 13 weeks.

DR. LIEBLER: I agree with Curt.

DR. BELSITO: If it's GRAS, if it's a food, if we have a 13-week oral, those would be safe as used.

DR. LIEBLER: Thirteen weeks, we only have --

DR. BELSITO: I mean, 4-week oral. If it's GRAS, if it's a food, if we have a 4-week oral, then we'd be comfortable with it, is that what I'm hearing?

DR. SNYDER: That's my sense. That's why I said, at the beginning, there doesn't appear to be any red flags for anything that we have data on. Even though we don't have data on as many as I would like to see us have data on. Or we don't have composition data on as many as I'd like to see us have data on. It's just difficult. It's a very large, complex group. And it's hard to get your head around it.

DR. BELSITO: I agree.

DR. SNYDER: But there is no real red flag that I have a big concern about.

DR. BELSITO: Curt, do you have your hand on the mic?

DR. KLAASSEN: Yeah. I was going to ask a general question. Plants often contain these polyphenolic compounds and terpenoids. Are any of those known to be allergens? I assume they probably are not because so many plants have them.

DR. LIEBLER: You mean sensitizers?

DR. KLAASSEN: Yeah, sensitizer is what I meant. Can we make a generalization that basically

they're not sensitizers?

DR. LIEBLER: We don't have the data on whether they contain any of those compounds. I would expect they must. But it hasn't been measured and reported in any of the tables we're given.

DR. KLAASSEN: I think there is one table on the terpenoids, maybe. But I agree, they weren't in here. But they most likely do contain them. But just getting back to the general question, what do we know about the allergenicity. Are these classes of compounds, terpenoids, et cetera. Are they generally not allergens?

DR. BELSITO: Terpenes are, but not terpenoids.

DR. LIEBLER: Terpenoids is another name that encompasses the terpenes.

DR. BELSITO: Okay.

DR. LIEBLER: So yes, it's true, Curt. That class does include sensitizers. And it's like with citrus. No, citrus isn't a good example. But it's like with a lot of botanicals, where one particular plant may have high levels of a sensitizing terpene. And then others in that family of ingredients don't. And so, that's when we have to start looking at sensitization data and formulated to be non-sensitizing, and so forth.

Here we don't have anything on the reported levels of those, because nobody's apparently made the measurement.

DR. BELSITO: But then can we say when formulated to be non-sensitizing?

DR. LIEBLER: We could. I mean, we usually do that when we know there's a sensitizer there. We could extend that logic to say, we don't know that there's a sensitizer there, but just in case, formulate to be non-sensitizing.

DR. BELSITO: And we know they are terpenoids.

DR. LIEBLER: I'm comfortable assuming -- well, put it this way; I would bet in a card game that there are terpenoids, but we don't have any data confirming that.

MS. FIUME: But to take that one step further, when we do that with botanicals, when formulated to be non-sensitizing, it's because of the overall composition of the ingredient; not because of the concern about the individual botanical, but botanical in formulation with other botanicals.

DR. LIEBLER: Correct. We almost always do that, because there's some evidence, under some condition, that this ingredient that we're looking at could be sensitizing.

DR. SNYDER: Yes.

DR. LIEBLER: Has constituents of concern. And we don't have that here, at all.

DR. SNYDER: I don't think we should use that approach for an absence of data.

DR. BERGFELD: Otherwise, you pass everything.

DR. SNYDER: Yeah. It's just not the way, scientifically, you look at stuff.

DR. BELSITO: So then, even if we accept the GRAS, the food, the 4-week oral, we're really not going to meet the sensitization, except for a few of these. But then we only know that the individual component was not sensitizing. But in the absence of knowing whether the constituents of that are, and whether there are any constituents of concern, how do we handle that?

DR. LIEBLER: Well, I think there in the case of the food additives and the foods, in the absence of data, suggests that these are allergen containing; and as long as a composition of the cosmetic ingredient is similar, or identical, to the food grade, or whatever, then we are okay with it. Right? Because there are no glaring reports of people having allergies to the consumption of these products.

DR. BELSITO: But there's a phenomenon called oral tolerance.

DR. SNYDER: Yes. Right.

DR. BELSITO: And it could simply be that these people are orally tolerized, because they're fed these foods from childhood.

DR. SNYDER: Yes. That's a good point.

DR. LIEBLER: So, if we had a larger body of sensitization data, at concentration of use, even if we didn't have it for everything, would that move you closer to comfort on evaluating sensitization? In other words, how much further would we need to go with human-test data? HRIPTs or something that would alleviate your concern? Or do you just need sensitization at concentration of use for everything?

DR. BELSITO: Personally, I have not been overwhelmingly concerned with these, as sensitizers, just looking at the composition. I think you're largely just putting fiber and carbohydrates on the skin, is what I see when I look at the overwhelming constituents of these materials. And my only concern is heavy metal and arsenic, when I look at it. But you're right, we don't have the data.

DR. LIEBLER: Right. When you analyze something, you analyze it for specific substances, or groups of substances, depending on what the analytical method is that you use. And it appears they just haven't done the kind of analysis that would identify and quantify flavonoids, polyphenolics, terpenoids, et cetera. It

appears that that hasn't been done.

We don't have a column for terpenoids that says, below limit of detection. We have nothing. So, I think when we say we don't see any constituents of concern, it's because nobody looked. It doesn't mean they're not there.

We, basically, have two ways to know if there is a problem there. One is do the measurement, and then two is do the experiment in the person. And it's one or the other.

DR. KLAASSEN: In this day and age, looking at the constituents in these ground up plants, let's say, is not that difficult anymore. It's not like it was 30 years ago. And why people don't have this information is really kind of amazing. These kinds of studies, analytically, can be done relatively easy in this day and age. And we would know what flavonoids were there, and triterpenoids, and et cetera. And if there might be some compounds that we know that are bad. So I guess I'm a little disappointed that there isn't more information on this.

DR. LIEBLER: They don't want to know. They don't want to pay.

DR. BERGFELD: Yes. But if you go back to your tables, which you've been reflecting on intermittently here today, Table 29, Table 30 -- wrong Table 30, does cite some of the irritation studies. They call it human-irritation sensitization. But they've only commented on the irritation. So, there are some endpoints using something -- there must be about 30 of these in here or more -- I haven't counted them -- where we actually have an ingredient that's had clinical human testing.

DR. BELSITO: But it's most irritations.

DR. BERGFELD: I said mostly irritation. It says irritating and non-sensitizing a few, but.

DR. BELSITO: But irritation is just a 24-hour patch. So, I mean, the sensitization is much more limited.

DR. BERGFELD: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14. Fourteen and one.

DR. BELSITO: Right. But in terms of the actual ingredients, the number is smaller. But it doesn't address any tox endpoints on these. And so, what I'm hearing is there's also a concern in the absence of dermal absorption about toxicity.

DR. LIEBLER: If we have oral tox, acute and repeat dose, then I'm not really worried about dermal tox. If it's clean by oral and these are all clean by oral. The only limitation is the number of compounds for which we have data. And then with dermal irritation and sensitization, I leave it to you guys to determine if we got a

sufficient body of data. On PDF, I guess it's, 99 -- 98-99 is what Wilma was looking at. We have about a dozen.

DR. BELSITO: Well, irritation. But again --

DR. LIEBLER: No, sensitization.

DR. BELSITO: Sensitization. Table 30. But I mean, a lot of them -- you have two on Fucus Spiralis. A lot of them are on the same ingredient.

DR. BERGFELD: It won't support the whole body, but it might support that ingredient.

DR. BELSITO: No. So let me just recap what you're saying. If we take and create a list of those that are GRAS, those that are food, and those for which we have a four-week oral or longer, and we cross reference it to those that have been studied for sensitization, we would go safe as used for that group that falls into those two columns.

DR. LIEBLER: Correct.

DR. BELSITO: And the rest would be insufficient.

DR. LIEBLER: Correct.

DR. BELSITO: For composition.

DR. LIEBLER: I would say they'd be insufficient for the tox data or the sensitization data. Because I don't think we can use the composition to infer safety. The only way that we would be able to use the composition data, perhaps in a limited sense, is if there was a particular constituent of concern and there was sensitization occurring. Then we could look at that constituent of concern and maybe help use that to drive our conclusion. But we're nowhere near having that type of data.

DR. BELSITO: Okay. So, is anyone going to be able to create this list by tomorrow?

MS. CHERIAN: I'll give it a try, yes.

DR. SNYDER: The good thing is the one that's most used, the Laminaria Digitata, it's GRAS. It's going to clear one of the major -- the Macrocystis I think too, isn't it? Macrocystis?

DR. BELSITO: Yes. Macrocystis is GRAS.

DR. SNYDER: Yeah. So, I think the two major ones will be cleared, which is probably pretty good, all things considered.

DR. LIEBLER: I think we're inevitably heading towards a split conclusion here.

DR. BELSITO: The only issue will be that the Laminaria Digitata and the Macrocystis Pyrifera

were not tested at the concentrations that we're told they're used at, which is 40 and 36.4 percent respectively. Again, I don't have an issue with it, I'm just pointing that out, that we don't have the sensitization data at the concentration that we're told they're used at.

DR. SNYDER: We have an HRIPT at 10 and 20 percent. So I mean, would we expect something different?

DR. BELSITO: No. I mean, again, I'm fine.

DR. SNYDER: Okay.

DR. LIEBLER: Yep. I am as well, Dan.

DR. BELSITO: Okay.

MS. CHERIAN: The HRIPT that came in as Wave 3, I think that it might have been diluted down. So it said 10 and 20 percent, and then when it was actually tested, it was diluted down to 20 percent.

DR. LIEBLER: Oh, I didn't see that. Your heading, you had tested at 8 to 12 and then 20. So, we need that clarification in there. So it wasn't down 10 fold or 100 fold.

DR. BELSITO: Again, I'm not really concerned with these as sensitizers.

DR. BERGFELD: It has to be based on your clinical experience or what you're seeing? Broadview or everything?

DR. BELSITO: Just looking at the bulk of the material, when you look at --

DR. BERGFELD: We don't have that.

DR. BELSITO: I understand that, Wilma. But when you look at the fact that -- look at the composition. I mean it's carbohydrate and it's fiber. And there is all this other stuff.

DR. BERGFELD: I know. But the other stuff is what we're talking about.

DR. LIEBLER: It's organic, which we originally had a problem with.

DR. BELSITO: Right. Let's just go back. That's what, Table 8 and 9? Where's the composition? It's Table 8 and 9, right?

MS. FIUME: Yes. Is that right, Priya? Constituents are in Table 8, on PDF Page 74.

DR. BELSITO: Right.

MS. FIUME: And then Table 9.

DR. BELSITO: So you have, in general, the protein fraction of brown algae is low, 1 to 24

percent dry weight compared to the green. Most have a protein content of 15 percent. Sterols found in brown algae, we're not really concerned about those. Terpenes, phenolic compounds and meroterpenes make up three major classes of secondary metabolites. Reference 41 doesn't tell us how much.

MS. CHERIAN: Specifics, no.

DR. BELSITO: And then in Table 9, the only one we really have fairly good data on is fucus vesiculosus.

MS. FIUME: And that references Dr. Duke's.

DR. BELSITO: Right. And, I mean, when you look at it, it's huge carbohydrates, huge fiber, metals, some beta carotene. I just think that's what all of these are going to look like with variations, but we don't know. We're sort of beating a dead horse. So, where are we going?

DR. SNYDER: Right. I mean, yeah. We're just chasing our tail here. The composition and impurities we have, we know the constituents of concern, we can deal with those. The problem is we have to make a broad assumption, for those we don't have data for, that we would consider the composition and impurity levels to be similar to those we have. But that's a greater leap than we normally make.

I'm comfortable with it, because I can't understand why they would be different. But I'm not an algae expert, and so -- I think the way that you said, we go with the food, the food additives, the ones we have composition tox data on, and then we see what it looks like. And we may be ending up with a handful that are even remotely used. And so, I get we just don't know, and see what the data looks like.

DR. BELSITO: Okay. Let me go back. We're going to ask Priya to put a table together that groups GRAS food or more than 4-week oral. That's one list. And then anther list where we have sensitization data. And any material that appears in both of those lists, we'll go safe as used. And anything not, we'll go insufficient for what?

DR. LIEBLER: For the missing piece.

DR. BELSITO: For the missing piece.

DR. LIEBLER: Either the tox or the sensitization.

DR. BELSITO: Or the sensitization.

DR. SNYDER: And that would be consistent with what we asked for first. The first cut, was we wanted composition and organic impurities. And then we wanted the 28-day dermal absorption and, if not, other tox

data. So, it's consistent with what we've asked for previously.

MS. FIUME: So, for the purpose of the discussion, when you say tox, as the missing piece, do you want it to read as 28-day dermal, or do you want it to read --

DR. BELSITO: Twenty-eight-day oral or longer.

MS. FIUME: Okay.

DR. BERGFELD: It's acute tox.

DR. LIEBLER: I think the acute tox in a repeat dose.

DR. SNYDER: Yeah. We were saying 4-week, right? That's not acute tox, that would be short term.

DR. LIEBLER: No. No.

DR. SNYDER: Yeah.

DR. LIEBLER: Okay. Short-term tox, but it could be either oral or dermal.

MS. FIUME: That was the piece that I wanted to make sure we had clarification on.

DR. BELSITO: Oral or dermal.

DR. LIEBLER: That makes sense, doesn't it?

DR. KLAASSEN: Yeah. I agree.

MS. FIUME: It does. Especially, since the discussion we'll be stating that you used 4-weeks oral tox to support safety. So, then that would make sense for the insufficient piece.

DR. LIEBLER: I mean, oral will be satisfactory, dermal will be better.

DR. BELSITO: Okay. So, we don't know what those ingredients are yet. But if it's GRAS, food or we have a greater than 28-day oral or dermal tox, and we also have sensitization on that, it'll be safe. All the others will be insufficient for whatever that missing piece is.

DR. LIEBLER: So, if we're going to have a conclusion tomorrow that we vote on, we're going to have to actually be able to assign the ingredients to the conclusion as either safe as used or --

DR. BELSITO: Yes.

DR. LIEBLER: And I'm not sure that we'll be there tomorrow. I don't know, Priya, you got a lot on your plate. I don't know if it's possible or not. I mean, is this something that we might need to table until the next meeting?

MS. CHERIAN: I think I could come up with a list.

DR. KLAASSEN: Make that decision tomorrow.

DR. LIEBLER: I tried to give you a place to hide.

MS. CHERIAN: I appreciate that.

MS. FIUME: She'll make her best effort to have it for you tomorrow.

DR. EISENMANN: I have one comment that I would like to see corrected in the report. In the impurity section, there's a study on phthalates in the --

DR. LIEBLER: What page?

DR. BELSITO: PDF?

DR. EISENMANN: It's the paragraph right before the use, I don't have the PDF --

MS. FIUME: Forty-seven.

DR. EISENMANN: -- page. It says that phthalates are at a concentration of 60 to 70 percent in the algae. I looked that up. The paper actually does say that, but it's out of context. There's no way that could be that much phthalate in it.

What they were doing -- it's an isotope study, and they were trying to determine if the algae is actually making the phthalates. And so, they concentrated it very much. And I think those are the concentrations in the concentrate, in which they were determining how much 14C was in it.

So that their conclusion was, yes, algae can make some phthalates. But they never said how much is actually in the algae. So, I'd like to see that corrected in the report.

DR. LIEBLER: Yeah, that makes sense. I mean, there's no way that they could contain 60/70 percent phthalate.

DR. BELSITO: They'd be rather plastic, wouldn't they?

DR. LIEBLER: That's right.

DR. EISENMANN: Right. Did they use a (inaudible) -- I mean, why isn't industry using a (inaudible) to isolate them, rather than making it from oil?

DR. LIEBLER: You ought to start a company.

DR. EISENMANN: Right.

DR. BELSITO: So, how would you like that changed?

DR. EISENMANN: To really focus on the conclusion of the paper, that they've determined that they make these phthalates. That they don't give the concentration of the phthalates in the algae. That's the concentration of the phthalates in the material they could measure. I mean, they had to really clean up the algae and get rid of all the fatty acid and all the other things in order to focus on the --

DR. BELSITO: So, just say they can make phthalates and end it there?

DR. EISENMANN: Right.

DR. LIEBLER: Right. Leave it at that.

DR. KLAASSEN: Leave out the 60 and 70. No quantification. It's a qualitative statement here.

DR. BELSITO: So get rid of just the concentration. I'm fine with that. Everyone else?

DR. LIEBLER: Yes.

MS. CHERIAN: Are there any other discussion points that need to be addressed, such as heavy metals?

DR. BELSITO: Yes. Heavy metals and arsenic.

DR. EISENMANN: What about iodine? Do you want to discuss iodine? Because what this is used as, is a dietary supplement to provide iodine. And I don't know if you want that in the discussion or not.

DR. BERGFELD: Yes.

DR. BELSITO: So, exactly -- there were some case reports on this of toxicity from dermal exposure or just is it oral?

DR. SNYDER: Mic.

DR. BELSITO: Case reports of toxicity affecting thyroid, but that was oral, right? It really wasn't -- it was just one.

DR. SNYDER: The thyroid hormone, they increased, but they still were within normal range.

DR. BELSITO: Right.

DR. SNYDER: I didn't flag that at all.

DR. BELSITO: These were extracts for potassium iodine.

DR. SNYDER: We don't have any composition data on that, that's the problem, so I don't know. I mean, it's hard to --

DR. BELSITO: Right. Like you said, it was within normal limits.

DR. SNYDER: Yeah. So I didn't flag it at all.

DR. BELSITO: I think we're okay with that. I think the biggest concern is arsenic and heavy metal.

DR. SNYDER: And pesticides.

DR. BELSITO: Anything else? Shall we take a little break, give our minds a break? It's 10:16, regroup in ten minutes. Is that enough? 10:25, 10:30 at the latest.

Group 2 – Day 1

DR. MARKS: Next -- oh. Brown algae. There's brown algae. We got a lot of supplemental data.

DR. SLAGA: A lot of it.

DR. MARKS: Where is -- yeah. Here we go. So, team -- Priya, you're up again, huh? You're the brown algae expert now. I guess I'll wait until Ron Hill gets back in here. So, Ron Hill already knows this, I'll start.

At the September 18th meeting, the panel issued an insufficient data announcement for these 82 ingredients. And Priya listed the needs composition organic constituent, 28-day dermal toxicity, if the ingredients are not GRAS. I didn't see which ingredients were GRAS-identified, but I may have overlooked that. Sensitization data and genotox for ingredients that are not GRAS.

I guess we'd better start. Better wait for Ron Hill. I suspect we're gonna be issuing a tentative report with insufficient data, but --

DR. SHANK: For sensitization, right?

DR. MARKS: Yep. How important are the GRAS, Ron, at this point? Was there GRAS identified in this?

DR. SHANK: Yes.

DR. MARKS: It was. Okay. I missed that.

DR. SHANK: Yeah, it's in here.

DR. MARKS: Okay. Good.

MS. CHERIAN: Table 23.

DR. SHANK: Table 23.

DR. MARKS: Oh, that's it. Thank you.

DR. SLAGA: We got a lot of data to go on and read.

DR. MARKS: So, you had the same sensitization I did, Ron Shank, the Laminaria Digitata Powder at 40 percent, and the Macrocystis Pyrifera Extract at 36 percent? I thought those would be the lead ingredients for sensitization.

DR. SHANK: And how about Japonica? Laminaria Japonica Powder, 5 percent?

DR. MARKS: Yeah. We could --

DR. SHANK: We have no data.

DR. MARKS: Okay. Well -- so, Ron Hill, basically, I summarize where we were at that point now to the moving on to a tentative report. We got a lot of data. I think Tom has mentioned that two or three times, that we got a lot of data, so --

DR. SLAGA: If we wait one more time, we'll have even more.

DR. MARKS: Yeah. Are the composition and -- so, composition and organic, let's go down these one at a time on the data needs. Are the composition and organic constituents now, are they okay? We do have that issue with heavy metals and arsenic, but I assume we'll take care of that with the boilerplate.

DR. SLAGA: Yeah.

DR. MARKS: So, Ron Shank, what did you think about the composition constituents?

DR. SHANK: As far as I was concerned, it was okay. Most of these have low use concentrations in leave-on products.

DR. HILL: Yeah, that's the thing.

DR. SHANK: And the weight of evidence on the sensitization studies, for most of them, seems to say they're okay. And the same thing, weight of evidence and systemic toxicology supports at these low doses, they're safe. So, it was just insufficient for three, which we've identified. Want me to say it again?

DR. MARKS: Yeah. Repeat that. Well, the third one.

DR. ANSELL: Which are the non-GRAS.

DR. MARKS: So, the sensitization, I had the Laminaria Digitata Powder at 40 percent and Macrocystis Pyrifera (kelp) Extract, at 36 percent.

DR. SHANK: Right.

DR. MARKS: And then, the third one you had, Ron?

DR. SHANK: Laminaria Japonica Powder at 5 percent.

DR. MARKS: Okay.

DR. SHANK: So the only need that I had --

DR. SLAGA: Well, there are plenty of genotoxicity dermal irritation.

DR. SHANK: Right.

DR. MARKS: Okay.

DR. SHANK: One minor point. We might check something on Page 47, under impurities. Near the top of Page 47, under phthalates, it has dibutyl phthalate and ethylhexyl phthalate at 60 to 70 percent of the plant. I don't think that could be right.

DR. ANSELL: No.

DR. SHANK: Now, is that -- maybe have a plant extract**?**

DR. ANSELL: No. We think it's 60 or 70 percent of the phthalates found in algae are those two.

DR. SHANK: Oh.

DR. HILL: That sounds --

DR. SHANK: Okay, okay. That makes sense.

DR. ANSELL: Which is substantively different than a material which is 90 percent water, also containing 70 percent of another material.

DR. HILL: I know of no production of phthalates, by natural organisms, as esters like that. I guess it's possible, but I might have not encountered it.

DR. ANSELL: Okay. We would just ask that the paper be reviewed more carefully.

DR. MARKS: Okay. So you have that, Priya?

MS. CHERIAN: Um-hmm.

DR. MARKS: Okay. So, tomorrow -- any other comments? Otherwise --

DR. HILL: Just a general comment. Who normally does the bookmarking of the PDF before it comes to us?

DR. HELDRETH: The bookmarking kind of occurs automated. We take the different pieces of

a report and form the report.

DR. HILL: I'm talking about in the report. Because most of them will be bookmarked where the sections of the report are bookmarked

DR. HELDRETH: Right.

DR. HILL: I mean, usually, it's just one for the tables, but --

DR. HELDRETH: When we bring it into Acrobat, it makes the whole portfolio, it automatically bookmarks the different pieces that were put in.

DR. HILL: The only reason why I ask is because in this particular case there's just one bookmark, for the whole report, and there's no subsections.

DR. HELDRETH: Yeah. I see that.

DR. HILL: And when we have a really long report with big long tables, it -- that's why I didn't know if that was down to the writers or --

DR. ANSELL: No, that's at, like, Kevin stage, Kevin and Julia (phonetic) stage. So, we'll make sure we fix that.

DR. HILL: Okay. Then it might have just been an oversight in this case, given the timeline which was tight, really tight.

DR. MARKS: Out of interest, Ron Shank, why did you pick the Laminaria Japonica Powder at 5 percent? The ones I chose are high use, high concentration. There must've been something stood out that you wanted that. And I'm fine. I mean, obviously.

DR. SHANK: Okay. I had that there are four ingredients used in leave-on products at concentrations greater than 1 percent. And that's why that one fell in. One of them, Laminaria Digitata Extract, at 5 percent, was tested HRIPT, and not a sensitizer.

DR. MARKS: Right. That was the Wave 3 data on that. Yep.

DR. SHANK: Right.

DR. MARKS: Okay. Good.

DR. HILL: And if you don't have composition, to know how similar it is to the Laminaria Digitata, for example, then --

DR. HELDRETH: The conclusion will be --

DR. MARKS: Conclusion will be insufficient data for sensitization of the three ingredients that we mentioned before.

DR. HELDRETH: Okay.

DR. MARKS: So, all the other ingredients will be safe, and insufficient for these 3.

DR. SHANK: Amazing. That huge list of all kinds of funny things, handled very well. Congratulations.

MS. CHERIAN: Thank you.

DR. SHANK: You had a very difficult task there.

DR. HELDRETH: She came in midstream, too. She didn't get to build it from scratch.

DR. MARKS: So, basically, safe for 79 ingredients and insufficient data for sensitization, HRIPT for 3 ingredients. I wouldn't be surprised that we see the sensitization data for those 3, since there are a lot of uses, at least for two of them.

DR. SLAGA: Yep. A lot of uses.

DR. MARKS: Okay. So, presumably, we'll be seconding a tentative report tomorrow. Let me save this. And then we'll make a decision about the next group of ingredients. I had figured that that would take the whole half, until lunch, but we've got 20 minutes more. So, team, I would move on.

DR. SLAGA: Sure.

DR. SHANK: Good.

Day 2

DR. BERGFELD: We did have a handout that came. I guess you received this, Don.

DR. MARKS: Wave 6.

DR. BERGFELD: This is Wave 6.

DR. MARKS: This morning.

DR. BERGFELD: This morning.

DR. BELSITO: This is brown algae. And at the September meeting, we issued an

insufficient data announcement for the 82 ingredients. We wanted composition organic constituent data for each. Twenty-eight-day dermal toxicity for those that were not GRAS, sensitization data at relevant use concentrations for all the ingredients, and genotoxicity for those listed that were not GRAS. We received quite a bit of data, but not necessarily all of the data that we asked for.

We gave Priya a homework assignment, and I'm not going to read all of these. But if you take out what was handed out this morning by her, the conclusion of our team was that it was GRAS, if it was a food, if we had oral toxicity studies of four weeks or longer, and -- so, if we had any of those three, and we also had sensitization data, they would be safe as used. For those that don't have some degree of either GRAS, food, oral toxicity and sensitization, they'd be insufficient for whatever part was missing.

If you look at the list that was provided, we're prepared to say that Undaria pinnatifida extract and Undaria pinnatifida cell culture extract, Macrocystis pyrifera (kelp) extract, Alaria esculenta extract, Laminaria digitata extract, and Laminaria saccharina extract are safe as used.

Going down that list on the first page, all of those ingredients would be insufficient for sensitization data, as would be the first two ingredients on the second page. The last of the ingredients in the table would be insufficient for some degree of oral toxicity 4 weeks or longer. And then the remaining 45 ingredients, at the bottom of the page, would be insufficient for both some form of oral toxicity and sensitization data. That was our conclusion.

DR. BERGFELD: Dr. Marks, comment? Second?

DR. MARKS: I'll second, I think. I want to go back. We, actually, were much more liberal in the approach. I kind of like how specific you were in creating this table. We felt we could get a safe for 79 ingredient and insufficient data for sensitization on 3 ingredients.

Did you say sensitization for Laminaria digitata powder at 40 percent as safe? And the other one we had was Macrocystis pyrifera (kelp) extract at 36 percent. We didn't feel there was enough sensitization data for that. Then the Laminaria japonica powder at five percent. You know what's interesting because these are botanicals; and if we used the precedent we've set in the past, that as long as it's formulated to nonsensitizing, we probably could wave the sensitization. Team, do you want to respond to the Belsito's

proposal?

DR. HELDRETH: Historically, for the nonsensitizing caveat with botanicals, we used that merely for a cumulative effect, not one specific ingredient.

DR. MARKS: Yeah. So, this would go out as a tentative report, so we'd have time to relook at the proposed conclusions, Don, correct?

DR. BELSITO: Yeah.

DR. MARKS: Yeah.

DR. SLAGA: My concern with the table, it would take me a little time to analyze what you said, to make sure, with concentrating and everything, that I agree with it, and right now I cannot. It's a lot to try to -- whereas we picked out the high levels for needing sensitization data, and that's understandable to me, but I would have to study each one of the ones, and how you have it listed, and I just can't do that this quickly at the meeting. So, we could table or something else.

DR. MARKS: Yeah, Tom, and Ron, and Ron, so why did -- we have GRAS, and food, and tox columns here; why was it that we felt that the systemic toxicity was not going to be an issue for 79 of the ingrediants -- for all the ingredient, essentially? We just had sensitization concerns.

DR. HILL: I think the basis was -- and I was going to ask this sort of rhetorical question, why do we care about oral toxicology information when these are used primarily -- well, maybe exclusively -- dermal roots of exposure at low concentrations of use. We may have substances in there that would be taken out by -- unless you use huge whopping doses for the oral toxicology study, by first-pass metabolism, and we wouldn't know about anything that was happening in the skin or in nearby areas. On the other side is, they're used at low concentrations. So, I'm not sure that oral systemic toxicology tells us anything of any use informing -- versus the art of use.

DR. SNYDER: We could modify that to say that we want -- instead of oral tox, we can modify it to our standard 28-day dermal, and if absorbed, then we may want additional tox data.

DR. BELSITO: I think our issue -- and I'll let Dan address this -- is we don't really have good data on constituents. We have very broad ranges, like it contains terpenoid; but what terpenes does it contain? We have asked for composition data and we really never got a lot of specific composition data. So, yeah, there's a lot of fiber, it's a lot of carbohydrate, but what else is in these? And that we don't really know.

DR. LIEBLER: So, when we use the formulated to be nonsensitizing construct, to my recollection, we've always had some data indicating that there was a sensitizing chemical of concern in the ingredient; and we just didn't know how much would be applied and that's why we used this construct. Here, we don't even have that information for any of them. It's just a glaring omission, in my view. Nothing on polyphenols or -- it says there are polyphenols, but doesn't say which ones. Nothing on terpenoids. It says they're there, we don't know which ones.

Some of these are going to be the ones that are going to produce the problems. If we had representative data, we could probably deal with it. I'm not necessarily objecting to the formulated to be nonsensitizing here, but I think we've always done that when we had evidence that there is something sensitizing in there. All we have here are the test data from the limited number of compounds that have actually been tested. And then other than that, we've got nothing.

DR. BERGFELD: Any other discussion or a second to the motion? Or a new motion?

DR. HILL: So, if we have GRAS, we're still not sure -- is what you're saying -- about dermal sensitization?

DR. LIEBLER: Right. So, the GRAS and food additives, actually, as I recall, it was Ron Shank's suggestion how to take a first cut out of these ingredients. Those that were GRAS for some sort of use, or also consumed in foods, could be safely presumed to not have a systemic toxicity risk; and then it would be more of an issue of skin sensitization or irritation. I thought that was reasonable, but I didn't have a good feel for how many of those actually fell into that category. Then we had some that were the tox data and that's why I asked Priya if she could make this little table for us, which helps clarify my thinking on this.

So, I'm not sure how we bring in the others with the lack of sensitization data, and without making some assumptions and going a little bit beyond our approach to formulated to be nonsensitizing. I

don't necessarily object to it, but I wanted to point out that this is different from the situation that we've applied this to in the past.

DR. MARKS: Yeah, I think my response to that was because we had three ingredients, we identified we wanted to see sensitization data. With you having a long list of ingredients, it's quite a bit. Team, should we -- this is going to go out as a tentative report. I don't want to delay that.

DR. BERGFELD: It's not been seconded. That's the motion on the table.

DR. MARKS: I know. So, should we second and then go and deal with the information from the table? I'd like Ron Shank to comment, because Ron surprised me when he suggested that all would be safe other than the three ingredients for sensitization. I'd be interested in how you got past GRAS and the ones that are not GRAS.

DR. SHANK: I looked at the use concentration in leave-on products, and for most of them the concentrations are very, very low, where I would not expect systemic toxicity from this class of compounds. It's a weight of evidence based on the whole lot at such low concentrations. The sensitization, we agree with you on some of them. But if you're going to ask for sensitization on every one, now we go back to Dr. Belsito's concern, what kind of sensitization data do you want? LLNA's enough? Or you could do an HRIPT on every one and then you say, well, that's not very good because you don't know where it's applied.

DR. BELSITO: I mean, the LLNA would give us the best data if you can clear it with LLNA concentrations that are very high. I would agree with you, just looking at these, I doubt that they would be sensitizers. But we don't have information on composition. And as Dan pointed out, the ones that we're worried about are just listed as being present. They're are terpenes. What terpenes? What percentage? We don't have that information.

One of the other things we kicked around was trying to look at compositions of families to see how similar, across the board, rather than asking for compositions for all of these, take one representative family and look at it. But we don't have that data. It's just that we're dealing here with a lot of absence of data. A lot of these aren't used. I think we're clearing -- at least, my suggestion would clear those that are in

major use. It's just that we're making decisions, again, without any information.

And I would agree with Bart's point, and Dan's point, formulated to be nonsensitizing is when we have a signal. If a botanical contains limonene, and we don't want to add it with another botanical, that contains limonene, that could get it to a sensitizing concentration; or we have a positive LLNA, or we have a positive guinea pig maximization test.

The sensitization data that we have is clean. So, what is the rationale for asking, or saying, to be formulated when nonsensitizing when we don't have that data? I had issues with that. And it may be that we never get this data.

But I think we've cleared the majority of those that are used by saying, okay, if we have oral tox, or some degree of safety in terms of internal side effects, 28-day dermal, however you want to do it, and it clears sensitization, than that's fine. Perhaps the easiest way for industry to do this would be to get us some further data on composition of the families, so we could compare across and then we could probably say all of them are safe as used.

DR. BERGFELD: So, we have a motion that Dr. Belsito's put on. You want to restate that motion, and we can see if we can move forward?

DR. BELSITO: The motion was to look at those ingredients that were GRAS, food, or we had a four-week or longer oral study that was negative, meeting any of those three criteria. And then some degree of sensitization data. I would agree with Jim, for laminaria digitata, we don't have it up to 40 percent; for Macrocystis, we don't have it up to 36.4 percent. But as Carol pointed out, it's really not clear that those are the actual concentrations being used.

From reading the data, I would suspect that that is, in fact, correct; because these are not provided as a hundred percent pure substances and they're diluted down. We do have the Laminaria, maybe at 20 percent, maybe not at 20 percent. We're not even sure on that, which comes close to 40.

I think that we have at least some data to go on to suggest they're not sensitizing. So, there were one, two, three, four, five, six. The top six were fine, safe as used. The whole rest of the first page, and

the first two on the second page, needed sensitization data. The remaining in the table required some degree of lack of systemic toxicity out of the 28-day dermal, oral, they're not GRAS or food. And the other 45, we absolutely had no data on.

DR. BERGFELD: That's a motion to move forward with?

DR. BELSITO: That was a motion.

DR. MARKS: Second.

DR. BERGFELD: Second. Any further discussion then? I'm going to call the question. All those in favor of safe with these limited numbers of ingredients within this document? Okay. Unanimous.

Now, on the ones that we do not have data on, do we need to make a list of things that we need? Obviously, composition, sensation, and acute toxicity or 28-day?

DR. BELSITO: Well, I mean, from the list Priya put together, we have those that require sensitization. We have those that require some degree of systemic toxicity or lack thereof, and those that require both. Or the alternative is to have industry look at the different families and get us some better composition data; and then that way, we might be able to read across all of them and say they're all fine.

DR. BERGFELD: So, there are two opportunities offered here?

DR. BELSITO: Mm-hmm.

DR. BERGFELD: Okay. And, Monice, are you okay with this?

MS. FIUME: Yes.

DR. LIEBLER: Well, one minor point for Priya. Priya, thank you for putting figure one in the flowchart on the ingredient preparation. I think it needs one more iteration. What I was hoping, is that at the bottoms of the branches would end in like, extract, powder. You know, so you can see where these are going, because it's not clear what this means right now. I think that might be helpful, and I'm sure you can do

that. Thank you.

DR. BERGFELD: Alex, any comment? Carol? You understand what's needed then? All right. Then we'll move on. Oh, Ron Hill, excuse me.

DR. HILL: Ten-second clarification. So, when you say systemic toxicity, did we want to specify that our preference would be 28-day dermal? Or are we leaving it open-ended for now?

DR. BELSITO: I think 28-day dermal, 4-week oral; I mean, there are many ways of satisfying this, leave it open. Or provide us with composition that we can read across to others.

DR. BERGFELD: Okay. All right. Let's move on the next ingredient in this reports advancing group, the Basic Red 76. Dr. Marks.

Safety Assessment of Brown Algae-Derived Ingredients as Used in Cosmetics

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The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Lillian C. Becker, former Scientific Analyst/Writer and Priya Cherian, Scientific Analyst/Writer.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of brown algae-derived ingredients; 82 brown algae-derived ingredients were found in the in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), however, several of these ingredients may be equivalent according to accepted scientific names. The Panel reviewed the available data to determine the safety of these ingredients, which are frequently reported to function in cosmetics as skin-conditioning agents. Impurities, particularly arsenic, may be present in these ingredients. Industry should continue to use good manufacturing practices to limit these possible impurities. The Panel concluded that 6 brown algae-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the data are insufficient to determine the safety of the remaining ingredients under the intended conditions of use in cosmetic formulations. [Please note, these numbers may change based on additional information that was submitted after the Tentative Report was issued.]

INTRODUCTION

This is a safety assessment of brown algae-derived ingredients as used in cosmetics. The ingredients in this review are extracts, powders, juices, or waters derived from one or multiple species of brown algae. A total of 82 International Nomenclature Cosmetic Ingredient (INCI) names identifying brown algae-derived ingredients (Table 1) were found in the *Dictionary*; however, several of these ingredients appear to be equivalent based on the accepted scientific name, as given in the definition (Table 2).[1] Accordingly, the total number of distinct cosmetic ingredients is 74.

These ingredients are a highly complex group, all of which are marine-derived, with intricate chemistry and compositions. According to the *Dictionary*, these brown algae-derived ingredients are most commonly used as skin conditioning agents (Table 2).[1] These ingredients are also reported to be used as absorbents, antioxidants, binders, hair conditioning agents, oxidizing agents, pH adjusters, and viscosity increasing agents. The safety of these ingredients was assessed based on the availability of systemic toxicity data, via oral repeated dose toxicity studies, use in food, generally recognized as safe (GRAS) status, and on local effects such as sensitization.

There are several major groups of algae (as described in "Algae Identification" section). However, this safety assessment focuses only on brown algae. The names of the ingredients in this report are written in accordance with the INCI naming conventions, i.e., capitalized without italics or abbreviations. When referring to the algae from which these ingredients are derived, the standard taxonomic practice of using *italics* is followed (e.g., *Agarum cribrosum*). The term "kelp" is commonly used when referring to brown algae. Kelp are large brown algae that belong to the order Laminariales.[2]

Several brown algae constituents, such as phytosterols,[3] phytosteryl ingredients,[3] and alginic acid[4] were found to be safe as used by the Panel. The full reports on these ingredients can be accessed on the CIR website (https://www.cir-safety.org/ingredients); therefore, information regarding these ingredients will not be included in this report.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (https://www.cir-safety.org/ supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

The European Chemical Agency (ECHA)[5,6] website provides summaries of data generated by industry, and is cited throughout the report as appropriate. Also referenced in this safety assessment are summary data found in other reports, including those published by the European Medicines Agency (EMA),[7,8] the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA),[9] and Food Standards Australia New Zealand (FSANZ).[10,11]

CHEMISTRY

Definitions

The ingredients in this safety assessment are derived from various species of brown algae. "Algae" is not a taxonomic group, but a functional group of convenience.[12] Not all algae should be considered to be plant-like (seaweed; macroalgae). While some algae are seaweed, some are protozoa, and some are unique and belong in other kingdoms. However, these aquatic and oxygenic organisms are all part of the eclectic group called "algae."

Algae Identification

There are several major groups of algae, and they are commonly referred to as brown algae (*Phaeophyceae)*, green algae (*Chlorophyta*), diatoms (*Bacillariophyceae*), chrysophytes (*Chrysophyta*), blue-green algae (*Cyanophyta*), red algae (*Rhodophyta*), dinoflagellates (*Pyrrhophyta*), and euglenoids (*Euglenophyta*). A description of these major algal groups can be seen in Table 3. The different types of algae are differentiated by storage products, pigmentation, and cell wall composition.[12] A list of the brown algae-derived ingredients, based on their subclass, order, family and genus, is presented in Table 4.

Brown algae are mostly comprised of large, leathery seaweeds and are classified in about 265 genera with more than 1500 species.[12,13] The actual color varies depending on the proportion of brown pigment (fucoxanthin) to green pigment (chlorophyll). This algal group contains alginic acid and fucoidan in its complex cell walls. General characteristics and the geographic distribution of the specific species of brown algae included in this report are presented in Table 5**.**

As with plant-derived ingredients, the constituent composition of these seaweed ingredients can vary widely depending on growing conditions, age of the organisms, local environmental aspects, harvesting conditions, methods of extraction, and many other variables. For example, the concentration of the most abundant carotenoid pigment in brown algae, fucoxanthin, varies remarkably depending on the age of the alga, and the protein content in brown algae varies considerably depending on the season in which it is harvested.[14,15]

Physical and Chemical Properties

Physical and chemical properties of Ascophyllum Nodosum Extract, Ascophyllum Nodosum Powder, Ecklonia Cava Extract, and Halidrys Siliquosa Extract (aq.) are presented in Table 6. Using the sieve method, 93.5% of the particle sizes of Ascophyllum Nodosum Extract, as a fully dried extract, were less than 0.250 mm and greater than 0.045 mm.[6]

Harvesting

Originally, the only source of brown algae was in the wild; but since the mid-twentieth century, demand has exceeded the supply that could be harvested from wild sources, and methods for cultivation have been developed.[16] Consequently, today, commercial brown seaweed comes mainly from farming rather than wild sources. *Laminaria japonica* and *Undaria pinnatifida* are among the most cultivated species of brown algae.[17] Several species, such as *Laminaria japonica*, are grown on suspended ropes in the ocean.[16] Repeated harvesting of *Macrocystis pyrifera* over a 3-month period did not significantly impact tissue chemical properties (i.e. alginate yield; viscosity and strength; nutritional quality, such as protein, carbohydrate, lipid, crude fiber, ash, and energy content; and tissue carbon/nitrogen ratios).[18]

Method of Manufacture

Numerous methods of manufacture are provided in Table 7. Several of these methods have a target constituent or composition (e.g., high in fucoidan). The characterization of the final extract is provided in the table. A general overview of a method of manufacture for the relevant brown algae-derived ingredients can be seen in Figure 1.

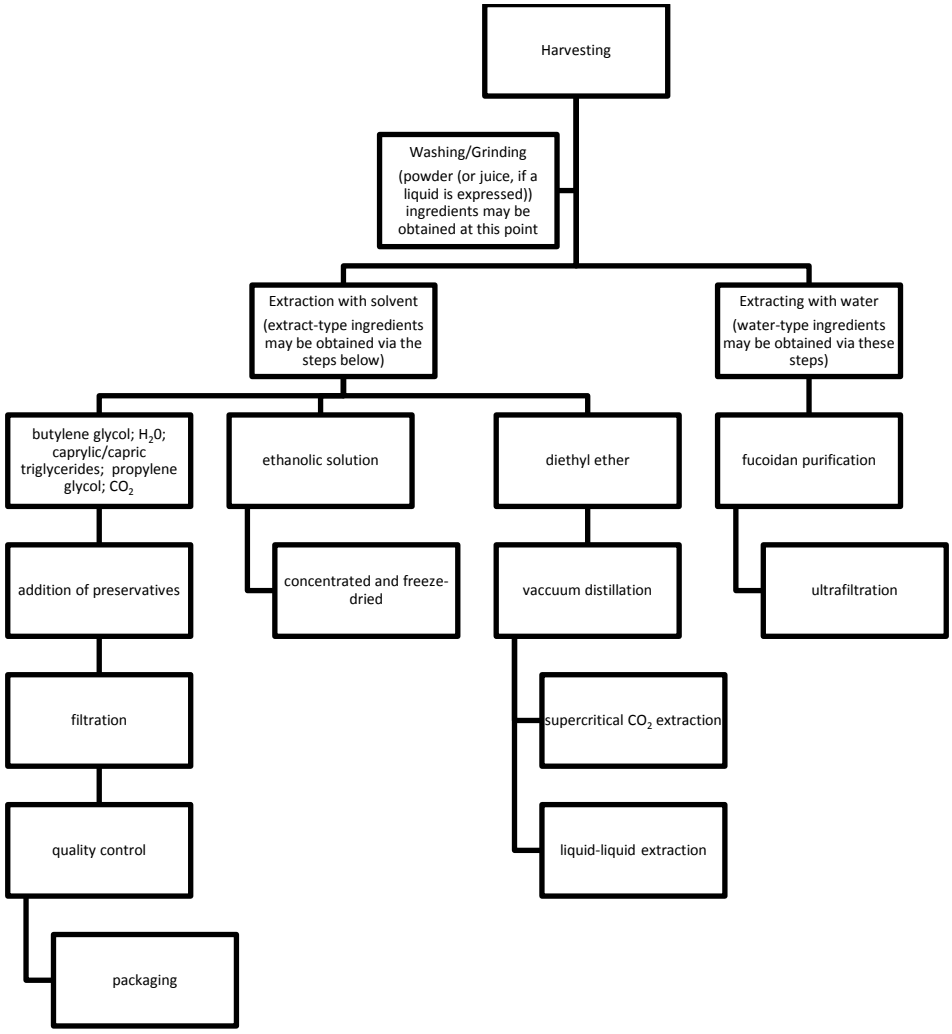

Figure 1. Overview of methods of manufacture for brown algae-derived ingredients. [1,9,19-28,28-52, CIR STAFF]

Arsenic is a constituent of concern in certain brown algae [see Constituents of Concern].[10,11,53,54] There are methods to remove the arsenic, including extraction with water, methanol, or water/methanol mixtures accompanied with sonication or mechanical agitation.[55] Extraction with microwave-assisted heating and accelerated solvent extraction systems are described in the literature.[55] Soaking the algae in water at room temperature followed by simmering in the water is shown to be effective for removing inorganic arsenic.[56] Another variation entails repeated boiling in seawater, and replacing the water three times, after initial soaking.[53] Soaking the algae in a simmering 4% acetic acid or a 4% sodium hydrogen carbonate aqueous solution has also been shown to remove arsenic.[57]

Composition

Some constituents and constituent groups that are found in brown algae, in general, are presented in Table 8; included therein are alkaloids, laminarins, pheromones, phytohormones, terpenoids, amino acids, betaines, and characteristic pigments such as chlorophyll *a* and *c*, β-carotene, fucoxanthin, and several other xanthophylls.[58] Constituents found in *Ascophyllum nodosum*, *Fucus vesiculosus*, and *Laminaria digitata* are listed in Table 9.

According to a study, Sargassacean brown algae species biosynthesize mainly meroditerpenes and linear diterpenes, whereas most compounds from the Dictyotacean species are cyclic diterpenoids, sesquiterpenes, and various types of meroterpenes.[59] Algae of the family Sargassaceae are among the most prolific in terms of terpene yield. In the genera *Cystoseira*, *Sargassum*, and *Halidrys*, meroditerpenoids constitute the most common metabolites. In the genus *Cystoseira*, meroditerpinoids could be classified into specific groups dependent upon the structure of their diterpene side chain: linear, monocyclic, bicyclic, or rearranged. The organic extracts of *Cystoseira amentacea* var. *stricta* contain high amounts of methoxybifurcarenone.

Sterols are also found in brown algae.[60,61] Sterols reported to be in *Cystoseira tamariscifolia*, *Fucus spiralis*, and *Sargassum vulgare* are provided in Table 10.

Methanol, hexane, and chloroform extracts from *Cystoseira compressa* were examined for flavonoid and phenolic content.[62] The flavonoid content of the methanol, hexane, and chloroform extract, were 0.291 ± 0.02, 0.88 ± 0.07, and 0.804 ± 0.07 mg/g, respectively. The phenolic content of hexane (1.541 ± 0.09 mg/g) was considerably higher than the phenolic content of the methanol (0.161 ± 0.08 mg/g) and chloroform (0.45 ± 0.04 mg/g) extracts.

Constituents of ethanolic extracts of *Fucus spiralis* and *Sargassum vulgare* are presented in Table 11. The constituent with the highest concentration in both extracts is vaccenic acid (21,690 and 2848 ppm, respectively).[63]

Approximately 0.64 – 1.99 grams of polyphenols can be found in *Himanthalia elongata* extract.[64] In addition, phlorotannins can also be found in this extract (0.2 % dry weight). These include fucols, diphloroethol, and several fucophloroethols. Polyphenols are also found in *Undaria pinnatifida* extract in amounts of 0.08 – 0.60 g/ 100 g extract. Fucoidans extracted from the sporophylls of *Undaria pinnatifida* show a higher sulfate and l-fucose content than other fucoidans. The concentration of polyphenols in an aqueous extract of *Halidrys siliquosa* was reported to be 0.16 %.[65] The total protein and mineral content present in *Halidrys siliquosa* is approximately 9.6 and 11.19%, respectively.

The composition of a water/propylene glycol extract of *Laminaria japonica* is provided in Table 12.[51] The compositions of extracts of *Laminaria japonica*[52] that are produced via enzyme hydrolysis are presented in Table 13.

The specifications for an alcohol extract of *Ecklonia cava*, as a food/dietary supplement, include a combined phlorotannin content of 90.0 ± 5.0%; the content of dieckol, a specific phlorotannin, is 6.6% to 9.9% (Table 14).[9] The extract is to contain no insoluble substances, and it is reported to contain calcium (4800 ± 400 mg/kg), magnesium (1300 mg/kg), potassium (700 ± 200 mg/kg), and iodine (220 ± 40 mg/kg).

An *Undaria pinnatifida* extract rich in fucoidan was characterized as having 27% uronic acid, 53% monosaccharides, and 7.4% sulfate.[66] Major monosaccharides included 54% fucose and 35% galactose. The minor monosaccharides were 3% rhamnose, 4% arabinose, and 1% xylose, glucose, and mannose.

A desalinated *Undaria pinnatifida* powder was reported to consist of 532 mg/g dietary fiber, mostly in the form of alginates, and 209 mg/g protein.[67] The composition profile is presented in Table 15.

A study was performed to determine the flavonoid content of several species of algae.[68] Results of this study are presented in Table 16.

Impurities/Constituents of Concern

Possible allergens listed in Annex III of EU Cosmetic Regulation (EC) No. 1223/2009 found in trade name mixtures containing relevant brown algae-derived ingredients can be found in Table 17.

Arsenic

Arsenic, usually in the form of arsenosugars, is a natural constituent of some brown algae, including *Ecklonia radiate*, *Laminaria japonica*, and *Sargassum fusiforme*.[10,11,52,54,69] The amount of arsenic is inconsistent due to varied uptake of inorganic arsenic by brown algae varieties and the influence of external factors (e.g., temperature, season, and pH). A trade name mixture containing 4.7% Ascophyllum Nodosum Extract in 94.5% water was reported to have ≤ 2 ppm arsenic.[70] The amounts of arsenic that have been measured in various brown algae are presented in Table 18. The different arsenic-containing moieties found in four brown algae species are presented in Table 19. A comparison of the amount of arsenic found in *Laminaria japonica* and a *Laminaria japonica* extract (equivalence to cosmetic ingredients not confirmed) is presented in Table 20.

Heavy Metals

Brown algae, in general, exhibit an affinity for heavy metals, which are believed to be absorbed from the water column.[58,71] Heavy metal concentrations in algae are strongly dependent on environmental parameters of the sampling sites (e.g., salinity, temperature, pH, light, nutrient concentrations, oxygen, etc.) and the structural differences among the algae. These seaweeds also absorb heavy metals from the sediment.[72,73] A trade name mixture containing 4.7% Ascophyllum Nodosum Extract in 94.5% water was reported to have ≤ 20 ppm heavy metals.[70] An overview of the amount of heavy metals found in brown algae species is provided in Table 21. Information regarding heavy metal impurities in trade name mixtures containing brown algae can be found in Table 22.

An edible, phlorotannin-rich, ethanol extract of *Ecklonia cava* has specifications issued by the European Commission.[9] According to the Commission, this extract must contain < 3 mg/kg lead, < 0.1 mg/kg mercury, < 3 mg/kg cadmium, < 25 mg/kg arsenic, and 150 - 650 mg/kg iodine.

Phthalates

Dibutyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) were shown to occur naturally in *Laminaria japonica*.[74] These phthalates were also present in *Undaria pinnatifida*.

USE

Cosmetic

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

According to VCRP data received in 2019, Laminaria Digitata Extract is reported to be used in 310 formulations (229 in leave-on formulations, 74 in rinse-off formulations, and 7 diluted for the bath; Table 23).[75] Fucus Vesiculosus Extract is reported to be used in 291 formulations, Macrocystis Pyrifera (Kelp) Extract in 199 formulations, and Ascophyllum Nodosum Extract is used in 140 formulations. All other in-use ingredients are reported to be used in 136 formulations or fewer.

Ascophyllum Nodosum Extract was reported in the VCRP as Ascophyllum Nodosum (Seaweed) Extract and Fucus Vesiculosus Extract was reported as Fucus Vesiculosus (Bladderwrack) Extract. Laminaria Saccharina Extract is reported in the VCRP as Saccharina Latissima (Kelp) Extract; the accepted scientific name for *Laminaria saccharina* is *Saccharina latissima*.

The results of the concentration of use surveys conducted by the Council in 2015 and 2016 indicate Laminaria Digitata Powder has the highest reported maximum concentration of use; it is used at up to 40% in face and neck formulations.[76,77] Macrocystis Pyrifera (Kelp) Extract is reported to be used at up to 36.4% in eye lotions. The other ingredients are reported to be used at 6% or less.

In some cases, reports of uses were received in the VCRP, but concentration of use data were not provided. For example, Ascophyllum Nodosum Powder is reported to be used in 4 cosmetic formulations, but no use concentration data were reported. In other cases, no uses were reported in the VCRP, but concentration of use data were reported in the industry survey; Fucus Vesiculosus had no reported uses in the VCRP, but a use concentration in shampoos, moisturizing formulations, and suntan formulations was provided in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported. The ingredients not in use according to 2019 VCRP data and the 2015 and 2016 Council surveys are listed in Table 24.

Several of these ingredients are used in formulations that are used near the eye (e.g., Macrocystis Pyrifera (Kelp) Extract at up to 36.4% in eye lotion and Fucus Vesiculosus Extract in mascara at up to 5%), incidentally ingested (e.g., Macrocystis Pyrifera (Kelp) Extract in lipsticks at up to 0.079%), and in formulations that come in contact with mucous membranes (e.g., Fucus Vesiculosus Extract and Laminaria Digitata Extract at up to 5% in bubble baths and Laminaria Japonica Extract and Macrocystis Pyrifera (Kelp) Extract at up to 5% in bath oils, tablets and salts).

Additionally, some of the brown algae-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Macrocystis Pyrifera (Kelp) Extract is reported to be used at up to 0.79% in spray face and neck products. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[78,79] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[80,81] Laminaria Japonica Extract and Macrocystis Pyrifera (Kelp) Extract were reported to be used in face powders at concentrations up to 0.0035%. Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400- to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[82-84]

None of the brown algae-derived ingredients named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[85]

Non-Cosmetic

Brown seaweeds are consumed around the world and come mostly, but not only, from the *Laminaria*, *Undaria*, and *Hizikia* genus.[16] According to the US FDA, brown algae (i.e., several species of seaweeds that are harvested principally in coastal waters of the northern Atlantic and Pacific oceans) are direct food substances that are GRAS for human consumption for use as flavor enhancers and flavor adjuvants, when the maximum level in food does not exceed the current good manufacturing practice (cGMP). [21CFR184.1120] "Kelp" (the dehydrated, ground product prepared from *Macrocystis pyrifera*, *Laminaria digitata*, *Laminaria saccharina*, and *Laminaria cloustoni*) is approved as a food additive for direct addition to food for human consumption as a source of iodine or as a dietary supplement. [21CFR172.365] An overview of the species of brown algae that are GRAS in the US can be seen in Table 25. In New Zealand, Japan and other Asian countries, dried sea kelp is a common food; the exact species of kelp used varies according to location.[16] The EFSA NDA Panel concluded that an alcohol extract of *Ecklonia cava* is safe for the use in food supplements at a maximum intake level of 163 mg/day for adolescents from 12 to 14 years of age, 230 mg/day for adolescents above 14 years of age, and 263 mg/day for adults.[9] In addition, a listing of brown algae species that are frequently ingested by humans is provided in Table 26.

Several genuses of edible brown algae include *Alaria, Himanthalia, Laminaria, Saccharina, Undaria, Ascophyllum, Fucus, Sargassum, Hizikia, Dictyotales,* and *Eisenia*. [86]

In France, some varieties of seaweed have been authorized for use as vegetables and condiments.[87] These include *Ascophyllum nodosum, Fucus vesiculosus, Fucus serratus, Himanthalia elongata, Undaria pinnatifida, Laminaria digitata, Laminaria saccharina, Laminaria japonica,* and *Alaria esculenta*. These algae, when used in this manner, must not exceed certain levels of toxic minerals (≤ 3 mg/kg arsenic, ≤ 0.5 mg/kg cadmium, ≤ 0.1 mg/kg mercury, ≤ 5 mg/kg lead, ≤ 5 mg/kg tin, and ≤ 2000 mg/kg iodine.

In animal drugs, feeds, and related products, brown algae (kelp; *Laminaria* spp. and *Nereocystis* spp.) are GRAS as natural substances [21CFR582.30] and as solvent-free natural extractives [21CFR582.40] used in conjunction with spices and other natural seasonings and flavorings.

In the US, "kelp" is present in OTC dietary supplements for weight loss. [21CFR310.545] However, there are inadequate data to establish a general recognition of the safety and effectiveness of this ingredient for that specified use. Several other sources refer to the use of *Fucus vesiculosus* for weight loss.[88,89]

Pastes of seaweed, made by cold grinding or freeze crushing, are used in thalassotherapy, in which the pastes are applied to the body and then warmed under infrared radiation.[16] This treatment, in conjunction with seawater hydrotherapy, is said to provide relief for rheumatism and osteoporosis. In folk medicine, preparations of *Fucus vesiculosus* are used to treat hypothyroidism, iodine deficiency, arteriosclerosis, digestive disorders, menstrual abnormalities, cellulite, and sprains.[88,90] In herbal folk medicine, *Laminaria hyperborea* is used for thyroid regulation, and *Macrocystis Pyrifera* is used to treat thyroid conditions, anemia in pregnancy, and hypertension, for bringing about weight loss, and as an immunity booster.[88]

Brown algae have been used as fertilizers and soil conditioners (*Ascophyllum*, *Sargassum*, *Ecklonia*, and *Fucus* species), animal feed for sheep, cattle, horses, pigs, and chickens (*Alaria esculenta,* and *Ascophyllum* and *Laminaria* species), feed and feed binder for fish and abalone (*Macrocystis pyrifera*), and biomass fuel (*Macrocystis pyrifera*), and they have been used for waste water/effluent treatment and removal of heavy metals (*Sargassum*, *Laminaria*, and *Ecklonia* species).[16,58] Brown algae are used as biomonitors for heavy metal pollution in estuarine and coastal waters worldwide, and to evaluate the quality of their surrounding environment.[71]

TOXICOKINETIC STUDIES

Obtaining data on the toxicokinetics of uncharacterized, complex mixtures would be impractical, as is the case with many botanical ingredients. No toxicokinetics studies were discovered in the published literature, and no unpublished data were submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

No acute dermal or inhalation toxicity studies were discovered in the published literature, and no unpublished data were submitted. Acute oral toxicity studies summarized below are presented in Table 27**.**

Oral

The LD_{50} was > 2000 mg/kg when Sprague-Dawley rats were dosed with Ascophyllum Nodosum Extract. No other details regarding this study were provided.[91] Cystoseira Compressa Extract was not toxic to mice when given a single dose of up to 2000 mg/kg by gavage.[62] No animals died when Sprague Dawley rats (10/sex) were given 2000 mg/kg Ecklonia Cava Extract (alcohol extract) by gavage.[9] Similarly, no abnormalities were seen when Ecklonia Cava Extract (enzyme extract; 3000 mg) was given to SD rats (5/sex) or Beagle dogs (2/sex) by oral gavage.[92] The oral LD_{50}s of two Fucus Vesiculosus Extracts were 1000 and 500 mg/kg for male mice and between 1000 and 2000 mg/kg and < 750 mg/kg for female mice.[93] In rats (sex not stated), the oral LD_{50}s of two Fucus Vesiculosus Extracts were between 1000 and 2000 mg/kg for one extract and > 2000 mg/kg for the second extract.[93] The oral LD_{50} of rats given 20% of a test substance containing Laminaria Digitata Extract (≤ 10%), artemisia vulgaris extract (≤ 10%), and phenoxyethanol (0.8%), in water, was > 5000 mg/kg.[94] Sargassum Fulvellum Extract and Sargassum Thunbergii Extract were not toxic to mice that were given a single dose of 5000 mg in 10 mL Tween-80 via gavage.[50]

Short-Term, Subchronic, and Chronic Toxicity Studies

No repeated dose dermal or inhalation toxicity studies were discovered in the published literature, and no unpublished data were submitted. Short-term, subchronic, and chronic oral toxicity studies summarized below are presented in Table 28.

Oral

Ascophyllum Nodosum was not toxic when it was fed to pigs at up to 10% via feed for 23 days, or to rats at up to 15% in the diet for 4 weeks.[45,95] Vomiting was the only adverse effect when Ecklonia Cava Extract in capsules was orally

administered (in increasing amounts up to 1000 mg/kg over 8 days) to dogs.[9] Ecklonia Cava Extract was not toxic to rats dosed with up to 3000 mg/kg via oral gavage once daily in rats, and twice daily in dogs, for 13 weeks.[9,92] An enzyme extract of Ecklonia Cava Extract (starting at doses of 2000 mg/kg) administered by gavage for 2 weeks caused reduced ovary and brain weights in female rats.[92] Hepatic effects in rats were observed when animals were dosed with 2000 mg/kg/day via gavage of an alcohol Ecklonia Cava Extract for 4 weeks.[9] While consuming high-fat diets, there were no adverse effects caused by alcohol Ecklonia Cava Extract when mice were given doses of up to 5 mg/day via gavage for 4 weeks.[96] When rats were dosed with the same extract at doses of 1500 mg/kg/day for 13 weeks, there were also decreases in body weight gain and organ weights (the hepatic effects resolved after 4 weeks recovery).[9]

Increased liver weights were apparent when two ethanol Fucus Vesiculosus Extracts (starting at doses of 200 mg/kg/day) were administered by gavage for 4 weeks in male rats.[93] No treatment-related effects were noted in females. An ethanol Laminaria Japonica Extract (up to 400 mg/kg) administered by gavage for 6 weeks caused decreased body weight gain, fat-pad weights, and serum and hepatic lipid levels in rats.[46]

In rats, doses of 1200 to 4000 mg/kg Cladosiphon Okamuranus Extract given once a day for 3 months via gavage caused a dose-dependent increase in clotting time and decrease in alkaline phosphatase (ALP) that was not observed with lower doses.[47] There were no other adverse effects reported.

Laminaria Japonica Powder (up to 5%) was incorporated in the feed of mice from the age of 7 weeks until death. There were no dose-dependent effects on the lifespan of mice.[48] Undaria Pinnatifida Extract administered via drinking water (1.5 g in 1000 mL water) did not cause any toxic effects in rats when administered for 32 weeks.[97] Undaria Pinnatifida Powder (0.1, 1, or 5%) was given to 5 female SD rats for 36 weeks via diet.[98] No adverse effects were reported.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

No DART studies were discovered in the published literature, and no unpublished data were submitted.

GENOTOXICITY STUDIES

The in vitro and in vivo genotoxicity studies summarized below are presented in Table 29.

In Vitro

Ascophyllum Nodosum Extract was not genotoxic in two Ames assays (up to 5000 µg/plate), a mammalian cell gene mutation test (up to 500 µg/mL), or in chromosomal aberration assays (up to 5 mg/mL); in a mammalian cell gene mutation test, Ascophyllum Nodosum Extract was genotoxic to Chinese hamster ovary (CHO) cells starting at 1500 µg/mL.[6,91] An Ames test was performed according to the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 471 on a trade name mixture containing 4.7% Ascophyllum Nodosum Extract in 94.5% water.[70] No mutagenic activity was reported. Cystoseira Compressa Extract was not mutagenic in an Ames assay performed with and without metabolic activation at up to 5 mg/plate.[62] Ecklonia Cava Extract was not genotoxic in Ames assays (up to 5000 µg/plate) or chromosomal aberration assays (up to 350 µg/plate).[9,92] Halidrys Siliquosa Extract was non-mutagenic in an Ames assay, performed according to OECD TG 471, at up to 5 µL/plate.[65] Another Ames assay performed according to OECD TG 471 resulted in negative results when testing the genotoxic potential of a mixture consisting of Fucus Spiralis Extract (12%), tetraselmis chui extract (8%), and water (80%) (up to 5 µL/plate).[99] Aqueous Fucus Vesiculosus Extract was not genotoxic in a chromosomal aberration assay (up to 1 mg/mL; human peripheral lymphocytes) or a comet assay (up to 1 mg/mL; human peripheral lymphocytes).[100] *Laminaria digitata* was non-mutagenic in an ames assay performed with and without metabolic activation (concentrations not stated).[101] A trade name mixture containing Laminaria Saccharina Extract in sea water and methylpropandiol was non-mutagenic in an Ames assay (up to 5000 µg/plate).[102] Macrocystis Pyrifera (Kelp) Extract was non-mutagenic in an Ames assay (1 mL test substance in 10 mL 0.9% sodium chloride; concentration of extract was approximately 4%).[103] A trade name mixture containing 24% Undaria Pinnatifida Cell Culture Extract was not mutagenic in a bacterial reverse mutation assay (up to 5000 µg/plate).[104] No genotoxicity was reported in a chemiluminescent 3D assay using water (52%) and Cystoseira Amentacea/ Caespitosa/Brachycarpa Extract (48%) as the test substance at up to 10%.[105] The test system for this study was not reported.

In Vivo

Ecklonia Cava Extract was not genotoxic in micronucleus assays up to 3000 mg/kg using male CD1 mice.[9,92]

CARCINOGENICITY STUDIES

No carcinogenicity studies were discovered in the published literature, and no unpublished data were submitted.

Tumor Promotion

Tumor promotion studies summarized below are presented in Table 30. The brown algae-derived ingredients that were tested were not tumor promoters; instead, decreases in the number, incidence, and size of tumors in rats and mice were

observed.

Dermal

Mice were treated dermally with a single dose of 7,12-dimethylbenz[a]anthracene (DMBA; a carcinogen) followed by biweekly treatments for fifteen weeks with 12-*O*-tetradecanoylphorbol-13-acetate (TPA; a tumor promotor) or Undaria Pinnatifida Extract (1 mg).[106] The mice treated with Undaria Pinnatifida Extract had a delayed appearance of skin tumors (14 vs 8 weeks) and fewer tumors (average 0.2 vs 3.7) compared to the TPA-treated mice.

Oral

Rats injected with azoxymethane (AOM; a carcinogen) and then fed a diet containing Hizikia Fusiforme Extract (2% and 6%) had a reduced number of colorectal tumors (21 vs 58) compared to rats injected with AOM and fed a normal diet.[107] A *Saccharina angustata* powder (5%; inference for Saccharina Angustata Extract) in feed delayed the appearance and reduced the incidences of mammary tumors in rats orally administered DMBA.[108]

Rats administered *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG; a carcinogen) followed by Sargassum Pallidum Extract (0, 400, 600 and 800 mg/kg/day) in drinking water for 8 weeks had decreased inflammatory responses; serum IL-6, IL-1β, and TNF-α levels and concentration of serum and gastric mucosa malondialdehyde (MDA; an oxidant) were decreased in a dose-dependent manner.[109] In rats administered Undaria Pinnatifida Powder (0, 1.0% or 5.0% in feed) for 8 weeks after oral administration of DMBA, the mean combined weight of all mammary tumors of each rat in treatment groups was lower than that in the control group (approximately 7 vs 20 g).[98] Undaria Pinnatifida Extract (100% as drinking water) for 32 weeks reduced the incidence of mammary tumors (22% vs 100%) after female rats were orally administered DMBA.[97]

OTHER RELEVANT STUDIES

Endocrine Effects

In Vitro

Fucus vesiculosus extract

Human granulosa cells (obtained from 8 women) were treated with a water:ethanol (1:1) *Fucus vesiculosus* extract (25, 50, or 75 µmol/l) for 9 days.[110] Ethanol (50%) served as the vehicle control. At 50 and 75 µmol/l, the extract significantly reduced 17-β-estradiol levels in human granulosa cells and also competed with estradiol (E2) and progesterone for binding to their receptors.

Affinity of this extract for estrogen receptor-α (ERα), ERβ, and progesterone receptor (PR)-B was determined by radiometric competitive binding assays.[110] Dried extract (0.5, 5, or 50 µmol/l final concentration) was re-solubilized in dimethyl sulfoxide and combined with ERα or ERβ and 0.5 nmol/l estradiol. Non-specific binding was estimated in the presence of 1 µmol/l diethylstilbesterol. To test PR-B binding, the extract was incubated with PR-B and 1.4 nmol/l radiolabeled progesterone. Non-specific binding was estimated in the presence of 1 µmol/l progesterone. The extract competed for and bound to ERα (IC_{50} = 42.2 µmol/l), ERβ (IC_{50} = 31.8 µmol/l), and PR-B (IC_{50} = 31.8 µmol/l), with a slightly greater affinity for ERβ. The inhibition of progesterone production was less prominent, and there was no concentration-response relationship. In contrast, there was a concentration-dependent occupancy of the estrogen and progesterone receptors. Compounds found in *Fucus vesiculosus* could act as estradiol antagonists by decreasing the affinity of either ERα or ERβ for its ligand.

In competitive radio-ligand binding assays, aromatase activity was estimated by measuring the incorporation of tritium from androstenedione into water in the presence or absence of a *Fucus vesiculosus* extract (10, 50, or 100 µmol/L).[110] Aromatase activity following treatment of human luteinized granulosa cells (hLGCs) with this extract did not change.

A chemically activated luciferase reporter (CALUX®) assay was used to determine the effect of an aqueous *Fucus vesiculosus* extract on activation of the ER.[111] Aromatase enzymatic activity was measured to determine the potential effect of this extract on E2 biosynthesis. In co-treatments with E2, this extract (2%) reduced the activation of the luciferase reporter by up to 50%, exhibiting ER antagonistic effects. The effect of this extract (0 to 2%) on aromatase activity was measured using recombinant human CYP19 enzymatic hydrolysis of the fluorescent substrate, 7-methoxy-4-trifluoromethyl coumarin, in a 96-well plate. Ketoconazole was used as the positive marker of aromatase inhibition. This extract inhibited aromatase activity (IC_{50} 2.0%). ER-dependent and -independent cancer cell lines showed significantly decreased viability with increasing *Fucus vesiculosus* extract concentrations; altered morphological features suggested apoptosis and autophagy. The cell line-specific sensitivity suggests that *Fucus vesiculosus* extract was not toxic at up to 2%, but instead induces cell death through modulated pathways.

Animal

Fucus vesiculosus powder

Female Sprague-Dawley rats (n = 8), that had two confirmed normal estrous cycles, were administered a *Fucus vesiculosus* powder (0, 175, or 350 mg/kg/day) on an apple wedge daily for 4 weeks.[110] Vaginal smears were obtained and daily logs were maintained to monitor estrous cycling. No adverse effects were observed during the course of the experiment. Administration of this powder resulted in a statistically-significant, dose-dependent increase in the length of the estrous cycle in the treated rats. In the control group, the mean number of days of the estrous cycle was 4.3 ± 0.96 days compared to 5.4 ± 1.7 days in the low-dose group and 5.9 ± 1.9 days in the high-dose group. Treatment with this powder caused an overall 100% increase in the mean length of the diestrus phase of the estrous cycle. The mean number of days in diestrus was 0.97 ± 0.22 among the controls compared to 1.4 ± 0.54 in the low-dose group and 2.1 ± 0.88 days in the high-dose group. Treatment had no significant effect on the number of days in estrus, proestrus, or metestrus during the mean estrous cycle. After treatment was stopped, five rats stopped normal estrous cycling; one remained in estrus and four in diestrus.

Blood samples were collected from female Sprague-Dawley rats (n = 19) before treatment with dried *Fucus vesiculosus* powder, and at 2 and 4 weeks of the oral administration of this powder (0 or 175 mg/kg/d) on apple wedges.[110] At 2 weeks, mean serum 17β-estradiol levels were reduced from 48.9 ± 4.5 to 40.2 ± 3.2 ng/l and, after 4 weeks, reduced the levels from baseline to 36.7 ± 2.2 ng/l (25% decrease), suggesting an effect of dosing over time. Serum progesterone levels between controls and the treatment groups did not differ.

Blood samples were collected from female Sprague-Dawley rats (n = 8), that had naturally high circulating estradiol levels (≥ 50 µg/l), before, and after 1 week of the oral administration of *Fucus vesiculosus* powder (350 mg/kg/day) on apple wedges.[110] Median serum 17-β-estradiol levels decreased by 38%. The range in reduction of serum 17-β-estradiol levels in 6 of the rats was 25% to 58%, whereas 2 rats had levels similar to their baseline levels. Progesterone levels were not significantly affected following this treatment. This could be due to the fact that in the studies with rats the blood samples were collected in the morning, and in the morning the 17-β-estradiol levels were at their peak but the progesterone levels were not.

Photoprotection

Sargassum muticum

The effect of the ethyl acetate fraction of *Sargassum muticum* extract against cell death induced by mid-wavelength ultraviolet (UVB) radiation was studied.[112] Cells were seeded in a 96-well plate at a concentration of $1x10^{-5}$ cells/mL. Sixteen hours after plating, 100 µg/mL of *Sargassum muticum* extract were added to the cells and exposed to UVB radiation at a dose of 150 mJ/cm^2. Cell viability was 61% in UVB (150 mJ/cm^2) irradiated cells and 70% in UVB-irradiated cells treated with *Sargassum muticum* extract. Decreased numbers of apoptotic bodies as well as DNA fragmentation was apparent in cells exposed to *Sargassum muticum* extract and UVB, versus UVB exposure alone.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below are presented in Table 32.

Irritation

In Vitro

In vitro dermal irritation assays were performed on a mixture containing 24% Undaria Pinnatifida Cell Culture Extract in water; a mixture containing Laminaria Japonica (7%), Nereocystis Leutkeana (7%), Macrocystis Pyrifera Extract (7%), and pentaerythrityl tetraethylhexanoate; and a mixture containing Sargassum Filipendula Extract (1.3%), water (81.78%), sorbitol (14%), hypnea musciformis extract (1.4%), gellidiela acerosa extract (1.3%), methylparaben (0.2%), and propylparaben (0.2%).[113,114,115] These trade name mixtures were considered to be non-irritating.

Animal

Ascophyllum Nodosum Extract (4.7%; aqueous), Laminaria Digitata Extract (0.5 %) with dipropylene glycol and water or water and sea salt, and Laminaria Digitata Extract (0.5 %) with artemisia vulgaris extract, phenoxyethanol, and water, were non-irritating in animal dermal irritation studies.[6,49,94,91]

Human

Many human irritation studies were provided using test substances containing a brown algae ingredient, or combination of ingredients, along with other substances such as caprylic/capric triglycerides, butylene glycol, water, sea salt, propylene glycol, phenoxyethanol, panthenol, or dipropylene glycol. The majority of these studies resulted in negative results; however, irritation was seen in several studies after treatment with high concentrations or short periods of exposure.

In a study using a trade name mixture consisting of Fucus Spiralis Extract (< 5%) in caprylic/capric triglycerides as the test substance, slight irritation was observed after 30 minutes, however, no irritation was reported after 24 hours.[116] A trade name mixture containing 20% Himanthalia Elongata Extract, 37% Undaria Pinnatifida Extract, and 43% water, was considered to be very slightly irritating to human skin.[64] When a test substance consisting of Laminaria Digitata Extract (1.5 - 2.5%) in water and propylene glycol was applied to the skin, moderate irritation was observed after 30 minutes, and slight irritation was observed after 24 hours.[117] In a different study, Laminaria Saccharina Extract (1 - 3%) in water and propylene glycol was applied at concentrations of 8, 16, and 100% to 10 subjects.[118] Slight irritation was observed at the 100% dose level, and no irritation was observed at the lower doses. When a trade name mixture containing Pelvetia Canaliculata Extract (1 - 3%) in propylene glycol and water was applied to the skin, moderate irritation was noted after 30 minutes, and slight irritation was noted after 24 hours.[119] Similar results were observed when a trade name mixture consisting of Undaria Pinnatifida Extract (< 5%) in water and propylene glycol was applied to the skin of 12 subjects.[120] In a different study, the test substance (trade name mixture containing Pelvetia Canaliculata Extract and Laminaria Digitata Extract extracted in propylene glycol with panthenol (the amount of dry extract of both extracts combined is estimated to be 5.5 - 9.0%)) was applied to the skin of 10 subjects at concentrations of 5, 10, and 100%.[121] Mild irritation was observed at the 100% concentration, minimal concentration was observed at the 10% concentration, and no irritation was reported at the 5% concentration.

Sensitization

In Vitro

An ARE-Nfr2 Luciferase Test utilizing human keratinocyte cells at concentrations up to 2000 µM was performed to study the sensitization potential of Undaria Pinnatifida Cell Culture Extract (24%).[122] The test substance was non-sensitizing. A direct peptide reactivity assay (DPRA) performed testing the sensitizing potential of the same ingredient yielded negative results.[123] An ARE-Nfr2 Luciferase Test was also performed on a trade name mixture containing Sargassum Filipendula Extract (1.3%), water (81.78%), sorbitol (14%), Hypnea Musciformis Extract (1.4%), gellidiela acerosa extract (1.3%), methylparaben (0.2%), and propylparaben (0.025%).[123] No sensitization potential was observed.

Animal

Ascophyllum Nodosum Extract (25% - 75%), was non-sensitizing when applied to the skin of 20 guinea pigs.[91] No sensitization was noted when a cream containing 0.0023% Cystoseira Amentacea/Caespitosa/Brachycarpa Extract was applied to 25 animals in a maximization test.[124]

Human

All in vivo sensitization studies performed on humans, regarding several brown algae ingredients (Alaria Esculenta Extract (0.5 - 2.5% and < 5%), Ascophyllum Nodosum Extract (0.5% - 75%), Cystoseira Baccata Extract (0.5 – 10%), Cystoseira Tamariscifolia Extract (0.5 -10%), Dictyopteris Polypodioides Extract (0.5 – 10%), Fucus Spiralis (1 -3%), Fucus Vesiculosus Extract (5%), Halidrys Siliquosa Extract (48%), Halopteris Scoparia Extract (0.5 – 10%), Himanthalia Elongata Extract (0.2%), Macrocystis Pyrifera (Kelp) Extract (4%), Laminaria Digitata Extract (< 12%), Laminaria Saccharina Extract (< 3%), Pelvetia Canaliculata Extract (< 44%), Phyllacantha Fibrosa Extract (< 10%), Sphacelaria Scoparia Extract, Sargassum Filipendula Extract (1.2%), Sargassum Muticum Extract (0.076%), and Undaria Pinnatifida Extract (<5%)), were negative.[49,65,94,103,116,124-129,129-141]

Phototoxicity

In Vitro

Ascophyllum Nodosum Extract

A phototoxicity study was performed according to OECD TG 432 (3T3 NRU phototoxicity test) using a trade name mixture containing 4.7% Ascophyllum Nodosum Extract in 94.5% water.[70] No additional details were provided. No phototoxic activity was reported.

OCULAR IRRITATION STUDIES

The studies summarized below are presented in Table 32.

In Vitro

Many in vitro HET-CAM tests were performed. The majority of these tests resulted in no irritation or slight irritation; however, some studies resulted in moderate irritation. Macrocystis Pyrifera (Kelp) Extract was moderately irritating when used in a HET-CAM test.[103] Moderate irritation was also noted when a cosmetic product consisting of Laminaria Ochroleuca Extract (5%), caprylic/capric triglycerides (94.75%), and tocopherols (0.25%), was used in a HET-CAM assay.[142]

Animal

Ascophyllum nodosum extract (100 mg; concentration not stated) was mildly irritating when applied ot the eyes of New Zealand White rabbits.[6] In a different study performed according to OECD TG 405, Ascophyllum Nodosum Extract was slightly irritating.[143] A test substance (diluted to 22% in water; 0.1 mL) containing Laminaria Digitata Extract (≤ 10%), artemisia vulgaris extract (≤ 10%), phenoxyethanol (0.8%), and water, was non-irritating when placed in the eyes of New Zealand White rabbits.[94]

Human

The ophthalmic irritation potential of an eye cream containing 0.076% Sargassum Muticum Extract was tested in 31 subjects, approximately 50% of which wore soft contact lenses.[144] The test material did not indicate a potential for ophthalmologic irritation and was considered safe for use by both contact and non-contact lens wearers.

CLINICAL STUDIES

Case Reports

Oral case reports regarding brown algae-derived supplements are presented in Table 33. Decreased platelet count and an increased amount of arsenic in the blood were noted in subjects taking kelp supplements. [145,146]

Clinical Trials

Dermal

A gel formulation containing 1% of an aqueous extract of *Fucus vesiculosus* (0.2 mL) was tested in a double-blind, placebo-controlled experiment.[44] Female subjects (n = 10) applied the gel to one cheek at least twice per day (morning and evening) for 5 weeks. The same gel, without the extract, was applied to the other cheek. The skin was examined before the experiment began, daily, and after the experiment ended. There were no signs of erythema or edema during the experiment.

Oral

Clinical trials summarized below are presented in Table 34.

In an oral clinical trial in which an *Ascophyllum nodosum* powder (0.5g/d) was administered to healthy female subjects, median urinary iodine concentrations increased from 78 mg/l to 140 mg/l, and thyroid-stimulating hormone (TSH) concentrations increased slightly, but remained within the normal range.[147] There were no adverse events reported. Administration of an alcohol extract of *Ecklonia cava* (400 mg/day) to subjects with hypercholesterolaemia for 12 weeks did not have an effect on hematology, clinical chemistry, or urinalysis parameters; however, one instance (2.2%) each of nausea, dyspepsia, diarrhea, and alopecia were reported.[9,148] A phlorotannin-rich extract of *Ecklonia cava* (0, 72, or 144 mg/day) was administered for 12 weeks to overweight patients in a randomized, double-blind study. Hematological and clinical chemistry did not reveal any adverse effects; the 144 mg/d group showed decreases in serum glucose and systolic blood pressure (SBP).[9] No adverse effects were reported when Ecklonia Cava Extract (alcohol extract; 400 mg) was given to 40 overweight subjcts for 12 weeks.[24] Administration of capsules containing a desalinated *Undaria pinnatifida* powder (average intake estimated to be 3.3 g per day) to hypertensive subjects for 8 weeks resulted in a decrease in the average SBP, diastolic blood pressure (DBP), and total cholesterol; adverse effects included two cases of indigestion and one case of diarrhea, both of which resolved quickly without treatment.[67]

Three pre-menopausal women with irregular menstrual cycles were administered a *Fucus vesiculosus* powder.[149] Subject number 1 was 43 years old with hypermenorrhea, polymenorrhea, dysmenorrhea, luteal phase deficiency, and endometriosis. Subject number 2 was 42 years old with hypermenorrhea, polymenorrhea, and dysmenorrhea. Subject number 3 was 21 years old with hypermenorrhea, dysmenorrhea, and endometriosis. Menstrual cycles were tracked for three cycles and serum 17β-estradiol and progesterone levels were measured before treatment started. Then the women were administered this powder in capsules (700 mg/day) for two menstrual cycles. Serum 17-β-estradiol and progesterone levels were measured again. Subject 2 stopped treatment at this point and subjects 1 and 3 continued treatment with a greater dose of this powder (1400 mg/day) for two more cycles. This powder increased the menstrual cycle length and reduced the days of menstruation in a dose-dependent manner (Table 35). In subject 1, the plasma estradiol levels were decreased (before: 626 ± 91 pg/mL; low dose: 164 ± 30 pg/mL; high dose: 92.5 ± 3.5 pg/mL) and the progesterone levels were increased (before: 0.58 ± 0.14 ng/mL; low-dose: 8.4 ± 2.6 ng/mL; high-dose: 16.8 ±0.7 ng/mL).[149]

SUMMARY

This is a review of the safety of 82 brown algae-derived ingredients; however, several of these ingredients may be equivalent according to accepted scientific names. Accordingly, the number of distinct cosmetic ingredients is 74. The ingredients in this review are extracts, powders, juices, or waters derived from one or multiple species of brown algae and may be derived from the whole or a defined part of the seaweed. "Brown algae" is a common name for seaweeds of the class *Phaeophyceae*, which have an abundance of xanthophyll pigments and are a known source of alginate. The most frequently reported function of brown algae ingredients in cosmetics is as a skin-conditioning agent; other reported functions include absorbent, antioxidant, binder, hair conditioning agent, oxidizing agent, and viscosity increasing agent.

Extraction methods and solvents vary, depending on the desired composition of the final ingredient. Powders, however, are generally the dried algae pulverized by milling. Arsenic, usually in the form of arsenosugars, is a natural constituent of brown algae and the amount in harvested algae can be reduced by several methods. In addition to arsenic, brown algae exhibit an affinity for heavy metals and uptake is strongly dependent on environmental parameters.

According to VCRP data received in 2019, Laminaria Digitata Extract is reported to be used in 310 formulations (229 in leave-on formulations, 74 in rinse-off formulations, and 7 diluted for the bath; Table 23).[75] Fucus Vesiculosus Extract is reported to be used in 291 formulations, Macrocystis Pyrifera (Kelp) Extract in 199 formulations, and Ascophyllum Nodosum Extract is used in 140 formulations. The results of the concentration of use surveys conducted by the Council in 2015 and 2016 indicate Laminaria Digitata Powder has the highest reported maximum concentration of use; it is used at up to 40% in face and neck formulations. Macrocystis Pyrifera (Kelp) Extract is reported to be used at up to 36.4% in eye lotions. The rest of these ingredients are reported to be used at 6% or less.

According to the US FDA, brown algae (i.e., several species of seaweeds that are harvested principally in coastal waters of the northern Atlantic and Pacific oceans) are direct food substances that are GRAS for human consumption for use as flavor enhancers and flavor adjuvants, when the maximum level in food does not exceed the cGMP). "Kelp" (the dehydrated, ground product prepared from Macrocystis pyrifera, Laminaria digitata, Laminaria saccharina, and Laminaria cloustoni) is approved as a food additive for direct addition to food for human consumption as a source of iodine or as a dietary supplement. In animal drugs, feeds, and related products, brown algae (kelp; *Laminaria* spp. and *Nereocystis* spp.) are GRAS as natural substances and as solvent-free natural extractives used in conjunction with spices and other natural seasonings and flavorings.

Acute oral administration of brown algae extracts was not toxic to mice, rats, and dogs. The LD_{50} was reported to be > 2000 mg/kg when Sprague-Dawley rats were given Ascophyllum Nodosum extract. Cystoseira Compressa Extract was not toxic to mice up to 2000 mg/kg by gavage. Ecklonia Cava Extract was not toxic to rats and dogs up to 3000 mg/kg by gavage. The oral LD_{50}s of two different Fucus Vesiculosus Extracts were 500 mg/kg and greater for mice and rats. Sargassum Fulvellum Extract and Sargassum Thunbergii Extract administered by gavage were not toxic to mice. The oral LD_{50} of rats given 20% of a test substance containing Laminaria Digitata Extract (≤ 10%), artemisia vulgaris extract (≤ 10%), and phenoxyethanol (0.8%), in water, was > 5000 mg/kg.

In oral short-term and subchronic studies, there were some adverse effects observed. In rats, Cladosiphon Okamuranus Extract (1200 to 4000 mg/kg by gavage) caused a dose-dependent increase in clotting time and decrease in ALP; there were no other adverse effects reported. An enzyme extract of Ecklonia Cava Extract (starting at 2000 mg/kg) administered by gavage for 2 weeks caused reduced ovary and brain weights in female rats. Hepatic effects in rats were observed when animals were treated with an alcohol Ecklonia Cava Extract at 2000 mg/kg/day for 4 weeks and at 1500 mg/kg/day for 13 weeks (the hepatic effects resolved after 4 weeks of recovery). There were increased liver weights in male rats treated with two ethanol Fucus Vesiculosus Extracts (starting at 200 mg/kg/day) administered by gavage for 4 weeks. Vomiting was the only adverse effect when Ecklonia Cava Extract capsules (in increasing amounts up to 1000 mg/kg over 8 days) were orally administered to dogs.

In other oral short-term and subchronic studies, there were no adverse effects observed. Ascophyllum Nodosum was not toxic to pigs for 23 days or to rats for 4 weeks administered in feed at up to 10% and 15%, respectively. While consuming high-fat diets, there were no adverse effects caused by alcohol Ecklonia Cava Extract (up to 5 mg/day) administered to mice by gavage daily for 4 weeks and an ethanol Laminaria Japonica Extract (up to 400 mg/kg) administered by gavage for 6 weeks caused decreased body weight gain, fat-pad weights, and serum and hepatic lipid levels in rats. An *Ecklonia cava* powder (up to 0.15%; inference for Ecklonia Cava Extract and Ecklonia Cava Water) administered in feed for 28 days was not toxic to weanling pigs.

In a chronic oral toxicity study, the NOAEL of a Laminaria Japonica Extract administered to rats by gavage for 6 months was 300 mg/kg/day. In females, a decrease in AST was observed starting at 300 mg/kg/day and, at 2500 mg/kg/day, there was decreased serum glucose concentration; all effects returned to baseline after a 1-month recovery. Laminaria Japonica Powder incorporated into feed did not affect the lifespan of mice at up to 5%. In rats, Undaria Pinnatifida Extract administered as drinking water at a concentration of 1.5 g/L for 32 weeks and incorporated into the feed (at up to 5%) for 36 weeks did not cause any toxic effects.

In genotoxicity assays of several of the brown algae-derived ingredients, all results were negative with the exception of an Ascophyllum Nodosum Extract in one mammalian cell gene mutation test in which the extract was genotoxic starting at 1500 µg/mL in CHO cells. With metabolic activation, Ascophyllum Nodosum Extract was not genotoxic in CHO cells.

Ascophyllum Nodosum Extract was not genotoxic in two Ames assays and a mammalian cell gene mutation test (up to 500 µg/mL), and in chromosome aberration assays (up to 5 mg/mL). Cystoseira Compressa Extract (up to 5 mg/plate) was not genotoxic in an Ames assay. Ecklonia Cava Extract was not genotoxic in Ames assays (up to 5000 µg/plate) and chromosome aberration assays (up to 350 µg/plate). Fucus Spiralis Extract in water and tetraselmis chui extract was non-genotoxic in an Ames assay (up to 5 µg/plate). Aqueous Fucus Vesiculosus Extract was not genotoxic in a chromosome aberration assay and a comet assay (up to 1 mg/mL). Halidrys Siliquosa Extract was non-mutagenic in an Ames assay (up to 5 µL/plate). Laminaria Japonica Extract (up to 5000 µg/plate) was not mutagenic in an Ames assay and a chromosome aberration assay. Macrocystis Pyrifera (Kelp) Extract was non-mutagenic in an Ames assay (1 mL test substance in 10 mL 0.9% sodium chloride; concentration of extract not provided). Undaria Pinnatifida Extract was not genotoxic in Ames assays and chromosome aberration assays (up to 5000 µg/mL). In a micronucleus assay, Ecklonia Cava Extract (up to 3000 mg/kg), was not genotoxic. An Ames test performed using a trade name mixture containing Laminaria Saccharina Extract in sea water and methylpropandiol at up to 5000 µg/plate resulted in negative results. A different Ames test was performed according to OECD TG 471 using a trade name mixture containing 4.7% Ascophyllum Nodosum Extract in 94.5% water. No mutagenic activity was reported. In a bacterial reverse mutation assay performed according to OECD TG 471, a trade name mixture containing 24% Undaria Pinnatifida Extract was not mutagenic (up to 5000 µg/plate). No genotoxicity was reported in a chemiluminescent 3D assay using water 52% and Cystoseira Amentacea/Caespitosa/ Brachycarpa Extract (48%) as the test substance.

None of the orally or dermally administered brown algae-derived ingredients tested (e.g., Hizikia Fusiforme Extract, Saccharina Angustata Extract (inference from *Saccharina angustata* powder), Undaria Pinnatifida Extract, and Undaria Pinnatifida Powder) were tumor (mammary and colorectal) promoters; instead, decreases in the number, incidence, and/or size of tumors in rats were reported. Rats administered MNNG followed by 8 weeks of Sargassum Pallidum Extract (400 to 800 mg/kg/day) in drinking water exhibited decreased inflammatory responses.

A *Fucus vesiculosus* extract exhibited estrogen effects in several in vitro studies. This extract (50 and 75 µmol/l) reduced 17-β-estradiol levels in human granulosa cells and also competed with estradiol and progesterone for binding to the respective receptors. In another study, a *Fucus vesiculosus* extract competed for, and bound to, ERα (IC_{50} = 42.2 µmol/l), ERβ (IC_{50} = 31.8 µmol/l), and PR-B (IC_{50} = 31.8 µmol/l), with a slightly higher affinity for ERβ. In co-treatments with E2 (12.5 pM; EC_{50}), a *Fucus vesiculosus* extract (2%) reduced the activation of the luciferase reporter by up to 50%, exhibiting ER antagonistic effects. ER-dependent and -independent cancer cell lines showed significantly decreased viability with increasing test material concentrations. The cell line-specific sensitivity suggests that *Fucus vesiculosus* extract was not toxic at up to 2%, but instead induces cell death through modulated pathways. In one study, aromatase activity following treatment of hLGCs with a *Fucus vesiculosus* extract (10 to 100 µmol/L) did not change.

In in vivo studies, a *Fucus vesiculosus* powder exhibited estrogenic effects. Oral administration (175 and 350 mg/kg/day) for 4 weeks resulted in a dose-dependent increase in the length of the estrous cycle and an overall 100% increase in the mean length of the diestrus phase of the estrous cycle in the treated rats. Mean serum 17-β-estradiol levels were reduced at 2 weeks and further reduced at 4 weeks. Female rats that had naturally high circulating estradiol had reduced serum 17-β-estradiol (25% to 58% in 2/8 rats) after 1 week oral administration of a *Fucus vesiculosus* powder (350 mg/kg/day). This powder (700 and 1400 mg/day) increased the menstrual cycle length and reduced the days of menstruation in a dose-dependent manner in three female human subjects with hypermenorrhea, dysmenorrhea, and other related ailments. In one subject, the plasma estradiol levels were decreased and the progesterone levels were increased in a dose-dependent manner.

In an in vitro study examining the photo-protection potential involving a *Sargassum muticum* extract, the effect of this extract against cell death induced by UVB radiation was studied. Cell viability was 61% in UVB (150 mJ/cm^2) irradiated cells and 70% in UVB-irradiated cells treated with *Sargassum muticum* exract. Decreased numbers of apoptotic bodies as well as DNA fragmentation was apparent in cells exposed to *Sargassum muticum* extract and UVB versus UVB exposure alone.

In vitro dermal irritation assays were performed on a mixture containing 24% Undaria Pinnatifida Cell Culture Extract in water; a mixture containing Laminaria Japonica (7%), Nereocystis Leutkeana (7%), Macrocystis Pyrifera Extract (7%), and pentaerythrityl tetraethylhexanoate; and a mixture containing Sargassum Filipendula Extract (1.3%), water (81.78%), sorbitol (14%), hypnea musciformis extract (1.4%), gellidiela acerosa extract (1.3%), methylparaben (0.2%), and propylparaben (0.2%). These trade name mixtures were considered to be non-irritating.

Ascophyllum Nodosum Extract (4.7%), Laminaria Digitata Extract (0.5%) with dipropylene glycol and water or water and sea salt, and Laminaria Digitata Extract (0.5%) with artemisia vulgaris extract, phenoxyethanol, and water, were non-irritating in animal dermal irritation studies. Many human irritation studies were provided using test substances containing a brown algae ingredient, or combination of ingredients, along with other substances such as caprylic/capric triglycerides, butylene glycol, water, sea salt, propylene glycol, phenoxyethanol, panthenol, or dipropylene glycol. The majority of these studies resulted in negative results; however, irritation was seen in several studies after treatment with high concentrations or short periods of exposure. In a study using a trade name mixture consisting of Fucus Spiralis Extract (< 5%) in caprylic/capric triglycerides as the test substance, slight irritation was observed after 30 minutes, however, no irritation was reported after 24 hours. A trade name mixture containing 20% Himanthalia Elongata Extract, 37% Undaria Pinnatifida Extract, and 43% water, was considered to be very slightly irritating to human skin. When a test substance

consisting of Laminaria Digitata Extract (1.5 - 2.5%) in water and propylene glycol was applied to the skin, moderate irritation was observed after 30 minutes, and slight irritation was observed after 24 hours. In a different study, Laminaria Saccharina Extract (1 - 3%) in water and propylene glycol was applied at concentrations of 8, 16, and 100% to 10 subjects. Slight irritation was observed at the 100% dose level, and no irritation was observed at the lower doses. When a trade name mixture containing Pelvetia Canaliculata Extract (1 - 3%) in propylene glycol and water was applied to the skin, moderate irritation was noted after 30 minutes, and slight irritation was noted after 24 hours. Similar results were observed when a trade name mixture consisting of Undaria Pinnatifida Extract (< 5%) in water and propylene glycol was applied to the skin of 12 subjects. In a different study, the test substance (trade name mixture containing Pelvetia Canaliculata Extract and Laminaria Digitata Extract extracted in propylene glycol with panthenol (the amount of dry extract of both extracts combined is estimated to be 5.5 - 9.0%)) was applied to the skin of 10 subjects at concentrations of 5, 10, and 100%. Mild irritation was observed at the 100% concentration, minimal concentration was observed at the 10% concentration, and no irritation was reported at the 5% concentration.

An ARE-Nfr2 Luciferase Test utilizing human keratinocyte cells at concentrations up to 2000 µM was performed to study the sensitization potential of Undaria Pinnatifida Cell Culture Extract (24%) The test substance was considered to be non-sensitizing. A DPRA performed testing the sensitizing potential of the same ingredient yielded negative results. An ARE-Nfr2 Luciferase Test was also performed on a trade name mixture containing Sargassum Filipendula Extract (1.3%), water (81.78%), sorbitol (14%), Hypnea Musciformis Extract (1.4%), gellidiela acerosa extract (1.3%), methylparaben (0.2%), and propylparaben (0.025%). No sensitization potential was observed. Ascophyllum Nodosum Extract (25% - 75%), was non-sensitizing when applied to the skin of 20 guinea pigs. No sensitization was noted when a cream containing 0.0023% Cystoseira Amentacea/Caespitosa/Brachycarpa Extract was applied to 25 animals in a maximization test. All in vivo sensitization studies performed on humans, regarding several brown algae ingredients (Alaria Esculenta Extract (0.5 - 2.5% and < 5%), Ascophyllum Nodosum Extract (0.5% - 75%), Cystoseira Tamariscifolia Extract (0.5 -10%), Dictyopteris Polypodioides Extract (0.5 – 10%), Fucus Spiralis (1 -3%), Fucus Vesiculosus Extract (5%), Halidrys Siliquosa Extract (48%), Halopteris Scoparia Extract (0.5 – 10%), Himanthalia Elongata Extract (0.2%), Macrocystis Pyrifera (Kelp) Extract (4%), Laminaria Digitata Extract (< 12%), Laminaria Saccharina Extract (< 3%), Pelvetia Canaliculata Extract (< 44%), Phyllacantha Fibrosa Extract (< 10%), Sphacelaria Scoparia Extract, Sargassum Filipendula Extract (1.2%), Sargassum Muticum Extract (0.076%), and Undaria Pinnatifida Extract (<5%)), were negative.

A phototoxicity study was performed according to OECD TG 432 using a trade name mixture containing 4.7% Ascophyllum Nodosum Extract in 94.5% water. No phototoxic activity was reported.

Many in vitro HET-CAM tests were performed. The majority of these tests resulted in no irritation or slight irritation; however, some studies resulted in moderate irritation. Macrocystis Pyrifera (Kelp) Extract was moderately irritating when used in a HET-CAM test. Moderate irritation was also noted when a cosmetic product consisting of Laminaria Ochroleuca Extract (5%), caprylic/capric triglycerides (94.75%), and tocopherols (0.25%), was used in a HET-CAM assay.

An *Ascophyllum nodosum* extract (100 mg) administered to the eyes of rabbits had a maximum irritation score of 6.7 out of 8 at 1 h post-instillation. The score decreased to 0 by day 7 and was rated as a mild ocular irritant. Ascophyllum Nodosum Extract was slightly irritating in an ocular irritation study performed according to OECD TG 405. No other details were provided for this study. The ophthalmic irritation potential of an eye cream containing 0.076% Sargassum Muticum Extract was tested in 31 subjects. The test material did not indicate a potential for ophthalmologic irritation and was considered safe for use by both contact and non-contact lens wearers. A test substance diluted to 20% containing Laminaria Digitata Extract (≤ 10%), artemisia vulgaris extract (≤ 10%), phenoxyethanol (0.8%), and water was considered non-irritating when placed in the eyes of New Zealand White rabbits.

No signs of edema or erythema were noted when a gel formulation containing 1% of an aqueous extract of *Fucus vesiculosus* (0.2 mL) was applied to the cheeks of 10 female subjects. In oral human clinical trials, adverse effects of an *Ascophyllum nodosum* powder (0.5 g/d), an *Ecklonia cava* extract (up to 400 mg/day), and an *Undaria pinnatifida* powder (average intake 3.3 g/d) were mild and transient. The adverse effects included nausea, indigestion, dyspepsia, and diarrhea.

DISCUSSION

The Panel reviewed the ingredients in this report and concluded that 6 of the 82 ingredients are safe as used in cosmetics in the present practices of use, while the remaining ingredients had insufficient data to issue a safety conclusion. The ingredients that are considered safe were given this status due to availability of systemic toxicity data, via either a GRAS status or oral exposure data, and sensitization data. Those ingredients that were considered insufficient did not meet these two requirements, therefore, in order to issue a safety conclusion for these ingredients, both systemic toxicity and sensitization data are required.

The Panel noted an elevated amount of heavy metals and arsenic, which may be present in these brown algae-derived ingredients. They stressed that the cosmetics industry should continue to use cGMPs to limit these impurities. In addition, possible estrogenic effects were noted, however, the concern for these effects were mitigated as they were only seen at concentrations much higher than what would be used in cosmetics. Clinical studies suggesting the toxic potential of

iodine via brown algae consumption as a dietary supplement were noted. However, the systemic exposure to iodine via the use of brown algae ingredients in cosmetics would be far less than that resulting from ingestion.

The Panel discussed the issue of incidental inhalation exposure from formulations that may be aerosolized (e.g., face/neck products at up to 0.79% (Macrocystis Pyrifera (Kelp) Extract). The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

In addition to the requested systemic toxicity data and sensitization data for all ingredients that are lacking these data, the Panel has requested data regarding the possible constituents of concern of these brown-algae derived ingredients (e.g., specific terpenoids and flavonoids, and concentrations of such). As an alternative, the Panel suggested obtaining representative data for each genus, which may be used to formulate decisions regarding other ingredients of the same genus.

CONCLUSION

The CIR Expert Panel concluded that the following 6 of the 82 reviewed brown algae-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Alaria Esculenta Extract
Laminaria Digitata Extract
Laminaria Saccharina Extract
Macrocystis Pyrifera (Kelp) Extract
Undaria Pinnatifida Extract
Undaria Pinnatifida Cell Culture Extract*

**Not reported to be in current use. Were this ingredient not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.*

The CIR Expert Panel also concluded that the available data are insufficient to make a determination that the remaining 76 ingredients are safe under the intended conditions of use in cosmetic formulations.

Agarum Cribrosum Extract
Ascophyllum Nodosum**
Ascophyllum Nodosum Extract
Ascophyllum Nodosum Powder
Cladosiphon Novae-Caledoniae Extract**
Cladosiphon Okamuranus Extract
Cystoseira Amentacea/Caespitosa/Branchycarpa Extract**
Cystoseira Baccata Extract**
Cystoseira Balearica Extract*
Cystoseira Caespitosa Extract*
Cystoseira Compressa Extract**
Cystoseira Compressa Powder**
Cystoseira Tamariscifolia Extract**
Dictyopteris Polypodioides Extract
Dictyota Coriacea Extract**
Durvillaea Antarctica Extract
Ecklonia Cava Extract**
Ecklonia Cava Water**
Ecklonia Kurome Extract**
Ecklonia Kurome Powder**
Ecklonia/Laminaria Extract**
Ecklonia Maxima Extract**
Ecklonia Maxima Powder**
Ecklonia Radiata Extract
Eisenia Arborea Extract**
Fucus Serratus Extract
Fucus Spiralis Extract**
Fucus Vesiculosus
Fucus Vesiculosus Extract
Fucus Vesiculosus Powder
Halidrys Siliquosa Extract**
Halopteris Scoparia Extract
Himanthalia Elongata Extract
Himanthalia Elongata Powder**
Hizikia Fusiforme Extract*
Hizikia Fusiformis Water*
Hizikia Fusiformis Callus Culture Extract**
Hydrolyzed Ecklonia Cava Extract**
Hydrolyzed Fucus Vesiculosus Extract**
Hydrolyzed Fucus Vesiculosus Protein**
Laminaria Cloustoni Extract
Laminaria Diabolica Extract**
Laminaria Digitata Powder
Laminaria Hyperborea Extract
Laminaria Japonica Extract
Laminaria Japonica Powder**
Laminaria Longissima Extract**
Laminaria Ochroleuca Extract
Lessonia Nigrescens Extract
Lessonia Nigrescens Powder**
Macrocystis Pyrifera (Kelp)
Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract**
Macrocystis Pyrifera (Kelp) Juice**
Macrocystis Pyrifera (Kelp) Protein
Nereocystis Luetkeana Extract
Pelvetia Canaliculata Extract
Pelvetia Siliquosa Extract**
Phyllacantha Fibrosa Extract**
Saccharina Angustata Extract**
Saccharina Japonica Extract**
Saccharina Longicruris Extract
Sargassum Filipendula Extract
Sargassum Fulvellum Extract
Sargassum Fusiforme Extract
Sargassum Glaucescens Extract**
Sargassum Horneri Extract**
Sargassum Muticum Extract
Sargassum Pallidum Extract**
Sargassum Siliquastrum Extract**
Sargassum Thunbergii Extract**
Sargassum Vulgare Extract
Sphacelaria Scoparia Extract
Undaria Peterseniana Extract**
Undaria Pinnatifida Leaf/Stem Extract**
Undaria Pinnatifida Powder
Undaria Pinnatifida Root Powder**

***Not reported to be in current use.*

Ingredients in green type have sufficient systemic toxicity data, however, sensitization data are insufficient to determine safety.

Ingredients in blue type have sufficient sensitization data, however, systemic toxicity data are insufficient to determine safety.

Ingredients in black type have insufficient systemic toxicity and sensitization data.

TABLES

Table 1. Brown algae INCI names

Agarum Cribrosum Extract	Halopteris Scoparia Extract (equivalent to Sphacelaria Scoparia Extract)	Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract
Alaria Esculenta Extract	Himanthalia Elongata Extract	Macrocystis Pyrifera (Kelp) Extract
Ascophyllum Nodosum	Himanthalia Elongata Powder	Macrocystis Pyrifera (Kelp) Juice
Ascophyllum Nodosum Extract	Hizikia Fusiforme Extract (equivalent to Sargassum Fusiforme Extract)	Macrocystis Pyrifera (Kelp) Protein
Ascophyllum Nodosum Powder	Hizikia Fusiformis Water	Nereocystis Luetkeana Extract
Cladosiphon Novae-Caledoniae Extract	Hizikia Fusiformis Callus Culture Extract	Pelvetia Canaliculata Extract
Cladosiphon Okamuranus Extract	Hydrolyzed Ecklonia Cava Extract	Pelvetia Siliquosa Extract
Cystoseira Amentacea/Caespitosa/ Branchycarpa Extract	Hydrolyzed Fucus Vesiculosus Extract	Phyllacantha Fibrosa Extract (equivalent to Cystoseira Baccata Extract)
Cystoseira Baccata Extract (equivalent to Phyllacantha Fibrosa Extract)	Hydrolyzed Fucus Vesiculosus Protein	Saccharina Angustata Extract
Cystoseira Balearica Extract (equivalent to Cystoseira Caespitosa Extract)	Laminaria Cloustoni Extract (equivalent to Laminaria Hyperborea Extract)	Saccharina Japonica Extract (equivalent to Laminaria Diabolica Extract; Laminaria Japonica Extract; and Laminaria Ochroleuca Extract)
Cystoseira Caespitosa Extract (equivalent to Cystoseira Balearica Extract)	Laminaria Diabolica Extract (equivalent to Laminaria Japonica Extract; Laminaria Ochroleuca Extract; and Saccharina Japonica Extract)	Saccharina Longicruris Extract
Cystoseira Compressa Extract	Laminaria Digitata Extract	Sargassum Filipendula Extract
Cystoseira Compressa Powder	Laminaria Digitata Powder	Sargassum Fulvellum Extract
Cystoseira Tamariscifolia Extract	Laminaria Hyperborea Extract (equivalent to Laminaria Cloustoni Extract)	Sargassum Fusiforme Extract (equivalent to Hizikia Fusiforme Extract)
Dictyopteris Polypodioides Extract	Laminaria Japonica Extract (equivalent to Laminaria Diabolica Extract; Laminaria Ochroleuca Extract; and Saccharina Japonica Extract)	Sargassum Glaucescens Extract
Dictyota Coriacea Extract	Laminaria Japonica Powder	Sargassum Horneri Extract
Durvillaea Antarctica Extract	Laminaria Longissima Extract	Sargassum Muticum Extract
Ecklonia Cava Extract	Laminaria Ochroleuca Extract (equivalent to Laminaria Diabolica Extract; Laminaria Japonica Extract; and Saccharina Japonica Extract)	Sargassum Pallidum Extract
Ecklonia Cava Water	Laminaria Saccharina Extract	Sargassum Siliquastrum Extract
Ecklonia Kurome Extract	Lessonia Nigrescens Extract	Sargassum Thunbergii Extract
Ecklonia Kurome Powder	Lessonia Nigrescens Powder	Sargassum Vulgare Extract
Ecklonia/Laminaria Extract	Macrocystis Pyrifera (Kelp)	Sphacelaria Scoparia Extract (equivalent to Halopteris Scoparia Extract)
Ecklonia Maxima Extract		Undaria Peterseniana Extract
Ecklonia Maxima Powder		Undaria Pinnatifida Extract
Ecklonia Radiata Extract		Undaria Pinnatifida Cell Culture Extract
Eisenia Arborea Extract		Undaria Pinnatifida Leaf/Stem Extract
Fucus Serratus Extract		Undaria Pinnatifida Powder
Fucus Spiralis Extract		Undaria Pinnatifida Root Powder
Fucus Vesiculosus		
Fucus Vesiculosus Extract		
Fucus Vesiculosus Powder		
Halidrys Siliquosa Extract		

Table 2. Current and retired INCI names, definitions, and functions of the brown algae-derived ingredients in this safety assessment[1]

Ingredient	Definition	Function
Agarum Cribrosum Extract	Agarum Cribrosum Extract is the extract of the alga, *Agarum cribrosum.*	Skin-conditioning agent - miscellaneous
Alaria Esculenta Extract	Alaria Esculenta Extract is the extract of the alga, *Alaria esculenta*.	Hair conditioning agent; skin protectant
Ascophyllum Nodosum	Ascophyllum Nodosum is the alga, *Ascophyllum nodosum.*	Skin-conditioning agent - miscellaneous
Ascophyllum Nodosum Extract 84775-78-0	Ascophyllum Nodosum Extract is the extract of the alga, *Ascophyllum nodosum.*	Skin-conditioning agent - miscellaneous
Ascophyllum Nodosum Powder	Ascophyllum Nodosum Powder is the powder obtained from the dried, ground alga, *Ascophyllum nodosum.*	Skin-conditioning agent - miscellaneous
Cladosiphon Novae-Caledoniae Extract	Cladosiphon Novae-Caledoniae Extract is the extract of the alga, *Cladosiphon novae-caledoniae.*	Humectant; skin protectant
Cladosiphon Okamuranus Extract	Cladosiphon Okamuranus Extract is the extract of the alga, *Cladosiphon okamuranus.*	Skin-conditioning agent - miscellaneous
Cystoseira Amentacea/Caespitosa/ Branchycarpa Extract	Cystoseira Amentacea/Caespitosa/Branchycarpa Extract is the extract of the algae, *Cystoseira amentacea*, *Cystoseira caespitosa*, and *Cystoseira branchycarpa*.	Skin-conditioning agent - miscellaneous
Cystoseira Baccata Extract	Cystoseira Baccata Extract is the extract of the alga, *Cystoseira baccata*.	Skin-conditioning agent - miscellaneous
Phyllacantha Fibrosa Extract	*Phyllacantha Fibrosa Extract is the extract of the alga, Phyllacantha fibrosa. The accepted scientific name for Phyllacantha fibrosa is Cystoseira baccata.*	*Skin-conditioning agent - miscellaneous*

Table 2. Current and retired INCI names, definitions, and functions of the brown algae-derived ingredients in this safety assessment[1]

Ingredient	Definition	Function
Cystoseira Balearica Extract	Cystoseira Balearica Extract is the extract of the alga, *Cystoseira balearica.* The accepted scientific name for *Cystoseira balearica* is *Cystoseira brachycarpa.*	Skin-conditioning agent - miscellaneous
Cystoseira Caespitosa Extract	*Cystoseira Caespitosa Extract is the extract of the alga, Cystoseira caespitosa. The accepted scientific name for Cystoseira caespitosa is Cystoseira brachycarpa.*	*Skin protectant*
Cystoseira Caespitosa Extract	*See Cystoseira Balearica Extract.*	
Cystoseira Compressa Extract	Cystoseira Compressa Extract is the extract of the alga, *Cystoseira compressa.*	Skin-conditioning agent - miscellaneous
Cystoseira Compressa Powder	Cystoseira Compressa Powder is the dried, ground powder obtained from the alga, *Cystoseira compressa.*	Skin-conditioning agent - miscellaneous
Cystoseira Tamariscifolia Extract	Cystoseira Tamariscifolia Extract is the extract of the alga, *Cystoseira tamarisfolia*.	Skin-conditioning agent - miscellaneous
Dictyopteris Polypodioides Extract	Dictyopteris Polypodioides Extract is the extract of the alga, *Dictyopteris polypodioides.*	Skin-conditioning agent – emollient; skin-conditioning agent - miscellaneous
Dictyopteris Membranacea Extract (Retired)	Dictyopteris Membranacea Extract (Retired) is the extract of the alga, *Dictyopteris membranacea*. The INCI Name, Dictyopteris Membranacea Extract, originally published in 2007, was designated with a retired status in 2015. For an interim period of time, trade name assignments formerly published with the INCI Name Dictyopteris Membranacea Extract will be retained in the retired monograph, and also published with the new name assignment based on the current genus and species name, Dictyopteris Polypodioides Extract.	Antioxidant
Dictyota Coriacea Extract	Dictyota Coriacea Extract is the extract of the alga, *Dictyota coriacea.*	Oxidizing agent
Durvillaea Antarctica Extract	Durvillaea Antarctica Extract is the extract of the alga, *Durvillaea antarctica.*	Skin-conditioning agent - miscellaneous
Ecklonia Cava Extract	Ecklonia Cava Extract is the extract of the alga, *Ecklonia cava.*	Humectant; skin-conditioning agent - humectant
Ecklonia Cava Water	Ecklonia Cava Water is the aqueous solution of the steam distillates obtained from the alga, *Ecklonia cava*.	Skin protectant
Ecklonia Kurome Extract	Ecklonia Kurome Extract is the extract of the alga, *Ecklonia kurome.*	Skin-conditioning agent – humectant; skin-conditioning agent - miscellaneous
Ecklonia Kurome Powder	Ecklonia Kurome Powder is the powder obtained from the dried, ground alga, *Ecklonia kurome.*	Skin-conditioning agent - humectant
Ecklonia/Laminaria Extract	Ecklonia/Laminaria Extract is the extract of a mixture of the algae, *Ecklonia* and *Laminaria*.	Skin-conditioning agent - miscellaneous
Ecklonia Maxima Extract	Ecklonia Maxima Extract is the extract of the alga, *Ecklonia maxima*.	Skin-conditioning agent - miscellaneous
Ecklonia Maxima Powder	Ecklonia Maxima Powder is the powder obtained from the dried, ground alga, *Ecklonia maxima.*	Skin-conditioning agent - miscellaneous
Ecklonia Radiata Extract	Ecklonia Radiata Extract is the extract of the alga, *Ecklonia radiata.*	Hair conditioning agent; skin-conditioning agent - miscellaneous
Eisenia Arborea Extract	Eisenia Arborea Extract is the extract of the alga, *Eisenia arborea.*	Skin-conditioning agent - miscellaneous
Fucus Serratus Extract 94167-02-9	Fucus Serratus Extract is the extract of the alga, *Fucus serratus.*	Skin-conditioning agent - miscellaneous
Fucus Spiralis Extract	Fucus Spiralis Extract is the extract of the alga, *Fucus spiralis.*	Skin-conditioning agent – emollient; skin-conditioning agent - miscellaneous
Fucus Vesiculosus	Fucus Vesiculosus is the alga, *Fucus vesiculosus.*	Skin-conditioning agent - miscellaneous
Fucus Vesiculosus Extract 283-633-7	Fucus Vesiculosus Extract is the extract of the alga, *Fucus vesiculosus.*	Fragrance ingredient; skin-conditioning agent - miscellaneous
Fucus Vesiculosus Powder	Fucus Vesiculosus Powder is the powder obtained from dried, ground *Fucus vesiculosus.*	Skin-conditioning agent - miscellaneous
Halidrys Siliquosa Extract	Halidrys Siliquosa Extract is the extract of the alga, *Halidrys siliquosa.*	Skin-conditioning agent - miscellaneous
Halopteris Scoparia Extract	Halopteris Scoparia Extract is the extract of the alga, *Halopteris scoparia.*	Skin-conditioning agent - miscellaneous
Sphacelaria Scoparia Extract	*Sphacelaria Scoparia Extract is the extract of the alga, Sphacelaria scoparia. The accepted scientific name for Sphacelaria scoparia is Halopteris scoparia.*	*Corn/callus/wart remover*
Himanthalia Elongata Extract	Himanthalia Elongata Extract is the extract of the thallus of the alga, *Himanthalia elongata*.	Skin-conditioning agent - miscellaneous

Table 2. Current and retired INCI names, definitions, and functions of the brown algae-derived ingredients in this safety assessment[1]

Ingredient	Definition	Function
Himanthalia Elongata Powder	Himanthalia Elongata Powder is the powder obtained from the dried, ground alga, *Himanthalia elongata.*	Absorbent; binder; viscosity increasing agent -aqueous
Hizikia Fusiforme Extract	*See Sargassum Fusiforme Extract*	
Hizikia Fusiformis Water	Hizikia Fusiformis Water is the aqueous solution of the steam distillates obtained from the alga, *Hizikia fusiformis.* The accepted scientific name for *Hizikia fusiformis* is *Sargassum fusiforme.* .	Skin protectant
Hizikia Fusiformis Callus Culture Extract	Hizikia Fusiformis Callus Culture Extract is the extract of a culture of the callus of *Hizikia fusiformis.* The accepted scientific name for *Hizikia fusiformis* is *Sargassum fusiforme.*	Antifungal agent; antioxidant; hair conditioning agent; skin-conditioning agent - miscellaneous
Hydrolyzed Ecklonia Cava Extract	Hydrolyzed Ecklonia Cava Extract is the hydrolysate of an extract of the alga, *Ecklonia cava* derived by acid, enzyme or other method of hydrolysis.	Skin-conditioning agent - miscellaneous
Hydrolyzed Fucus Vesiculosus Extract 84696-13-9	Fucus Vesiculosus Extract is the extract of the alga, *Fucus vesiculosus.*	Fragrance ingredient; skin-conditioning agent – miscellaneous
Hydrolyzed Fucus Vesiculosus Protein	Hydrolyzed Fucus Vesiculosus Extract is the extract of the hydrolysate of *Fucus vesiculosus* derived by acid, enzyme or other method of hydrolysis.	None reported
Laminaria Cloustoni Extract	*See Laminaria Hyperborea Extract.*	
Laminaria Diabolica Extract	*See Saccharina Japonica Extract.*	
Laminaria Digitata Extract 90046-12-1 92128-82-0	Laminaria Digitata Extract is the extract of the alga, *Laminaria digitata.*	Fragrance ingredient; skin protectant; skin-conditioning agent - miscellaneous
Laminaria Digitata Powder	Laminaria Digitata Powder is the powder obtained from the dried, ground thallus of the alga, *Laminaria digitata.*	Skin-conditioning agent - miscellaneous
Laminaria Hyperborea Extract 90046-13-2 92128-82-0	Laminaria Hyperborea Extract is the extract of the alga, *Laminaria hyperborea.*	Fragrance ingredient; skin protectant
Laminaria Cloustoni Extract *90046-11-0* *92128-82-0*	Laminaria Cloustoni Extract is the extract of the alga, *Laminaria cloustoni*. The accepted scientific name for *Laminaria cloustoni* is *Laminaria hyperborea.*	Fragrance ingredient
Laminaria Japonica Extract	*See Saccharina Japonica Extract.*	
Laminaria Japonica Powder	Laminaria Japonica Powder is the powder obtained from the dried, ground alga, *Laminaria japonica.* The accepted scientific name for *Laminaria japonica* is *Saccharina japonica.*	Skin-conditioning agent - miscellaneous
Laminaria Longissima Extract	Laminaria Longissima Extract is the extract of the alga, *Laminaria longissima.* The accepted scientific name for *Laminaria longissima* is *Saccharina longissima*	Skin-conditioning agent - humectant
Laminaria Ochroleuca Extract	*See Saccharina Japonica Extract.*	
Laminaria Saccharina Extract 90046-14-3 92128-82-0	Laminaria Saccharina Extract is the extract of the thallus of the alga, *Laminaria saccharina.* The accepted scientific name for *Laminaria saccharina* is *Saccharina latissima.*	Fragrance ingredient; skin-conditioning agent - miscellaneous
Lessonia Nigrescens Extract	Lessonia Nigrescens Extract is the extract of the alga, *Lessonia nigrescens.*	Skin protectant
Lessonia Nigrescens Powder	Lessonia Nigrescens Powder is the powder obtained from the dried, ground alga, *Lessonia nigrescens.*	Binder
Macrocystis Pyrifera (Kelp)	Macrocystis Pyrifera (Kelp) is the alga, *Macrocystis pyriferae.*	Viscosity increasing agent - aqueous
Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract	Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract is the extract of the juice derived from the blade, pneumatocyst and stipe of the alga, *Macrocystis pyrifera.*	Skin-conditioning agent - miscellaneous
Macrocystis Pyrifera (Kelp) Extract 347174-92-9	Macrocystis Pyrifera (Kelp) Extract is the extract of the alga, *Macrocystis pyrifera.*	Skin-conditioning agent - miscellaneous
Macrocystis Pyrifera (Kelp) Juice	Macrocystis Pyrifera (Kelp) Juice is the juice expressed from the alga, *Macrocystis pyrifera.*	Skin-conditioning agent - miscellaneous
Macrocystis Pyrifera (Kelp) Protein	Macrocystis Pyrifera (Kelp) Protein is the protein derived from the alga, *Macrocystis pyrifera.*	Skin-conditioning agent - miscellaneous
Nereocystis Luetkeana Extract	Nereocystis Luetkeana Extract is the extract of the alga, *Nereocystis luetkeana.*	Hair conditioning agent; skin-conditioning agent - miscellaneous
Pelvetia Canaliculata Extract 223751-75-5	Pelvetia Canaliculata Extract is the extract of the alga, *Pelvetia canaliculata.*	Skin protectant; skin-conditioning agent - miscellaneous
Pelvetia Siliquosa Extract	Pelvetia Siliquosa Extract is the extract of the alga, *Pelvetia siliquosa.*	Antioxidant; skin protectant; skin-conditioning agent - humectant
Phyllacantha Fibrosa Extract	*See Cystoseira Baccata Extract.*	

Table 2. Current and retired INCI names, definitions, and functions of the brown algae-derived ingredients in this safety assessment[1]

Ingredient	Definition	Function
Saccharina Angustata Extract	Saccharina Angustata Extract is the extract of the alga, *Saccharina angustata*.	Skin-conditioning agent - emollient; skin-conditioning agent - miscellaneous
Laminaria Angustata Extract (Retired)	Laminaria Angustata Extract (Retired) is the extract of the alga, *Laminaria angustata*. The INCI Name, Laminaria Angustata Extract, originally published in 2003, was designated with a retired status in 2015. For an interim period of time, trade name assignments formerly published with the INCI Name Laminaria Angustata Extract will be retained in the retired monograph, and also published with the new name assignment based on the current genus and species name, Saccharina Angustata Extract.	Skin-conditioning agent - miscellaneous
Saccharina Japonica Extract	Saccharina Japonica Extract is the extract of the alga, *Saccharina japonica*.	Skin-conditioning agent - miscellaneous
Laminaria Ochotensis Extract (Retired)	Laminaria Ochotensis Extract (Retired) is the extract of the alga, *Laminaria ochotensis*. The INCI Name, Laminaria Ochotensis Extract, originally published in 2008, was designated with a retired status in 2015. For an interim period of time, trade name assignments formerly published with the INCI Name Laminaria Ochotensis Extract will be retained in the retired monograph, and also published with the new name assignment based on the current genus and species name, Saccharina Japonica Extract.	Skin-conditioning agent - emollient
Laminaria Diabolica Extract	*Laminaria Diabolica Extract is the extract of the alga, Laminaria diabolica. The accepted scientific name for Laminaria diabolica is Saccharina japonica.*	*Skin-conditioning agent - humectant*
Laminaria Japonica Extract 92128-82-0	*Laminaria Japonica Extract is the extract of the alga, Laminaria japonica. The accepted scientific name for Laminaria japonica is Saccharina japonica.*	*Fragrance ingredient*
Laminaria Ochroleuca Extract 92128-82-0	*Laminaria Ochroleuca Extract is the extract of the alga, Laminaria ochroleuca. The accepted scientific name for Laminaria ochroleuca is Saccharina japonica.*	*Fragrance ingredient; skin-conditioning agent - miscellaneous*
Saccharina Longicruris Extract	Saccharina Longicruris Extract is the extract of the alga, *Saccharina longicruris.*	Skin-conditioning agent - humectant
Sargassum Filipendula Extract	Sargassum Filipendula Extract is the extract of the brown alga, *Sargassum filipendula*.	Skin-conditioning agent - miscellaneous
Sargassum Fulvellum Extract	Sargassum Fulvellum Extract is the extract of the alga, *Sargassum fulvellum.*	Skin-conditioning agent - miscellaneous
Sargassum Fusiforme Extract	Sargassum Fusiforme Extract is the extract of the brown alga, *Sargassum fusiforme.*	Skin-conditioning agent - miscellaneous
Hizikia Fusiforme Extract	*Hizikia Fusiforme Extract is the extract of the alga, Hizikia fusiforme. The accepted scientific name for Hizikia fusiforme is Sargassum fusiforme.*	*Skin protectant; skin-conditioning agent - miscellaneous*
Sargassum Glaucescens Extract	Sargassum Glaucescens Extract is the extract of the alga, *Sargassum glaucescens.*	Antioxidant
Sargassum Horneri Extract	Sargassum Horneri Extract is the extract of the alga, *Sargassum horneri*.	Skin-conditioning agent - miscellaneous
Sargassum Muticum Extract	Sargassum Muticum Extract is the extract of the alga *Sargassum muticum.*	Skin-conditioning agent - miscellaneous
Sargassum Pallidum Extract	Sargassum Pallidum Extract is the extract of the alga, *Sargassum pallidum.*	Antifungal agent; antioxidant
Sargassum Siliquastrum Extract	Sargassum Siliquastrum Extract is the extract of the alga, *Sargassum siliquastrum.*	Skin-conditioning agent - miscellaneous
Sargassum Thunbergii Extract	Sargassum Thunbergii Extract is the extract of the alga, *Sargassum thunbergii.*	Antimicrobial agent
Sargassum Vulgare Extract	Sargassum Vulgare Extract is the extract of the alga, *Sargassum vulgare.*	Skin-conditioning agent - miscellaneous
Sphacelaria Scoparia Extract	*See Halopteris Scoparia Extract.*	
Undaria Peterseniana Extract	Undaria Peterseniana Extract is the extract of the alga *Undaria peterseniana.*	Skin-conditioning agent - miscellaneous
Undaria Pinnatifida Extract	Undaria Pinnatifida Extract is the extract of the alga, *Undaria pinnatifida.*	Skin protectant; skin-conditioning agent - miscellaneous
Undaria Pinnatifida Cell Culture Extract	Undaria Pinnatifida Cell Culture Extract is the extract of a cell culture suspension of *Undaria pinnatifida.*	Hair conditioning agent; skin-conditioning agent - miscellaneous
Undaria Pinnatifida Leaf/Stem Extract	Undaria Pinnatifida Leaf/Stem Extract is the extract of the leaves and stems of *Undaria pinnatifida.*	Skin-conditioning agent – emollient
Undaria Pinnatifida Powder	Undaria Pinnatifida Powder is the powder obtained from the dried, ground alga, *Undaria pinnatifida.*	Absorbent; binder; viscosity increasing agent - nonaqueous
Undaria Pinnatifida Root Powder	Undaria Pinnatifida Root Powder is the powder obtained from the dried, ground root-like structures of the alga, *Undaria pinnatifida.*	Humectant; skin-conditioning agent - humectant

Table 3. Descriptions of major algae groups

Common Name	Kingdom	Class	Description	Reference
Brown Algae	Chromista	Phaeophyceae	-mostly large, leathery seaweeds -cellulose wall with alginic acid and fucoidan -derived alginic acid is used as a suspending, emulsifying, gel-forming and film-forming agent	12
Green Algae	Plantae	Chlorophyta	-usually green in color -cellulose cell walls -store starch -beta carotene -chlorophyll a & b	12
Diatoms	Stramenopila	Bacillariophyceae	-golden brown in color -silica cell walls -store oil as food reserve -carotenoids -chlorophyll a & c	12
Chrysophytes	Stramenopila	Chrysophyta	-consists of diatoms, golden-brown algae and yellow-green algae -cellulose cell walls with large amounts of silica -chlorophyll a &c	12,150
Blue Green Algae	Monera	Cyanophyta	-phycobilins present -store glycogen -prokaryotic -chlorophyll a -some are toxic	12
Red Algae	Plantae	Rhodophyta	-phycobilins present -store floridean starch -cellulose cell wall -chlorophyll a & d -source of agar -used as a stabilizer and thickener in many products	12
Dinoflagellates	Alveolata	Pyrrhophyta	-some produce toxins -mostly marine	12,151
Euglenoids	Euglenozoa	Euglenophyta	-common in freshwater -can be parasitic	12,152

Table 4. Taxonomy of brown-algae derived ingredients based on currently accepted scientific name[153]

Subclass	Order	Family	Genus	Ingredient
Dictyotophycidae	Dictyotales	Dictyotacaea	Dictyopteris	Dictyopteris Polypodioides Extract
Dictyotophycidae	Dictyotales	Dictyotacaea	Dictyota	Dictyota Coriacea Extract
Dictyotophycidae	Sphacelariales	Sphacelariaceae	Sphacelaria	Sphacelaria Scoparia Extract
Dictyotophycidae	Sphacelariales	Sphacelariaceae	Sphacelaria	Halopteris Scoparia Extract
Fucophycidae	Ectocarpales	Chordariaceae	Cladosiphon	Cladosiphon Novae-Caledoniae Extract
Fucophycidae	Ectocarpales	Chordariaceae	Cladosiphon	Cladosiphon Okamuranus Extract
Fucophycidae	Fucales	Durvillaeaceae	Durvillaea	Durvillaea Antarctica Extract
Fucophycidae	Fucales	Fucaceae	Ascophyllum	Ascophyllum Nodosum
Fucophycidae	Fucales	Fucaceae	Ascophyllum	Ascophyllum Nodosum Extract
Fucophycidae	Fucales	Fucaceae	Ascophyllum	Ascophyllum Nodosum Powder
Fucophycidae	Fucales	Fucaceae	Fucus	Fucus Serratus Extract
Fucophycidae	Fucales	Fucaceae	Fucus	Fucus Spiralis Extract
Fucophycidae	Fucales	Fucaceae	Fucus	Fucus Vesiculosus
Fucophycidae	Fucales	Fucaceae	Fucus	Fucus Vesiculosus Extract
Fucophycidae	Fucales	Fucaceae	Fucus	Fucus Vesiculosus Powder
Fucophycidae	Fucales	Fucaceae	Fucus	Hydrolyzed Fucus Vesiculosus Extract
Fucophycidae	Fucales	Fucaceae	Fucus	Hydrolyzed Fucus Vesiculosus Protein
Fucophycidae	Fucales	Fucaceae	Pelvitia	Pelvetia Canaliculata Extract
Fucophycidae	Fucales	Fucaceae	Pelvitia	Pelvetia Siliquosa Extract
Fucophycidae	Fucales	Himanthaliaceae	Himanthalia	Himanthalia Elongata Extract
Fucophycidae	Fucales	Himanthaliaceae	Himanthalia	Himanthalia Elongata Powder
Fucophycidae	Fucales	Sargassaceae	Cystoseira	Cystoseira Amentacea/Caespitosa/ Branchycarpa Extract
Fucophycidae	Fucales	Sargassaceae	Cystoseira	Cystoseira Baccata Extract
Fucophycidae	Fucales	Sargassaceae	Cystoseira	Cystoseira Balearica Extract
Fucophycidae	Fucales	Sargassaceae	Cystoseira	Cystoseira Caespitosa Extract
Fucophycidae	Fucales	Sargassaceae	Cystoseira	Cystoseira Compressa Extract
Fucophycidae	Fucales	Sargassaceae	Cystoseira	Cystoseira Compressa Powder
Fucophycidae	Fucales	Sargassaceae	Cystoseira	Cystoseira Tamariscifolia Extract
Fucophycidae	Fucales	Sargassaceae	Halidrys	Halidrys Siliquosa Extract
Fucophycidae	Fucales	Sargassaceae	Hizikia	Hizikia Fusiforme Extract

Table 4. Taxonomy of brown-algae derived ingredients based on currently accepted scientific name[153]

Subclass	Order	Family	Genus	Ingredient
Fucophycidae	Fucales	Sargassaceae	Sargassum	Hizikia Fusiformis Water
Fucophycidae	Fucales	Sargassaceae	Hizikia	Hizikia Fusiformis Callus Culture Extract
Fucophycidae	Fucales	Sargassaceae	Cystoseira	Phyllacantha Fibrosa Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Filipendula Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Fulvellum Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Fusiforme Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Glaucescens Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Horneri Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Muticum Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Pallidum Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Siliquastrum Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Thunbergii Extract
Fucophycidae	Fucales	Sargassaceae	Sargassum	Sargassum Vulgare Extract
Fucophycidae	Laminariales	Agaraceae	Agarum	Agarum Cribrosum Extract
Fucophycidae	Laminariales	Agaraceae	Alaria	Alaria Esculenta Extract
Fucophycidae	Laminariales	Alariaceae	Undaria	Undaria Peterseniana Extract
Fucophycidae	Laminariales	Alariaceae	Undaria	Undaria Pinnatifida Extract
Fucophycidae	Laminariales	Alariaceae	Undaria	Undaria Pinnatifida Cell Culture Extract
Fucophycidae	Laminariales	Alariaceae	Undaria	Undaria Pinnatifida Leaf/Stem Extract
Fucophycidae	Laminariales	Alariaceae	Undaria	Undaria Pinnatifida Powder
Fucophycidae	Laminariales	Alariaceae	Undaria	Undaria Pinnatifida Root Powder
Fucophycidae	Laminariales	Laminariaceae	Laminaria	Laminaria Cloustoni Extract
Fucophycidae	Laminariales	Laminariaceae	Saccharina	Laminaria Diabolica Extract
Fucophycidae	Laminariales	Laminariaceae	Laminaria	Laminaria Digitata Extract
Fucophycidae	Laminariales	Laminariaceae	Laminaria	Laminaria Digitata Powder
Fucophycidae	Laminariales	Laminariaceae	Laminaria	Laminaria Hyperborea Extract
Fucophycidae	Laminariales	Laminariaceae	Saccharina	Laminaria Japonica Extract
Fucophycidae	Laminariales	Laminariaceae	Saccharina	Laminaria Japonica Powder
Fucophycidae	Laminariales	Laminariaceae	Laminaria	Laminaria Longissima Extract
Fucophycidae	Laminariales	Laminariaceae	Saccharina	Laminaria Ochroleuca Extract
Fucophycidae	Laminariales	Laminariaceae	Laminaria	Laminaria Saccharina Extract
Fucophycidae	Laminariales	Laminariaceae	Macrocystis	Macrocystis Pyrifera (Kelp)
Fucophycidae	Laminariales	Laminariaceae	Macrocystis	Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract
Fucophycidae	Laminariales	Laminariaceae	Macrocystis	Macrocystis Pyrifera (Kelp) Extract
Fucophycidae	Laminariales	Laminariaceae	Macrocystis	Macrocystis Pyrifera (Kelp) Juice
Fucophycidae	Laminariales	Laminariaceae	Macrocystis	Macrocystis Pyrifera (Kelp) Protein
Fucophycidae	Laminariales	Laminariaceae	Nereocystis	Nereocystis Luetkeana Extract
Fucophycidae	Laminariales	Laminariaceae	Saccharina	Saccharina Angustata Extract
Fucophycidae	Laminariales	Laminariaceae	Saccharina	Saccharina Japonica Extract
Fucophycidae	Laminariales	Laminariaceae	Saccharina	Saccharina Longicruris Extract
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Ecklonia Cava Extract
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Ecklonia Cava Water
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Ecklonia Kurome Extract
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Ecklonia Kurome Powder
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Ecklonia/Laminaria Extract
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Ecklonia Maxima Extract
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Ecklonia Maxima Powder
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Ecklonia Radiata Extract
Fucophycidae	Laminariales	Lessoniaceae	Ecklonia	Hydrolyzed Ecklonia Cava Extract
Fucophycidae	Laminariales	Lessoniaceae	Eisenia	Eisenia Arborea Extract
Fucophycidae	Laminariales	Lessoniaceae	Lessonia	Lessonia Nigrescens Extract
Fucophycidae	Laminariales	Lessoniaceae	Lessonia	Lessonia Nigrescens Powder

Table 5. General characteristics and geographic distribution of brown algae species

Species (common name)	Description	Distribution/Habitat/Ecology	References
Agarum cribrosum	-	North Atlantic (Massachusetts to east Greenland) and North Pacific (Washington state to Japan and Russia) Forms thick beds at depths of 10-12 m	153
Alaria esculenta (dabberlocks, badderlocks, winged kelp)	Olive or yellow-brown fronds to 4 m long and 25 cm wide, more often about 1 m and 7.5 cm wide. Attached by a root-like holdfast at the base from which a narrow flexible stipe arises which continues into the leafy part of thealgae as a distinct mid-rib, generally with a yellow-brown color. The reproductive structures, apparent as dark-brown areas, are confined to unbranched leafy appendages borne on the stipe, usually in two rows.	North Atlantic Ocean Generally growing on rock in wave-exposed places, often forming a band at low water and in the shallow subtidal, but also occurring in tidal pools in the lower shore.	153,154
Ascophyllum nodosum (asco, sea whistle, bladderwrack, rockweed)	Closely related to *Fucus*. Up to 3 m in height and is yellow in areas exposed to sunlight and dark green or brown in its shaded parts. Single bladders are central in long, strap-like fronds. Fronds hang downwards. Multiple fronds grow from each basal holdfast; generally regenerates new fronds from base when one of the larger fronds is damaged. Reproduction takes place in spring in yellow receptacles, which develop in response to short days in autumn, mature during winter, and are at their most prolific in spring. Eggs and sperm are released into water, and eggs release a low molecular weight pheromone, finnavarene.	North Atlantic basin (Virginia to Spain) Has been observed in San Francisco Bay, but does not persist there. Sheltered intertidal rocks in shallow (usually where it is exposed at low or extreme low tides)	153-156
Cystoseira baccata (bushy berry wrack) also known as *Phyllacantha fibrosa*	Thallus to 1 m long, usually solitary, attached by a thick, conical attachment disc. Axis simple or branched, and flattened; apex smooth and surrounded during periods of active growth by incurved young laterals. Lateral branch systems alternate, radially symmetrical, profusely branched in a repeatedly pinnate fashion and bearing sparse, filiform, occasionally bifurcated appendages on the branches; deciduous, leaving decurrent bases which give an irregular, zigzag outline to the axis. Air vesicles present in axes of branches of higher order, sometimes in chains; seasonal, particularly numerous in autumn. Receptacles 1-5 cm long, formed from axes of ultimate ramuli, irregularly nodose and bearing simple, filiform appendages.	S England, W Ireland north to W Scotland. Has been noted down to Morocco and in Mediterranean Sea. Lower intertidal in large sandy pools or lagoons, mostly in persistent stands.	153,154
Cystoseira tamariscifolia (bushy rainbow wrack)	Solitary thalli, up to 1 m long, bushy, with a pronounced greenish or bluish iridescence when submerged or wet; attached by a conical disc. Axis is cylindrical, up to 60 cm long, usually branched and with an inconspicuous apex. Lateral branch systems arising in spiral sequence, up to 60 cm long, profusely branched in a repeatedly pinnate fashion, showing radial symmetry with simple or bifid spine-like appendages: deciduous, leaving prominent scars or stumps. Cryptostomata present on branches and appendages. Ovoid air vesicles often present in axes of ultimate ramuli. Receptacles 1-2 cm long, formed from terminal regions of ultimate ramuli.	Western Mediterranean Sea/northern Africa to Ireland Large intertidal rock pools and lagoons and shallow subtidal shores	153,154
Dictyopteris polypodioides [*Dictyopteris membranacea* (Retired)]	Thallus flat and leaf-like, to 300 mm long and 20 - 30 mm broad; fronds olive to yellow-brown, translucent, and somewhat regularly dichotomously forked with a prominent midrib extending to the apices. Margins sometimes split to midrib. Has an unpleasant smell shortly after collection, which degenerates quickly.	Ireland (except for east coast), west Scotland, Wales, southwest England, to Portugal and West Africa Large pools at low water and shallow subtidal shores	153,154
Fucus serratus (serrated wrack, saw wrack, toothed wrack)	Dichotomously branched fronds arising from a small disc via a short stipe; distinct midrib.Algae grows to 300 mm with terminal, compressed receptacles with warty conceptacles. It is easily recognized by its saw-toothed frond, and a lack of swollen receptacles.	Widely distributed on all coasts of Britain and Ireland. Baltic Sea to Spain and Canary Islands. Introduced to Nova Scotia and has spread to New Brunswick and Maine. Zone forming on sheltered and semi-exposed shores.	153-155
Fucus spiralis (jelly bags, spiral wrack, flat wrack spiraled wrack)	Fronds lack bladders; elongated air bladders are on either side of the midrib. Fronds have twisted, dichotomous branches. This species is up to 20 cm long, attached to the substratum with a discoid holdfast. Color ranges from dark brown to olive-green.	North Atlantic and North Pacific; Baltic Sea to Morocco/Canary Islands and New York; Alaska to California. Introduced to Mediterranean Sea (France). Uppermost species of *Fucus* that occurs on shore.	155

Table 5. General characteristics and geographic distribution of brown algae species

Species (common name)	Description	Distribution/Habitat/Ecology	References
Fucus vesiculosus (paddy tang, red fucus, dyers fucus, swine tang, sea ware, bladder, rockweed, bladderwrack, popping wrack, wrack)	Paired bladders occur on either side of a prominent midrib. Frond is generally not strongly spiraled and receptacles do not have a sterile rim, and frond does not have a serrated margin. Attached by a small, strong disc which gives rise to a short stipe. This species is 15 to 90 cm long and 0.6 to 2.5 cm wide. Reproductive receptacles are swollen areas at tips of fronds that have many flask-shaped cavities called conceptacles, which house male and female reproductive structures known as antheridia (borne on antheridiophores) and oogonia (containing 8 eggs), respectively. Eggs and sperm are liberated onto surface of receptacles and a pheromone (sex-attracting substance) is released by eggs that attract sperm. Fertilization results in a zygote that forms a new *Fucus* adult.	North Atlantic (Canadian Arctic, Russia, White Sea, Baltic Sea) south to Canary Islands and West Indies Midshore zone A bladderless form occurs on more wave-exposed shores in the NE Atlantic. Grows in various conditions, from saline lagoons to exposed rocky shores, as well as on sheltered rocky shores. Forms dense canopies.	153-155,157
Halidrys siliquosa (podweed, sea oak)	Thallus 30 - 130 cm long, tawny to yellow-brown ochre, tough and leathery; attached by a large, discoid holdfast, giving rise to compressed, irregularly alternately branched fronds, with several orders of close branching in the same plane. Pod-shaped, segmented air bladders are produced replacing some lateral branches. Reproductive conceptacles forming in swollen conceptacles at apices of branches	Northeast Atlantic (Norway/Baltic Sea to Morocco) Large, mid-intertidal pools, often dominating in very large, sunny pools, but more often forming occasional stands. Occasionally forming extensive forests in shallow subtidal to about 10 m, generally in current-exposed locations. Widespread and common. Halidrys produces meroditerpenoids that seemingly act as antifouling agents preventing other organisms adhering to surface of the algae.	153,154
Halopteris scoparia (sea flax weed) also known as *Sphacelaris scoparia*	*Stypocaulon scoparium* may be synonymous	Northwest Atlantic (Baltic Sea to Canary Islands) and Mediterranean Sea	153
Himanthalia elongata (thongweed, buttonweed, sea spaghetti, sea thong, sea haricots)	Long thong-like fronds, basal mushroom-like buttons. Thallus consisting of a button-shaped vegetative thallus to 30 mm wide and 25 mm high, and a long, narrow, strap-like, sparingly branched, light yellow-brown reproductive receptacle to 2 m in length and up to 10 mm in width, on which conceptacles are borne. Buttons, initially club-shaped but later mushroom-like, develop from zygotes in late summer, mature in winter, and begin to form reproductive receptacles in January/February. Some 4-6 dichotomies are produced at this stage, and fronds then elongate and thicken, developing no further branches, and become reproductively mature in July-September.	Northwest Atlantic Ocean (Scandinavia to Spain) Gently sloping rocks, particularly on semi-wave-exposed shore, on which they may form a distinct zone at low water. Sparse populations sometimes develop in sheltered lagoons where thealgae are more yellow and less flattened.	153,154
Laminaria cloustoni [*Laminaria hyperborea*] (kelp, may weed, kelpie, liver weed, mirkle, pennant weed, strapwrack, cuvie, tangle, split whip wrack, sea rods, forest kelp, northern kelp)	Dark brown, to 2 m in length; with a claw-like, conical holdfast, a rough, rigid stipe which generally rises up out of the water, and is covered in epiphytes when older, and a laminate blade to 1.5 m long dividing into finger-like segments. Stipe is rugose (rough) when older, circular in cross-section, and snaps easily when bent; the holdfast is conical.	Northwest Atlantic Ocean (Scandinavia to Spain) Common at extreme low water in wave-exposed areas, and in the subtidal in optically clear water growing on rock to a depth of 32 m. Forms extensive closed communities at depths of 0 - 24 m. There are usually large quantities of ephytic red algae growing on the older stipes; the old fronds are cast off in spring and new ones grow below for a time.	153,154
Laminaria digitata (kelp)	Dark brown, to 2 m in length; with a claw-like holdfast, a smooth, flexible stipe, and a laminate blade to 1.5 m long split into finger-like segments. The stipe is oval in cross-section, and does not snap easily when bent. Underwater algae are more golden in color in sunlight.	North Atlantic (Arctic Canada/ Baltic Sea/Russia to Spain and New England) Very common in lower intertidal and shallow subtidal growing on rock. May form extensive meadows at low tide.	153,154
Laminaria hyperborea (kelpie, liver weed, mirkle, pennant weed, strapwrack, cuvie, tangle, split whip wrack)	Dark brown, to 2 m in length; with a claw-like, conical holdfast, a rough, rigid stipe which generally sticks up out of the water, and is covered in epiphytes when older, and a laminate blade to 1.5 m long dividing into finger-like segments. Stipe is rugose (rough) when older, circular in cross-section, and snaps easily when bent; the holdfast is conical.	Northeast Atlantic (Scandinavia/Iceland to Spain and Canary Islands) Common at extreme low water in wave-exposed areas, and in subtidal in optically clear water growing on rock to a depth of 32 m. Forms extensive closed communities at depths of 0-24 m; there are usually large quantities of ephytic red algae growing on the older stipes; the old fronds are cast off in spring and new ones grow below for a time.	153,154,158

Table 5. General characteristics and geographic distribution of brown algae species

Species (common name)	Description	Distribution/Habitat/Ecology	References
Laminaria saccharina [The accepted scientific name is *Saccharina latissima*] (sea belt, poor man's weather glass, sweet wrack, sugar wrack, sugar tang, oarweed, tangle, kelp, sugar sea belt, sweet tangle, sugarwrack, zuckertang)	Yellow brown, to 3 m in length; with a claw-like holdfast, a small, smooth, flexible stipe, and an undivided laminate blade to 3 m long with parallel, ruffled sides and an elongated, tongue-like appearance. Frond is characteristically dimpled with regular bullations (depressions). Stipe is relatively small, cylindrical in section and more flexible than those of *Laminaria digitata* and *Laminaria hyperborea*. It is only species in the NE Atlantic Ocean with an undivided frond, distinct bullations, and a frilly margin.	Circumboreal (Atlantic Ocean: Canada, Scandinavia, Greenland, Iceland to Galicia, Spain and Maine, but not known in the Bay of Biscay; Pacific Ocean: Alaska to California, Japan, Korea, Central Polynesia, India, New Zealand) Intertidal pools and occasional in shallow subtidal areas, becoming more abundant at low water in sheltered localities with fast-moving water, such as rapids systems. In subtidal, it is characteristic of intermittently disturbed areas.	153,154
Macrocystis pyrifera (giant kelp, sea ivy, giant pacific kelp)	This species reaches 45 meters long and grow in waters 6 - 20 (possibly up to 80) m deep, and grow at up to 30 cm per day. Now believed to be a monospecific genera ranging from intertidal to deep water with environments dictating morphology.	Eastern and southern Pacific Ocean in both hemispheres (Alaska to New Zealand and Australia) Dominant canopy-forming algae in southern and central California.	153,159,160
Pelvetia canaliculata (channeled wrack, cow tang)	This species is 80-120 mm long, yellow-brown in color, turning black when dry, and often so dry that fronds disintegrate when trodden upon; regularly dichotomously branched with a distinct channel on underside (side nearest rock), which holds moisture and apparently helps algae survive at very high levels on shore. Reproduction in conceptacles visible as dots on warty terminal receptacles. Usually infected by a fungus which may assist in allowing it to survive high in intertidal zone.	NE Atlantic from the Faroe Islands to Portugal Occurring very high on shore, generally above mean high water neap tides, on wave-exposed and sheltered shores, but absent from very exposed rocky shores.	153-155
Sargassum muticum	Thallus bushy, elongated, yellowish-tawny to dark brown, generally to 4 m long; tough, cylindrical, repeatedly alternately pinnately branched to the third or fourth order; whorls of distinctly flattened sculpted leaves at the base (resembling the leaves of Holly); with characteristic rounded-elliptical air bladders above and below, formed terminally. Reproductive receptacles below, formed in the axils of spiny leaves; spectacularly fecund. Basal holdfast penetrating and conical, persisting for several years. Reproductive plants detach easily, and continue to reproduce while drifting, and spreading the reproductive zygotes that develop on the surfaces of the receptacles. Terminal air bladders below; receptacles in the axils of spiny leaves.	Native to Japan; spread to China and Korea. Invasive in France, Spain and Portugal; western Mediterranean; Alaska south to Mexico. Throughout the intertidal in pools, but largest and commonest at low water.	153,154
Undaria pinnatifida (sea mustard, precious sea grass, wakame)	Thallus laminate, yellowish to dark brown, usually 1 - 2 m, occasionally 3 m or more in length; holdfast spreading, dichotomously branched and claw-like, giving rise to a flattened oar-like stipe with a "fried-egg" like margin with small proliferations and basally with beautifully lobed sporophylls that coil around it when mature; stipe continuing into the fond as a flattened midrib that bears broadly lobed laciniate fronds with a roughly pyramidal shape. Frilly sporophylls coiling around the base of the flattened stipe at the base. A similar flattened midrib is not found in any other kelp in the Atlantic. *Alaria esculenta* has a midrib which is not flattened and the frond of *Alaria* is not lobed, although it may be similarly laciniate.	Native to Pacific Russia, Japan, China and Korea. NE Ireland, S England, NW France, NW Spain, Mediterranean Lower intertidal and very shallow subtidal (no more than a few m), particularly in sheltered locations, growing particularly on marinas, buoys, and similar floating structures in harbors. Often occurring on boat-hulls.	153

Table 6. Chemical and physical properties of some brown algae-derived ingredients

Property	Value	Reference
Ascophyllum Nodosum Extract		
Physical Form	Liquid	161,162
	Viscous liquid	163
	Solid flakes	6
Color	Black	6,161
	Dark brown	162
	Dark brown (aq. ext)	163
Odor	Marine-like/Fish-like	161,162
	Characteristic, seaweed (aq. ext)	163
	Odorless	6
Density/Specific Gravity	1.17	161
	1.1 (aq. ext.)	163
Bulk Density (g/mL)	0.58	6
Viscosity kg/(s m)	< 0.1	161
Melting Point °C	0 (aq. ext.)	163
	> 300	6
Boiling Point °C	100	161
	100 (aq. ext.)	163
	65 – 96	162
Water Solubility g/L @ 20 °C & pH 7.4 – 7.5	> 10,000	6
@ 20 °C	100%	161,162
	100%	163
Other Solubility g/L		
Acetone @ 22 °C	0.007	6
Ethyl acetate @ 22°C	0.009	6
Methanol @ 22 °C	0.251	6
log P_{ow}	-3.3 est.	5,6
Particle size	> 0.250 mm, 93.5%	6
	< 0.045 mm, none	
Ascophyllum Nodosum Powder		
Physical Form	Flakes or powder	164
	Powder	165
Color	Olive green	164
	Green	165
Odor	Marine-like	164
	Characteristic, fish-like	165
Water Solubility g/L	Insoluble	164
Ecklonia Cava Extract		
Physical Form	Powder (alcohol ext)	9
Color	Brown (alcohol ext)	9
Halidrys Siliquosa Extract (aq.)		
Physical Form	Liquid	65
pH	5	65
Density	1.02	65

aq. = aqueous; ext. = extract

Table 7. Methods of manufacture for brown algae-derived ingredients

Ingredient (characterization)	Method of Manufacture	Reference
Alaria Esculenta Extract	trade name mixture consisting of Alaria Esculenta Extract in butylene glycol and water: harvesting/identification → washing → grinding → extraction with the solvents and butylene glycol and water → filtration → quality control → packaging → quality control	19
Alaria Esculenta Extract	trade name mixture consisting of Alaria Esculenta Extract in butylene glycol and water – dried before extraction: harvesting/identification → washing → drying → grinding → extraction with the solvents butylene glycol and water → filtration → quality control → packaging → quality control	19
Alaria Esculenta Extract	trade name mixture containing Alaria Esculenta Extract in Caprylic/Capric Triglycerides: harvesting/identification → drying → grinding → extraction with solvent caprylic/capric triglyceride → filtration → quality control → packaging → quality control	20
Ascophyllum Nodosum Extract	A trade name mixture containing 4.7% Ascophyllum Nodosum Extract in 94.5% water, reported a manufacturing process consisting of grinding the algae, extraction by water, fucoidan purification and ultrafiltration.	21
Ascophyllum Nodosum Extract	The species *Ascophyllum nodosum* is grinded, extracted by water, then undergoes fucoidan purification and ultrafiltration.	22
Cladosiphon Okamuranus Extract (high in fucoidan)	*Cladosiphon okamuranus* is hydrolyzed in 0.05 M or 0.5 M hydrochloric acid at 80°C for 30 min and then is neutralized with sodium hydroxide. Salt is removed by electrodialysis and then hydrolysate is lyophilized.	47
Cystoseira Tamariscifolia Extract	Cystoseira Tamariscifolia Extract and Caprylic/Capric Triglycerides: extraction with supercritical carbon dioxide	49
Dictyopteris Polypodioides Extract (high fractions of C_{11} hydrocarbons and sulfur compounds)	Air-dried algae material is extracted with diethyl ether. Solvent is removed vacuum distillation leaving a crude concrete extract. Crude extract is treated with hydrodistillation followed by liquid-liquid extraction with diethyl ether to obtain the essential oil.	23
Dictyopteris Polypodioides Extract (high fraction of sulfur compounds)	Air-dried algae material is extracted with diethyl ether. Solvent is removed by vacuum distillation leaving a crude concrete extract. Crude extract is then subjected to supercritical fluid (CO_2) extraction.	23
Dictyopteris Polypodioides Extract (high fractions of sesquiterpenes)	Air-dried algae material is extracted with diethyl ether. Solvent is removed vacuum distillation leaving a crude concrete extract. Crude extract is mixed with water and irradiated in a microwave oven (focused microwave-assisted hydrodistillation).	23
Ecklonia Cava Extract	Fresh, semidried *Ecklonia cava* seaweed is dried and crushed followed by alcohol (i.e., food-grade ethanol) extraction, purification, filtration, and concentration steps.	9
Ecklonia Cava Extract	Small pieces of *Ecklonia cava* fronds (~ 5 cm; 30 kg) are placed in 750 L of distilled water in the presence of enzymes (300 g pectinase and 300 g cellulase). Suspension is stirred for 24 h at 50°C, centrifuged at 3000 g for 20 min at 4°C, and vacuum filtered. Three volumes of 60% ethanol are then added for 18 h of extraction. Solution is filtered and concentrated using a rotary evaporator. Concentrated solution is made into powder using a spray dryer.	92
Ecklonia Cava Extract (high in polyphenols)	Dried *Ecklonia cava* powder is extracted with ethanol, concentrated, and freeze-dried.	24
Fucus Spiralis Extract	trade name mixture containing Fucus Spiralis Extract ("1 - 3% dry extract" (further details not provided)) in butylene glycol and water: harvesting/identification → washing → grinding → extraction with the solvents butylene glycol and water → addition of phenyllactic acid → filtration → quality control → packaging → quality control	25
Fucus Vesiculosus Extract	trade name mixture containing water, alcohol and Fucus Vesiculosus Extract: dried raw material → extract with 30% ethanolic solution → filtrate → concentration → filtrate → packaging	26
Fucus Vesiculosus Extract	trade name mixture containing sodium sulfate and Fucus Vesiculosus Extract: dried raw material → extract with 30% ethanolic solution → filtrate → concentration → add anhydrous sodium sulfate → packaging	26
Fucus Vesiculosus Extract	trade name mixture containing Fucus Vesiculosus Extract in caprylic/capric triglyceride: harvesting/identification → washing → grinding → extraction with the solvent caprylic/capric triglyceride → filtration → quality control → packaging → quality control	27
Fucus Vesiculosus Extract (28.8% polyphenols)	Ethanol (30% - 35% aq.) extraction of *Fucus vesiculosus* (10% w/w) is performed at room temperature under mechanical stirring for 4 h. After filtration on a filter press, liquid phase undergoes an initial purification step to remove alginates by precipitation in presence of excess calcium chloride. Liquid phase undergoes a second purification step involving diafiltration to remove iodine and low molecular weight compounds. Extract is freeze-dried to obtain a powder extract.	93
Fucus Vesiculosus Extract (18% polyphenols plus 0.0012% fucoxanthin)	Ethanol (50% - 70% aq.) extraction of *Fucus vesiculosus* (10% w/w) is performed to solubilize a greater amount of carotenoids at room temperature under mechanical stirring for 2 h. After filtration on a filter press, liquid phase undergoes an initial purification step to remove alginates by precipitating them in presence of excess calcium chloride. After solid-liquid separation, a second extraction is performed under same conditions. Two liquid phases are then blended, submitted to diafiltration to remove iodine and low molecular weight compounds, and freeze-dried to obtain a powder extract.	93
Fucus Vesiculosus Extract	Dried algae material is extracted with water for 24 h, with stirring at room temperature. Residue is then removed by filtration to give a slightly brown colored extract.	44
Hizikia Fusiforme Extract	trade name mixture containing water butylene glycol and Hizikia Fusiforme Extract: dried raw material → extract with 80% ethanolic solution → filtrate → concentration → add 50% 1,3-butylene glycolic solution → filtrate → packaging	26

Table 7. Methods of manufacture for brown algae-derived ingredients

Ingredient (characterization)	Method of Manufacture	Reference
Laminaria Digitata Extract (high in oligosaccharides)	An aqueous extraction is conducted followed by enzymatic depolymerization that breaks the polysaccharide into oligosaccharides (e.g., smaller polymers with 3 to 10 sugar components). Final process involves chelating oligosaccharide with zinc sulfate (0.1% zinc-pyrrolidone).	[29]
Laminaria Digitata Extract	trade name mixture containing Laminaria Digitata Extract in caprylic/capric triglyceride: harvesting/identification → washing → drying → grinding → extraction with the solvent caprylic/capric Triglyceride → filtration → quality control → packaging → quality control	[28]
Laminaria Digitata Extract	trade name mixture containing Laminaria Digitata Extract in water and propylene glycol: harvesting/identification → washing → grinding → extraction with the solvents water and propylene glycol → addition of methylparaben and propylparaben → filtration → quality control → packaging → quality control	[30]
Laminaria Hyperborea Extract	trade name mixture containing Laminaria Hyperborea Extract in water: harvesting/identification → washing → grinding → extraction with water → addition of benzylic alcohol and dehydroacetic alcohol → filtration → quality control → packaging → packaging → quality control	[31]
Laminaria Japonica Extract (low-molecular weight fucoidan)	Enzyme hydrolysis	[52]
Laminaria Japonica Extract	Algae is rinsed with tap water to remove salt and dried in an air dryer at 60◦C for 40 h. Dried material is ground with a hammer mill, and powder stored at −20◦C until used. Dried powder (2.5 kg) is extracted 3 times with 96% (v/v) ethanol for 3 h at 70°C. Combined extracts are filtered and concentrated under reduced pressure to obtain ethanol extracts	[46]
Laminaria Japonica Extract	Freshly collected algae material is air dried with a fan for 24 h then ground into a fine powder. 5 g of powder is added to 100 mL of 1:1 water:propylene glycol at room temperature for 1 day. This procedure is repeated 2 times, and the combined extracts were stored at −20°C until use.	[51]
Laminaria Japonica Extract, Nereocystis Leutkeana, and Macrocystis Pyrifera	trade name mixture containing Laminaria Japonica, Nereocystis Leutkeana, and Macrocystis Pyrifera Extract: test of acceptance → processing (mechanical grinding/milling) → extraction with pentaerythrityl tetraethylhexanoate at specific pH and temperature for specific duration → filtration → batch adjustments (refiltration) → sample for QC → pack → sample for Micro → shipping	[32]
Laminaria Japonica Powder	Dried algae is pulverized to desired size.	[48]
Laminaria Ochroleuca Extract	trade name mixture consisting on Laminaria Ochroleuca extract in Caprylic/Capric Triglyceride: harvesting/identification → washing → grinding → extraction with the solvent caprylic/capric triglyceride → filtration → quality control → packaging → quality control	[33]
Laminaria Saccharina Extract	trade name mixture containing Laminaria Saccharina Extract in water and propylene glycol: harvesting/identification → washing → grinding → extraction with solvents: water + propylene glycol → mixture (addition of preservatives) → filtration → quality control	[34]
Laminaria Saccharina Extract	trade name mixture containing Laminaria Saccharina Extract ("1-2.5% dry extract" (no other details provided)) in water and butylene glycol: harvesting/identification → washing → grinding → extraction with the solvents water and butylene glycol → mixture → addition of preservatives → filtration → quality control	[34]
Macrocystis Pyrifera Extract	Macrocystis Pyrifera Extract ("1-3% dry extract (no other details provided)) – extracted in water with added methylpropanediol: harvesting → washing → grinding → extraction (water) → centrifugation → filtration → addition of 20% Methylpropanediol → filtration	[35]
Pelvetia Canaliculata Extract	trade name mixture containing Pelvetia Canaliculata Extract ("1 - 3% dry extract" (no other details provided)) in butylene glycol and water: harvesting/identification → washing → drying → grinding → extraction with the solvents vegetable butylene glycol and water → filtration → quality control → packaging → quality control	[36]
Pelvetia Canaliculata Extract	trade name mixture containing Pelvetia Canaliculata Extract ("1 - 3% dry extract" (no other details provided)) in water and propylene glycol: harvesting/identification → washing → grinding → extraction with the solvents water and propylene glycol → addition of methylparaben and propylparaben → filtration → quality control → packaging → quality control	[36]
Pelvetia Canaliculata Extract	trade name mixture containing Pelvetia Canaliculata Extract ("0.5 - 3% dry extract" (no other details provided)) in water: harvesting/identification → washing → grinding → extraction with water → addition of benzylic alcohol and dehydroacetic acid → filtration → addition of trisodium citrate dehydrate → filtration → quality control → packaging → quality control	[37]
Pelvetia Canaliculata Extract	trade name mixture containing Pelvetia Canaliculata Extract in water: harvesting/identification → washing → grinding → extraction with water → addition of phenoxyethanol and sorbic acid → filtration → quality control → packaging → quality control	[38]
Pelvetia Canaliculata and Laminaria Digitata Extract	trade name mixture containing Pelvetia Canaliculata and Laminaria Digitata extracted in propylene glycol with panthenol: harvesting/identification → washing → grinding → extraction with the solvent propylene glycol → filtration → quality control → mixture → filtration → quality control → packaging → quality control	[39]
Pelvetia Canaliculata and Laminaria Digitata Extract	trade name mixture containing Pelvetia Canaliculata and Laminaria Digitata extracted in butylene glycol with preservatives: harvesting/identification → washing → grinding → extraction with butylene glycol → filtration → quality control → mixture → filtration → quality control → packaging → quality control	[39]
Pelvetia Canaliculata and Laminaria Digitata Extract	trade name mixture containing Pelvetia Canaliculata and Laminaria Digitata extracted in butylene glycol without preservatives: harvesting/identification → washing → grinding → extraction with butylene glycol → filtration → quality control → mixture → filtration → quality control → packaging → quality control	[40]
Sargassum Fusiforme Extract and Undaria Pinnatifida Extract (high in fucosterol and phytol)	Microwave-assisted extraction coupled with high-speed countercurrent chromatography.	[41]

Table 7. Methods of manufacture for brown algae-derived ingredients

Ingredient (characterization)	Method of Manufacture	Reference
Sargassum Fusiforme Extract and Undaria Pinnatifida Extract (high in lipids and antioxidant compounds)	Supercritical fluid extraction and subcritical water extraction.	[41]
Sargassum Glaucescens Extract	trade name mixture containing 20% Sargassum Glaucescens Extract, 79% water and 1% phenoxyethanol: grinding → extraction → preservative addition → sterilization → filtration → packaging → storage	[166]
Undaria Pinnatifida Extract (high in fucoidan)	Algae material is hydrolyzed in 0.05 or 0.5 M hydrochloric acid at 80°C for 30 min then neutralized with 1 M sodium hydroxide. Resulting material is desalted by gel filtration and hydrolysate lyophilized.	[66]
Undaria Pinnatifida Extract	trade name mixture containing Undaria Pinnatifida Extract in water and propylene glycol: harvesting/identification → drying → grinding → extraction with solvents water and propylene glycol, and addition of preservatives (methylparaben and propylparaben) → filtration → quality control → packaging → quality control	[43]
Undaria Pinnatifida Extract	trade name mixture containing Undaria Pinnatifida Extract in Caprylic/Capric Triglyceride: harvesting of fertile sporophytes → fragment isolation of gametophyte → culture in liquid medium → gametophyte separation → freeze-dried gametophyte -→ quality control → extraction with the solvent caprylic/capric triglyceride → filtration → quality control → packaging → quality control	[42]

Abbreviations: aq. = aqueous; HPLC = high-performance liquid chromatography

Table 8. Constituents in brown algae

Constituent(s)	Description
Alkaloids	Tyramine (TYR, 4-hydroxyphenylethylamine) has been detected in *Laminaria saccharina*.[167] The alkaloids found in marine algae may be divided into three groups: phenylethylamine alkaloids, indole and halogenated indole alkaloids, and other alkaloids.
Amino acids	Brown algae contain all of the essential amino acids and are greater in threonine, valine, leucine, lysine, glycine, and alanine than are the green and blue algaes.[41] *Fucus spiralis* was reported to contain 63.5% essential amino acids per total protein, containing leucine (5.5 mg/g protein), isoleucine (15.3 mg/g protein), lysine (12.5 mg/g protein), glutamic acid (12.1 mg/g protein), arginine (11.7 mg/g protein), serine (11.5 mg/g protein), valine (11.1 mg/g protein), and threonine (10.9 mg/g protein).[168]
Betaines	Glycinebetaine, γ-aminobutyric acid betaine, and/or trigonelline have been found in Alaria esculenta, Ecklonia maxima, Ecklonia radiata, Eisenia arborea, Laminaria digitata Macrocystis pyrifera, Nereocystis luetkeana, Saccharina angustata, Saccharina japonica, and Undaria pinnatifida.[169]
Iodine	The concentration of iodine in *Alaria esculenta* was reported to have a range of approximately 200 mg/kg (dry wt) to approximately 700 mg/kg (dry wt) depending on year, season, location, and whether it was collected in the wild, a monoculture, or an integrated culture.[170] *Fucus vesiculosus* contains between 0.03% and 0.2% iodine in dried material.[171] The iodine content is highest in the spring in freshly cut young blades. In *Laminaria digitata*, iodine content is highest in late autumn and winter (0.75% to 1.20% dry wt) and lowest in summer (0.25% to 0.60% dry wt).[172] Iodine content for *Fucus spiralis* and *Laminaria ochroleuca* have been reported to be 232.7 and 883.5 mg/kg dry wt.[168]
Laminarins	Laminarins are basically a class of low molecular weight storage β-glucans. These are composed of (1,3)-β-D-glucan and can be up to 35% of the dry weight of brown algae.[173]
Lipids	Fucosterol and fucosterol derivatives are present in brown algae.[41] Tocopherols, and sterols are also found in brown algae.
Omega-3 fatty acids	Omega-3 fatty acids include stearidonic acid and hexadecatetraenoic acid.[174] These make up to 40% of the total fatty acid content in *Undaria pinnatifida*.
Phenolic compounds, polyphenols, and phlorotannins	Phlorotannins are found in brown algae.[41] Flavonoids are integral structural components of cell walls (e.g., eckol, phlorofucofuroeckol A, dieckol, catechin, and epigallocatechin).
Pheromones	The pheromones include lamoxirene 4 (e.g., Agarum cribrosum, Ecklonia radiata, Eisenia arborea, Laminaria digitata, Laminaria hyperborea, Laminaria japonica, Laminaria saccharina, Saccharina angustata, Undaria pinnatifida, Macrocystis pyrifera, and Nereocystis luetkeana), fucoserratene 6 (e.g., Fucus serratus, Fucus spiralis, and Fucus vesiculosus), hormonsirene 8 (e.g., Durvillaea antarctica), and finavarrene 12 (Ascophyllum nodosum). The major constituents of the essential oil of Dictyopteris polypodioides are C_{11} hydrocarbons sulfur products such as 3-hexyl-4,5-dithiacycloheptanone.[23]
Phytohormones	Auxins (plant hormones that cause the elongation of cells in shoots and are involved in regulating plant growth), such as indoleacetic acid are found in the genera *Macrocystis*, *Laminaria*, *Fucus*, *Ascophyllum*).[41,175] Cytokinins (genera *Fucus*, *Ascophyllum*, *Sargassum*, *Macrocystis*), gibberellins (genus *Fucus*), abscisic acid (genera *Ascophyllum*, *Laminaria*), and polyamines (genus *Dyctiota*) are also found.
Pigments	Carotenoids including fucoxanthin, β-carotene, zeaxanthin, violaxanthin, and antheraxanthin are found in brown algae.[41] These vary with season.
Protein	The protein content of algae varies according to species and season.[14,41] In general, the protein fraction of brown algae is low (1% to 24% dry wt.) compared with that of green or red algae (4% to 50% dry wt). Except for the species *Undaria pinnatifida*, which has a protein content between 11% and 24% (dry wt.), most commercial brown algae have a protein content lower than 15% (dry wt; e.g., *Ascophyllum nodosum*, 3% to 15%; *Fucus vesiculosus*, *Himanthalia elongate*, and *Laminaria digitata*, 8% to 15%). The protein content of *Fucus* sp. tend to range from 3% to 11% (e.g., *Fucus spiralis*, 9.71% dry weight).[168]
Sterols	Sterols found in brown algae include desmosterol, ergosterol, fucosterol, cholesterol, campesterol, stigmasterol, and β-sterol.[60,61]
Terpenoids	Terpenes, phenolic compounds, and meroterpenes make up the three major classes of secondary metabolites in brown seaweed.[41]

Table 9. Constituents in *Ascophyllum nodosum*, *Fucus vesiculosus,* and *Laminaria digitata*

	Ascophyllum nodosum (ppm) [176]	*Fucus vesiculosus (*ppm) [177]	*Fucus vesiculosus* (ppm) [176]	*Laminaria digitata* (ppm) [29]
Algin	NR	41300 – 500000	NR	NR
Alginic acid	NR	NR	NR	200000 – 450000
Aluminum	NR	75.0 - 631.0	NR	NR
Arsenic	NR	68.0	NR	NR
Ascorbic-acid	NR	30.0 - 258.0	NR	NR
Bromine	NR	150.0	NR	NR
Calcium	9847	3587 – 30400	11600	NR
Carbohydrates	NR	77290 – 655000	NR	10000 – 20000
β-carotene	NR	5.0 – 40.0	NR	NR
Chromium	NR	0.1 – 0.7	NR	NR
Cobalt	NR	0.2 – 1.6	NR	NR
Fat	NR	3540 – 30000	NR	10000 – 20000
Fiber	NR	98000	NR	NR
Fiber(crude)	NR	98000	NR	NR
Fiber(dietary)	NR	482000	NR	NR
Fucinicacid	NR	1000	NR	NR
Fucoidin	NR	600000	NR	20000 – 40000
Fucose	NR	240000	NR	NR
Iodine	NR	64.0 – 540.0	NR	3000 – 1100
Iron	133.4	2.0 – 16.0	189.9	NR
Kilocalories	NR	2490	NR	NR
Lead	NR	91.0	NR	NR
γ-Linolenic acid	NR	NR	NR	NR
Magnesium	8678	1023 – 8670	7320	5000 – 8000
Mannitol	NR	NR	NR	40000 – 160000
Manganese	19.6	0.9 – 7.6	82.8	NR
Mercury	NR	40.0	NR	NR
Niacin	NR	6.0 – 47.0	NR	NR
Phosphorus	NR	294.0 -2490	1935.7	NR
Potassium	37810	2490 – 21,100	37450	13000 – 38000
Selenium	NR	0.2 – 1.7	NR	NR
Silicon	NR	0.9 – 7.6	NR	NR
Sodium	45757	6620 – 56,100	21875	9000 – 22000
Sugars	NR	2360 – 20000	NR	NR
Tin	NR	3.0 – 24.0	NR	NR
Water	NR	882000	NR	730000 – 900000
Zinc	NR	0.1 – 0.6	NR	NR

NR = not reported

Table 10. Sterols in several brown algae

Species	Desmosterol (mg/kg)	Ergosterol (mg/kg)	Fucosterol (mg/kg)	Cholesterol (mg/kg)	Campesterol + Stigmasterol (mg/kg)	β-Sterol (mg/kg)	Brassicasterol (mg/kg)	Ssaringosterol (mg/kg)	24-ketocholesterol (mg/kg)	Total[a] (mg/kg)	Reference
Cystoseira tamariscifolia	44.1 ± 3.4	-	5260.2 ± 14.9	500.4 ± 2.6	680.9 ± 21.4	17.0 ± 0.3	NR	NR	NR	6502.6	[61]
Fucus spiralis	37.6 ± 3.8	-	3815.1 ± 329.5	325.1 ± 13.5	183.4 ± 0.3	-	NR	NR	NR	4361.0	[61]
Sargassum vulgare	47.2 ± 0.2	5.6 ± 0.4	4451.5 ± 16.7	406.3 ± 13.2	303.3 ± 18.9	15.2 ± 2.8	NR	NR	NR	5229.1	[61]

NR = not reported; - = not found

[a] Total may not be exact due to rounding.

Table 11. Constituents of ethanol extracts of *Fucus spiralis* and *Sargassum vulgare*[63]

	Range (if provide; ppm)	
Constituent	***Fucus spiralis* extract**	***Sargassum vulgare* extract**
Arachidic Acid	ND	ND
Arachidonic Acid	465.6 ± 29.0	ND
Cholesterol	ND	127.4 ± 11.6
Eicosapentaenoic Acid	217.0 ± 11.4	ND
Fucosterol	317.6 ± 9.4	257.6 ± 43.6
γ-Linolenic Acid	ND	2413.6 ± 57.6
Mannitol (Total)	1273.8 ± 34.8	394.6 ± 15.2
Myristic Acid	69.8 ± 2.7	ND
Palmitic Acid	606.0 ± 20.6	340.4 ± 95.0
Phloroglucinol	< LOD	ND
Proline	396.8 ± 96.8	117.4 ± 11.0
β-Sitosterol	ND	ND
Stearic Acid	208.4 ± 21.4	204.0 ± 26.0
Vaccenic Acid	21,690.6 ± 1667.6	2848.6 ± 71.2

LOD = limit of detection; ND = not detected

Table 12. Composition of a 50/50 water/propylene glycol extract of *Laminaria japonica*[51]

Constituent	**Amount**
Constituent Groups (mg/g)	
Carbohydrate	6
Sugars	5
Proteins	2
Crude fat	2
Saturated fatty acid	1
Unsaturated fatty acid	None detected
Amino Acids (mg/L)	
Alanine	42.3
Ammonium chloride	16.2
Arginine	20.3
Aspartic acid	424.7
Glutamic acid	689.4
Glycine	1.7
Hydroxyproline	381.4
Phosphoserine	3.7
Serine	8.6
Threonine	4.2
Minerals (mg/g)	
Sodium	404
Calcium	300
Potassium	1022
Magnesium	35
Iron	0.5
Zinc	0.2

Table 13. Composition of enzyme hydrolysis extracts of *Laminaria japonica*[52]

Constituent	**Concentration (% w/w)**
	***Laminaria japonica* extract[52]**
Ash	4.1 ± 0.1
Fat	0.6 ± 0.1
Fucose	85.9
Moisture	3.9 ± 0.8
Monosaccharides (neutral)	NR
Protein	4.3 ± 0.3%
Sulfate	28.4 ± 2.1

NR = not reported

Table 14. Specifications of an alcohol extract of *Ecklonia cava* for use as a food supplement[9]

Parameter	Specification
Phlorotannin	90 ± 5.0%
Dieckol	6.6% – 9.9%
Moisture content	< 5%
Ash	< 5%
Insoluble substances	Negative
Substances not originating from *E. cava*	Negative
Viable cell count	< 3000 CFU/g
Staphylococcus aureus	Negative
Molds and yeasts	< 300 CFU/g
Salmonella spp.	Negative
Coliforms	Negative
Lead	< 3 mg/kg
Mercury	< 0.1 mg/kg
Cadmium	< 3 mg/kg
Arsenic	< 25 mg/kg
Iodine	150.0 – 650.0 mg/kg
Sieving size	> 60 (0.250 mm)

CFU = colony-forming unit

Table 15. Constituents of desalinated Undaria pinnatifida powder[67]

Constituent	Amount (mg/g)
Ash	147
Calcium	13.6
Copper	0.00130
Dietary fiber	532
Iron	0.107
Lipid	14
Magnesium	13.4
Protein	209
Sodium	25.4
Zinc	0.02

Table 16. Flavonoid content of brown algae species (µg/g dry weight)[68]

Flavonoid	*Undaria pinnatifida*	*Hizikia fusiformis*	*Ecklonia cava*	*Sargassum muticum*
Rutin	457 ± 6.3	-	2730 ± 190	-
Quercitrin	202 ± 26	-	-	-
Hesperidin	-	-	4240 ± 380	+
Myricetin	-	-	-	-
Morin	1020 ± 110	1010 ± 11	2360 ± 280	927 ± 30
Caffeic acid	53.6 ± 60	-	-	-

-: not detected; + = trace amounts detected

Table 17. Allergens found in trade name mixtures containing brown algae-derived ingredients.

	Amount (ppm)		
Allergen	**Undaria Pinnatifida Cell Culture Extract (0.5-2%)[178]**	**Hydrolyzed Fucus Vesiculosus Protein (98.9%)[179]**	**Sargassum Filipendula Extract (1.3%)[180]**
Alpha-IsoMethyl Ionone	< 0.02	0.00	< 0.02
Amyl Cinnamal	< 0.10	0.00	< 0.10
Anise Alcohol	< 0.00	0.00	< 0.00
Benzyl Alcohol	< 0.01	0.00	< 0.01
Benzyl Benzoate	< 0.09	0.00	< 0.09
Benzyl Cinnamate	< 0.30	0.00	< 0.30
Benzyl Salicylate	< 0.06	0.00	< 0.06
Butylphenyl Methylpropional	< 0.50	0.00	< 0.50
Cinnamal	< 0.01	0.00	< 0.01
Cinnamyl Alcohol	< 0.30	0.00	< 0.30
Citral	< 1.00	0.00	< 1.00
Citronellol	< 1.00	0.00	< 1.00
Coumarin	< 0.00	0.00	< 0.00
Eugenol	< 0.70	0.00	< 0.70
Farnesol	< 0.04	0.00	< 0.04
Geraniol	< 0.08	0.00	< 0.08
Hexyl Cinnamal	< 0.40	0.00	< 0.40
Hydroxycintronellal	<1.00	0.00	<1.00
Hydroxymethylpentyl 3-Cyclohexene carboxaldehyde	< 0.00	0.00	< 0.00
Isoeugenol	< 0.06	0.00	< 0.06
Limonene	< 0.05	0.00	< 0.05
Linalool	< 0.00	0.00	< 0.00
Methyl 2-Octynoate	< 0.20	0.00	< 0.20
Evernia prunastri	< 0.02	0.00	< 0.02
Evernia furfuracea	< 0.00	0.00	< 0.00
Amylcinnamyl Alcohol	< 1.00	0.00	< 1.00

Table 18. Concentration of arsenic found in several brown algae species[54]

Species	Arsenic Concentration (mg/kg wet wt.)	Arsenic Concentration (mg/kg dry wt.)
Ecklonia radiate	10[54]	-
Hizikia fusiforme	10[54]	-
Laminaria japonica	4[54]	-
Laminaria ochroleuca	-	56.8 ± 2.4[69]
Laminaria saccharina	-	52.4 ± 2.1[69]
Saccharina (spp)	-	< 0.3[181]
Sargassum fusiforme	-	67 - 96[181]
Sargassum thunbergii	4[54]	-
Unidaria pinnatifida	2.8 – 4.5[54]	< 0.3[181] 115 ± 9[69]

- = no data

Table 19. Arsenic -containing moieties found in various brown algae[69]

	Amount (mg/kg)			
Arsenic-Containing Moiety	***Laminaria ochroleuca***	***Laminaria saccharina***	***Sargassum fulvellum***	***Undaria pinnatifida***
Arsenic III	ND	ND	ND	ND
Arsenic V	ND	ND	69.9 ± 1.0	0.29 ± 0.03
Methylarsonate	ND	0.21 ± 0.03	ND	ND
Dimethylarsinate	0.26 ± 0.08	0.67 ± 0.02	2.1 ± 0.1	0.13 ± 0.03
Trimethylarsine oxide	ND	ND	ND	ND
Arsenobetaine	0.20 ± 0.02	0.09 ± 0.02	ND	ND
Phospate-sug po4	6.2 ± 0.1	6.9 ± 0.1	2.2 ± 0.1	0.30 ± 0.02
Sulfonate-sug so3	39.4 ± 1.6	30.7 ± 1.2	1.80 ± 0.10	ND
Sulfate-sug so4	ND	ND	9.0 ± 0.7	ND
Glycerol-sug gly	2.71 ± 0.04	2.9 ± 0.1	1.2 ± 0.2	0.87 ± 0.03
Arsenocholine	ND	ND	ND	ND
Inorganic arsenic	ND	ND	69.9	0.29

ND = not detected

Table 20. Arsenic species found in *Laminaria japonica* and an extract of *Laminaria japonica*[52]

	Amount (mg/kg)	
Arsenic Species	***Laminaria japonica***	***Laminaria japonica* extract[a]**
Arsenic III	ND	ND
Arsenic V	ND	ND
Monomethylarsonic Acid	9.27 ± 0.96	1.35 ± 0.63
Dimethylarsinic Acid	9.23 ± 0.83	ND
Arsenobetaine	34.31 ±1.21	4.77 ± 0.88
Arsenocholine	6.19 ± 2.17	ND
Arsenic (sum)	59.00 ± 1.65	6.12 ± 2.005

ND = not detected
[a] Extracted by enzyme hydrolysis, high in low-molecular-weight fucoidan

Table 21. Heavy metals and arsenic in brown algae

	Concentration of heavy metals and arsenic (mg/kg dry weight)							Reference
Species	**Cadmium**	**Lead**	**Mercury**	**Copper**	**Zinc**	**Arsenic**	**Inorganic Arsenic**	
Alaria esculenta	0.22 – 7.9	0.2 – 1.9	< 0.005 - <0.071	0.39 - 4	7 - 45	<0.074 - 100	-	[182]
Fucus vesiculosus	1.7	11	-	12.7	89	13.5	-	[157]
Himanthalia elongata	0.310 – 0.326	0.203 – 0.259	0.008 – 0.016	1.14 – 1.25	48.5 – 48.7	32.9 – 36.7	0.166 – 0.245	[71]
Hizikia fusiforme	0.988 – 2.50	< 0.008[a] – 0.531	0.015 – 0.050	1.78 – 7.70	4.72 – 19.5	103 – 147	32.1 – 69.5	[71]
Laminaria spp.	0.085 – 1.83	< 0.008[a] – 0.460	0.001 – 0.005	0.91 – 2.50	10.3 – 23.2	51.7 – 68.3	0.052 – 0.443	[71]
Undaria pinnatifida	0.267 – 4.82	< 0.008[a] – 1.28	0.010 – 0.057	1.07 – 1.70	8.25 – 26.6	42.1 – 76.9	0.045 – 0.346	[71]

[a] Limit of detection.
spp. = multiple species

Table 22. Heavy metal, arsenic, and iodine impurities in trade name mixtures containing brown algae species

	Concentration of heavy metals (ppm)							Reference
Trade name mixture	**Arsenic**	**Cadmium**	**Lead**	**Nickel**	**Silver**	**Iodine**	**Mercury**	
Alaria Esculenta Extract (< 5%) in butylene glycol and water	< 5	< 3	< 5	< 2	< 5	< 10	-	[183]
Alaria Esculenta Extract (< 5%) in butylene glycol and water – dried before extraction	< 5	< 3	< 5	< 2	< 5	< 10	-	[184]
Alaria Esculenta Extract (< 5%) in Caprylic/Capric Triglycerides	< 2	< 3	< 5	< 2	< 5	< 1	< 1	[185]
Ascophyllum Nodosum Extract (40.5%), Halopteris Scoparia Extract (13.5%), water	1.683	< 0.010	< 0.010	-	-	-	< 0.010	[186]
Cystoseira Amentacea/ Caespitosa/Brachycarpa Extracts (48%) in water	7.303	< 0.010	< 0.010	-	-	-	< 0.010	[105]
Cystoseira Tamariscifolia Extract (0.5%) and Caprylic/Capric Triglycerides	-	-	-	-	-	1	-	[49]
Cystoseira Tamariscifolia Extract (0.5%), water, and glycerin	1.35	-	-	-	-	1.4	-	[125]
Dictyopteris Polypodioides Extract (0.5%), water, and glycerin	0.809	-	-	-	-	19	-	[125]
Dictyopteris Polypodioides Extract (0.5%), water, and glycerin	0.602	-	-	-	-	19	-	[125]
Dictyopteris Polypodioides Extract (0.5%) and caprylic/capric triglyceride	0.051	-	-	-	-	< 9	-	[125]
Fucus Vesiculosus Extract, water and alcohol	< 10	-	-	-	-	-	-	[187]
Fucus Vesiculosus Extract and sodium sulfate	< 10	-	-	-	-	-	-	[187]
Fucus Vesiculosus Extract (< 5%) in caprylic/capric triglyceride	< 2	< 3	< 5	< 2	< 5	< 1	-	[188]
Fucus Vesiculosus Extract (0.5%), dipropylene glycol, and water	-	-	-	-	-	< 9	-	[125]

Table 22. Heavy metal, arsenic, and iodine impurities in trade name mixtures containing brown algae species

	Concentration of heavy metals (ppm)							Reference
Trade name mixture	**Arsenic**	**Cadmium**	**Lead**	**Nickel**	**Silver**	**Iodine**	**Mercury**	
Fucus Serratus Extract (44%) and water	3.691	0.011	< 0.010	-	-	-	< 0.010	189
Fucus Spiralis Extract (1-3%), butylene glycol, water	< 2	< 3	< 5	< 2	< 5	< 10	-	190
Fucus Spiralis Extract (12%), tetraselmis chui extract (8%), and water	0.65	< 0.05	< 0.05	-	-	-	< 0.05	191
Halidrys Siliquosa Extract (48%) in water	0.01	< 0.010	< 0.010	-	-	-	< 0.010	65
Halopteris Scoparia Extract (0.5%), water, and dipropylene glycol	0.73	-	-	-	-	15	-	125
Himanthalia Elongata Extract (0.5%), water, and dipropylene glycol	-	-	-	-	-	< 9	-	49
Himanthalia Elongata Extract (20%), Undaria Pinnatifida Extract (30%), and water	0.510	0.010	-	-	-	-	0.010	64
Himanthalia Elongata Extract (62%), saccharomyces cerevisiae extract (0.1%), Fucus Vesiculosus Extract (1.4%), and water	1.264	< 0.010	0.210	-	-	-	< 0.010	192
Hizikia Fusiforme Extract, water, and butylene glycol	<10	-	-	-	-	-	-	26
Laminaria Digitata Extract (0.5%), water, and sea salt	1.5	-	-	-	-	62	-	49
Laminaria Digitata Extract (0.5%), water, dipropylene glycol	2.37	-	-	-	-	87	-	49
Laminaria Digitata Extract (0.5%) and water	< 10	-	-	-	-	550 ± 150	-	49
Laminaria Digitata Extract (0.5%) and water	19.06	-	-	-	-	192	-	49
Laminaria Digitata Extract (0.5%) and water	2.69	-	-	-	-	41	-	125
Laminaria Digitata Extract (< 5%) in caprylic/capric triglyceride	< 2	< 3	< 5	< 2	< 5	< 300	-	193
Laminaria Digitata Extract (1.5 – 2.5%) in water and propylene glycol	< 5	< 10	< 5	< 2	< 5	< 400	-	194
Laminaria Japonica Extract (7%), Nereocystis Leutkeana Extract (7%), Macrocystis Pyrifera Extract (7%), and pentaerythrityl tetraethylhexanoate	< 2	< 1	<10	-	-	-	-	195
Laminaria Hyperborea Extract (<5%)	< 2	< 3	< 5	< 2	< 5	< 320	-	196
Laminaria Ochroleuca Extract (<5%), caprylic/capric triglyceride, and tocopherols	< 0.025	< 0.025	< 0.025	-	-	-	< 0.025	197
Laminaria Saccharina, water, and propylene glycol	< 2	< 3	< 5	< 2	< 5	< 200	< 1	198
Laminaria Saccharina Extract in water and propylene glycol	< 2	< 3	< 5	< 2	< 5	< 200	< 1	198
Laminaria Saccharina Extract in water and butylene glycol	< 2	< 3	< 5	< 2	< 5	< 200	< 1	199
Lessonia Nigrescens Extract (12%), water, and butylene glycol	2.628	0.050	< 0.010	-	-	-	0.012	200
Macrocystis Pyrifera (1-3%) in water and methylpropanediol	< 5	< 10	< 5	< 2	< 5	< 5	-	35
Pelvetia Canaliculata Extract (44%) and water	2.383	< 0.010	< 0.010	-	-	-	< 0.010	201
Pelvetia Canaliculata Extract (0.5 – 3%) in butylene glycol and water	< 3	< 3	< 5	< 2	< 5	< 10	-	202
Pelvetia Canaliculata Extract (5.5 – 9% dry extract) in propylene glycol and water	< 2	< 3	< 5	< 2	< 5	< 10	-	203

Table 22. Heavy metal, arsenic, and iodine impurities in trade name mixtures containing brown algae species

	Concentration of heavy metals (ppm)							Reference
Trade name mixture	**Arsenic**	**Cadmium**	**Lead**	**Nickel**	**Silver**	**Iodine**	**Mercury**	
Pelvetia Canaliculata and Laminaria Digitata (5.5 – 9% dry extract) extracted in propylene glycol with panthenol	< 5	< 3	< 5	< 2	< 5	< 100	-	204
Pelvetia Canaliculata and Laminaria Digitata (5.5 – 9% dry extract) extracted in butylene glycol with preservatives	< 5	< 10	< 5	< 2	< 5	< 100	-	205
Pelvetia Canaliculata and Laminaria Digitata (5.5 – 9% dry extract)extracted in butylene glycol without preservatives	< 5	< 10	< 5	< 2	< 5	< 100	-	202
Phyllacantha Fibrosa Extract (0.5%) and water	11.35	-	-	-	-	140	-	49
Phyllacantha Fibrosa Extract (0.5%) and water	11.35	-	-	-	-	97	-	125
Sargassum Glaucescens Extract (20%), water (79%), phenoxyethanol (1%)	< 2.5	-	< 1	< 230	-	-	-	206
Sargassum Muticum Extract (46%) and water	1.562	< 0.010	< 0.010	-	-	-	< 0.010	207
Undaria Pinnatifida Cell Culture Extract (0.5%)	< 2	< 1	< 10	-	-	-	-	208
Sphacelaria Scoparia Extract (0.5%)	0.73	-	-	-	-	15	-	49
Undaria Pinnatifida Extract (0.5%) in glycerin and water	0.837	-	-	-	-	<1	-	125
Undaria Pinnatifida Extract (0.5%) in water and propylene glycol	< 5	< 10	< 5	< 2	< 5	< 1	< 1	209
Undaria Pinnatifida Extract (0.5%) in caprylic/capric triglyceride	< 0.025	-	-	-	-	1.2	-	125
Undaria Pinnatifida Extract (0.5%) in caprylic/capric triglyceride	< 2	< 3	< 5	< 2	< 5	< 1	< 1	210

- = not reported

Table 23. Frequency (2019) and concentration of use (2015 - 2016) according to duration and exposure of brown algae-derived ingredients[75-77,211]

Use type	*# Uses*	*Max. Conc. (%)*	*# Uses*	*Max. Conc.(%)*	*# Uses*	*Max. Conc.(%)*	*# Uses*	*Max.Conc. (%)*
	Agarum Cribrosum Extract		**Alaria Esculenta Extract**		**Ascophyllum Nodosum Extract**		**Ascophyllum Nodosum Powder**	
Total/range	**1**	**0.012**	**41**	**0.0005-0.05**	**140**	**0.0000004-0.2**	**5**	**NR**
Duration of use[a]								
Leave-on	*1*	*0.012*	*41*	*0.0005-0.05*	*111*	*0.0000004-0.2*	*3*	*NR*
Rinse-off	*NR*	*NR*	*NR*	*0.0015*	*29*	*0.00004-0.0032*	*1*	*NR*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*1*	*NR*
Exposure type								
Eye area	NR	NR	12	NR	17	0.025-0.2	NR	NR
Incidental Ingestion	NR	NR	3	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[b]	NR	6[a]; 6[b]	0.0005[a]	23[a]; 62[b]	0.002[a]	2[a]	NR
Incidental Inhalation-Powder	1[b]	NR	5; 6[b]	0.0015-0.05[c]	1; 62[b]	0.0000004-0.03[c]	NR	NR
Dermal Contact	1	0.012	37	0.0005-0.05	124	0.0000004-0.2	5	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Non-Coloring	NR	NR	1	NR	13	0.00005-0.002	NR	NR
Hair- Coloring	NR	NR	NR	NR	NR		NR	NR
Nail	NR	NR	NR	NR	3	0.000065-0.02	NR	NR
Mucous Membrane	NR	NR	3	NR	6	0.00004	1	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 23. Frequency (2019) and concentration of use (2015 - 2016) according to duration and exposure of brown algae-derived ingredients[75-77,211]

Use type	# Uses	Max. Conc. (%)	# Uses	Max. Conc.(%)	# Uses	Max. Conc.(%)	# Uses	Max.Conc. (%)
	Cladosiphon Okamuranus Extract		**Dictyopteris Polypodioides Extract**[d]		**Ecklonia Cava Extract**		**Ecklonia Radiata Extract**	
Total/range	**10**	**0.005-0.05**	**6**	**0.01**	**18**	**0.0001**	**82**	**0.005-0.0051**
Duration of use								
Leave-on	*9*	*0.025-0.05*	*5*	*0.01*	*15*	*0.0001*	*13*	*0.0051*
Rinse-off	*1*	*0.005*	*1*	*NR*	*3*	*NR*	*69*	*0.005*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure type								
Eye area	1	0.025	NR	NR	1	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.01	NR	NR	NR	NR
Incidental Inhalation-Spray	4[a]; 3[b]	NR	4[a]; 1[b]	NR	5[a]; 8[b]	NR	7; 6[a]	0.0051
Incidental Inhalation-Powder	3[b]	0.025[b]	1[b]	NR	8[b]; 1[c]	NR	NR	NR
Dermal Contact	10	0.005-0.05	6	NR	17	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Non-Coloring	NR	NR	NR	NR	1	NR	82	0.0051
Hair- Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	0.001	NR	NR
Mucous Membrane	NR	NR	NR	0.01	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

	Fucus Serratus Extract		**Fucus Vesiculosus**		**Fucus Vesiculosus Extract**		**Fucus Vesiculosus Powder**	
Total/range	**8**	**0.00001-0.05**	**NR**	**0.0003-0.0051**	**291**	**0.00002-5**	**4**	**NR**
Duration of use								
Leave-on	*8*	*0.05*	*NR*	*0.00098-0.0051*	*192*	*0.000032-5*	*1*	*NR*
Rinse-off	*NR*	*0.00001-0.05*	*NR*	*0.0003*	*90*	*0.00002-5*	*2*	*NR*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*9*	*0.0001-5*	*1*	*NR*
Exposure type								
Eye area	8	0.05	NR	NR	5	0.01-5	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	0.0005	NR	NR
Incidental Inhalation-Spray	3[a]; 4[b]	NR	NR	0.00098	3; 81[a]; 78[b]	0.00018-0.12; 0.0001-0.1[a]	1[b]	NR
Incidental Inhalation-Powder	4[b]	0.05[c]	NR	NR	78[b]	0.000032-.05[c]	1[b]	NR
Dermal Contact	8	NR	NR	0.00098-0.0051	260	0.00002-5	4	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair- Non-Coloring	NR	0.000010	NR	0.0003	29	0.0001-5	NR	NR
Hair- Coloring	NR	NR	NR	NR	NR	0.0001-0.001	NR	NR
Nail	NR	NR	NR	NR	NR	0.02	NR	NR
Mucous Membrane	NR	NR	NR	NR	39	0.00002-5	1	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Himanthalia Elongata Extract		**Laminaria Cloustoni Extract**		**Laminaria Digitata Extract**		**Laminaria Digitata Powder**	
Total/range	**14**	**0.2**	**15**	**NR**	**310**	**0.00004-5**	**18**	**40**
Duration of use								
Leave-on	*11*	*0.2*	*11*	*NR*	*229*	*0.0001-5*	*2*	*40*
Rinse-off	*3*	*NR*	*4*	*NR*	*74*	*0.00004-5*	*13*	*NR*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*7*	*0.1-5*	*3*	*NR*
Exposure type								
Eye area	1	NR	1	NR	20	0.0035-0.5	NR	NR
Incidental Ingestion	NR	NR	NR	NR	2	NR	NR	NR
Incidental Inhalation-Spray	2[a]; 7[b]	NR	5[a]; 4[b]	NR	3; 71[a]; 88[b]	0.0007; 0.0035-5[a]	1[b]	NR
Incidental Inhalation-Powder	7[b]	NR	4[b]	NR	2; 88[b]	0.0001-0.1[c]	1[b]	40[b]
Dermal Contact	11	0.2	15	NR	266	0.0001-5	15	40
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair- Non-Coloring	3	NR	NR	NR	36	0.0007-5	3	NR
Hair- Coloring	NR	NR	NR	NR	1	0.00004-0.0007	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	23	0.06-5	4	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 23. Frequency (2019) and concentration of use (2015 - 2016) according to duration and exposure of brown algae-derived ingredients[75-77,211]

Use type	# Uses	Max. Conc. (%)	# Uses	Max. Conc.(%)	# Uses	Max. Conc.(%)	# Uses	Max.Conc. (%)
	Laminaria Hyperborea Extract		**Laminaria Japonica Extract**		**Laminaria Ochroleuca Extract**		**Laminaria Saccharina Extract**	
Total/range	**14**	**0.03**	**98**	**0.005-5**	**54**	**0.000024-0.63**	**136**	**0.00001-0.54**
Duration of use								
Leave-on	*14*	*0.03*	*81*	*0.0005-5*	*48*	*0.00017-0.63*	*89*	*0.000092-0.54*
Rinse-off	*1*	*NR*	*17*	*0.0005-5*	*6*	*0.000024-0.017*	*47*	*0.00001-0.51*
Diluted for (bath) use	*NR*	*NR*	*NR*	*0.011-5*	*NR*	*NR*	*NR*	*NR*
Exposure type								
Eye area	NR	NR	4	0.0005-0.007	7	0.0034-0.63	NR	0.000092-0.019
Incidental ingestion	NR	NR	1	NR	1	NR	NR	NR
Incidental Inhalation-Spray	2; 7[a]; 3[b]	NR	14[a]; 40[b]	0.3-5[a]	16[a]; 12[b]	0.017; 0.017[a]	42[a]; 20[b]	0.001-0.005
Incidental Inhalation-Powder	3[b]	0.03[c]	3; 2[c]; 40[b]	0.0035; 0.0055-5[c]	3; 12[b]	0.0005-0.17[c]	20[b]	0.0008; 0.000092-0.1[c]
Dermal Contact	14	0.03	92	0.0005-5	53	0.000024-0.63	124	0.000092-0.54
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.15[e]
Hair- Non-Coloring	1	NR	2	0.0005-0.3	NR	0.017	12	0.00001-0.045
Hair- Coloring	NR	NR	NR	NR	NR	0.017	NR	
Nail	NR	NR	2	NR	NR	NR	NR	0.001
Mucous Membrane	1	NR	6	0.011-5	3	NR	4	0.51
Baby Products	NR	NR	2	NR	NR	NR	NR	NR

	Lessonia Nigrescens Extract		**Macrocystis Pyrifera (Kelp)**		**Macrocystis Pyrifera (Kelp) Extract**		**Macrocystis Pyrifera (Kelp) Protein**	
Total/range	**NR**	**0.032**	**2**	**NR**	**199**	**0.00005-36.4**	**3**	**NR**
Duration of use								
Leave-on	*NR*	*NR*	*1*	*NR*	*114*	*0.0002-36.4*	*1*	*NR*
Rinse-off	*NR*	*0.032*	*1*	*NR*	*81*	*0.00005-5*	*2*	*NR*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*4*	*0.0051-1*	*NR*	*NR*
Exposure type								
Eye area	NR	NR	NR	NR	5	0.007-36.4	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	0.079	NR	NR
Incidental Inhalation-Spray	NR	NR	1[a]	NR	10; 40[a]; 27[b]	0.042-0.79; 0.0036-5[a]; 0.17[b]	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	2; 27[b]	0.0035; 0.001-33.3[c]; 0.17[b]	NR	NR
Dermal Contact	NR	0.032	2	NR	134	0.00005-36.4	3	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair- Non-Coloring	NR	NR	NR	NR	56	0.001-5	NR	NR
Hair- Coloring	NR	NR	NR	NR	4		NR	NR
Nail	NR	NR	NR	NR	5	0.0002-0.0011	NR	NR
Mucous Membrane	NR	NR	1	NR	39	0.0051-5	1	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

	Pelvetia Canaliculata Extract		**Sargassum Filipendula Extract**		**Sargassum Fusiforme Extract**		**Sargassum Muticum Extract**	
Total/range	**47**	**0.00002-0.018**	**46**	**0.0001-1.2**	**17**	**NR**	**1**	**0.01-0.076**
Duration of use								
Leave-on	*34*	*0.00002-0.018*	*14*	*0.0001-1.2*	*13*	*NR*	*NR*	*0.076*
Rinse-off	*13*	*0.00004-0.0018*	*32*	*0.002-0.29*	*4*	*NR*	*1*	*0.01*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure type[a]								
Eye area	6	0.00002-0.0007	2	NR	NR	NR	NR	0.076
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1; 18[a]; 8[b]	0.00004-0.0007; 0.002-0.0035[a]	3; 5[a]; 1[b]	0.0001[a]	7[a]; 4[b]	NR	NR	NR
Incidental Inhalation-Powder	8[b]	0.002-0.018[c]	1[b]	0.8[c]	4[b]; 1[c]	NR	NR	NR
Dermal Contact	19	0.00002-0.018	16	0.002-1.2	17	NR	1	0.076
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair- Non-Coloring	24	0.00004-0.0025	7	0.0001-0.29	NR	NR	NR	NR
Hair- Coloring	1	0.0000-0.0007	23	0.011-0.29	NR	NR	NR	NR
Nail			NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

Table 23. Frequency (2019) and concentration of use (2015 - 2016) according to duration and exposure of brown algae-derived ingredients[75-77,211]

Use type	# Uses	Max. Conc. (%)	# Uses	Max. Conc.(%)	# Uses	Max. Conc.(%)	# Uses	Max.Conc. (%)
	Sargassum Vulgare Extract		**Sphacelaria Scoparia Extract**		**Undaria Pinnatifida Extract**		**Undaria Pinnatifida Powder**	
Total/range	**NR**	**0.0075-0.016**	**8**	**0.016**	**90**	**0.00001-5**	**NR**	**0.1**
Duration of use								
Leave-on	*NR*	*0.009-0.016*	*6*	*0.016*	*76*	*0.00001-5*	*NR*	*NR*
Rinse-off	*NR*	*0.0075*	*2*	*NR*	*14*	*0.0001-5*	*NR*	*0.1*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*NR*	*0.0001*	*NR*	*NR*
Exposure type								
Eye area	NR	0.011	NR	NR	4	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	0.009[a]	1[a]; 4[c]	NR	18[a]; 42[b]	0.002[a]	NR	NR
Incidental Inhalation-Powder	NR	0.011[c]	4[c]	NR	2; 42[b]; 3[c]	0.00001-5; 0.00001-5[c]	NR	NR
Dermal Contact	NR	0.011-0.016	8	0.016	80	0.00001-5	NR	0.1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair- Non-Coloring	NR	0.0075-0.009	NR	NR	10	0.002-5	NR	NR
Hair- Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	NR	4	0.0001	NR	NR
Baby Products	NR	NR	NR	NR	4	NR	NR	NR

	Nereocystis Luetkeana Extract		**Sargassum Fulvellum Extract**		**Saccharina Longicruris Extract**		**Halidrys Siliquosa Extract**	
Total/range	**6**	**NR**	**2**	**NR**	**2**	**2**	**NR**	**0.029 – 0.29**
Duration of use								
Leave-on	*6*	*NR*	*2*	*NR*	*NR*	*NR*	*NR*	*0.29*
Rinse-off	*0*	*NR*	*NR*	*NR*	*2*	*2*	*NR*	*0.029*
Diluted for (bath) use	*0*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	NR	0.29
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	2[b]	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	2	NR	2[b]	NR	NR	NR	NR	0.29[c]
Dermal Contact	6	NR	2	NR	NR	NR	NR	0.029–0.29
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair- Non-Coloring	NR	NR	NR	NR	2	2	NR	NR
Hair- Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.
[a] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[c] It is possible these products may be powders, but it is not specified whether the reported uses are powders.
[d] Frequency of use and concentration of use were reported under the INCI name Dictyopteris Membranacea Extract (Retired).
[e] Not spray.

Table 24. Brown algae-derived ingredients with no reported uses in the VCRP or the Council survey[75-77]

Ascophyllum Nodosum
Cladosiphon Novae-Caledoniae Extract
Cystoseira Amentacea/Caespitosa / Branchycarpa Extract
Cystoseira Baccata Extract
Cystoseira Balearica Extract
Cystoseira Caespitosa Extract
Cystoseira Compressa Extract
Cystoseira Compressa Powder
Cystoseira Tamariscifolia Extract
Dictyota Coriacea Extract
Ecklonia Cava Extract
Ecklonia Cava Water
Ecklonia Kurome Extract
Ecklonia Kurome Powder
Ecklonia Maxima Extract
Ecklonia Maxima Powder
Ecklonia/Laminaria Extract
Eisenia Arborea Extract
Fucus Spiralis Extract
Halidrys Siliquosa Extract
Himanthalia Elongata Powder
Hizikia Fusiforme Extract
Hizikia Fusiformis Callus Culture Extract
Hizikia Fusiformis Water
Hizikia Fusiformis Water
Hydrolyzed Ecklonia Cava Extract
Hydrolyzed Fucus Vesiculosus Extract
Hydrolyzed Fucus Vesiculosus Extract
Hydrolyzed Fucus Vesiculosus Protein
Laminaria Diabolica Extract
Laminaria Japonica Powder
Laminaria Longissima Extract
Laminaria Longissima Extract
Lessonia Nigrescens Powder
Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract
Macrocystis Pyrifera (Kelp) Juice
Macrocystis Pyrifera (Kelp) Juice
Pelvetia Siliquosa Extract
Phyllacantha Fibrosa Extract
Saccharina Angustata Extract [Laminaria Angustata Extract (Retired)]
Saccharina Japonica Extract [Laminaria Ochotensis Extract (Retired)]
Sargassum Glaucescens Extract
Sargassum Horneri Extract
Sargassum Pallidum Extract
Sargassum Siliquastrum Extract
Sargassum Thunbergii Extract
Undaria Peterseniana Extract
Undaria Pinnatifida Cell Culture Extract
Undaria Pinnatifida Leaf/Stem Extract
Undaria Pinnatifida Root Powder

Table 25. GRAS brown algae-derived ingredients

Species	Functional Use in Food	CFR Citation
Hizikia fusiforme	Spices, seasoning, flavoring	21CFR184.1120
Laminaria spp.	Natural substances; solvent-free natural extractives	21CFR582.30; 21CFR582.40
Laminaria claustonia	Spices, seasoning, flavoring; dietary supplement	21CFR184.1120; 21CFR172.365
Laminaria digitata	Spices, seasoning, flavoring; dietary supplement	21CFR184.1120; 21CFR172.365
Laminaria japonica	Spices, seasoning, flavoring	21CFR184.1120
Laminaria longissima	Spices, seasoning, flavoring	21CFR184.1120
Laminaria saccharina	Spices, seasoning, flavoring; dietary supplement	21CFR184.1120; 21CFR172.365
Nereocystis spp.	Natural substances; solvent-free natural extractives	21CFR582.30; 21CFR582.40
Macrocystis pyrifera	Spices, seasoning, flavoring; dietary supplement	21CFR184.1120; 21CFR172.365
Undaria pinnatifida	Spices, seasoning, flavoring	21CFR184.1120

Table 26. Brown algae species used in food products[16]

Species	Methods of consumption	Reference
Alaria esculenta	Eaten either fresh or cooked	16
Ascophyllum nodosum	Eaten either fresh or cooked	212
Cladosiphon okamuranus	Eaten fresh and in seaweed salads	16
Ecklonia cava	Used in addition to *Hizikia* as pigment replacer; typically cooked into stir fries	16
Fucus vesiculosus	Eaten as a vegetable or condiment	87
Fucus serratus	Eaten as a vegetable or condiment	87
Hizikia fusiforme	Steamed to remove phlorotannins, and cooked into stir fries; used as a spice	16
Himanthalia elongata	Eaten dried or pickled	213,214
Laminaria angustata (also known as Saccharina angustata)	Typically cooked in soups; can be powdered and added to sauces and soups; used in tea	16
Laminaria digitata	Eaten dried, fresh, or cooked	212
Laminaria japonica	Typically cooked in soups; can be powdered and added to sauces and soups; used in tea	16
Laminaria longissima	Typically cooked in soups; can be powdered and added to sauces and soups; used in tea	16
Laminaria ochotensis	Typically cooked in soups; can be powdered and added to sauces and soups; used in tea	16
Laminaria ochroleuca	Eaten dried, fresh, or cooked	215
Laminaria saccharina	Eaten dried, fresh, or cooked	212
Macrocystis pyrifera	Used as spices, seasonings	16
Undaria pinnatifida	Eaten raw in dehydrated form; used in instant foods such as noodles and soups; used as spice, seasoning	16

Table 27. Acute oral toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
ORAL						
Ascophyllum Nodosum Extract	Sprague-Dawley rats	NR	NR	OECD TG 401	LD_{50} > 2000 mg/kg	91
Cystoseira Compressa Extract (methanol, hexane, and chloroform extracts)	Albino mice	2	Not specified	Up to 2000 mg/kg by gavage. Observed for 24 h.	There were no mortalities or clinical signs for any of the extracts.	62
Ecklonia Cava Extract (alcohol extract)	Sprague-Dawley (Crl:DC(DS)) rats	10/sex	Not specified	2000 mg/kg by gavage. Observed for 2 weeks.	There were no mortalities. Clinical signs were soft stools, diarrhea, mucus stools, compound-colored feces, and soiled perineal region from the day of administration until day 2.	9
Ecklonia Cava Extract (enzyme extract)	SD rats	5/sex	Distilled water	0 or 3000 mg/kg by oral gavage. Rats were observed for 14 days.	No abnormal changes in body weights, clinical signs, or mortalities were observed. Necropsy results showed no macroscopic lesions in any organs of treatment group.	92
Ecklonia Cava Extract (enzyme extract)	Beagle dogs	2/sex	Distilled water	3000 mg/kg by oral gavage in two equally divided doses approximately 6 h apart. Dogs were observed for 14 days.	No abnormal changes in body weights, clinical signs, or mortalities were observed. Necropsy results showed no macroscopic lesions in any organs of treatment group.	92
Fucus Vesiculosus Extract (28.8% polyphenols)	Swiss mice	7/sex	1% carboxymethyl-cellulose	1000 - 2000 mg/kg OECD TG 425 Administered by gavage. An Irwin test (determines the general effects of a test substance on the central nervous system and physiological functions) was performed at 1 and 5 h after administration of the extracts to detect motor, respiratory, temperature, circulatory, behavior, or other alterations. Mice were observed for 7 days.	LD_{50}: Males = 1000 mg/kg; females = between 1000 and 2000 mg/kg	93
Fucus Vesiculosus Extract (18% polyphenols plus 0.0012% fucoxanthin)	Swiss mice	7/sex	1% carboxymethyl-cellulose	200 - 750 mg/kg OECD TG 425 Administered by gavage. Irwin test was performed at 1 and 5 h after administration of the extracts to detect motor, respiratory, temperature, circulatory, behavior, or other alterations. Mice were observed for 7 days.	LD_{50}: Males = 500 mg/kg; females = < 750 mg/kg	93
Fucus Vesiculosus Extract (28.8% polyphenols)	Sprague-Dawley rats	7/sex	1% carboxymethyl-cellulose	1000 - 2000 mg/kg OECD TG 425 Administered by gavage. Irwin test was performed at 1 and 5 h after administration of the extracts to detect motor, respiratory, temperature, circulatory, behavior, or other alterations. Rats were observed for 7 days.	LD_{50}: Males and females = between 1000 and 2000 mg/kg	93

Table 27. Acute oral toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
Fucus Vesiculosus Extract (18% polyphenols plus 0.0012% fucoxanthin)	Sprague-Dawley rats	7/sex	1% carboxymethyl-cellulose	1000 - 2000 mg/kg OECD TG 425 Administered by gavage. Irwin test was performed at 1 and 5 h after administration of the extracts to detect motor, respiratory, temperature, circulatory, behavior, or other alterations. Rats were observed for 7 days.	LD_{50}: Males and females = > 2000 mg/kg	93
Laminaria Digitata Extract (≤ 10%), artemisia vulgaris extract (≤ 10%), phenoxyethanol (0.8%), and water	Wistar rats	5/sex	Feed or water	20%; administered via food or water ad-libitum	No significant changes were reported for each of the 10 rats tested. LD_{50}: Males and females = > 5 g/kg	94
Sargassum Fulvellum Extract (dichloromethane, ethanol, and water extracts)	BALB/c mice	5	Tween-80 (5%)	5000 mg in 10 mL vehicle by gavage. Observed for 2 weeks.	There were no mortalities. Most of the mice reacted immediately by perpetual gagging, jumping, sleeping, scaling, and writhing for 5–10 min.	50
Sargassum Thunbergii Extract	BALB/c mice	5	Tween-80 (5%)	5000 mg in 10 mL vehicle by gavage. Observed for 2 weeks.	There were no mortalities. Most of the mice reacted immediately by perpetual gagging, jumping, sleeping, scaling, and writhing for 5–10 min.	50

OECD TG = Organisation for Economic Co-operation and Development Test Guideline

Table 28. Oral repeated dose studies

Test Article	Extraction Solvent/Method or Composition	Animals (n)	Study Duration	Vehicle	Dose / Concentration	Results	Reference
			Short-Term				
Ascophyllum nodosum	Dried	Topigs Hybrid X Piétrain weanling pigs (20)	23 days	Feed	0, 2.5, 5.0, or 10.0 g/kg feed (0.25%, 0.5%, or 1.0%)	There were no adverse effects from treated feed. There were no effects on weight gain, feed consumption. Digestion characteristics were similar to controls (pH, fresh matter weight, and dry matter content), except for pH of part of the intestine was increased in the high-dose group (6.28 vs.5.96).	95
Ascophyllum nodosum	Freeze-dried and powdered	Male Sprague-Dawley rats (6)	4 weeks	Feed	0, 5%, 10%, or 15% in feed	Food intake, weight gain, and serum enzyme (alanine transaminase and aspartate transaminase) levels indicated that seaweed diets were well tolerated.	45
Ecklonia Cava Extract	Alcohol extract	Male ICR mice (10)	4 weeks	None	0, 1.25, 2.5 or 5 mg/d Mice were fed high fat diet (20% fat) or normal diet (5% to 10% fat). After 1 week, mice in high fat diets were administered Ecklonia Cava Extract by gavage while continuing on the high fat diet.	There were no mortalities. There was a dose-dependent lower body weight of ~ 12% - ~ 16% in the mice administered the extract compared to control group. Triglycerides, total cholesterol and LDL cholesterol were decreased in all treated groups. Liver enzymes (GPT and GOT), BUN, and creatinine values in serum were similar to controls. No data on feed consumption provided.	96

Table 28. Oral repeated dose studies

Test Article	Extraction Solvent/Method or Composition	Animals (n)	Study Duration	Vehicle	Dose / Concentration	Results	Reference
Ecklonia Cava Extract	Enzyme extract	SD rats (5/sex)	14 days	Water	0, 1000, 2000, or 5000 mg/kg by gavage	- There were no mortalities. No dose-related clinical abnormalities or body weight changes. - Macroscopic examination did not reveal any treatment-related abnormal lesions in males or females at necropsy; although redness in thymus, red spot in lung, and congestion and red spot in cervical lymph node were sporadically observed without a dose-dependent relationship. - Females in the 2000 and 5000 mg/kg groups had decreases in absolute and relative left ovary weights relative to control group and decreases in absolute brain weights were observed in females in 5000 mg/kg group.	92
Ecklonia Cava Extract	Alcohol extract	Sprague-Dawley (Crl:CD(SD)) rats (5/sex)	4 weeks	None	0, 500, 1000, or 2000 mg/kg/d by gavage.	- Compound-colored stools were observed in all rats in all dosing groups starting from day 1 of dosing. Salivation after dosing was observed sporadically in 1 female in the 1000 mg/kg/d group and in 2 males and 2 females in the 2000 mg/kg/d group on days 5 to 17 of dosing. - In clinical chemical investigations in 2000 mg/kg/d group, increases in ALT, and decreases in total protein, triglycerides and glucose were observed in males. Absolute and relative liver weights and absolute kidney weights were increased in males in 2000 mg/kg/d group. In females, relative heart weights were decreased in 1000 and 2000 mg/kg/d groups. There were no differences between study groups concerning body weight. Histopathologically, atrophy of periportal hepatocytes in livers was detected in male rats in 2000 mg/kg/d group.	9
Ecklonia Cava Extract	Alcohol extract	Beagle dogs (2/sex)	8 days 2-week observation period	Capsule	Day 1, 100 mg/kg; Day 4, 300 mg/kg; and Day 8, 1000 mg/kg	There were no mortalities. Compound-colored stools were observed in all dogs in 300 and 1000 mg/kg groups. Vomiting was observed in 1 male and 1 female dog when treated at 1000 mg/kg.	9
Fucus Vesiculosus Extract (28.8% polyphenols)	Ethanol (30% - 35% aq)	Sprague-Dawley rats (7/sex)	4 weeks	1% CMC	0, 200, or 750 mg/kg/d by gavage	- There were no mortalities. -Males: body and most organ weights were similar to controls. Livers had an increase weight (21%) at necropsy. - Females: body and organ weights were similar to controls.	93
Fucus Vesiculosus Extract (18% polyphenols plus 0.0012% fucoxanthin)	Ethanol (50% - 70% aq.)	Sprague-Dawley rats (7/sex)	4 weeks	1% CMC	0, 200, or 750 mg/kg/d by gavage	- There were no mortalities. - Males: body and most organ weights were similar to controls. Livers had an increase weight (25%) at necropsy. - Females: body and organ weights were similar to controls.	93
Laminaria Japonica Extract	Ethanol extract	Sprague-Dawley rats (6)	6 weeks	Not clear (probably daily gavage)	0, 100, 200, or 400 mg/kg starting after 6 weeks of a 12-week high-fat diet	- There were no mortalities. - Treatment groups had decreased the body weight gain, fat-pad weights, and serum and hepatic lipid levels in high-fat-induced obese rats. Histological analysis showed that treated groups had decreased number of lipid droplets and size of adipocytes compared to untreated high-fat diet group.	46

Table 28. Oral repeated dose studies

Test Article	Extraction Solvent/Method or Composition	Animals (n)	Study Duration	Vehicle	Dose / Concentration	Results	Reference
					Subchronic Oral		
Cladosiphon Okamuranus Extract	hydrolyzing in HCl	Wistar Rats (12/group)	3 months	Water	300, 600, 1299, 2400, 4000 mg/kg bw/d by gavage	A dose-dependent increase in clotting time and decrease in alkaline phosphatase (ALP) was noted in high doses. No significant differences compares to control. No treatment-related changes in organ weights reported. No abnormalities is morphology of brain, thymus, lungs, heart, spleen, liver, adrenal glands, kidneys, testes, thyroids, prostate gland, uterus or ovaries.	47
Ecklonia Cava Extract	Alcohol extract	Sprague–Dawley (Crl:CD(SD)) rats (10/sex;5 additional in control and high-dose groups)	13 weeks 4-week recovery period for 5 rats in control and high-dose group	Water	0, 375, 750, or 1500 mg/kg/d	- Compound-colored stools in all dose levels; not considered to be of toxicological significance. -At 750 and 1500 mg/kg/d, BUN was decreased in males, glucose was decreased in females, and neutrophil counts were increased in females, compared to controls. Sporadic salivation occurred in females. - At 1500 mg/kg/d, incidence of salivation in females increased and occurred in male rats. Salivation was mainly observed after gavage, but to some degree also before. It was considered by authors to be a temporary sign caused by the test substance, since it was no longer evident later in the day. Number of rats with salivation increased with study duration. -At 1500 mg/kg/d, males and females had a lower body weight (11.7% and 8.7%, respectively) at end of study compared to controls (not statistically significant). This effect was dose related, appearing to a minor degree also at lower dose levels. Body weight effects were more pronounced in recovery group in both sexes. Feed consumption was not decreased. Blood chemistry analyses showed increases of phosphorus and ALT concentrations and a decrease of triglycerides in males, and a decrease of glucose in females, compared to controls. Prothrombin time was increased in males compared to controls. These changes were not evident after recovery period. There were no compound related findings in histopathological investigations including liver.	9
Ecklonia Cava Extract	Enzyme extract	SD rats (5/sex)	13 weeks	Water	0, 500, 1000, 2000, or 3000 mg/kg by gavage	- There were no mortalities. None of groups had any dose-related clinical abnormalities or body weight changes. - Urinalysis and hematological analysis showed no treatment-related adverse effects. - Serum biochemistry and organ weights showed sporadic changes. However, sporadic changes might not have any relationship with treatment because these changes were very minimal within physiologically acceptable ranges without consistency between male and female rats. - Gross visual and macroscopic changes were not observed in organs of treated rats. Histopathological examination of sampled organs revealed a few spontaneous lesions which might be unrelated to treatment because there was no difference in incidence between control and treatment groups.	92
					Chronic Oral		
Laminaria Japonica Powder	Dried and powdered	Male CDF1 mice (6)	Life time	Feed	0, 2%, 5%	Mean lifespans were similar in all groups: 907 ± 135, 746 ± 183, and 851 ± 225 days for 0, 2%, and 5%, respectively.	48

Table 28. Oral repeated dose studies

Test Article	Extraction Solvent/Method or Composition	Animals (n)	Study Duration	Vehicle	Dose / Concentration	Results	Reference
Undaria Pinnatifida Extract	Filtered aqueous extract of powdered stems and thick leaves	Female Sprague-Dawley (SD) rats (12)	32 weeks	Drinking water	1.5 g in 1000 mL water	There were no mortalities. Body weight changes were similar between groups.	97
Undaria Pinnatifida Powder	Dried and ground	Female SD rats (5)	36 weeks	Feed	0, 1.0%, or 5.0%	There were no mortalities. Body weight changes, thyroid weights, and T4 levels were similar between groups.	98

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMP = adenosine monophosphate; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMC = carboxymethylcellulose; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; HDL = high-density lipoprotein; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LDL = low-density lipoprotein; MCHC = mean corpuscular hemoglobin concentration; T4 = thyroxin

Table 29. Genotoxicity studies

Ingredient/Test Article	Extraction Solvent/ Method	Concentration/ Vehicle	Procedure	Test System	Results	Reference
			In Vitro			
Ascophyllum Nodosum Extract	Not specified	Not specified	Ames assay performed according to OECD TG 471. No other details provided.	Not specified	Non-mutagenic.	91
Ascophyllum Nodosum Extract	Not specified	50, 150, 500, 1500, or 5000 µg/plate; in water	Ames assay, with and without metabolic activation in accordance with OECD TG 471 (bacterial reverse mutation test). Negative control: histidine; positive control: 4-nitroquinoline-N-oxide, 3-methylmethane sulphonate, 2-aminoanthracene, and sodium azide. There was no solvent control.	*S. typhimurium* (strains TA97, TA98, TA100, TA102, and TA1535)	Not genotoxic in all strains	6
Ascophyllum Nodosum Extract	Not specified	150, 500, 1500, or 5000 µg/mL; in water	Mammalian cell gene mutation test accordance with OECD TG 476 (in vitro mammalian cell gene mutation test) with and without metabolic activation. Positive control without metabolic activation: ethylmethanesulphonate, with metabolic activation: BaP	CHO; K1 sub clone CHO K1	Increased mutant frequencies at 1500 and 5000 µg/mL without metabolic activation; no increase in mutation frequencies at lower concentrations. No increase in mutation frequencies at any concentration with metabolic activation.	6
Ascophyllum Nodosum Extract	Not specified	With metabolic activation: 0.63, 1.25, 2.5, or 5 mg/mL; without metabolic activation: 1.25, 2.5, or 5 mg/mL	Chromosome aberration assay in accordance with OECD TG 487 (in vitro mammalian chromosome aberration test) with and without metabolic activation. Negative control: medium (serum free cell culture medium); positive controls: CPA, MMC, and colchicine	Human lymphocytes	Not genotoxic	6

Table 29. Genotoxicity studies

Ingredient/Test Article	Extraction Solvent/ Method	Concentration/ Vehicle	Procedure	Test System	Results	Reference
Ascophyllum Nodosum Extract	Not specified	Experiment I: With metabolic activation: 1.25, 2.5, or 5 mg/mL; without metabolic activation: 1.25, 2.5, or 5 mg/mL Experiment II: without metabolic activation: 0.63, 1.25, 2.5, or 5 mg/mL Serum free cell culture medium	Chromosome aberration assay in accordance with OECD TG 487 with and without metabolic activation. Negative control: solvent (serum free cell culture medium); Positive control: CPA, MMC, colchicine	Human peripheral lymphocytes	Not genotoxic or cytotoxic	6
Ascophyllum Nodosum Extract (4.7%) in water	Not specified	4.7% Ascophyllum Nodosum Extract	An Ames test was performed using a trade name mixture containing 4.7% Ascophyllum nodosum extract in 94.5% water. The procedure was done in accordance to OECD TG 471.	Not specified	Not mutagenic or pro-mutagenic activity	70
Cystoseira Compressa Extract	n-Hexane, chloroform, and methanol	1, 2.5, or 5 mg/plate	Ames Assay with and without metabolic activation. Negative control: DMSO. Positive controls: BaP, 2-nitrofluorene, and sodium azide.	*S. typhimurium* (strains TA 98 and TA 100)	Not mutagenic	62
Ecklonia Cava Extract	Enzymatic extraction	911 - 3500 µg/plate; distilled water	Ames assay, with and without metabolic activation. OECD TG 471	*S. typhimurium* (strains TA 98, TA 100, TA 1535, and TA 1537) and *E. coli* (WP2uvrA)	Not genotoxic	92
Ecklonia Cava Extract	Alcohol	Up to 5000 µg/plate; vehicle not specified	Ames assay, with and without metabolic activation	*S. typhimurium* (strains TA 98, TA 100, TA 1535, and TA 1537) and *E. coli* (WP2uvrA(pKM101))	Not genotoxic or cytotoxic	9
Ecklonia Cava Extract	Alcohol	Up to 290 µg/mL	Chromosome aberration test, with and without metabolic activation	CHL cells	Not genotoxic	9
Ecklonia Cava Extract	Enzymatic extraction	87.5 – 350 µg/plate; distilled water	Chromosome aberration test, with and without metabolic activation. OECD TG 473	CHL cells	Not genotoxic	92
Fucus Spiralis Extract (12%), tetraselmis chui extract (8%), water (80%)	Not specified	0.06 – 5 µL/plate	Ames assay, OECD TG 471; with and without metabolic activation	Not specified.	Non-mutagenic; Non-promutagenic	99
Fucus Vesiculosus Extract	Aqueous	0, 0.25, 0.5, or 1 mg/mL; cell medium	Chromosome aberration assay OECD TG 487	Human peripheral lymphocytes	Frequency of chromosome aberrations, mitotic index and extent of DNA damage in cells treated with extract were similar to controls at all concentrations.	100
Fucus Vesiculosus Extract	Aqueous	0, 0.25, 0.5, or 1 mg/mL; cell medium	Comet assay	Human peripheral lymphocytes	Extent of DNA damage in cells treated with extract was similar to controls at all concentrations.	100
Halidrys Siliquosa Extract (48%) in water (52%)	Water	0.06 µL – 5 µL/plate	Ames assay; OECD TG 471; with and without metabolic activation	*S. typhimurium* (strains TA 98, TA 100, TA 102, TA 1535)	Non-mutagenic; Non-promutagenic	65

Table 29. Genotoxicity studies

Ingredient/Test Article	Extraction Solvent/ Method	Concentration/ Vehicle	Procedure	Test System	Results	Reference
Laminaria digitata	Not specified	Not specified	Ames assay, with and without metabolic activation	*S. typhimurium*	No evidence of mutagenicity	101
Laminaria Saccharina Extract	NR	50, 150, 500, 1500 and 5000 µg/plate; sea water and methylpropandiol	Ames test with and without metabolic activation	*S. typhimurium* (TA 1535, TA 1537, TA 102, TA98, and TA 100)	Non-mutagenic	102
Macrocystis Pyrifera (Kelp) Extract	Water	1 mL extract in 10 mL 0.9% sodium chloride (concentration of extract was approximately 4%)	Ames test with and without metabolic activation	*S. typhimurium* (TA 98, TA 100, TA 1535, TA 1537, TA1538)	Non-mutagenic	103
Trade name mixture containing 24% Undaria Pinnatifida Cell Culture Extract	Aqueous	1.5, 5, 15, 50, 150, 500, 1500, and 5000 µg/plate	Bacterial reverse mutation assay performed with and without metabolic activation; OECD TG 471	*S. typhimurium* (strains TA 98, TA 100, TA 1537, TA 1535) and tryptophan-dependent *E. coli* (strain WPRuvrA)	Non-mutagenic	104
Cystoseira Amentacea/ Caespitosa/ Brachycarpa Extract (48%), Water (52%)	Water	0.01, 0.1, 1, and 10%	A chemiluminescent 3D Assay was performed by using plasmid DNA adsorbed on sensitized microplates as the substrate	NR	No direct genotoxicity.	105
			In Vivo			
Ecklonia Cava Extract	Alcohol	0 or 2000 mg/kg	Micronucleus assay. Test substance administered via oral gavage. Bone marrow (2,000 erythrocytes) was checked for frequency of micronuclei, after 24, 48, and 72 h.	Male Crlj:CD1(ICR) mice (n = 3)	There was no increase in frequency of micronuclei in any of the time points.	9
Ecklonia Cava Extract	Alcohol	0, 500, 1000, or 2000 mg/kg	Micronucleus assay. Test substance administered via oral gavage. Bone marrow (2,000 erythrocytes) was checked for the frequency of micronuclei, after 24 h.	Male Crlj:CD1(ICR) mice (n = 5)	There was no increase in frequency of micronuclei polychromatic erythrocytes (PCE)/(PCE + normochromatic erythrocytes (NCE)) ratio was not significantly different between treatment groups and control groups. No evidence of genotoxicity.	9
Ecklonia Cava Extract	Enzymatic extraction	1000, 2000, or 3000 mg/kg; distilled water	Mouse micronucleus assay. The number of mice used in the study was not provided. Administered by gavage. Saline and MMC were the controls. OECD TG 474	Male ICR mice	There were no mortalities or abnormal clinical signs in any group. There were no increases in structural or numerical chromosomal aberrations at any dose compared to the negative control.	92

BaP = benzo(a)pyrene; CHL = Chinese hamster lung; CHO = Chinese hamster ovary; CPA = cyclophosphamide; HCl = hydrochloric acid; MMC = mitomycin C; MNPCE = micronucleated polychromatic erythrocyte; NCE = normochromatic erythrocyte; NR = Not Reported; PBS = phosphate-buffered saline; PCE = polychromatic erythrocytes

Table 30. Tumor promotion studies

Test Article	Extraction/solvent/ method	Dose/Exposure Route	Species (n)	Tumor Type	Carcinogenicity Model	Results	Reference
				Dermal			
Undaria Pinnatifida Extract	Dichloromethane extract	1 mg	Female ICR mice (n not specified)	Skin	- Initiation: a single dermal dose of DMBA (50 µg) - 1 week later, mice were dermally treated twice per week with TPA (1 µg) or Undaria Pinnatifida Extract (1 mg) 1 h prior to treatment with TPA for 15 weeks	TPA: tumors > 1 mm were observed after week 8; average number of tumors was 3.7. Undaria Pinnatifida Extract and TPA: mice did not show 1-mm tumors until week 14 (< 5%); average number of tumors was 0.2.	106
				Oral			
Hizikia Fusiforme Extract	95% Ethanol aq.	0, 2%, or 6% in feed	Male F344 rats (10, control, 8)	Colorectal	- Group 1 – standard diet - Group 2 – injected with AOM (15 mg/1 mL/kg once a week for 2 weeks) and standard diet - Group 3 – Injected with AOM and diet with 2% Hizikia Fusiforme Extract - Group 4 – Injected with AOM and diet with 6% Hizikia Fusiforme Extract - After 8 weeks, the rats were killed and necropsied.	- Body weights were similar among groups at 11 weeks. - No tumors were found in the negative control group and 58 tumors were found in the positive control group. Treatment groups had reduced number of tumors (21 each). - Immuno-histochemistry analysis of PCNA expression, a marker of tumor cell proliferation and apoptosis, was lower in treatment groups than in treated control group.	107
Saccharina Angustata Extract (inference from *Saccharina angustata* powder)	Dried and milled	0 or 5% in feed	Female Sprague-Dawley rats (54)	Mammary	- After 50 days on respective diets, 4 rats in each group were killed and examined for abnormalities. None were found. - At 55 days treatment groups were administered DMBA by gavage after fasting. - Rats were palpated weekly for tumors. - The rats were killed at 181 - 188 days after DMBA administration and necropsied.	- Weight gains were similar among groups. - First tumors in the control group appeared at 11.0 weeks and 19.8 in the treatment group. - 41 of 54 rats (76%) in control group and 34 of 54 rats (63%) in the treatment group had 1 or more adenocarcinomas at necropsy. - During treatment, 13 rats (8 control and 5 experimental) were euthanized between 74 and 170 days post- DMBA. 10 of these rats had developed large (~ 4 cm in diameter) mammary tumors, 2 developed malignant lymphomas, and 1 developed a large necrotic ear gland tumor (Zymbal's gland carcinoma). There were no other deaths. - 12 tumor-free rats (6 from each group) were found to have small nonpalpable mammary masses; 11 of these were found to be adenocarcinomas and 1 to be an adenoma. 93% of all tumors found in the mammary gland region at necropsywere adenocarcinomas; 5 tumors, which were mostly fibroadenoma but which had focal proliferations of malignant epithelial cells. Other tumors consisted of 7 fibroadenomas, 5 adenomas, 3 epidermal inclusion cysts, and 1 adenocarcinoma of sebaceous glands.	108

Table 30. Tumor promotion studies

Test Article	Extraction/solvent/ method	Dose/Exposure Route	Species (n)	Tumor Type	Carcinogenicity Model	Results	Reference
Sargassum Pallidum Extract	Aqueous. Boiled under reflux and filtered.	400, 600 or 800 mg/kg/d	Male Wistar rats (10)	Gastric	- Group 1 – distilled water - Group 2 – 800 mg/kg/d Sargassum Pallidum Extract - Group 3 - 6 – MNNG (25 mg/mL) in drinking for 25 weeks; then 0, 400, 600, or 800 mg/kg Sargassum Pallidum Extract for 8 weeks - All rats were killed at 33 weeks, blood analyzed, and stomachs examined.	- There were no mortalities. - Compared to group 1 (control), Sargassum Pallidum Extract increased serum IL-2, IL-4, and IL-10 levels in group 2; serum IL-2, IL-4, and IL-10 levels in group 3 were decreased. - Compared to group 1, Sargassum Pallidum Extract decreased serum IL-6, IL-1β, and TNF-α levels in group 2; serum IL-6, IL-1β, and TNF-α levels in group 3 were increased. - Compared with group 3, Sargassum Pallidum Extract dose-dependently decreased serum IL-6, IL-1β, and TNF-α levels in groups 4, 5, and 6. - Concentration of serum and gastric mucosa MDA decreased in a dose-dependent manner in groups 4, 5, and 6. - Concentration of serum and gastric mucosa GSH and antioxidant enzyme activities increased in a dose-dependent manner in groups 4, 5, and 6. - Sargassum Pallidum Extract could decrease inflammatory response and improve immunity function partly through stimulating inflammatory cytokines (IL-2, IL-4, IL-10) production and inhibiting pro-inflammatory cytokines production.	[109]
Undaria Pinnatifida Powder	Not specified	0, 1.0% or 5.0% in feed	Female Sprague-Dawley (SD) rats (11)	Mammary	- Initiation: a single dose of DMBA (20 mg) by gastric intubation - Once tumors reached 1 cm, rats were divided between 3 treatment groups for 8 weeks - Rats were then killed and all mammary tumors were histologically examined and thyroid glands, ovaries, and adrenal glands were weighed. Blood samples collected for measurement of serum total iodine concentration and serum T4 levels.	No differences in body weight gains between groups. Tumors in control group increased by more than 450%; tumor growth was suppressed in the 1% group and there was almost no change in tumor size in the 5% group. Mean combined weight of all mammary tumors of each rat in treatment groups was lower than that in the control group (~ 7 vs 20 g) at end of experiment. Weights of thyroid glands, ovaries, and adrenal glands did not differ among groups. Concentration of serum iodine was greater in treatment groups compared to controls. Serum iodine concentration had a positive relationship with concentration of Undaria Pinnatifida Powder in diet. Serum T4 levels showed no differences among groups. Test substance did not promote mammary tumors and suppressed tumor growth after a single dose of DMBA.	[98]
Undaria Pinnatifida Extract	Filtered aqueous extract of powdered stems and thick leaves	1.5 g in 1000 mL water	Female Sprague-Dawley (SD) rats (12)	Mammary	- Initiation: a single dose of DMBA (20 mg) by gastric intubation - 1 week later, treatment began for 32 weeks - Mammary tumors were removed and measured	- Body weight gains were similar in both groups - Incidence of tumors at end of experiment was 22% vs 100% (controls) - The number of tumors was an average of < 1 vs. ~ 7 (controls) - Total tumor diameters was < 250 vs > 5000 mm - Histologically, mammary tumors were cystic adenocarcinoma, and tumors in treatment group had a decreased density of epithelial cells and fibrosis.	[97]

AOM = azoxymethane; DMBA = 7,12-dimethylbenz(*a*)anthracene; GSH = glutathione; MDA = malondialdehyde; MNNG = *N*-methyl-*N*′-nitro-N-nitrosoguanidine; PCNA = proliferating cell nuclear antigen; T4 = thyroxin; TPA = 12-*O*-tetradecanoylphorbol-13-acetate

Table 31. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population	Procedure	Results	Reference
Irritation						
IN VITRO						
Laminaria Japonica, Nereocystis Leutkeana, and Macrocystis Pyrifera Extract	Trade name mixture containing Laminaria Japonica (7%), Nereocystis Leutkeana (7%), Macrocystis Pyrifera Extract (7%), and pentaerythrityl tetraethylhexanoate (79%)	100%; 30 µL (liquid) or 25 mg (solid)	3	Reconstructed human epidermal model; 3 tissues treated with test substance and incubated for 60 minutes	Non-irritating	114
Sargassum Filipendula Extract	Trade name mixture containing Sargassum Filipendula Extract (1.3%), water (81.78%), Sorbitol (14%), hypnea musciformis Extract (1.4%), gellidiela acerosa Extract (1.3%), methylparaben (0.2%), propylparaben (0.025%)	100%	3	30 µL (liquid) or 25 mg (solid) of the test substance was applied to 3 tissue inserts and incubated for 60 minutes; inserts were then washed, transferred to fresh media	Non-irritating	115
Undaria Pinnatifida Cell Culture Extract	Trade name mixture containing Undaria Pinnatifida Cell Culture Extract (24%) with water as solvent	30 µL (liquid); 25 mg (solid)	3 per test concentration	The test substance, either liquid or solid, was applied to reconstructed human epidermis and incubated for 60 minutes. These tissue inserts were then washed and cell viability was measured.	Non-irritating	113
Undaria Pinnatifida Extract	Trade name mixture containing Undaria Pinnatifida Extract (0.5-2%) in caprylic/capric triglycerides	100%; 10 µL	3	OECD TG 439; 3 replicates of human skin cell models were treated with the test substance for approximately 15 minutes; time of recovery was 42 hours ± 1 hour	Non-irritating	216
ANIMAL						
Ascophyllum Nodosum Extract	Ascophyllum Nodosum extract	0.5 mL (liquid); 0.5 g (solid)	NR	Dermal irritation assay performed according to OECD TG 404; application for 4 hours	Non-irritating	91
Ascophyllum Nodosum Extract	*Ascophyllum nodosum* extract	0.5 g; concentration not stated	3 male rabbits	A dermal irritation assay was performed according to OECD TG 404 guidelines. The test substance was administered in three patches on areas of 12-20 cm^2 to the shaved backs of the rabbits under semi-occlusion for 3 min (patch 1), 1 h (patch 2), and 4 h (patch 3). There were no signs of irritation after the removal of patch 1 from one rabbit; patch 2 was then applied to the same rabbit. There were no signs of irritation after patch 2 was removed; patch 3 was then applied to all three rabbits. The test site was examined at 1, 24, 48, and 72 hours after removal of the last patch.	Non-irritating	6
Laminaria Digitata Extract	Trade name mixture containing Laminaria Digitata Extract (≤ 10%), artemisia vulgaris extract (≤ 10%), phenoxyethanol (0.8%), and water	20%; 0.5 mL	6 New Zealand White rabbits	The test material was applied to an area of 6 cm^2, and covered with an occlusive patch for 24 hours. Animals were examined 24 and 72 hours after administration of test material.	Non-irritating	94
Laminaria Digitata Extract	Trade name mixture containing Laminaria Digitata Extract, water, and dipropylene glycol	0.5 g; concentration not stated	Rabbits (# not stated)	Dermal irritation assay; details not available	Non-irritating	49

Table 31. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population	Procedure	Results	Reference
Laminaria Digitata Extract	Trade name mixture containing Laminaria Digitata Extract, water, and sea salt	0.5 g; concentration not stated	Rabbits (# not stated)	Dermal irritation assay; details not available	Non-irritating	49
			HUMAN			
Alaria Esculenta Extract	Trade name mixture containing Alaria Esculenta Extract (<5%) and in caprylic/capric triglycerides	100%; 20 µL	10	24-hour patch test; occlusive patch; over a surface of 50 mm^2	Non-irritating	217
Ascophyllum Nodosum Extract	Trade name mixture containing 4.7% Ascophyllum Nodosum Extract in 94.5% water	NR	NR	A cutaneous irritation test was performed according to OECD TG 439. No additional details were provided.	Non-irritating	70
Ascophyllum Nodosum Extract	Trade name mixture containing 0.5 – 10% Ascophyllum Nodosum Extract in water	100%	10	24-hour patch test; occlusive patch	Non-irritating	125
Ascophyllum Nodosum Extract and Halopteris Scoparia Extract	Ascophyllum Nodosum Extract (40.5%), Halopteris Scoparia Extract (13.5%), and water	100%; 0.02 mL	11	48-hour patch test; occlusive patch	Non-irritating	218
Cystoseira Amentacea/Caespitosa/ Brachycarpa Extract	52% water; 48% Cystoseira Amentacea/Caespitosa/ Brachycarpa Extract	NR	11	0.02 mL of test substance applied to back under an occlusive patch for 48 hours	Non-irritating	105
Cystoseira Baccata Extract	Cystoseira Baccata Extract in water (0.5 %)	100%	10	24-hour patch test; occlusive dressing	Non-irritating	49
Cystoseira Baccata Extract	Cystoseira Baccata Extract in water (0.5 %)	100%	50	24-hour patch test; occlusive dressing	Non-irritating	49
Cystoseira Tamariscifolia Extract	Trade name mixture containing Cystoseira Tamariscifolia Extract (0.5 %) and caprylic/capric triglycerides	100%	10	24-hour patch test; occlusive patch	Non-irritating	49
Cystoseira Tamariscifolia Extract	Cystoseira Tamariscifolia Extract (0.5 – 10%), glycerin, and water	20%	11	48-hour patch test; occlusive patch	Non-irritating	125
Dictyopteris Polypodioides Extract	Dictyopteris Polypodioides Extract (0.5 – 10%), water, and glycerin	100%	10	48-hour patch test; occlusive patch	Non-irritating	125
Dictyopteris Polypodioides Extract	Dictyopteris Polypodioides Extract (0.5 – 10%) and water	100%	10	48-hour patch test; occlusive patch	Non-irritating	125
Dictyopteris Polypodioides Extract	Dictyopteris Polypodioides Extract (0.5 – 10%) and caprylic/capric triglyceride	100%	10	48-hour patch test; occlusive patch	Non-irritating	125
Fucus Serratus Extract	Fucus Serratus Extract (44%) and water (56%)	5%; 0.02 mL	10	48-hour patch test; occlusive dressing	Non-irritating	219
Fucus Spiralis Extract	Trade name mixture consisting of Fucus Spiralis Extract (1 - 3%) in butylene glycol and water	100%; 20 µL	12	24-hour patch test; occlusive patch; application over an area of 50 mm^2	Non-irritating	220
Fucus Spiralis Extract	Trade name mixture consisting of Fucus Spiralis Extract (< 5%) in caprylic/capric triglycerides	100%; 20 µL	10	Test substance applied to an area of 50 mm^2 under an occlusive patch for 30 minutes and 24 hours	Slightly irritating at the 30 minute reading and non-irritating at the 24 hour reading	116

Table 31. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population	Procedure	Results	Reference
Fucus Spiralis Extract	Fucus Spiralis Extract (12%), tetraselmis chui extract (8%), water (80%)	10%; 0.02 mL	14	48-hour patch test; occlusive dressing	Non-irritating	221
Fucus Vesiculosus Extract	Fucus Vesiculosus Extract (0.5 – 10%), water, and dipropylene glycol	100%	10	24-hour patch test; occlusive dressing	Non-irritating	125
Fucus Vesiculosus Extract	Trade name mixture consisting of Fucus Vesiculosus Extract (5%) and caprylic/capric triglycerides (95%)	100%; 0.02 mL	10	24-hour patch test; occlusive dressing; application over an area of 50 mm^2	Non-irritating	116
Halidrys Siliquosa Extract	Halidrys Siliquosa Extract (52%) in water (48%)	5%; 0.02 mL	13	Test substance was diluted to 5% and applied to the back under an occlusive patch for 48 hours	Non-irritating	65
Halopteris Scoparia Extract	Halopteris Scoparia Extract (0.5 – 10%), water, and dipropylene glycol	100%	11	24-hour patch test; occlusive patch	Non-irritating	125
Himanthalia Elongata Extract	Trade name mixture containing Himanthalia Elongata Extract (0.5 %), water, and dipropylene glycol	100%	10	24-hour patch test; occlusive patch	Non-irritating	49
Himanthalia Elongata Extract and Undaria Pinnatifida Extract	Himanthalia Elongata Extract (20%), Undaria Pinnatifida Extract (37%), and water (43%)	NR	10	Test substance (0.02 mL) applied to the back under an occlusive patch for 48 hours	Very Slightly Irritating (average irritant score of 0.10)	64
Himanthalia Elongata Extract, Fucus Vesiculosus Extract, saccharomyces cerevisiae extract	Himanthalia Elongata Extract (62%), Fucus Vesiculosus Extract (1.4%), saccharomyces cerevisiae extract (0.1%), and water (36.5%)	10%; 160 µL	10 females	Test substance was applied to the back under a semi-occlusive patch for 48 h ± 4 h.	Non-irritating	222
Laminaria Digitata Extract	Laminaria Digitata Extract and water	0.5 %	10	24-hour patch test; occlusive patch	Non-irritating	49
Laminaria Digitata Extract	Trade name mixture containing Laminaria Digitata Extract (<5%) in caprylic/capric triglycerides	100%; 20 µL	12	24-hour patch test; test substance applied to an area of 50 mm^2; occlusive patch	Non-irritating	223
Laminaria Digitata Extract	Laminaria Digitata Extract (1.5-2.5%) in water and propylene glycol	100%; 20 µL	12	Test substance applied under an occlusive patch for 30 minutes or 24 hours over an area of 50 mm^2	Moderately irritating at the 30 minute reading; Slightly irritating at the 24 hour reading	117
Laminaria Hyperborea Extract	Trade name mixture containing Laminaria Hyperborea Extract (1-3%) in water	100%; 20 µL	10	24-hour patch test; occlusive patch	Non-irritating	224
Laminaria Japonica Extract	Skin cream containing a 50/50 aqueous propylene glycol extract of Laminaria japonica	10%; 20 mg	25	Patches were applied to the forearms of subjects using Finn chambers for up to 48 h and scored for irritation 6 h after patch removal.	Non-irritating	51
Laminaria Ochroleuca Extract	Trade name mixture consisting of Laminaria Ochroleuca Extract (<5%) in caprylic/capric triglycerides	2%; 20 µL	11	Single 24 hour application over an area of 50 mm^2; occlusive patch	Non-irritating	225

Table 31. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population	Procedure	Results	Reference
Laminaria Ochroleuca Extract	Cosmetic product containing Laminaria Ochroleuca Extract (5%), caprylic/capric triglyceride (94.75%), and tocopherols (0.25%)	10%; 0.02 mL	10	48-hour occlusive single patch test	Non-irritating	226
Lessonia Nigrescens Extract	Lessonia Nigrescens Extract (12%), water (44%), butylene glycol (44%)	5%; 0.02 mL	10	48-hour occlusive single patch test	Non-irritating	227
Laminaria Saccharina Extract	Trade name mixture containing Laminaria Saccharina Extract (1 -3%) in water and propylene glycol	8, 16, or 100%; 20 µL	10	Six occlusive patches (drenched with test substance) per concentration were applied to the arms over a 50 mm^2 surface for 24 and 48 hours	100% dose was slightly irritating; minimal erythema in 5/10 subjects; 16% dose was non-irritating; 8% dose was non-irritating	118
Macrocystis Pyrifera (Kelp) Extract	Macrocystis Pyrifera (Kelp) Extract (water extract)	4%	10	48-hour occlusive single patch test	Non-irritating	103
Pelvetia Canaliculata Extract	Trade name mixture containing Pelvetia Canaliculata Extract (1 - 3%) in butylene glycol and water	100%; 20 µL	12	Test substance was applied to skin under occlusive patches over a 50 mm^2 surface for 30 minutes and 24 hours	Non-irritating at the 30 minute reading; Slightly irritating at the 24 hour reading	228
Pelvetia Canaliculata Extract	Trade name mixture containing Pelvetia Canaliculata Extract (1 - 3%) in propylene glycol and water	100: 20 µL	12	Test substance was applied to skin under occlusive patches over a 50 mm^2 surface for 30 minutes and 24 hours	Moderately irritating at the 30 minute reading; slightly irritating at the 24 hour reading	119
Pelvetia Canaliculata Extract	Trade name mixture containing Pelvetia Canaliculata Extract (0.5 - 3%) in water	100%; 20 µL	11	24-hour patch test; occlusive patch	Non-irritating	136
Pelvetia Canaliculata Extract	Pelvetia Canaliculata Extract (44%) and water (56%)	100%; 0.02 mL	11	48-hour patch test; occlusive patch	Non-irritating	229
Pelvetia Canaliculata Extract and Laminaria Digitata Extract	Trade name mixture containing Pelvetia Canaliculata Extract and Laminaria Digitata Extract extracted in propylene glycol with panthenol (the amount of dry extract of both extracts combined is estimated to be 5.5-9.0%)	5, 10, and 100%; 20 µL	10	Test substance was applied to skin under occlusive patches over a 50 mm^2 surface for 24 and 48 hours	Mild irritation at the 100% concentration; Minimal irritation at the 10% concentration; No irritation at the 5% concentration	121
Phyllacantha Fibrosa Extract	Phyllacantha Fibrosa Extract (0.5 – 10%) in water	100%	10	24-hour patch test; occlusive patch	Non-irritating	125
Sargassum Glaucescens Extract	Trade name mixture containing 20% Sargassum Glaucescens Extract, 79% water, and 1% phenoxyethanol	10%	10	Test substance was applied under an occlusive patch for 48 hours	Non-irritating	166
Sargassum Muticum Extract	Sargassum Muticum Extract (46%) and water (54%)	100%; 0.02 mL	11	Test substance was applied under an occlusive patch for 48 hours	Non-irritating	230
Sphacelaria Scoparia Extract	Sphacelaria Scoparia Extract (0.5 %), water, and dipropylene glycol	100%; 15 mL	11	24-hour patch test; occlusive dressing	Non-irritating	49

Table 31. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population	Procedure	Results	Reference
Undaria Pinnatifida Extract	Trade name mixture containing Undaria Pinnatifida Extract (< 5%) in water and propylene glycol	100%; 20 µL	12	Test substance applied to the skin over an area of 50 mm^2 for either 30 minutes or 24 hours; occlusive patch	Moderately irritating after 30 minutes; Mildly irritating after 24 hours	120
Undaria Pinnatifida Extract	Trade name mixture containing Undaria Pinnatifida Extract (0.5%) in water and dipropylene glycol	NR	10	24-hour patch test; occlusive dressing	Non-irritating	49
Undaria Pinnatifida Extract	Undaria Pinnatifida Extract (0.5 – 10%) and caprylic/capric triglyceride	100%	10	24-hour patch test; occlusive dressing	Non-irritating	125
Sensitization						
IN VITRO						
Sargassum Filipendula Extract	Trade name mixture containing Sargassum Filipendula Extract (1.3%), water (81.78%), sorbitol (14%), hypnea musciformis extract (1.4%), gellidiela acerosa extract (1.3%), methylparaben (0.2%), propylparaben (0.025%)	0.98-2000 µM	2 per test concentration	ARE-Nrf2 Luciferase Test performed according to OECD TG 442D; immortalized adherent human keratinocyte cell line; 12 test concentrations ranging from 0.98 to 2000 µM were used	Non-sensitizing	231
Undaria Pinnatifida Cell Culture Extract	Trade name mixture containing Undaria Pinnatifida Cell Culture Extract (24%) with water as solvent	0.98 – 2000 µM	3 per test concentration	ARE-Nrf2 Luciferase Test performed according to OECD TG 442D; immortalized adherent human keratinocyte cell line; 12 test concentrations ranging from 0.98 to 2000 µM were used	Non-sensitizing	122
Undaria Pinnatifida Cell Culture Extract	Undaria Pinnatifida Cell Culture Extract (24%) with water as solvent in acetonitrile	5 mM or 25 mM	3 per test concentration	Direct Peptide Reactivity Assay (DPRA) performed according to OECD TG 442C; 1:10 ratio of Cysteine Peptide (0.5 mM) and test chemical (5 mM)) and 1:50 ratio of Lysine peptide (0.5 mM) and test chemical (25 mM)	Non-sensitizing	123
ANIMAL						
Ascophyllum Nodosum Extract	Ascophyllum Nodosum Extract	0.1 to 400 µL of 25% to 75% water solutions	20 test and 10 control guinea pigs	Magnusson and Kligman (guinea pig maximization test); OECD TG 406	Non-sensitizing	91
Cystoseira Amentacea/ Caespitosa/Brachycarpa Extract	Cream containing 0.0023% Cystoseira Amentacea/ Caespitosa/Brachycarpa Extract	100%	25	Maximization study. Product was applied under a semi-occlusive patch. No other details regarding this study were provided.	Non-sensitizing	124

Table 31. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population	Procedure	Results	Reference
			HUMAN			
Alaria Esculenta Extract	Trade name mixture consisting of Alaria Esculenta Extract (<5%) in caprylic/capric triglycerides – dried before extraction	100%; 25 µL	50	The sensitizing potential of the test substance was studied using a HRIPT. The test material was applied to the upper back under a patch. Occlusive conditions. During the induction phase, patches are applied 3 times per week for 3 weeks, for a total of 9 applications. If the test substance caused a moderate reaction (2-level), the application is moved to an adjacent area. If 3-level or 4-level reactions were noted, applications are discontinued. Two weeks after the final induction application, a challenge patch is applied to a previously untested site adjacent to the original patch site. Patches were removed and sites were scored 24 and 72 hours after application.	Non-irritating; Non-sensitizing	126
Alaria Esculenta Extract	Night cream containing 0.05% Alaria Esculenta Extract	0.2 g	105	A HRIPT was performed. Semi-occlusive conditions. The test material was applied to the 1 in^2 absorbent pad portion of a clear adhesive dressing.	Non-sensitizing	232
Alaria Esculenta Extract	Trade name mixture consisting of Alaria Esculenta Extract (0.5-2.5%) in butylene glycol and water	100%; 25 µL	50	The test substance was applied (under an occlusive patch) 3 times a week during the induction phase and once a week during challenge phase. The induction phase lasts for 3 weeks, followed by a latent phase which lasts for 2 weeks.	Non-irritating; Non-sensitizing	127
Ascophyllum Nodosum Extract	Ascophyllum Nodosum Extract (0.5 – 10%)	100%; 25 µL	50	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	125,233
Cystoseira Baccata Extract	Cystoseira Baccata Extract (0.5 – 10%) in water	100%; 25 mL	50	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	49,233
Cystoseira Tamariscifolia Extract	Cystoseira Tamariscifolia Extract (0.5 – 10%), glycerin, and water	20%; 25µL	105	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	125,233
Dictyopteris Polypodioides Extract	Dictyopteris Polypodioides Extract (0.5 – 10%), water, and glycerin	100%	50	Repeated epicutaneous applications. Occlusive conditions.	Non-irritating; Non-sensitizing	125
Dictyopteris Polypodioides Extract	Dictyopteris Polypodioides Extract (0.5 – 10%) and water	100%; 25 µL	50	Repeated epicutaneous applications. Occlusive conditions.	Non-irritating; Non-sensitizing	125,233
Dictyopteris Polypodioides Extract	Dictyopteris Polypodioides Extract (0.5 – 10%) , caprylic/capric triglyceride	100%; 25µL	50	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	125,233
Fucus Spiralis Extract	Trade name mixture consisting of Fucus Spiralis Extract (1-3%) in butylene glycol and water	100%; 200 µL	50	A HRIPT was performed. Occlusive conditions	Non-sensitizing	130
Fucus Spiralis Extract	Fucus Spiralis Extract (12%), tetraselmis chui extract (8%), and water (8%)	100%	105	A HRIPT was performed. No dosing details were provided.	Non-sensitizing	131
Fucus Vesiculosus Extract	Trade name mixture containing Fucus Vesiculosus Extract (0.1%)	10%; 0.2 mL	58	A HRIPT was performed. Semi-occlusive conditions.	Non-sensitizing	133
Fucus Vesiculosus Extract	Trade name mixture containing Fucus Vesiculosus Extract (0.1%)	100%; 0.2 mL	56	A HRIPT was performed. Semi-occlusive conditions.	Non-sensitizing	132
Fucus Vesiculosus Extract	Trade name mixture consisting of Fucus Vesiculosus Extract (5%) and caprylic/capric triglycerides (95%)	100%; 200 µL	52	A HRIPT was performed. Occlusive conditions.	Non-sensitizing	116

Table 31. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population	Procedure	Results	Reference
Halidrys Siliquosa Extract	Halidrys Siliquosa Extract (48%) and water (52%)	100%	107	A HRIPT was performed. Occlusive conditions.	Non-sensitizing	65
Halopteris Scoparia Extract	Halopteris Scoparia Extract (0.5 – 10%), water, dipropylene glycol	100%; 15 µL	50	Repeated epicutaneous applications. Occlusive conditions. 40 day test period.	Non-sensitizing	125,233
Himanthalia Elongata Extract	Cream containing 0.2% Himanthalia Elongata Extract	100%	102	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	124
Laminaria Digitata Extract	Laminaria Digitata Extract (<5%) in caprylic/capric triglycerides	100%; 20 µL	46	A HRIPT was performed. Occlusive conditions.	Non-sensitizing	134
Laminaria Digitata Extract	Trade name mixture containing Laminaria Digitata Extract (8-12%), urea (12-18%), synthetic glucosamine HCl (10-15%), saccharomyces cerevisiae extract (8-12%), and phenoxyethanol (0.8%)	10%; 0.2 mL (liquid) or 0.2 g (solid)	100	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	135
Laminaria Digitata Extract	Trade name mixture containing Laminaria Digitata Extract (≤ 10%), artemisia vulgaris extract (≤ 10%), phenoxyethanol (0.8%), and water	20%; 0.2 mL (liquid) or 0.2 g (solid)	100	A HRIPT was performed. Occlusive conditions/	Non-irritating; Non-sensitizing	94
Laminaria Saccharina Extract	Trade name mixture containing Laminaria Saccharina Extract (1-3%) in water and propylene glycol	20%; 25 µL	50	The test substance was applied (under an occlusive patch) 3 times a week during the induction phase and once a week during challenge phase. The induction phase lasts for 3 weeks, followed by a latent phase which lasts for 2 weeks.	Non-irritating; Non-sensitizing	129
Macrocystis Pyrifera (Kelp) Extract	Macrocystis Pyrifera (Kelp) Extract (water extract)	4%	53	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	103
Pelvetia Canaliculata Extract	Trade name mixture containing Pelvetia Canaliculata Extract (0.5-3%) in water	100%; 200 µL	55	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	136
Pelvetia Canaliculata Extract	Pelvetia Canaliculata Extract (44%) and water (56%)	100%	111	A HRIPT was performed. Occlusive conditions.	Non-sensitizing	137
Phyllacantha Fibrosa Extract	Phyllacantha Fibrosa Extract (0.5 – 10%) in water	100%; 25 µL	50	Repeated cutaneous applications. Occlusive conditions.	Non-sensitizing	125,233
Sargassum Filipendula Extract	Face cream containing 1.2% Sargassum Filipendula Extract	0.2 g	206	A HRIPT was performed. A 4 cm^2 occlusive patch was used.	Non-sensitizing	138
Sargassum Muticum Extract	Eye cream containing 0.076% Sargassum Muticum Extract	0.2 g	103	A HRIPT was performed. The test material was applied to the 1 $inch^2$ absorbent pad portion of a clear adhesive dressing.	Non-sensitizing	139
Sargassum Muticum Extract	Skin care product containing 0.076% Sargassum Muticum Extract	0.2 g	104	A HRIPT was performed. The test material was applied to the 1 $inch^2$ absorbent pad portion of a clear adhesive dressing.	Non-sensitizing	140
Sphacelaria Scoparia Extract	Sphacelaria Scoparia Extract, water, and dipropylene glycol (test concentration unknown)	100%	50	Repeated epicutaneous applications. Occlusive conditions.	Hypoallergenic	49
Undaria Pinnatifida Extract	Trade name mixture containing Undaria Pinnatifida Extract (<5%) in caprylic/capric triglycerides	100%; 50 µL	100	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	141
Undaria Pinnatifida Extract	Undaria Pinnatifida Extract in caprylic/capric triglycerides	100%	100	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	125

Table 31. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population	Procedure	Results	Reference
Undaria Pinnatifida Extract	Undaria Pinnatifida Extract (0.5 – 10%) in glycerin and water	100%	100	A HRIPT was performed. Occlusive conditions.	Non-irritating; Non-sensitizing	125

ARE = Antioxidant Response Elements; HRIPT = Human Repeat Insult Patch Test; Nrf2 = Nuclear factor-erythroid 2-related factor; NR = Not Reported

Table 32. Ocular Irritation Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IN VITRO					
Trade name mixture containing Ascophyllum Nodosum Extract (4.7%) in water (94.5%)	NR	NR	HET-CAM test	Non-irritating	70
Ascophyllum Nodosum Extract (40.5%), Halopteris Scoparia Extract (13.5%), and water	100%	NR	HET-CAM test; incubation for 11 days	Non-irritating	234
Cystoseira Amentacea/Caespitosa/Brachycarpa Extract (48%), water (52%)	100%	NR	HET-CAM test; incubation for 11 days	Slightly irritating	105
Fucus Serratus Extract (44%) and water (56%)	5%	NR	HET-CAM test; incubation for 11 days	Slightly irritating	235
Halidrys Siliquosa Extract (48%) in water (52%)	5%	NR	HET-CAM test; incubation for 11 days	Slightly irritating	65
Himanthalia Elongata Extract (20%), Undaria Pinnatifida Extract (37%), water (43%)	10%	NR	HET-CAM test	Slightly irritating	64
Himanthalia Elongata Extract (62%), Fucus Vesiculosus Extract (1.4%), saccharomyces cerevisiae extract (0.1%), water (36.5%)	10%	4	HET-CAM test	Slightly irritating	236
Trade name mixture containing Laminaria Digitata Extract (8-12%), urea (12-18%), synthetic glucosamine HCl (10-15%), saccharomyces cerevisiae extract (8-12%), and phenoxyethanol (0.8%)	5%; 0.3 mL (liquid) or 0.3 g (solid)	4	HET-CAM test; incubation for 10 days	Non-irritating	237
Laminaria Japonica Extract (7%), Nereocystis Leutkeana Extract (7%), Macrocystis Pyrifera Extract (7%), and pentaerythrityl tetraethylhexanoate	50 µL (liquid) or 50 mg (solid)	NR	Test substance was applied to reconstructed cornea epithelium; after application, epithelia was incubated for 30 (liquid) or 90 (solid) minutes	Non-irritating	114
Laminaria Ochroleuca Extract (5%), caprylic/capric triglyceride (94.75%), tocopherols (0.25%)	10%	NR	HET-CAM test	Moderately irritating	142
Lessonia Nigrescens Extract (12%), water (44%), butylene glycol (44%)	10%	NR	HET-CAM test	Non-irritating	238
Macrocystis Pyrifera (Kelp) Extract	4%	NR	HET-CAM test	Mildly irritating	103

Table 32. Ocular Irritation Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Trade name mixture containing Sargassum Filipendula Extract (1.3%), water (81.78%), sorbitol (14%), hypnea musciformis extract (1.4%), gellidiela acerosa extract (1.3%), methylparaben (0.2%), propylparaben (0.025%)	100%, 50 µL (liquid) or 50 mg (solid)	2	Test substance was applied to reconstructed cornea epithelium and allowed to incubate for 90 minutes	Non-irritating	115
Sargassum Muticum Extract (46%) and water (54%)	100%	NR	HET-CAM test; incubation for 11 days	Slightly-irritating	239
Undaria Pinatifida Cell Culture Extract (24%) in water	50 µL (liquid) or 50 mg (solid)	NR	Test substance was applied to reconstructed cornea epithelium; after application, epithelia was incubated for 30 (liquid) or 90 (solid) minutes	Non-irritating	113
			ANIMAL		
Ascophyllum Nodosum Extract	100 mg	3	OECD TG 405; New Zealand White rabbits; test substance was instilled into one eye of each rabbit and rinsed after 1 hour; examination occurred 1, 24, 48, and 72 hours, and 7 days after administration	The maximum irritation score was 6.7 out of 8 at 1 h post-instillation; the score decreased to 0 by day 7, which indicated that the induced changes were reversible, and thus, the effects of the test substance were classified as 'irritation' and not as 'corrosion.' The test substance was rated as a mild ocular irritant.	6
Ascophyllum Nodosum Extract	NR	NR	OECD TG 405; no other details were provided for this study	Slightly irritating	91
Trade name mixture containing Laminaria Digitata Extract (≤ 10%), artemisia vulgaris extract (≤ 10%), phenoxyethanol (0.8%), and water	20%; 0.1 mL	6	The test material was placed on the everted lower lid of one eye of each New Zealand White rabbit. The upper and lower lids were then gently held together for one second before releasing. Lesions were evaluated at 24 and 72 hours post instillation.	Non-irritating	94
			HUMAN		
Eye cream containing 0.076% Sargassum Muticum Extract	100%	31	Test substance was applied to the eye contour of 31 subjects. Half of the subjects were soft-contact lens wearers. Exam was performed 4 weeks after usage.	Non-irritating	144

NR = Not Reported

Table 33. Case Reports of brown algae

Ingredient/substance (dose, if known)	Details	Reference
Fucus vesiculosus supplement (1200 mg 3 times per day)	18-year-old female presented with polyuria, polydipsia, extreme faintness, and a general poor condition. She had been on a hypocaloric diet for 3 months and taking Fucus vesiculosus supplements. Renal biopsy showed widespread tubular degeneration, and diffuse lymphomonocytic infiltrate; the glomeruli displayed scarce and focal mesangial proliferation, but the basal membrane appeared intact. The supplement was tested for heavy metals: arsenic, 21.3 mg/kg; cadmium, 0.3 ppm; mercury, 0.06 ppm; and chrome, 4 ppm. The patient recovered within 1 year.	240
Kelp tablets	54-year-old female developed thrombocytopenia with mucocutaneous bleeding after ingesting kelp tablets (that contained 1.3 µg/g arsenic) twice daily for 6 weeks. Marrow aspirate demonstrated normal megakaryocytes and dyserythropoiesis. After discontinuation of the supplements and treatment with steroids and azathioprine, her platelet count recovered after 3 months.	145
Kelp supplements	A 54-year-old woman presented with a 2-year history of worsening alopecia and memory loss. She also had a rash, increasing fatigue, nausea, and vomiting to the point of disablement. She took daily kelp supplements. A urine sample showed an arsenic level of 83.6 µg/g creatinine (normal < 50 µg/g creatinine). A sample from her kelp supplements contained 8.5 mg/kg arsenic. Within weeks of discontinuing the supplements, her symptoms resolved and arsenic blood and urine levels were undetectable.	146

Table 34. Oral clinical trials

Test Article	Extraction/ Solvent Method or Characterization	Study group	Study Details	Results	Reference
Ascophyllum Nodosum Powder (0.5 g/d)	Powdered plant	Healthy female subjects (n = 42)	After a 4-day period of keeping a food diary, subjects were administered capsules containing extract or potassium iodide daily for 14 days, then repeated 4-day food diary. All-day urine sample was collected on fourth day of run-in period and last day of treatment period (day 19) and fasted blood samples were collected on fourth day of run-in period and on day after treatment period (day 20).	There was an increase in urinary iodine concentrations (median 140 mg/l vs78 mg/l) in the treatment group. TSH increased slightly but within normal range 2 subjects. Increase in TSH concentrations may be associated with iodine-induced hypothyroidism, especially in those subjects with low iodine stores, although no change in the concentrations of thyroid hormones was observed. There were no adverse events reported during this experiment.	147
Ecklonia Cava Extract (400 mg/d)	Alcohol	Subjects with hyper-cholesterolaemia (n = 52)	Uncontrolled, open-label, single-arm study for 12 weeks	Hematological, clinical chemistry, and urinalysis did not reveal any adverse effects. There was one instance (2.2%) each of nausea, dyspepsia, diarrhea, and alopecia reported.	9,148
Ecklonia Cava Extract (0, 72, or 144 mg/d)	Phlorotannin-rich	Overweight subjects (n = 32 or 33)	Randomized, double-blind, three-arm, parallel trial for 12 weeks	Hematological and clinical chemistry did not reveal any adverse effects. Only high-dose group showed significant decreases in serum glucose and systolic blood pressure. No adverse signs were observed during the trial.	9
Ecklonia Cava Extract (0 or 400 mg/d)	Alcohol	Overweight subjects (n = 40)	Randomized, double-blind, and placebo-controlled trial for 12 weeks. Administered as 200 mg twice per day in capsules	There were no adverse events reported that were related to the test substance.	24
Undaria Pinnatifida Powder (desalinated; 5040 mg/d)	Powdered	Hypertensive subjects (n = 18)	Subjects were gender and age matched to control group. Capsules (420 mg/capsule; 4 capsules/dose) 3 times/d with meals. Examined for body weight, BP, and blood chemistry parameters prior to experiment, at 4 weeks, and at 8 weeks. 1 subject in treatment group left study for personal reasons, so final number of paired subjects was 18, (some of her data (e.g., adverse effects) were used).	Compliance was not consistent; 6 subjects followed protocol; 1 ingested 9 capsules/d, 2 ingested 8 capsules/d, 6 ingested 6 capsules/d, and 3 ingested 3capsules/d. Average intake was estimated to be 7.9 capsules or 3.3 g/d. Average SBP in treatment group decreased by 13 mmHg from the baseline after 4 weeks, and was reduced by 8 mmHg below baseline after 8 weeks. Average DBP decreased by 9 mmHg from baseline after 4 weeks and by 8 mmHg after 8 weeks. There were no significant changes in either SBP or DBP in control group. However, the differences in reductions in SBP and DBP were significant between the treatment group and control group. Hypercholesterolemia subjects in treatment group had decreased total cholesterol by 8% after 4 weeks; no changes were observed in subjects with normal cholesterol levels. Adverse effects included 2 cases of indigestion and 1 case of diarrhea, all of which resolved quickly without treatment.	67

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; TSH = thyroid-stimulating hormone

Table 35. Change in menstrual cycle with the oral administration of Fucus Vesiculosus Powder[149]

	Menstrual cycle length			Days of Menstruation		
Subject	Baseline	Low-Dose	High-Dose	Baseline	Low-Dose	High-Dose
1	16.3 ± 0.6 days	26.0 ± 1.4 days	31.2 ± 1.1 days	9.3 ± 0.6 days	6.3 ± 1.8 days	4.5 ± 0.7 days
2	23.0 ± 1.7 days	28.5 ± 0.7 days	-	8.0 ± 1.0 days	5.3 ± 2.5 days	-
3	27.3 ± 0.6 days	31.5 ± 0.7 days	36.0 ± 2.8 days	6.3 ± 1.5 days	5.8 ± 0.4 days	3.5 ± 0.7 days

- = no data

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2019 FDA VCRP Data

1. **Agarum Cribrosum Extract***

12C - Face and Neck (exc shave)	1

2. **Alaria Esculenta Extract***

03C - Eye Shadow	8
03D - Eye Lotion	2
03G - Other Eye Makeup Preparations	2
05I - Other Hair Preparations	1
07A - Blushers (all types)	6
07B - Face Powders	5
07C - Foundations	1
07E - Lipstick	3
07I - Other Makeup Preparations	1
12C - Face and Neck (exc shave)	4
12D - Body and Hand (exc shave)	2
12F - Moisturizing	6

3. **Ascophyllum Nodosum**

NONE

4. **Ascophyllum Nodosum Extract***

03D - Eye Lotion	8
03G - Other Eye Makeup Preparations	9
05A - Hair Conditioner	6
05F - Shampoos (non-coloring)	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	4
07B - Face Powders	1
07F - Makeup Bases	2
08B - Cuticle Softeners	1
08G - Other Manicuring Preparations	2
10A - Bath Soaps and Detergents	6
11A - Aftershave Lotion	1
11E - Shaving Cream	1
12A - Cleansing	5
12C - Face and Neck (exc shave)	58
12D - Body and Hand (exc shave)	4
12F - Moisturizing	16
12G - Night	2

12H - Paste Masks (mud packs)	8
12I - Skin Fresheners	1
12J - Other Skin Care Preps	2

5. Ascophyllum Nodosum Powder*

02A - Bath Oils, Tablets, and Salts	1
12A - Cleansing	1
12F - Moisturizing	2
12J - Other Skin Care Preps	1

6. Cladosiphon Novae-Caledonia Extract

NONE

7. Cladosiphon Okamuranus Extract*

03G - Other Eye Makeup Preparations	1
07C - Foundations	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	3
12F - Moisturizing	2
12G - Night	2

8. Cystoseira Amentacea/Caespitosa/Branchycarpa Extract

12A - Cleansing	1

^^Cystoseira Foeniculacea/brachycarpa extract

9. Cystoseira Baccata Extract

None

10. Cystoseira Balearica Extract

None

11. Cystoseira Caespitosa Extract

None

12. Cystoseira Compressa Extract

None

13. Cystoseira Compressa Powder

None

14. Cystoseira Tamariscifolia Extract

None

15. Dictyopteris Polypodioides Extract*

12C - Face and Neck (exc shave)	1
12F - Moisturizing	4
12H - Paste Masks (mud packs)	1

16. Dictyota Coriacea Extract

None

17. Durvillaea Antarctica Extract*

None

18. Ecklonia Cava Extract

01B - Baby Lotions, Oils, Powders, and Creams	1
03D - Eye Lotion	1
05F - Shampoos (non-coloring)	1
12C - Face and Neck (exc shave)	8
12F - Moisturizing	5
12H - Paste Masks (mud packs)	2

19. Ecklonia Cava Water

None

20. Ecklonia Kurome Extract

None

21. Ecklonia Kurome Powder

None

22. Ecklonia/Laminaria Extract

None

23. Ecklonia Maxima Extract

None

24. Ecklonia Maxima Powder

None

25. Ecklonia Radiata Extract*

05A - Hair Conditioner	36
05B - Hair Spray (aerosol fixatives)	7
05F - Shampoos (non-coloring)	30
05G - Tonics, Dressings, and Other Hair Grooming Aids	6
05H - Wave Sets	3

26. Eisenia Arborea Extract

None

27. Fucus Serratus Extract*

03D - Eye Lotion	1
12C - Face and Neck (exc shave)	4
12F - Moisturizing	2
12G - Night	1

28. Fucus Spiralis Extract

None

29. Fucus Vesiculosus*

None

30. Fucus Vesiculosus Extract*

02A - Bath Oils, Tablets, and Salts	3
02B - Bubble Baths	2
02D - Other Bath Preparations	4
03D - Eye Lotion	2
03F - Mascara	2
03G - Other Eye Makeup Preparations	1
04E - Other Fragrance Preparation	3
05A - Hair Conditioner	10
05C - Hair Straighteners	2
05F - Shampoos (non-coloring)	9
05G - Tonics, Dressings, and Other Hair Grooming Aids	6
05I - Other Hair Preparations	2
07F - Makeup Bases	2
07I - Other Makeup Preparations	1
10A - Bath Soaps and Detergents	25
10E - Other Personal Cleanliness Products	5
11A - Aftershave Lotion	1
11E - Shaving Cream	1

11F - Shaving Soap	1
11G - Other Shaving Preparation Products	1
12A - Cleansing	12
12B - Depilatories	1
12C - Face and Neck (exc shave)	45
12D - Body and Hand (exc shave)	32
12E - Foot Powders and Sprays	1
12F - Moisturizing	44
12G - Night	1
12H - Paste Masks (mud packs)	23
12I - Skin Fresheners	4
12J - Other Skin Care Preps	19
13B - Indoor Tanning Preparations	25
13C - Other Suntan Preparations	1

31. Fucus Vesiculosus Powder*

02A - Bath Oils, Tablets, and Salts	1
12C - Face and Neck (exc shave)	1
12H - Paste Masks (mud packs)	2

32. Halidrys Siliquosa Extract

None

33. Halopteris Scoparia Extract

None

34. Himanthalia Elongata Extract*

03G - Other Eye Makeup Preparations	1
05A - Hair Conditioner	2
05I - Other Hair Preparations	1
12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	5
12F - Moisturizing	2
12H - Paste Masks (mud packs)	1

35. Himanthalia Elongata Powder

None

36. Hizikia Fusiforme Extract

None

37. Hizikia Fusiformis Water

None

38. Hizikia Fusiformis Callus Culture Extract

None

39. Hydrolyzed Ecklonia Cava Extract

None

40. Hydrolyzed Fucus Vesiculosus Extract

None

41. Hydrolyzed Fucus Vesiculosus Protein

None

42. Laminaria Cloustoni Extract*

03D - Eye Lotion	1
07F - Makeup Bases	1
12A - Cleansing	3
12C - Face and Neck (exc shave)	4
12F - Moisturizing	3
12G - Night	1
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	1

43. Laminaria Diabolica Extract

None

44. Laminaria Digitata Extract*

02A - Bath Oils, Tablets, and Salts	2
02B - Bubble Baths	3
02D - Other Bath Preparations	2
03D - Eye Lotion	5
03E - Eye Makeup Remover	2
03F - Mascara	4
03G - Other Eye Makeup Preparations	9
04E - Other Fragrance Preparation	2
05A - Hair Conditioner	4
05B - Hair Spray (aerosol fixatives)	1

05F - Shampoos (non-coloring)	12
05G - Tonics, Dressings, and Other Hair Grooming Aids	17
05I - Other Hair Preparations	2
06H - Other Hair Coloring Preparation	1
07B - Face Powders	2
07C - Foundations	3
07E - Lipstick	1
07F - Makeup Bases	1
07I - Other Makeup Preparations	3
09A - Dentifrices	1
10A - Bath Soaps and Detergents	8
10C - Douches	1
10E - Other Personal Cleanliness Products	5
11A - Aftershave Lotion	4
12A - Cleansing	21
12C - Face and Neck (exc shave)	49
12D - Body and Hand (exc shave)	39
12F - Moisturizing	40
12G - Night	6
12H - Paste Masks (mud packs)	19
12I - Skin Fresheners	3
12J - Other Skin Care Preps	33
13A - Suntan Gels, Creams, and Liquids	4
13C - Other Suntan Preparations	1

45. Laminaria Digitata Powder*

02A - Bath Oils, Tablets, and Salts	1
02D - Other Bath Preparations	2
05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	2
10E - Other Personal Cleanliness Products	1
12C - Face and Neck (exc shave)	1
12H - Paste Masks (mud packs)	9
12J - Other Skin Care Preps	1

46. Laminaria Hyperborea Extract*

04E - Other Fragrance Preparation	2
05I - Other Hair Preparations	1
10A - Bath Soaps and Detergents	1
12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	1

12F - Moisturizing	7
12J - Other Skin Care Preps	1

47. Laminaria Japonica Extract*

01B - Baby Lotions, Oils, Powders, and Creams	2
03D - Eye Lotion	2
03F - Mascara	1
03G - Other Eye Makeup Preparations	1
05F - Shampoos (non-coloring)	2
07A - Blushers (all types)	2
07B - Face Powders	3
07C - Foundations	7
07E - Lipstick	1
07F - Makeup Bases	2
08G - Other Manicuring Preparations	2
10A - Bath Soaps and Detergents	3
10E - Other Personal Cleanliness Products	2
12A - Cleansing	3
12C - Face and Neck (exc shave)	38
12D - Body and Hand (exc shave)	2
12F - Moisturizing	12
12G - Night	2
12H - Paste Masks (mud packs)	7
12J - Other Skin Care Preps	4

48. Laminaria Japonica Powder

None

49. Lamniara Logissima Extract

None

50. Laminaria Ochroleuca Extract*

03C - Eye Shadow	2
03D - Eye Lotion	3
03E - Eye Makeup Remover	2
07B - Face Powders	3
07C - Foundations	2
07E - Lipstick	1
07I - Other Makeup Preparations	2
10E - Other Personal Cleanliness Products	2

12A - Cleansing	1
12C - Face and Neck (exc shave)	8
12D - Body and Hand (exc shave)	4
12F - Moisturizing	15
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	7
13B - Indoor Tanning Preparations	1

51. Laminaria Saccharina Extract*

05A - Hair Conditioner	4
05F - Shampoos (non-coloring)	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	4
07C - Foundations	9
07I - Other Makeup Preparations	2
10A - Bath Soaps and Detergents	2
10E - Other Personal Cleanliness Products	2
11A - Aftershave Lotion	4
11D - Preshave Lotions (all types)	1
11E - Shaving Cream	1
12A - Cleansing	26
12C - Face and Neck (exc shave)	20
12F - Moisturizing	35
12G - Night	1
12H - Paste Masks (mud packs)	7
12I - Skin Fresheners	2
12J - Other Skin Care Preps	12

52. LEssonia Nigrescens Extract*

None

53. Lessonia Nigrescens Powder

None

54. Macrocystis Pyrifera (Kelp)*

10A - Bath Soaps and Detergents	1
12F - Moisturizing	1

55. Macrocystis Pyrifera (Kelp) Extract*

01B - Baby Lotions, Oils, Powders, and Creams	1
02A - Bath Oils, Tablets, and Salts	3
02B - Bubble Baths	1

03D - Eye Lotion	1
03E - Eye Makeup Remover	1
03G - Other Eye Makeup Preparations	3
04E - Other Fragrance Preparation	7
05A - Hair Conditioner	10
05B - Hair Spray (aerosol fixatives)	3
05F - Shampoos (non-coloring)	12
05G - Tonics, Dressings, and Other Hair Grooming Aids	20
05H - Wave Sets	1
05I - Other Hair Preparations	10
06H - Other Hair Coloring Preparation	4
07A - Blushers (all types)	2
07B - Face Powders	2
07C - Foundations	3
07H - Makeup Fixatives	1
08A - Basecoats and Undercoats	2
08E - Nail Polish and Enamel	2
08G - Other Manicuring Preparations	1
10A - Bath Soaps and Detergents	21
10E - Other Personal Cleanliness Products	14
11A - Aftershave Lotion	2
11E - Shaving Cream	1
12A - Cleansing	6
12B - Depilatories	6
12C - Face and Neck (exc shave)	14
12D - Body and Hand (exc shave)	13
12F - Moisturizing	16
12G - Night	1
12H - Paste Masks (mud packs)	5
12I - Skin Fresheners	3
12J - Other Skin Care Preps	7

56. Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract

None

57. Macrocystis Pyrifera (Kelp) Juice

None

58. Macrocystis Pyrifera (Kelp) Protein*

10A - Bath Soaps and Detergents	1
12H - Paste Masks (mud packs)	1

12J - Other Skin Care Preps	1

59. Nereocystis Luetkeana Extract

07A - Blushers (all types)	1
07B - Face Powders	2
07C - Foundations	3

60. Pelvetia Canaliculata Extract*

03D - Eye Lotion	1
03F - Mascara	3
03G - Other Eye Makeup Preparations	2
05A - Hair Conditioner	4
05B - Hair Spray (aerosol fixatives)	1
05F - Shampoos (non-coloring)	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	12
05I - Other Hair Preparations	1
06H - Other Hair Coloring Preparation	1
10E - Other Personal Cleanliness Products	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	8
12F - Moisturizing	4
12G - Night	2

61. Pelvetia Siliquosa Extract

None

62. Phyllacantha Fibrosa Extract

None

63. Saccharina Angustata Extract

None

64. Saccharina Japonica Extract

None

65. Saccharina Longicruris Extract

05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	1

66. Sargassum Filipendula Extract*

03D - Eye Lotion	2
05A - Hair Conditioner	1
05B - Hair Spray (aerosol fixatives)	3
05F - Shampoos (non-coloring)	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	23
07I - Other Makeup Preparations	1
11F - Shaving Soap	1
12A - Cleansing	2
12C - Face and Neck (exc shave)	1
12F - Moisturizing	4
12H - Paste Masks (mud packs)	3
12J - Other Skin Care Preps	2

67. Saragassum Fulvellum Extract

12C - Face and Neck (exc shave)	2

68. Sargassum Fusiforme Extract*

01B - Baby Lotions, Oils, Powders, and Creams	1
03G - Other Eye Makeup Preparations	1
12C - Face and Neck (exc shave)	4
12F - Moisturizing	7
12H - Paste Masks (mud packs)	4

69. Sargassum Glaucescens Extract

None

70. Sargassum Horneri Extract

None

71. Sargassum Muticum Extract*

12H - Paste Masks (mud packs)	1

72. Sargassum Pallidum Extract

None

73. Saragssum SIliquastrum Extract

None

74. Sargassum Thunbergii Extract

None

75. Sargassum Vugare Extract*

None

76. Sphacelaria Scoparia Extract*

10A - Bath Soaps and Detergents	2
12D - Body and Hand (exc shave)	4
12F - Moisturizing	1
12J - Other Skin Care Preps	1

77. Undaria Peterseniania Extract

None

78. Undaria Pinnatifida Cell Culture Extract

None

79. Undaria Pinnatifida Leaf/Stem Extract

None

80. Undaria Pinnatifida Extract*

01A - Baby Shampoos	1
01B - Baby Lotions, Oils, Powders, and Creams	3
03D - Eye Lotion	4
05A - Hair Conditioner	2
05F - Shampoos (non-coloring)	5
05I - Other Hair Preparations	2
07B - Face Powders	2
07C - Foundations	3
07I - Other Makeup Preparations	2
10A - Bath Soaps and Detergents	1
10E - Other Personal Cleanliness Products	3
12A - Cleansing	1
12C - Face and Neck (exc shave)	29
12D - Body and Hand (exc shave)	13
12F - Moisturizing	14

12G - Night	4
12H - Paste Masks (mud packs)	1

81. Undaria Pinnatifida Powder*

None

82. Undaria Pinnatifida Root Powder

None

Other:

Laminaria Extract*

05C - Hair Straighteners	1
05F - Shampoos (non-coloring)	1
12A - Cleansing	1
12D - Body and Hand (exc shave)	1
12J - Other Skin Care Preps	1

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Memorandum

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

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

DATE: January 23, 2019

SUBJECT: Summary of French Regulations Concerning Algae and Published Studies Concerning Brown Algae

CEVA. 2014. Summary of edible seaweed and French regulation.

The published papers listed below concern edible algae, including species of brown algae that are not currently listed among the food algae in Table 25 of the CIR report on brown algae-derived ingredients.

Brownlee I, Fairclough A, Hall A, et al. 2012. The potential health benefits of seaweed and seaweed extract. Sheffield Hallam University Research Archive.

Cofrades S, López-Lopez I, Brav L, et al. 2010. Nutritional and antioxidant properties of different brown and red Spanish edible seaweeds. *Food Science and Technology International*, 16(5): 361-370.

MacArtain P, Gill C, Brooks M, et al. 2007. Nutritional Value of Edible Seaweeds. *Nutrition Reviews* 65(12): 535-543.

Marhuenda J, Gironés-Vilaplana A, Galvez M, et al. 2016. Antioxidant capacity and totals phenolics in different types of edible seaweed after three times of cooking. Agro Food Industry Hi Tech 27(2): 57-59.

Pereira H, Barreira L, Figueiredo F, et al. 2012. Polyunsaturated fatty acids of marine macroalgae: Potential for nutritional and pharmaceutical applications. *Mar Drugs* 10: 1920-1935.

Edible seaweed and French regulation - Synthesis made by CEVA (31/03/2014)

In Europe, seaweeds are considered as novel food. Therefore they are considered as food if put on market as food or food ingredient and consumed to a signlficant degree before May 15 1997. The marine diatom Odontella aurita by Innovalg (France) has been approved since 9 December 2002 as a novel food ("substantially equivalent")

In France since 1990, some species of seaweed have been authorized for food consumption. France was the first European country to establish a specific regulation concerning the use of seaweeds for human consumption as non–traditlonal food substances.

Up to day, 21 macroalgae and 3 microalgae are authorized as vegetables and condiments (table 1). Moreover, maximum allowed levels of toxic minerals (lead, cadmium, tin, mercury, mineral arsenic and iodine) have been defined for all edible seaweed (table 2). These low levels are considered a high guarantee of food safety.

Scientlfic name	Common name
• **Brown seaweed**	
- *Ascophyllum nodosum*	
- *Fucus vesiculosus +serratus*	
- *Himanthalia elongata*	Sea spaghettl
- *Undaria pinnatifida*	Wakame
- *Laminaria digitata*	Kombu
- *Laminaria saccharina*	Royal Kombu
- *Laminaria japonica*	Kombu
- *Alaria esculenta*	Atlantic wakame
• **Red seaweed**	
- *Palmaria palmata*	Dulse
- *Porphyra umbilicalis*	Nori
- *Porphyra tenera*	"
- *Porphyra yezoensis*	"
- *Porphyra dioica*	"
- *Porphyra purpurea*	"
- *Porphyra laciniata*	"
- *Porphyra leucostica*	"
- *Chondrus crispus*	Pioca, lichen
- *Gracilaria verrucosa*	Ogonori
- *Lithothamnium calcareum*	Mäerl
• **Green seaweed**	
- *Ulva sp.*	Sea lettuce
- *Enteromorpha sp.*	Aonori
• **Microalgae**	
- *Spirulina sp.*	
- *Odontella aurita*	
- *Chlorella sp.*	

Table 1 : Synthesis of seaweed usable for food consumption in France

	Maximal level (mg/kg dry weight)
Inorganic Arsenic (As)	3
Cadmium (Cd)	0,5
Mercury (Hg)	0,1
Lead (Pb)	5
Tin (Sn)	5
Iodine (I)	2 000

Table 2. Maximal level of heavy metals and iodine authorized in seaweeds (mg/kg dry weight)

Remark for food supplement

According to the regulation (EC) No 629/2008 setting maximum levels for certain contaminants in Foodstuffs food supplements consisting exclusively or mainly of dried seaweed or of products derived from seaweed can therefore contain higher levels of cadmium than other food supplements. To take this into account, a higher maximum level for cadmium (3 mg/kg dry seaweed) is needed for food supplements consisting exclusively or mainly of seaweed.

Ingredients

- Algal oils rich in DHA have been approved by european commission decision as a novel food ingredient under regulation n° 258/97 : oil from the micro-algae *Schizochytrium sp* and oil from the microalgae *Ulkenia sp.*
- E160a : Mixed carotenes may also be produced from strains of the algae Dunaliella salina. Beta-carotene is extracted using an essential oil. The preparation is a 20 to 30 % suspension in edible oil. The ratio of trans-cis isomers is in the range of 50/50 to 71/29.
- E161j : astaxanthin as colouring substance for feeding-stuffs (salmons and trouts)

References

Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients

Oplnion of the French Higher Council for Public Health (CSHPF) issued of sessions of 14 June 1988, 13 December 1988, 9 January 1990 and 14 October 1997 (Bulletin Officiel du Mlnistère de la Santé (n°90/45, p. 103) et B.I.D n°2/98-03, BID n° 4/99-079)

Opinion of the French Food Safety Agency concerning the substantial equivalence of Odontella aurita with authorized seaweed (AFSSA Request n° 2001-SA-0082).

Opinion of the French Food Safety Agency on the recommended maximum inorganic arsenic content of laminaria and consumption of these seaweeds in light of their high iodine content (AFSSA Request no. 2007-SA-0007)

COMMISSION REGULATION (EC) No 629/2008 of 2 July 2008 amending Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs

COMMISSION DECISION of 5 June 2003 authorising the placing on the market of oil rich in DHA (docosahexaenoic acid) from the microalgae Schizochytrium sp. as a novel food ingredient under Regulation n° 258/97.

OPINION of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on an application for authorisation to market a novel food ingredient: DHA-EPA-rich oil from the micro-algae Schizochytrium sp. (Request no. 2011-Sa-034S)

COMMISSION DECISION of 21 October 2009 concerning the extension of uses of algal oil from the micro-algae Ulkenia sp. as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council

Commission Regulation (EU) No 1274/2013 of 6 December 2013 amending and correcting Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council and the Annex to Commission Regulation (EU) No 231/2012 as regards certain food additives

EFSA (2005) Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed on the request from the European Commission on the safety of use of colouring agents in animal nutrition. PART I. General Principles and Astaxanthin, The EFSA Journal, 291, 1-40.

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Memorandum

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

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

DATE: January 3, 2019

SUBJECT: Brown Algae Summary Information from UNITIS

UNITIS. 2019. UNITIS CIR Safety Report on Brown Algae-Derived Ingredients as Used in Cosmetics (additions January 2019).

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

UNITIS – CIR Safety Report on Brown Algae-Derived Ingredients as Used in Cosmetics – Additions January 2019

Please note that the % of brown algae contained in each below mentioned extract ranges between 0.5 and 10%

INCI Name	Dermal Toxicity Data	Dermal Irritation and Sensitization Data	Method of manufacture (solvent)	Arsenic	Iodine
Water (and) Ascophyllum Nodosum Extract	Acute cutaneous tolerance on the adult volunteer: patch test 24 hours. The results obtained under the experimental conditions showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 10 volunteers, was found to be non-irritating.	Evaluation of the allergenic potential after repeated cutaneous application over 50 volunteers. Results obtained under experimental conditions showed that the product was found to be very well tolerated on cutaneous level. It can be considered as hypoallergenic. Concentration tested: 100% (of the extract in water)	Extraction with Water	2.69 mg/kg (ICP-MS method)	41 mg/kg (alkaline mineralization and potentiometric method)
Water (and) Phyllacantha Fibrosa Extract	Acute cutaneous tolerance on the adult volunteer: patch test 24 hours. The results obtained under the experimental conditions showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 10 volunteers, with sensitive skin was	Evaluation of the allergenic potential after repeated cutaneous application over 50 volunteers. Results obtained under experimental conditions showed that the product was found to be non-irritant with regard to the cutaneous tolerance and did not induce any significant skin reaction of	Extraction with Water	11.35 ppm (ICP-MS method)	97 mg/L (ionic chromatography method)

	found to be non-irritating.	contact allergy. It can be thus qualified as hypoallergenic. Concentration tested: 100% (of the extract in water)			
Glycerin (and) Water (and) Undaria Pinnatifida Extract	Cytotoxicity assay on human fibroblasts by MTT method. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-cytotoxic.	Evaluation of the sensitizing potential with Marzulli-Maibach method on 100 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritant and no allergic reaction was observed. Concentration tested: 100% (of the extract in glycerin and water)	Extraction with Water and dilution with Glycerin	0.837 mg/kg (ICP-MS method)	<1 mg/kg (colorimetry method)
Caprylic/Capric Triglyceride (and) Undaria Pinnatifida Extract	Evaluation of the cutaneous compatibility with occlusive 24 hours patch test method. This study was completed on 10 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritating.	Evaluation of the sensitizing potential with Marzulli-Maibach method on 50 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritant and no allergic reaction was observed. Concentration tested: 100% (of the extract in	Extraction with supercritical CO_2 with Caprylic/Capric Triglyceride	<0.025 mg/kg (ICP-MS method)	1.2 mg/kg (ICP-MS method)

		Caprylic/Capric Triglyceride)			
Water (and) Dipropylene Glycol (and) Halopteris Scoparia Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 24 hours. The results obtained under the experimental conditions showed that the product applied pure and locally under an occlusive dressing during 24 hours on the skin of 11 volunteers was found to be non-irritating.	Evaluation of the allergic potential after repeated epicutaneous application on 50 volunteers. The results obtained in the experimental conditions retained permitted to conclude that the product was found to be very well tolerated at the cutaneous level, showing no significant irritative reaction or a contact allergy reaction. It can thus be qualified as hypoallergenic. Concentration tested: 100% (of the extract in Water and Dipropylene Glycol)	Extraction with Water and Dipropylene Glycol	0.73 mg/kg (ICP-MS method)	15 mg/kg (alkaline mineralization and potentiometric method)
Glycerin (and) Water (and) Cystoseira Tamariscifolia Extract	Evaluation of the cutaneous compatibility with occlusive 48 hours patch test method – applied diluted at 20%. This study was completed on 11 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the skin	Evaluation of the sensitizing potential with Marzulli-Maibach method on 105 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritating and non-sensitizing.	Extraction with water and depolymerization with enzyme and denaturation of the enzyme and addition of Glycerin	1.35 mg/kg (ICP-MS method)	1.4 mg/kg (ICP-MS method)

	compatibility is very good.	Concentration tested: 20% (of the extract in Glycerin and Water)			
Glycerin (and) Water (and) Dictyopteris Polypodioides Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 48 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 48 hours, on the skin of 10 volunteers, was found to be non-irritating.	See below	Extraction with Water and dilution in Glycerin	0.809 mg/kg (ICP-MS method)	19 mg/kg
Water and Dictyopteris Polypodioides Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 48 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 48 hours, on the skin of 10 volunteers, was found to be non-irritating.	Evaluation of the allergic potential after repeated epicutaneous application on 50 volunteers. The results obtained in the experimental conditions retained permitted to conclude that the product was found non-irritant at the cutaneous level, showing no significant reaction of a contact allergy. Concentration tested: 100% (of the extract in water)	Extraction with water	0.602 mg/kg (ICP-MS method)	19 mg/kg

Water (and) Dipropylene Glycol (and) Fucus Vesiculosis Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 24 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 24 hours , on the skin of 10 volunteers was found to be non-irritating.		Extraction with Water and Dipropylene Glycol		<9 mg/kg (alkaline mineralization and potentiometric method)
Caprylic/Capric Triglyceride (and) Dictyopteris Polypodioides Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 48 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 48 hours, on the skin of 10 volunteers, was found to be non-irritating.	Evaluation of the sensitizing potential with Marzulli-Maibach method. This study realized on 50 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritant and non-sensitizer. Concentration test: 100% (of the extract in Caprylic/Capric Triglyceride)	Extraction with supercritical CO_2 with Caprylic/Capric Triglyceride	0.051 mg/kg (ICP-MS method)	<9 mg/kg (FCC V method)

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Memorandum

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

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

DATE: January 23, 2019

SUBJECT: Information Cystoseira Amentacea/Caespitosa/Brachycarpa Extract and Himanthalia Elongata Extract

Anonymous. 2019. Summaries of Human Sensitization Studies of Products Containing Brown Algae-Derived Ingredients (Cystoseira Amentacea/Caespitosa/Branchycarpa Extract and Himanthalia Elongata Extract).

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January 2019

Summaries of Human Sensitization Studies of Products Containing Brown Algae-Derived Ingredients

Ingredient: Cystoseira Amentacea/Caespitosa/Branchycarpa Extract
Study Type: Maximization
Test Sample: Cream containing 0.0023% of the extract
Test Condition: Neat, semi-occlusive patch
Test Dates: Jan 2008-Feb. 2008
No. Completed Subjects: 25
Conclusion: No dermal sensitization potential

Ingredient: Himanthalia Elongata Extract
Study Type: HRIPT
Test Sample: Cream containing 0.2% of the extract
Test Condition: Neat, semi-occlusive patch
Test Dates: Oct 2018-Nov 2018
No. Completed Subjects: 102
Conclusion: No dermal irritation, nor dermal sensitization potential

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Memorandum

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

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

DATE: January 24, 2019

SUBJECT: Information on a Mixture Containing Water, Himanthalia Elongata Extract, Fucus Vesiculosus Extract and Saccharomyces Cerevisiae Extract

Anonymous. 2019. Specification data sheet for a mixture containing Water, Himanthalia Elongata Extract, Fucus Vesiculosus Extract and Saccharomyces Cerevisiae Extract.

Anonymous. 2019. Flow chart for a mixture containing Water, Himanthalia Elongata Extract, Fucus Vesiculosus Extract and Saccharomyces Cerevisiae Extract.

Anonymous. 2019. Attestation on heavy metals for a mixture containing Water, Himanthalia Elongata Extract, Fucus Vesiculosus Extract and Saccharomyces Cerevisiae Extract.

EVIC France. 2016. Summary: Assessment of the irritant potential of a test item after application to the embryonic hen's egg chorioallantoic membrane - HET-CAM (mixture containing Water, Himanthalia Elongata Extract, Fucus Vesiculosus Extract and Saccharomyces Cerevisiae Extract).

EVIC France. 2016. Summary: Human patch test under dermatological control (mixture containing Water, Himanthalia Elongata Extract, Fucus Vesiculosus Extract and Saccharomyces Cerevisiae Extract).

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SPECIFICATION DATA SHEET

Trade name:

Product: Version: 1.0 - 2019

Specification: Print date: 01 - 2019

is an association of algae extracts and yeast extract.

1 – Identification and composition of the preparation

Product	N° CAS	N°EINECS	Ingredients %
water	7732-18-5	231-791-2	36.5
Himanthalia elongata extract	223751-70-0	-	62.0
Fucus vesiculosus extract	84696-13-9	283-633-7	1.4
Saccharomyces cerevisiae extract	84604-16-0	283-294-5	0.1
Preservative	None		

2 – Characteristics (standard)

Aspect: liquid.

Colour: orange-amber .

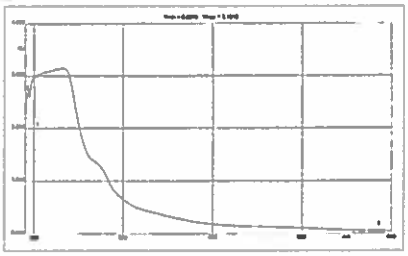
Odour: *sui generis.*

pH: 6.0 ± 1.0.

Relative density (20°C): 1.014 ± 0.01.

Dry residuals (%) 2.2 ± 0.5

Spectrum UV (5% in water):



Microbiology:

Total germs (germs/ml): < 100.
Pathogens: absence.
Yeasts /moulds: < 100.

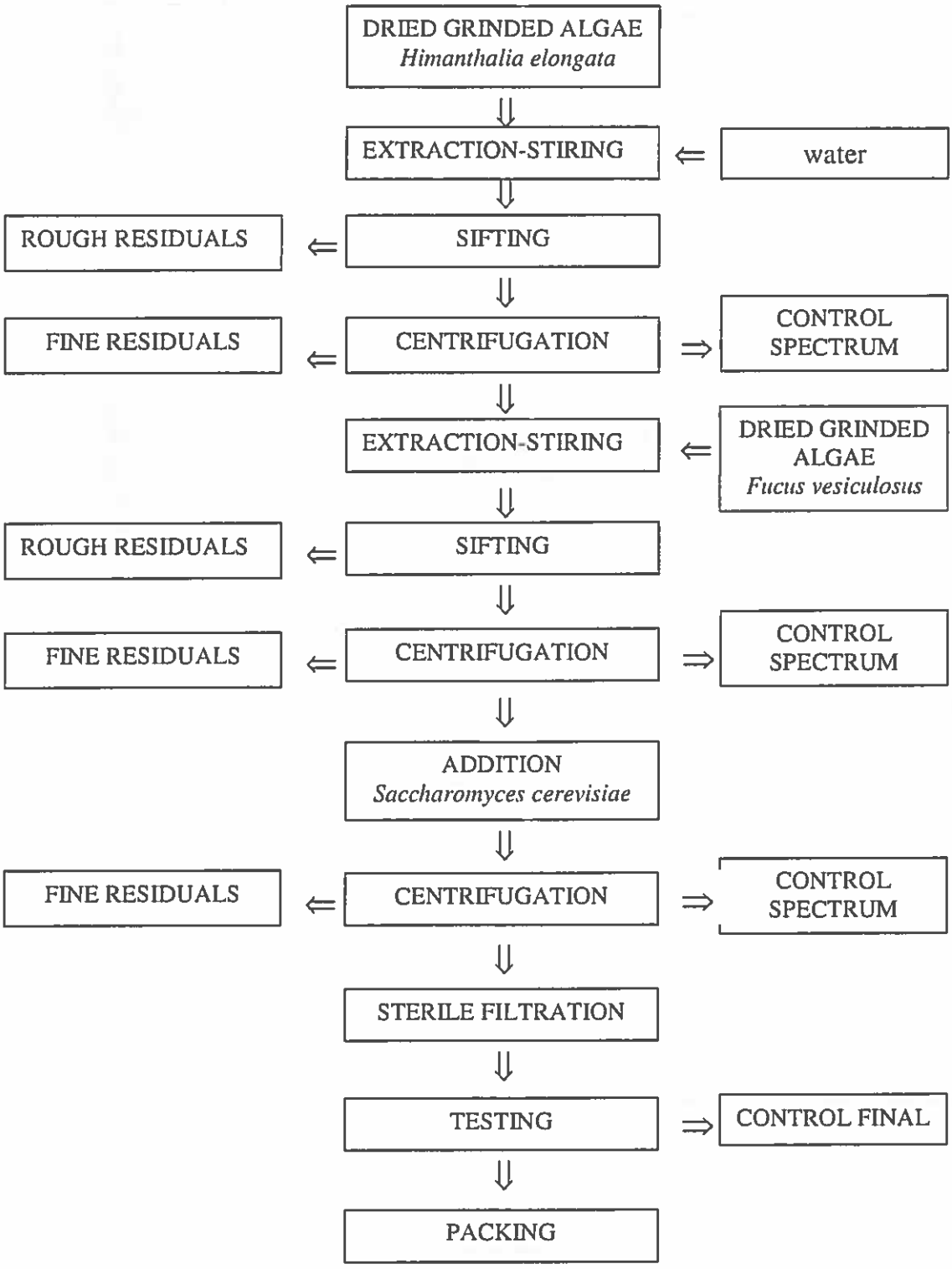
Storage: 15°C < store < 25°C.
Validity date: 12 months.

Remark: *No responsibility or liability for any consequences arising from the use of this technical data sheet can be accepted, including possible infringement of any patent.*

2019

FLOW CHART FOR

Water
Himanthalia Elongata Extract
Fucus Vesiculosus Extract
Saccharomyces Cerevisiae Extract



ATTESTATION ON HEAVY METALS

Product:

INCI names:

water	CAS n° 7732-18-5	EINECS n° 231-791-2
Himanthalia elongata extract	CAS n° 223751-70-0	
Fucus vesiculosus extract	CAS n° 84696-13-9	EINECS n° 283-633-7
Saccharomyces cerevisiae extract	CAS n° 84604-16-0	EINECS n° 283-294-5

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Some heavy metals in have been analysed. Based on these analysis, it is stated that the heavy metals content is below < 10 ppm in the above named product.

Arsenic : 1.264 ppm - Cadmium: < 0.010 ppm - Mercury: < 0.010 ppm - Lead : 0.210 ppm

Date : 04/01/2019

eurofins | EVIC

EVIC france

REFERENCES ETUDE/ELEMENT D'ESSAI : B16 0623 / 16-1325

DONNEUR D'ORDRE

ELEMENT D'ESSAI

Water
Himanthalia Elongata Extract 62% see specification sheet
Fucus Vesiculosus Extract 1.4%
Saccharomyces Cerevisiae Extract

EVALUATION DU POTENTIEL IRRITANT D'UN ELEMENT D'ESSAI PAR APPLICATION SUR LA MEMBRANE CHORIO-ALLANTOÏDIENNE DE L'ŒUF DE POULE EMBRYONNE

-HET-CAM-

Rapport Final

Bordeaux, le 19 juillet 2016

11 pages dans ce rapport

LABORATOIRES DE RECHERCHE ET D'EXPERIMENTATION

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EVALUATION DU POTENTIEL IRRITANT D'UN ELEMENT D'ESSAI PAR APPLICATION SUR LA MEMBRANE CHORIO-ALLANTOÏDIENNE DE L'ŒUF DE POULE EMBRYONNE - HET-CAM -

ASSESSMENT OF THE IRRITANT POTENTIAL OF A TEST ITEM AFTER APPLICATION TO THE EMBRYONIC HEN'S EGG CHORIOALLANTOIC MEMBRANE - HET-CAM -

RESUME/*SUMMARY*

- **PRINCIPE DE L'ETUDE/*PRINCIPLE OF THE STUDY***

L'étude a été basée sur l'observation, par une personne qualifiée, des effets irritants (hyperhémie, hémorragie, coagulation) pouvant survenir dans les cinq minutes suivant le dépôt d'un élément d'essai sur la membrane chorio-allantoïdienne (MCA) d'œufs de poule embryonnés au dixième jour d'incubation.
Le potentiel irritant a été scoré selon une échelle allant de 0 à 21. L'élément d'essai a été classé dans l'une des catégories définies en fonction du score moyen obtenu.

The study was based on the observation, by a trained person, of the irritant effects (hyperhemia, haemorrhage and coagulation) occurring during the five minutes after application of test item to the chorioallantoic membrane (CAM) of embryonic hen's eggs on the tenth day of incubation.
The irritant potential was scored according to a scale from 0 to 21. The test item was classified in one of the categories defined according to the mean score obtained.

Score moyen/*Mean Score* (Scm/*MSc*)	Classification/*Classification*
Scm/*MSc* < 1	Pratiquement non irritant/*Practically non irritant*
1 ≤ Scm/*MSc* < 5	Faiblement irritant/ *Slightly irritant*
5 ≤ Scm/*MSc* < 9	Modérément irritant/*Moderately irritant*
Scm/*MSc* ≥ 9	Irritant/*Irritant*

- **DATE(S) DE DEBUT ET DE FIN D'EXPERIMENTATION / *EXPERIMENTAL STARTING DATE AND EXPERIMENTAL COMPLETION DATE*** : 27 juin 2016 */ June 27, 2016*

- **RESULTATS/*RESULTS* :**

Elément d'essai *Test item*	Concentration testée *Tested concentration*	Score moyen sur 4 œufs ± écart type *Mean score on 4 eggs ±standard deviation*	Classification *Classification*	Comparaison par rapport à des éléments d'essai appartenant à la même catégorie *Comparison with test items belonging to the same category*
	Dilué à 10% dans l'eau p.p.i. / *Diluted at 10% with water for injection*	2.3 ± 1.5	Faiblement irritant/ *Slightly irritant*	pas de comparaison disponible / *no available comparison*

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EVIC france

PATCH TEST CHEZ L'HOMME SOUS CONTRÔLE DERMATOLOGIQUE

Rapport d'étude – version n° 1 du 11/07/2016

REFERENCES ETUDE	**EUROFINS EVIC france – I16 0486**
	E573367_P781565
PRODUIT D'INVESTIGATION	see specification sheet
Dénomination	Water
Référence / Numéro de formule	Himanthalia Elongata Extract
Numéro de lot	**16 06 090**
Catégorie cosmétique	**Ingrédient**
Forme galénique et caractères organoleptiques	**Liquide orangé**

Fucus Vesiculosus Extract

Saccharomyces Cerevisiae Extract

PROMOTEUR	
MONITEUR D'ETUDE	
CENTRE COORDINATEUR	**EUROFINS ATS** ZI Les Milles - Actimart 1140, rue Ampère 13851 AIX EN PROVENCE cedex 3 France
CENTRE D'INVESTIGATION	**EUROFINS EVIC france – Division Idec** 57, rue Ulysse Gayon 33000 - Bordeaux - France **Tél. : +33 5 57 14 00 80** Fax : +33 5 56 48 72 49 *e-mail : evic-idec@evic.fr*
INVESTIGATEUR PRINCIPAL	**Dr MAGNE Françoise (Dermatologue)**

HUMAN PATCH TEST UNDER DERMATOLOGICAL CONTROL

Résumé en anglais / English synopsis

STUDY OBJECTIVE	To confirm the skin compatibility of the investigational product in a panel of healthy human subjects after single application under maximising and controlled experimental conditions.
TYPE OF THE STUDY	Monocentric randomised clinical study performed in single blind and defined as a non interventional clinical research according to the French law 2004-806 of 09/08/2004 relating to the policy of public health. The test subject was used as own control.
DATES OF STUDY PERFORMANCE	**Initiation date:** 05/07/2016
	Completion date: 07/07/2016
STUDY POPULATION	**Number of test subjects: 10** valid cases **Inclusion criteria: test subjects** • suitable to participate in the study and corresponding to the quality of "healthy subject" • declaring to have a health coverage • signing an "informed consent form" for this study • certifying not to take part simultaneously in another clinical study which could interfere • certifying the truth of the personal information declared to the investigator • capable of following directions and reliable to respect the constraints of the protocol • free to ensure the visits to the investigating centre • aged from 18 to 70 • female/male • with all types of skin on back • with a phototype (Fitzpatrick): I to IV • declaring not to have exposed themselves to a risk of pregnancy for at least 3 months before the beginning of the study and committing themselves to use effective contraceptive method throughout the study (for the women of childbearing potential) **Non inclusion criteria: test subjects** • being in exclusion period • deprived of freedom by administrative or legal decision or under guardianship • who cannot be contacted in case of emergency • admitted in a residential care • planning an hospitalisation during the study • belonging to the staff of the investigating centre • being of age but protected by law • having received vaccination within the 3 weeks prior to the study or intending to be vaccinated during the course of the study • with personal history of adverse reactions to the same type of product as the investigational product • with personal history of adverse reaction to colophony, rubber, patch materials, adhesive plaster

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Résumé en anglais (suite) / English synopsis (continuation)

STUDY POPULATION	• with documented history of contact allergy • exhibiting skin marks and/or moles and/or freckles in too great quantity and/or hyperpilosity on the experimental area able to interfere with the assessment of the possible skin reactions • with still visible eczematous reaction, scar or pigmentary after-effects of previous tests on the experimental area • under treatment, prior to the study, able to interfere with the study results, • foreseeing, during the study, a treatment able to interfere with the interpretation of the study results (systemic or topical anti-acne medication, topical or systemic medication with anti-inflammatory or antihistamine, antibiotics, desensitisation treatment, ...) • having had a fever lasting more than 24 hours, within the 8 days prior to the study • having had any invasive aesthetic cares on chest and back (peeling, laser...) by a dermatologist within the 2 months prior to the study or foreseeing it for the duration of the study • having had any non invasive aesthetic cares on chest and back by an aesthetician within the month prior to the study or foreseeing it for the duration of the study • having received excessive or intensive exposure to sunlight (natural or artificial) within the month prior to the study or foreseeing UV exposures for the duration of the study • under treatment with PUVA or UVB within the month prior to the study • having participated in a human repeated insult patch test with challenge with or without sun exposure within the 4 months prior to the study • having participated in a cumulative irritability test within the 2 months prior to the study or in a single patch test within the month prior to the study • having already participated in 5 clinical studies involving patch test, including 3 human repeated patch tests maximum with or without challenge within the year prior to the study • foreseeing bath (in bathtub, sea or swimming pool), sauna or Turkish batch during the study period • regularly practicing intensive sport causing sweating and requiring frequent showers • breastfeeding or pregnant or planning a pregnancy during the study (for the women of childbearing potential) • having started or changed oestrogen-progesterone contraception or hormonal treatment, within the 3 months prior to the study or foreseeing it for the duration of the study
METHODOLOGY	**Definition and preparation of the experimental areas:** - Skin areas defined by the technician in charge of the study on the back of the test subjects, taking into account the skin appearance and avoiding the areas of friction with clothes - Before patching, wiping of the skin with a cotton pad **Application of the investigational product**, by the technician in charge of the study at the investigating centre: - once (on D1), - under maximising conditions of exposure (under Semi-occlusive patch - Trumed® : absorbent support in Webril® kept in position by a non woven medical adhesive (surface: 400 mm²) - quantity applied=160 µl; measured with a micropipette with disposable tip and put into the patch) - diluted at 10% in water for injection - during a defined time (48h ±4h) Application in parallel of water for injection (160 µl) to a skin area on back, under Semi-occlusive - Trumed® patch and during a defined time (48h ±4h) (control area, to take into account the possible effects not directly related to the investigational product but due to the patch material)

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Résumé en anglais (suite) / English synopsis (continuation)

METHODOLOGY	**Checking of the skin compatibility** based on: • a skin examination of the treated and control areas, visually, by the same investigator with the appropriate experience, under standard "daylight" source, on: ↓ D1/T0 before application ↓ D3/T15-30 minutes after patches removal • the analysis of the sensations of discomfort reported directly by the test subjects to the investigator during the study Descriptive analysis – Percentage of reactive test subjects (erythema and other visible signs of reactivity) Expression of the results: • **Percentage of reactive test subjects:** calculated taking into account only the following signs of reactivity: erythema, dryness, œdema, papula, vesicle, bulla, scab, soap effect, pruritus Description of the other reactivity clinical signs or sensations of discomfort and calculation of the corresponding percentage of test subjects if justified by the appearance frequency • **Individual daily irritation score (IDIS)** calculated for each test subject : **IDIS = sum of the marks obtained for all the signs observed** • **Mean daily irritation score (MDIS)** calculated for the panel : **MDIS = Σ (IDIS) / nb of valid cases** Classification of the reaction according to ICDRG scale in case of reaction of allergy Descriptive analysis of the data

RESULTS

Characteristics of the included panel

Number of included subjects: 10
Number of exclusions: 0
Number of withdrawals: 0
Number of valid cases: 10

- Age: 24 to 69 (Mean= 51 years old)
- Sex: female
- Phototype: II to IV
- All types of skin on the back

Résumé en anglais (suite) / English synopsis (continuation)

Checking of the skin compatibility

No reaction was noted on the control site

For the investigational product:

Control time after patch removal	Type of reaction	Number of reactive test subjects	% of reactive test subjects	Mean daily irritation score MDIS	Skin compatibility of the product
T15-30 minutes (D3)	/	0	0 %	0	**Very good skin compatibility**

Legend: / = none

OVERALL CONCLUSION

Under the experimental conditions adopted:

single application of the product diluted at 10% in water for injection, under semi-occlusive patch, on a panel of 10 women, aged between 24 and 69 years old, with phototype II to IV and with all types of skin on back,

the product · has a **very good** skin compatibility.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 24, 2019

SUBJECT: Information on a Mixture Containing Caprylic/Capric Triglyceride, Laminaria Ochroleuca Extract and Tocopherol

Anonymous. 2019. Specification data sheet for a mixture containing Caprylic/Capric Triglyceride, Laminaria Ochroleuca Extract and Tocopherol.

Anonymous. 2019. Flow chart for a mixture containing Caprylic/Capric Triglyceride, Laminaria Ochroleuca Extract and Tocopherol.

Anonymous. 2019. Attestation on heavy metals for a mixture containing Caprylic/Capric Triglyceride, Laminaria Ochroleuca Extract and Tocopherol.

Eurofins ATS. 2013. Summary: Assessment of the irritant potential of a test item after application to the embryonic hen's egg chorioallantoic membrane - HET-CAM (mixture containing Caprylic/Capric Triglyceride, Laminaria Ochroleuca Extract and Tocopherol).

Eurofins ATS. 2013. Summary: Assessment of skin tolerance of a cosmetic product after a single application under occluded patch test during 48 H on 10 volunteers: 48 hours patch test (mixture containing Caprylic/Capric Triglyceride, Laminaria Ochroleuca Extract and Tocopherol).

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SPECIFICATION DATA SHEET

Trade name:

Product: N° CCT-LAOC-00 Version : 1.0 - 2019
Specification: N° S.00 Print date: 01 - 2019

is an oily extract of *Laminaria ochroleuca* extract in caprylic capric triglycerides supplemented with tocopherols.

1 – Identification and composition of the preparation

Product	N° CAS	N°EINECS	EC N°1272/2008 (CLP)	67 / 548 EEC 1999/45/EC	Ingredients %
Caprylic/capric triglycéride	73398-61-5/65381-09-1	277-452-2/265-724-3	-	-	94.75
Laminaria ochroleuca extract	92128-82-0	295-780-4	-	-	5
Tocopherol (mixed)	59-02-9 16698-35-4 54-28-4 119-13-1	200-412-2 240-747-1 200-201-5 204-299-0	-	-	0.25
Preservative	None				

2 – Characteristics (standard)

Aspect : limpid liquid.

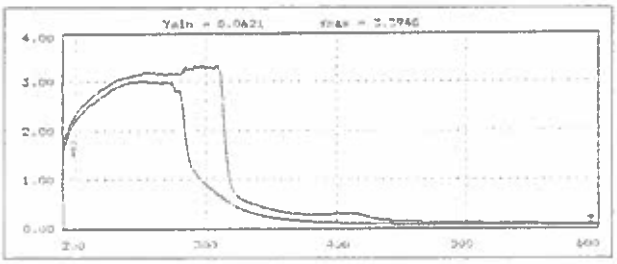
Color : transparent.

Odeur : *sui generis.*

Density : < 1.

Solubility : soluble in oils.

UV spectrum (dilution 1/5):



1 – Solvent alone
2 –

Microbiological quality:

Total germs (germs/ml)	< 100.
Pathogens	absence.
Yeasts /moulds	< 100.

Storage: 15°C < store <25°C - sheltered from light.
Can't stand the frost.
Validity date: 18 months.

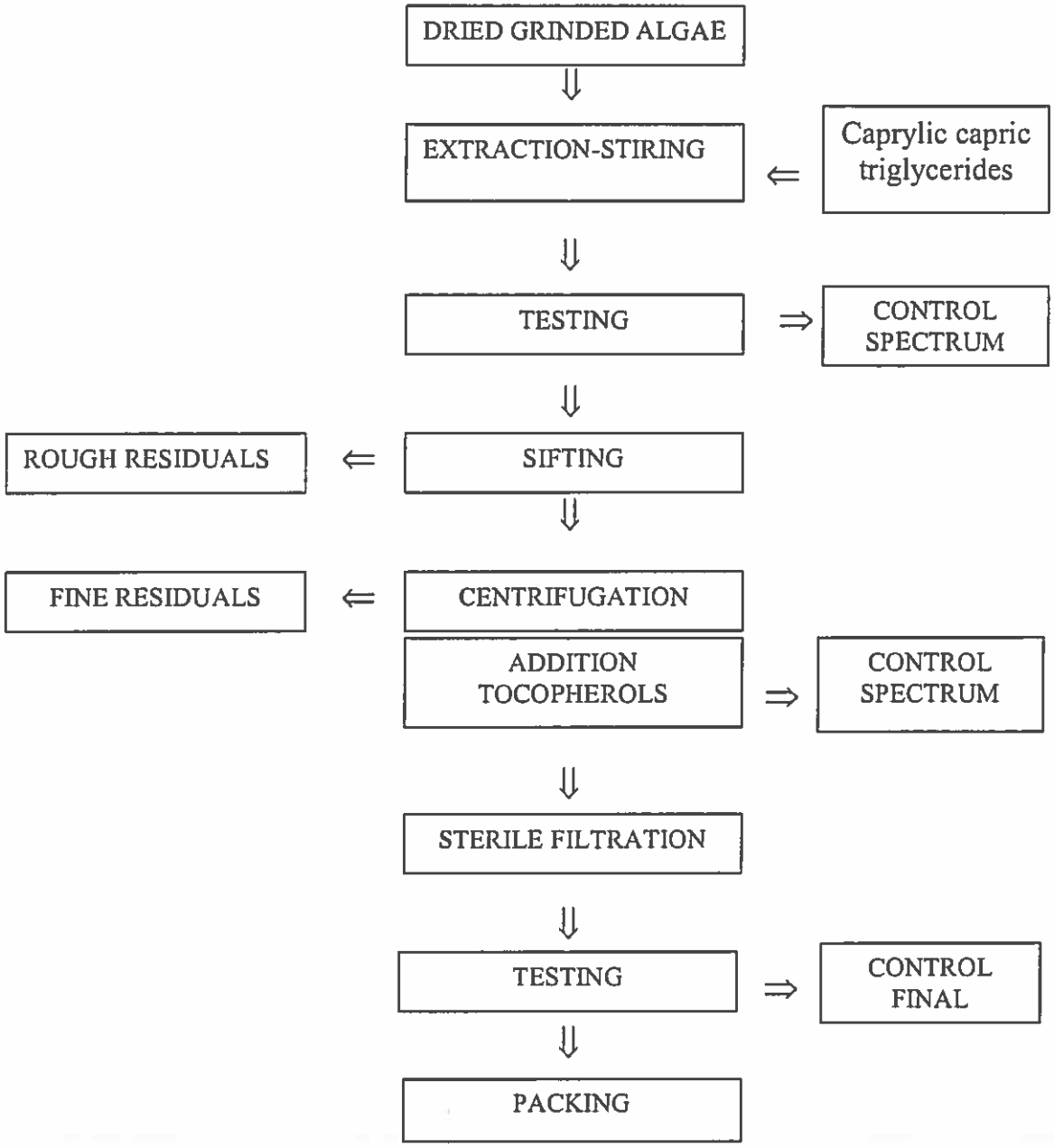
Remark: *No responsibility or liability for any consequences arising from the use of this technical data sheet can be accepted, including possible infringement of any patent.*

2019

FLOW CHART FOR

Bâtiment C4
1, Boulevard de l'Océan
13009 Marseille

Caprylic / Capric Triglyceride
Laminaria Ochroleuca Extrate
Tocopherol



ATTESTATION ON HEAVY METALS

Product:

INCI names: Caprylic capric triglycerides
CAS n° 73398-61-5/65381-09-1 EINECS n° 277-452-2/265-724-3
Laminaria ochroleuca extract
CAS n° 92128-82-0 EINECS n° 295-780-4
Tocopherol mixed
CAS n° 59-02-9 EINECS n° 200-412-2
16698-35-4 240-747-1
54-28-4 200-201-5
119-13-1 204-299-0

Some heavy metals in have been analysed. Based on these analysis, it is stated that the heavy metals content is below < 10 ppm in the above named product.

Arsenic : < 0.025 ppm - Cadmium: < 0.025 ppm - Mercury: < 0.025 ppm - Lead : < 0.025 ppm

Date : 04/01/2019

RAPPORT D'ETUDE

Caprylic / Capric Triglyceride
Laminaria Ochroleuca Extract 5%
Tocopherol

Le 11 février 2013

EVALUATION DU POTENTIEL IRRITANT D'UN PRODUIT PAR APPLICATION SUR LA MEMBRANE CHORIO-ALLANTOÏDIENNE DE L'ŒUF DE POULE : *Méthode du Het Cam*

Donneur d'ordre :

N° de devis : 2012 / 32164 / v1

N° d'étude : 515117

Elément d'essai :

- Dénomination :
- Référence client : 12 11 270
- N° échantillon ATS : 402964
- Marque : -

2013

Product tested: Caprylic / Capric Triglyceride
Laminaria Ochroleuca Extract 5%
Tocopherols

SUMMARY

The HET-CAM test is an organotypic method to detect the potential irritancy of compounds applied on the surface of the chorioallantoic membrane (CAM) of a fertilized hen's egg. The CAM is a vascular foetal membrane which represents an in vitro model to analyse the effects induced by chemicals that *in vivo* are observed on the conjunctiva.

The principle of this test is based on a visual observation, by a trained person, of the possible end-points (hyperaemia, haemorrhaging, coagulation / thrombosis) that may appear during the five minutes that follow the application of the product on this membrane.

This method is registered in the Official Journal of French Republic (JORF - Decree of 5 April 1971 modified by the decree of 29 November 1996).

In the performed experimental conditions, the **product** , tested by the HET-CAM method at 10 % and according to the JORF classification, is considered as **moderately irritant**.

2012

STUDY SUMMARY

ASSESSMENT OF SKIN TOLERANCE OF A COSMETIC PRODUCT AFTER A SINGLE APPLICATION UNDER OCCLUDED PATCH DURING 48H ON 10 VOLUNTEERS: *48 hours patch tests*

- **Product tested:** Caprylic / Capric Triglyceride
- **Promotor:** Laminaria Ochroleuca Extract 5% Tocopherol
- **Objective:** Assessment of the skin local tolerance of the studied product after an epicutaneous test performed in occluded conditions, during 48 hours, on healthy adult volunteers.
- **Investigator:** Doctor Chantal SOULIE-REGNIER, dermatologist
- **Place of the study:** EUROFINS ATS
  Pôle d'activité Aix-Les-Milles - ACTIMART
  3 allée des Ingénieurs
  1140 rue André Ampère
  13851 AIX EN PROVENCE cedex 3
- **Dates of study:** from 12/5/2012 to 12/7/2012
- **Method:**

✓ ***Application:***

Area: on the back
Quantity of product: 0.02 mL
Frequency and duration: only one application during 48 hours
Conditions of application: product applied diluted at 10% under occluded patch.

✓ ***Assessment method:***

A dermatologist performs the clinical observation, after the removal of the patches. The quantification of the skin irritation is given through a numeric scale (erythema, oedema, dryness/desquamation, vesicle). The average irritant score of the product to be tested is calculated from the average of the quotations obtained for each volunteer, allowing to rank the product from "non irritant to very irritant". The assessment is always made by comparison with the "negative" control.

- **Panel:** 10 healthy adult volunteers.
- **Result:** The average irritant score of the product is 0.00.
- **Conclusion:**

According to the experimental conditions of the study, **the** can be considered as **non irritant regarding its primary skin tolerance.**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 24, 2019

SUBJECT: Information on a Mixture Containing Water, Ascophyllum Nodosum Extract and Halopteris Scoparia Extract

Anonymous. 2019. Specification data sheet for a mixture containing Water, Ascophyllum Nodosum Extract and Halopteris Scoparia Extract.

Anonymous. 2019. Flow chart for a mixture containing Water, Ascophyllum Nodosum Extract and Halopteris Scoparia Extract.

Anonymous. 2019. Attestation on heavy metals for a mixture containing Water, Ascophyllum Nodosum Extract and Halopteris Scoparia Extract.

Eurofins ATS. 2006. Summary: Evaluation of a product through its application on the chorioallantoic membrane of a chicken eggshell: Het Cam method (mixture Water, Ascophyllum Nodosum Extract and Halopteris Scoparia Extract).

Eurofins ATS. 2006. Summary: Evaluation of the cutaneous tolerance of a cosmetic product after a single application under occlusive patch during 48 hours: patch test method (mixture containing Water, Ascophyllum Nodosum Extract and Halopteris Scoparia Extract).

SPECIFICATION DATA SHEET

Trade name:

Product: Version: 1.0 - 2019

Specification: Print date: 01 - 2019

is a patented algal complex based on the synergistic association of two aqueous and calibrated extracts prepared from the brown algae (*Phaeophyta*): *Ascophyllum nodosum* and *Halopteris scoparia (: Stypocaulon scoparium).* Patent :

1 – Identification and composition of the substance

Product	N° CAS	N°EINECS	Ingredients %	
Water	7732-18-5	231-791-2	46	
Ascophyllum nodosum extract	84775-78-0	283-907-6	40.5	54
Halopteris scoparia extract	-	-	13.5	
Preservative	None			

2 – Characteristics (standard)

Appearance: limpid liquid.

Color: amber.

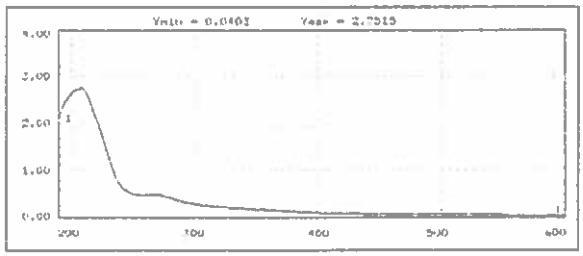
Odour: *sui generis.*

pH: 6.1 ± 1.0.

Relative density: 1.011 ± 0.010.

Dry residuals (%): 1.9 ± 0.3.

UV spectrum (5% in water):



Microbiological quality: Total germs (germs/ml): < 100.
Pathogens: absence.
Yeasts /moulds: < 100.

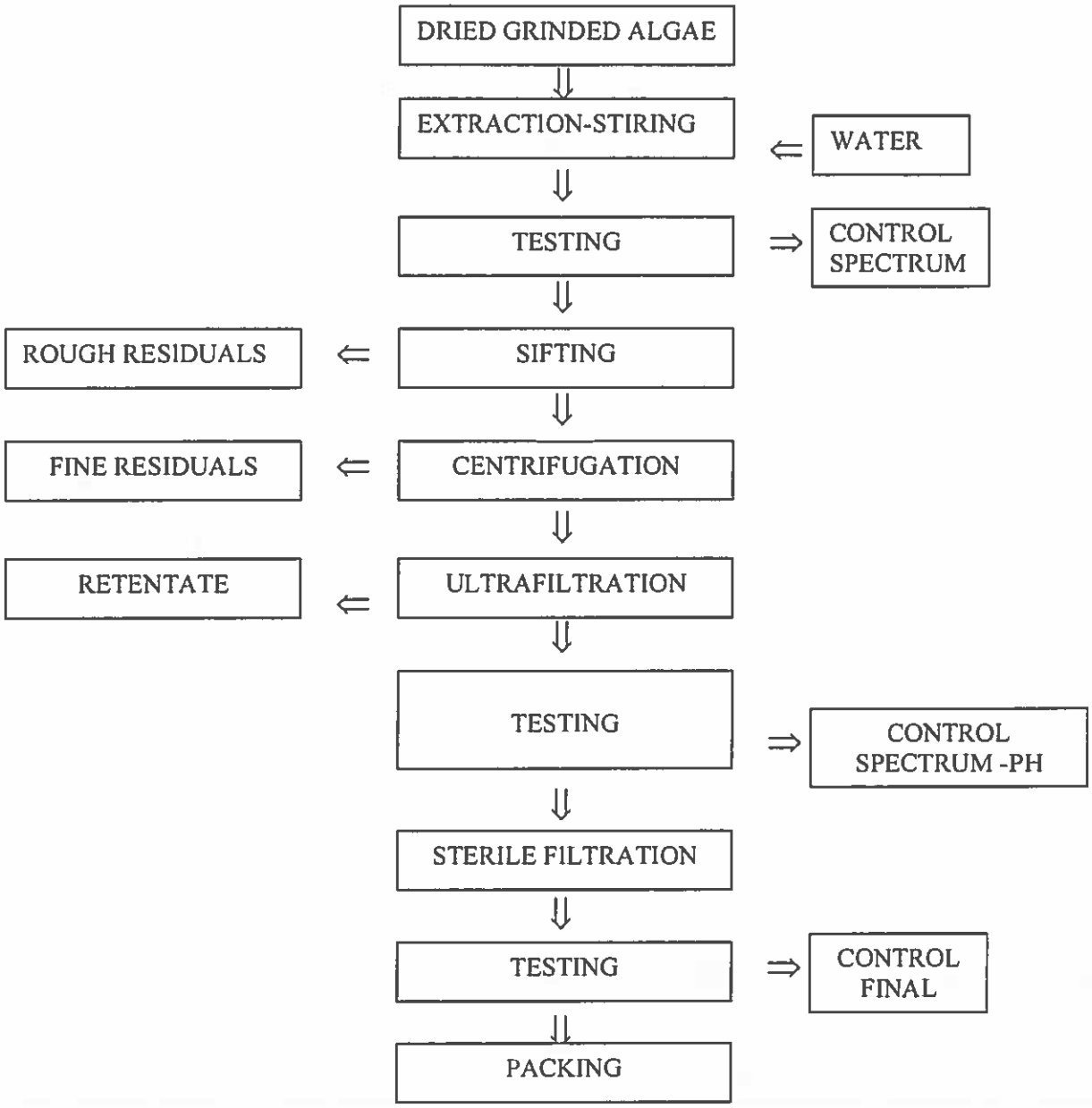
Storage: 15°C < store < 25°C.
Validity date: 6 months.

Remark*: No responsibility or liability for any consequences arising from the use of this technical data sheet can be accepted, including possible infringement of any patent.*

2019

FLOW CHART FOR

Water
Ascophyllum Nodosum Extract
Halopteris Scoparia Extract



ATTESTATION ON HEAVY METALS

Product :

INCI names:

water	CAS n° 7732-18-5	EINECS n° 231-791-2
Ascophyllum nodosum extract	CAS n° 84775-73-0	EINECS n° 283-907-6
Halopteris scoparia extract		

Some heavy metals in :ve been analysed. Based on these analysis, it is stated that the heavy metals content is below < 10 ppm in the above named product.

Arsenic : 1.683 ppm - Cadmium: < 0.010 ppm - Mercury: < 0.010 ppm - Lead : < 0.010 ppm

Date : 04/01/2019

eurofins | ATS

STUDY SUMMARY

EVALUATION OF THE POTENTIAL IRRITANCY OF A PRODUCT THROUGH ITS APPLICATION ON THE CHORIOALLANTOIC MEMBRANE OF A CHICKEN EGGSHELL: *Het Cam Method*

- **Tested product :** Water Ascophyllum Nodosum Extract 40.5%
- **Promoter :** Halopteris Scoparia Extract 13.5%
- **Objective:** To assess the irritant potential of the tested product
- **Methodology:** The principle of this study is based on the visual observation, by a trained person, of the possible irritations (hyperaemia, haemorrhaging, coagulation / thrombosis) that may appear during the five minutes that follow the application of the said product on the chorioallantoic membrane of an embryonic chicken egg after eleven days of incubation.
- **Dates of study :** 12/12/2006
- **Place of study:** EUROFINS ATS, Pôle d'activité d'Aix en Provence
  Actimart, 1140, rue Ampère,
  13851 AIX EN PROVENCE cedex 3
- **Results :**

Denomination	ATS Reference	Initial concentration	Results	
			Score	Classification
		100%	0	Practically no Irritant

- **Conclusion :**

According to the performed experimental conditions, the product tested by the HET CAM method, at 100 %, can be considered as practically no Irritant regarding its ocular primary tolerance.

STUDY SUMMARY

EVALUATION OF THE CUTANEOUS TOLERANCE OF A COSMETIC PRODUCT AFTER A SINGLE APPLICATION UNDER OCCLUSIVE PATCH DURING 48 HOURS:
Patch test method

- **Product tested :** Water
  Ascophyllum Nodosum Extract 40,5%
  Halopteris Scoparia Extract 13,5%
- **Promoter :**
- **Monitor :**
- **Objective :** Assessment of the cutaneous local tolerance of the studied product after an epicutaneous test performed in occlusive conditions, during 48 hours.
- **Place of the study:** EUROFINS SCIENTIFIC TEST CENTER,
  3 allée des Ingénieurs
  1140 rue André Ampère
  13851 AIX EN PROVENCE cedex 3
- **Investigator :** Doctor Mary CREST
- **Date of study:** from 28/11/06 to 30/11/06 and from 12/12/06 to 14/12/06
- **Methodology:**
  - ✓ ***Application modes:***

Area of application : on the back
Quantity of product : 0.02 ml
Frequency and duration : only one application during 48 hours
Conditions of application : product applied pure under occlusive patch.

- ✓ ***Assessment method:***

A dermatologist makes the clinical observation, after the removal of the patches. The quantification of the cutaneous irritation is given according to a numeric scale (rash, oedema, dryness, blister). The average Irritant score of the product to be tested is measured with the average of the quotations obtained for the whole volunteers, allowing ranking the product from "not irritant to very irritant". The assessment is always made by comparison with the "negative" control: patch alone.

- **Population:** 11 healthy adult volunteers.
- **Results:** The average irritant score of the product is 0,0.
- **Conclusion:**

According to the experimental conditions taken into account, after only one application of 0.02 ml of product, under occlusive patch and during 48 hours, on 11 healthy adult volunteers, and according to the scale used for the interpretation of the results, the raw material **"ACTISEANE", Lot 06 08 260, can be considered as not irritant regarding its primary cutaneous tolerance.**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 24, 2019

SUBJECT: Information on a Mixture Containing Water and Fucus Serratus Extract

Anonymous. 2019. Specification data sheet for a mixture containing Water and Fucus Serratus Extract.

Anonymous. 2019. Flow chart for a mixture containing Water and Fucus Serratus Extract.

Anonymous. 2019. Attestation on heavy metals for a mixture containing Water and Fucus Serratus Extract.

Eurofins ATS. 2005. Summary: Evaluation of a potential irritancy of a product through its application on the chorioallantoic membrane of a chicken eggshell: Het Cam method (mixture Water and Fucus Serratus Extract).

Eurofins ATS. 2005. Summary: Evaluation of the cutaneous tolerance of a cosmetic product after a single application under occlusive patch during 48 hours: patch test method (mixture Water and Fucus Serratus Extract).

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SPECIFICATION DATA SHEET

Trade name:

Product: -- Version: 1.0 - 2019

Specification: Print date: 01 - 2019

is a calibrated aqueous fraction from the brown algae *Fucus serratus.*

1 – Identification and composition of the substance

Product	N° CAS	N°EINECS	Ingredients %
Water	7732-18-5	231-791-2	56
Fucus serratus extract	94167-02-9	303-400-6	44
Preservative	None		

2 – Characteristics (standard)

Appearance: limpid liquid.

Color: yellow-orange.

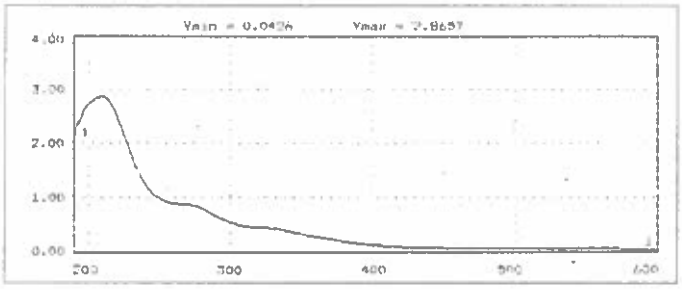
Odour: typical.

pH: 6.0 ± 1.0.

Relative density: 1.020 ± 0.025.

Dry residuals (%): 3.4 ± 0.6.

UV spectrum (5% in water):



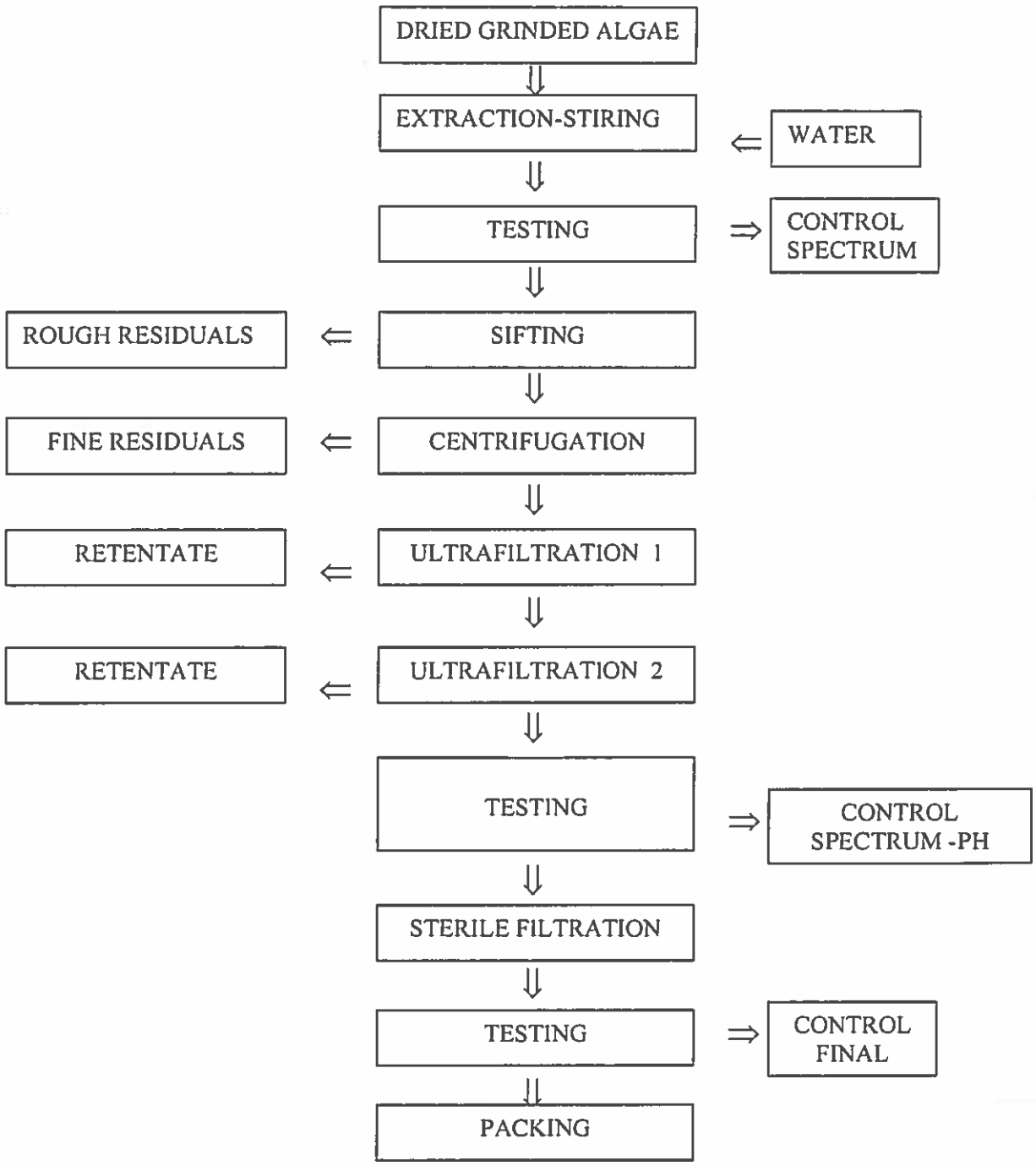
Microbiological quality:
- Total germs (germs/ml): < 100.
- Pathogens: absence.
- Yeasts /moulds: < 100.

Storage: 15°C < store < 25°C.
Validity date: 6 months.

Remark: *No responsibility or liability for any consequences arising from the use of this technical data sheet can be accepted, including possible infringement of any patent.*

FLOW CHART FOR

Water and Fucus Serratus Extract



ATTESTATION ON HEAVY METALS

Product:

INCI names:	Water	CAS n° 7732-18-5	EINECS n° 231-791-2
	Fucus serratus	CAS n° 94167-02-9	EINECS n° 303-400-6

Some heavy metals in SEAVIE® have been analysed. Based on these analysis, it is stated that the heavy metals content is below < 10 ppm in the above named product.

Arsenic : 3.691 ppm - Cadmium: 0.011 ppm - Mercury: < 0.010 ppm - Lead : < 0.010 ppm

Date : 04/01/2019

STUDY SUMMARY

EVALUATION OF THE POTENTIAL IRRITANCY OF A PRODUCT THROUGH ITS APPLICATION ON THE CHORIOALLANTOIC MEMBRANE OF A CHICKEN EGGSHELL: *Het Cam Method*

- **Tested product :** Water and Fucus Serratus Extract 44%
- **Promoter :**
- **Objective:** To assess the irritant potential of the tested product
- **Methodology:** The principle of this study is based on the visual observation, by a trained person, of the possible irritations (hyperaemia, haemorrhaging, coagulation / thrombosis) that may appear during the five minutes that follow the application of the said product on the chorioallantoic membrane of an embryonic chicken egg after eleven days of incubation.
- **Place of study:** EUROFINS ATS, Pôle d'activité d'Aix en Provence
  Actimart, 1140, rue Ampère,
  13851 AIX EN PROVENCE cedex 3
- **Dates of study :** 13/12/2005
- **Results :**

Denomination	ATS Reference	Initial concentration	Results	
			Score	Classification
SEAVIE	131728	5%	3.8	Slightly irritant

- **Conclusion :**

According to the performed experimental conditions, the product tested by the HET CAM method, at 5%, can be considered as slightly irritant regarding its ocular primary tolerance.

2005

eurofins | ATS

STUDY SUMMARY

EVALUATION OF THE CUTANEOUS TOLERANCE OF A COSMETIC PRODUCT AFTER A SINGLE APPLICATION UNDER OCCLUSIVE PATCH DURING 48 HOURS:
Patch test method

- **Product tested :** Water and Fucus Serratus Extract 44%
- **Promoter :**
- **Monitor :**
- **Objective :** Assessment of the cutaneous local tolerance of the studied product after an epicutaneous test performed in occlusive conditions, during 48 hours.
- **Place of the study:** EUROFINS SCIENTIFIC TEST CENTER,
  ACTIMART
  3 allée des Ingénieurs
  1140 rue André Ampère
  13851 AIX EN PROVENCE cedex 3
- **Investigator :** Docteur Amélie MENARD
- **Date of study:** from 13/12/05 to 15/12/05
- **Methodology:**
  - ✓ ***Application modes:***

Area of application : on the back
Quantity of product : 0.02 ml
Frequency and duration : only one application during 48 hours
Conditions of application : product applied at 5%, under occlusive patch.

- ✓ ***Assessment method:***

A dermatologist makes the clinical observation, after the removal of the patches. The quantification of the cutaneous irritation is given according to a numeric scale (rash, oedema, dryness, blister). The average irritant score of the product to be tested is measured with the average of the quotations obtained for the whole volunteers, allowing ranking the product from "not irritant to very irritant". The assessment is always made by comparison with the "negative" control: patch with demineralised water.

- **Population:** 10 healthy adult volunteers.
- **Results:** The average irritant score of the product is 0,0.
- **Conclusion:**

According to the experimental conditions taken into account, after only one application of 0.02 ml of product, under occlusive patch and during 48 hours, on 10 healthy adult volunteers, and according to the scale used for the interpretation of the results, the raw material ' ', **can be considered as not irritant regarding its primary cutaneous tolerance.**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 24, 2019

SUBJECT: Information on a Mixture Containing Water Butylene Glycol and Lessonia Nigrescens Extract

Anonymous. 2019. Specification data sheet for a mixture containing Water, Butylene Glycol and Lessonia Nigrescens Extract.

Anonymous. 2019. Flow chart for a mixture containing Water, Butylene Glycol and Lessonia Nigrescens Extract.

Anonymous. 2019. Attestation on heavy metals for a mixture containing Water, Butylene Glycol and Lessonia Nigrescens Extract.

Eurofins ATS. 2005. Summary: Evaluation du potentiel irritant d'un produit par application sur la membrane chorio-allantoidienne do l'oeuf de poule: methode du Het Cam (mixture Water, Butylene Glycol and Lessonia Nigrescens Extract).

Eurofins ATS. 2005. Summary: Evaluation de la tolerance cutanee d'un produit cosmetique apres application unique sous pansement occlusif pendant 48 heurs: methode des patchs tests (mixture Water, Butylene Glycol and Lessonia Nigrescens Extract).

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SPECIFICATIONS DATA SHHET

Trade name:

Product: N° BG-LENI-00 Version : 1.0 - 2019

Specification: N° S.00 Print date: 01 - 2019

is a standardized and concentrated hydroglycolic extract, selectively prepared from the Chilean brown alga *Lessonia nigrescens*.

1 – Identification of the substance

Product	N° CAS	N°EINECS	Ingredients %
Water	7732-18-5	231-791-2	44
Butylene glycol	107-88-0	203-529-7	44
Lessonia nigrescens extract	-	-	12
Preservative	None		

2 – Characteristics (standard)

Appearance: limpid liquid.

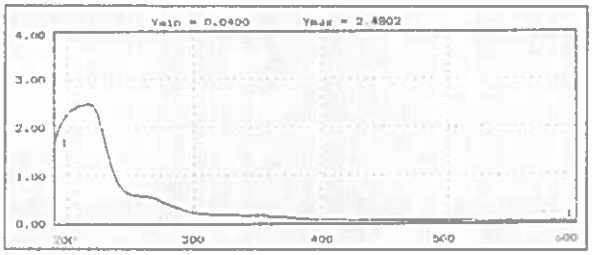
Color: yellow – light orange.

Odour: typical.

pH: 6.0 ± 1.0.

Relative density: 1.040 ± 0.030.

UV spectrum (5% in water)



Microbiological quality

Total germs (germs/ml): < 100.
Pathogens: absence.
Yeasts /moulds: < 100.

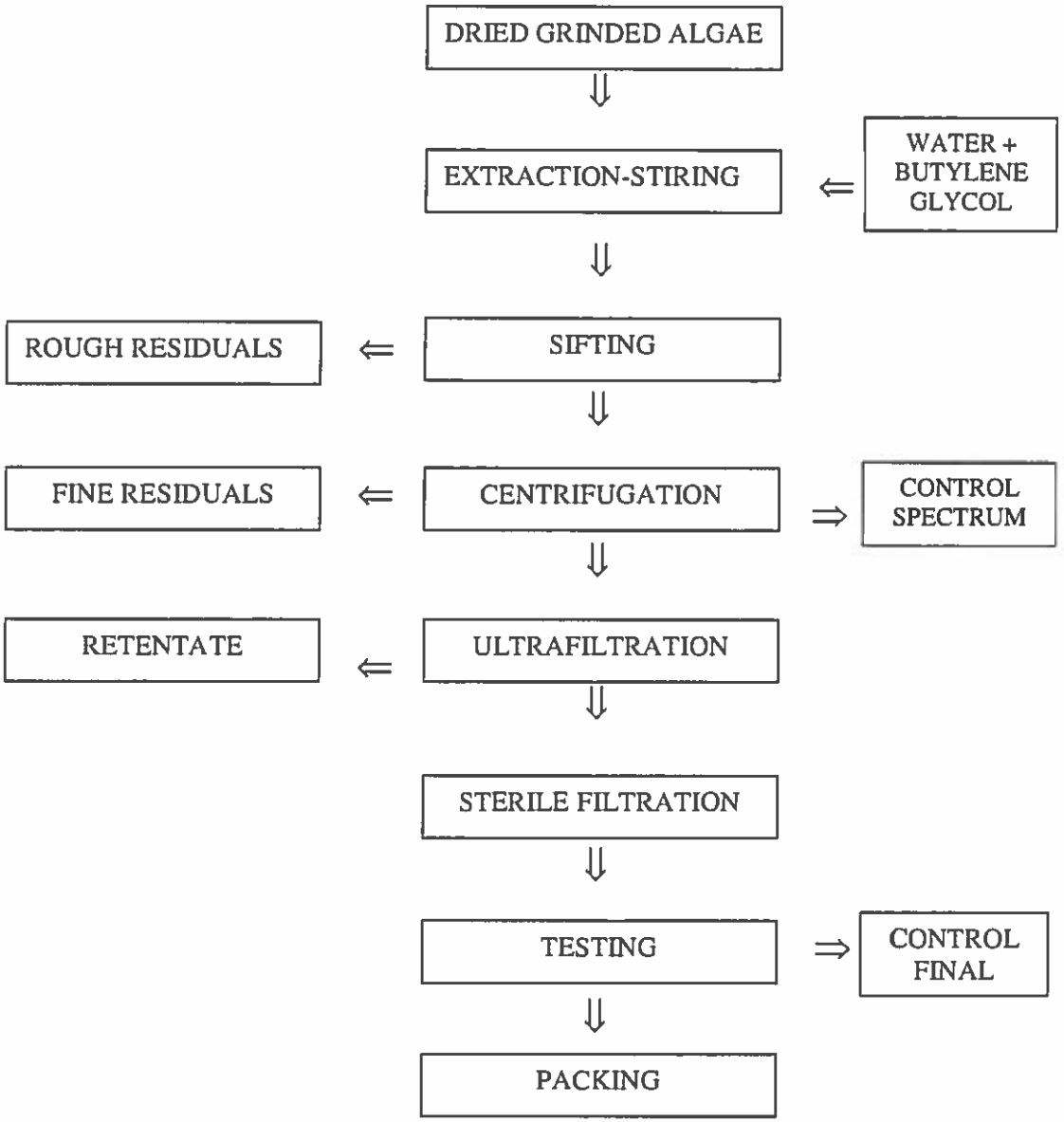
Storage

15°C < store < 25°C.
Validity date: 6 months.

Remark: *No responsibility or liability for any consequences arising from the use of this technical data sheet can be accepted, including possible infringement of any patent.*

FLOW CHART FOR

Water, Butylene Glycol and Lessonia Nigrescens Extract



ATTESTATION ON HEAVY METALS

Product :

INCI names	Water	CAS n° 7732-18-5	EINECS n° 231-791-2
	Butylene glycol	CAS n° 107-88-0	EINECS n° 203-529-7
	Lessonia nigrescens extract		

Some heavy metals in have been analysed. Based on these analysis, it is stated that the heavy metals content is below < 10 ppm in the above named product.

Arsenic : 2.628 ppm - Cadmium: 0.050 ppm - Mercury: 0.012 ppm - Lead : < 0.010 ppm

Date : 04/01/2019

RESULTATS

EVALUATION DU POTENTIEL IRRITANT D'UN PRODUIT PAR APPLICATION SUR LA MEMBRANE CHORIO-ALLANTOÏDIENNE DE L'ŒUF DE POULE : *Méthode du Het Cam*

- **Produit étudié :** Water, Butylene Glycol and
- **Promoteur :** Lessonia Nigrescens Extract 12%
- **Objectif de l'étude :** Evaluer le potentiel irritant du produit étudié
- **Méthodologie :** Le principe en est basé sur l'observation à l'œil nu, par une personne entraînée, des effets irritants (hyperémie, hémorragie, coagulation / thrombose), pouvant survenir dans les cinq minutes suivant le dépôt du produit sur la membrane chorio-allantoïdienne d'œuf de poule embryonné, au onzième jour d'incubation.
- **Lieu de l'étude :** EUROFINS ATS, Pôle d'activité d'Aix en Provence
  Actimart, 1140, rue Ampère,
  13851 AIX EN PROVENCE cedex 3
- **Dates de l'étude :** 20/12/2005
- **Résultats :**

Dénomination	Référence ATS	Concentration initiale	Résultats	
			Score	Classement
	133870	5%	0	Pratiquement non irritant

- **Conclusion :**

Dans les conditions expérimentales retenues, le produit , testé par la méthode officielle du HET CAM, à 5%, peut être considéré comme pratiquement non irritant du point de vue de sa tolérance primaire oculaire.

RESUME DE RAPPORT D'ETUDE

EVALUATION DE LA TOLERANCE CUTANEE D'UN PRODUIT COSMETIQUE APRES APPLICATION UNIQUE SOUS PANSEMENT OCCLUSIF PENDANT 48 HEURES :
Méthode des patchs tests

- **Produit étudié :** Water, Butylene Glycol and Lessonia Nigrescens Extract 12%
- **Promoteur :**
- **Objectif de l'étude :** L'objectif de l'étude est d'apprécier la tolérance locale épicutanée d'un produit cosmétique, après application unique sur la peau du dos et sous patch occlusif, pendant 48h, chez des volontaires adultes, sains.
- **Investigateur :** Docteur Mary CREST
- **Lieu de l'étude :** EUROFINS SCIENTIFIC TEST CENTER
  3 allée des Ingénieurs
  1140 rue André Ampère
  13851 AIX EN PROVENCE cedex 3
- **Dates de l'étude :** du 20/12/05 au 22/12/05
- **Méthodologie :**
  - ✓ ***Modalités d'application :***

Zones d'application : dos
Quantité de produit : 0.02 ml
Fréquence et durée : application unique pendant 48 heures.
Conditions d'application : produit déposé dilué à 5%, sous patch occlusif.

  - ✓ ***Méthode d'évaluation :***

L'observation clinique des effets provoqués est réalisée, par un dermatologue, après le retrait du patch. La cotation clinique est donnée selon une échelle numérique déterminée, en fonction de l'intensité des phénomènes d'irritation observés (érythème, œdème, sécheresse, vésicule). Le score irritant moyen du produit à l'essai est calculé en faisant la moyenne des cotations obtenues pour l'ensemble des volontaires, permettant ainsi de classer le produit de « non irritant à très irritant ». L'évaluation se fait toujours par comparaison au témoin "négatif" : patch contenant de l'eau déminéralisée.

- **Population :** 10 volontaires adultes, sains.
- **Résultats :** Le score irritant moyen du produit est de 0,0.
- **Conclusion :**

Dans les conditions expérimentales retenues, après application unique de 0.02ml de produit, sous patch occlusif pendant 48 heures, chez 10 volontaires adultes sains et selon le barème adopté pour l'interprétation des résultats, la matière première peut être considérée comme non irritante du point de vue de sa tolérance primaire cutanée.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 28, 2019

SUBJECT: Information on a Mixture Containing Water, Fucus Spiralis Extract and Tetraselmis Chi Extract

Anonymous. 2019. Specification data sheet for a mixture containing Water, Fucus Spiralis Extract and Tetraselmis Chi Extract.

Anonymous. 2019. Flow chart for a mixture containing Water, Fucus Spiralis Extract and Tetraselmis Chi Extract.

Anonymous. 2019. Attestation on heavy metals for a mixture containing Water, Fucus Spiralis Extract and Tetraselmis Chi Extract.

Eurofins ATS. 2011. Summary: Evaluation of skin tolerance of a cosmetic product after a single application under occluded patch during 48h on 14 volunteers: 48 hours patch test (Water, Fucus Spiralis Extract and Tetraselmis Chi Extract).

Vivotecnia. 2014. Summary: Bacterial reverse mutation test (Water, Fucus Spiralis Extract and Tetraselmis Chi Extract).

CTI. 2014. Summary: Assessment of sensitizing potential and cutaneous compatibility on healthy adult volunteers according to the Marzulli-Maibach sensitization method Water, Fucus Spiralis Extract and Tetraselmis Chi Extract).

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SPECIFICATION DATA SHEET

Trade name:

Product: Version: 1.0 - 2019

Specification: Print date: 01 - 2019

is an aqueous extract that combines the properties of two algae: the brown seaweed *Fucus spiralis* and the green microalga *Tetraselmis chui* cultured in metabolic induction.

Patent GELYMA: FR 29 80 698 A1

1 – Identification and composition of the substance

Product	N° CAS	N°EINECS	Ingredients %
Water	7732-18-5	231-791-2	80
Fucus spiralis extract	-	-	12
Tetraselmis chui extract	-	-	8
Preservative	None		

2 – Characteristics (standard)

Appearance: limpid liquid.

Color: amber.

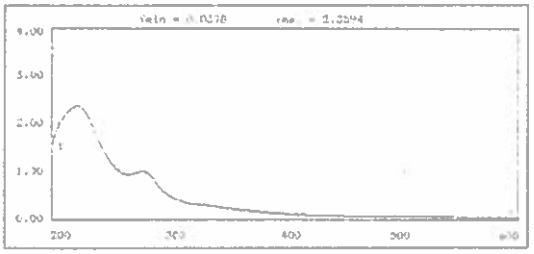
Odour: *sui generis.*

pH: 6.0 ± 1.0.

Relative density: 1.015 ± 0.015.

Dry residuals (%): 2.5 ± 0.5.

UV spectrum (5% in water):



Microbiological quality:
Total germs (germs/ml): < 100.
Pathogens: absence.
Yeasts /moulds: < 100.

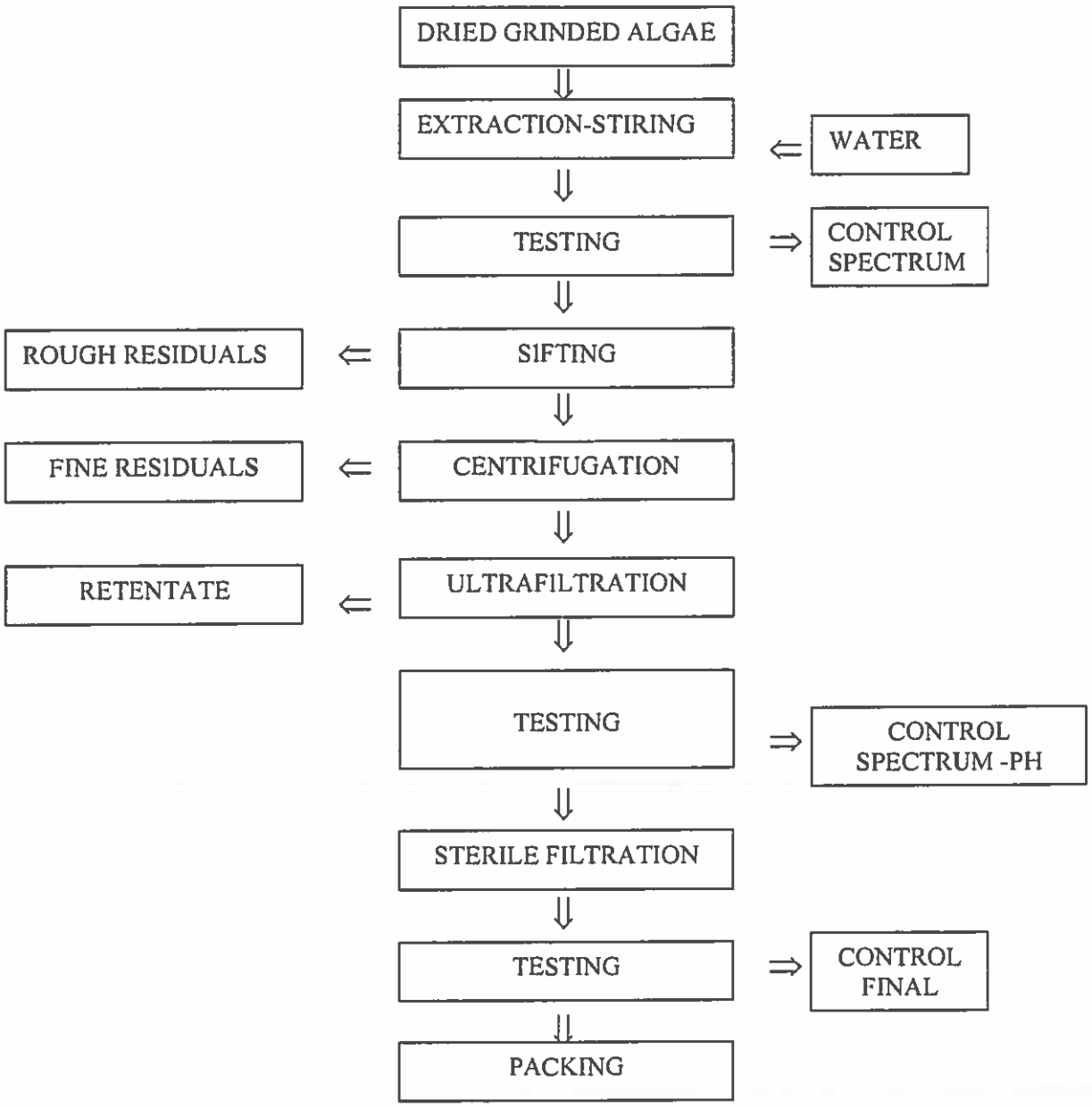
Storage: 15°C < store < 25°C.
Validity date: 6 months.

Remark: *No responsibility or liability for any consequences arising from the use of this technical data sheet can be accepted, including possible infringement of any patent.*

2019

FLOW CHART FOR

Water
Fucus spiralis Extract 12%
Tetraselmis Chui Extract



ATTESTATION ON HEAVY METALS

Product :

INCI names :

water CAS n° 7732-18-5 EINECS n° 231-791-2

Fucus spiralis extract

Tetraselmis chui extract

Some heavy metals in ' have been analysed. Based on these analysis, it is stated that the heavy metals content is below < 10 ppm in the above named product.

Arsenic : 0.65 ppm - Cadmium : < 0.05 ppm - Mercury: < 0.05 ppm - Lead : < 0.05 ppm

Date : 04/01/2019

2011

STUDY SUMMARY

EVALUATION OF SKIN TOLERANCE OF A COSMETIC PRODUCT AFTER A SINGLE APPLICATION UNDER OCCLUDED PATCH DURING 48H ON 14 VOLUNTEERS: *48 hours patch tests*

- **Product tested:** water Fucus Spiralis Extract 12% Tetraselmis Chui Extract
- **Promotor:**
- **Objective:** Assessment of the skin local tolerance of the studied product after an epicutaneous test performed in occluded conditions, during 48 hours.
- **Investigator:** Doctor Mary CREST, dermatologist
- **Place of the study:** EUROFINS ATS
  Pôle d'activité Aix-Les-Milles - ACTIMART
  3 allée des Ingénieurs
  1140 rue André Ampère
  13851 AIX EN PROVENCE cedex 3
- **Dates of study:** from 25/01/2011 to 27/01/2011
- **Method:**

✓ ***Application:***

Area: on the back
Quantity of product: 0.02 mL
Frequency and duration: only one application during 48 hours
Conditions of application: product applied diluted at 10% under occluded patch.

✓ ***Assessment method:***

A dermatologist performs the clinical observation, after the removal of the patches. The quantification of the skin irritation is given through a numeric scale (erythema, oedema, dryness/desquamation, vesicle). The average irritant score of the product to be tested is calculated from the average of the quotations obtained for each volunteer, allowing to rank the product from "non irritant to very irritant". The assessment is always made by comparison with the "negative" control.

- **Panel:** 14 healthy adult volunteers.
- **Result:** The average irritant score of the product is 0.00.
- **Conclusion:**

According to the experimental conditions of the study, **the product, referenced : n be considered as non irritant regarding its primary skin tolerance.**

2014

3 SUMMARY

The bacterial reverse mutation test (Ames test) assesses the mutagenic or promutagenic potential of the test item ..ne several bacterial strains. Water, Fucus Spiralis Extract 12% Tetraselmis Chui Extract

The test was performed in accordance with OECD Guideline 471 for the Testing of Chemicals (Bacterial Reverse Mutation Test. Adopted 21st July 1997) and the test Method B13/B14 of Commission Directive 2000/32/EC.

No cytotoxic activity was observed by the test item in the bacterial system at a concentration of 5 µL/plate.

Five test item doses ranged between 5,00 and 0,06 µL/plate. None of the concentrations assayed for the test item showed an increase in the R value either with or without S9 metabolic activation regardless of the procedure.

No dose response for the test item as observed in any of the tested bacterial strains.

Based on the results obtained in this study, it can be concluded that the test item does not induce point mutations or frame-shifts in the genome of the bacterial strains with or without metabolic activation regardless of the procedure.

Therefore, the test item is considered to be **NON MUTAGENIC / NON PRO-MUTAGENIC** under the experimental conditions assayed.

4 OBJECTIVE

The objective of the bacterial reverse mutation test (Ames test) was to assess the mutagenic or promutagenic potential of a given test item in a bacterial test system.

5 TEST PRINCIPLE

The Ames test evaluates the potential of the test item to revert mutations present in amino-acid requiring bacterial strains. The reversion restores the functional capability of the bacteria to synthesize the essential amino-acid thus enabling the bacterial culture to grow in the absence of the amino-acid required by the parent bacterial strain.

Many chemicals are not mutagenic in their native forms, but are converted into mutagenic substances by metabolism in the liver. Selected bacterial strains do not produce the enzymes required to transform these chemicals. To identify the promutagenic potential of a test item, the metabolic activation system (commercially available post-mitochondrial fraction (S9) from livers of rodents treated with the enzyme inducing agent Aroclor) is also used in the test.

The mutagenic or promutagenic potential of the test item is assessed by the increase in the number of revertant colonies upon exposure to the test item relative to the number of spontaneously occurring revertant colonies in the controls.

EVALUATION DU POTENTIEL SENSIBILISANT ET DE LA COMPATIBILITE CUTANEE CHEZ LE VOLONTAIRE ADULTE SAIN SELON LA METHODE DE MARZULLI-MAIBACH

ASSESSMENT OF SENSITISING POTENTIAL AND CUTANEOUS COMPATIBILITY ON HEALTHY ADULT VOLUNTEER ACCORDING TO THE MARZULLI-MAIBACH SENSITISATION METHOD

Etude clinique sur 105 volontaires (tout type de peau)
Clinical study in 105 volunteers (all type of skin)

- Code étude / *Study code* : 3.04
- Elément d'essai / *Test item* : CT14/0001

ELEMENT D'ESSAI / *TEST ITEM*	:	Water
CODE TESTS / *TESTS CODE*	:	Fucus Spiralis Extract 12%
DILUTION / *DILUTION*	:	**PUR** / *PURE*
INVESTIGATEUR / *INVESTIGATOR*	:	**DR. DALIA STANCIU** **DERMATOLOGUE** / *DERMATOLOGIST*
PROMOTEUR / *SPONSOR*	:	
DATE DU RAPPORT	:	20/05/2014

Tetraselmis Chui Extract

CTI
IULIU TEODORI, NR.1 SECTOR 5
010221 BUCAREST ROMANIA

8. RESULTAS ET DISCUSSION / *RESULTS AND DISCUSSION*

Le tableau 1 décrit les caractéristiques des volontaires, les tableaux 2 et 3 les scores individuels.
See Table 1 for Volunteer characteristics, Table 2 and Table 3 for Individual scores:

- ❖ 106 sujets ont été inclus dans cette étude :
  106 subjects were empanelled for this test:
  - Un total de 105 sujets a terminé l'étude sur l'élément d'essai :
    A total of 105 subjects satisfactorily completed the test procedure on test item:
  - 1 sujet n'a pas poursuivi l'étude, après la 2ème application, volontaire n°8, du 1er panel, abandon « perdu de vue ».
  - *1 subject was discontinued during the test procedure, after the 2nd application volunteer n° 8, of the 1st panel, withdrawal "lost to follow up".*

- ❖ Lors de la phase d'induction :
  During the induction phase:
  Il y a eu un érythème léger chez le volontaire n°44 du 1er panel.
  There was a mild erythema on subject n° 44 of the 1st panel

- ❖ Lors de la phase de révélation :
  During the challenge phase:
  Aucune réaction cutanée n'a été observée.
  There were no responses to any subject.

9. CONCLUSIONS / *CONCLUSIONS*

Dans les conditions de l'étude après applications répétées d'un patch occlusif sur un panel de 105 volontaires sains, ayant tout type de peau au niveau du corps, l'élément d'essai "testé dermatologiquement" n'a induit ni de réaction de type irritative, ni de réaction de type allergique chez l'homme.
Under the conditions of a repeated insult occlusive patch test procedure conducted in a panel of 105 healthy subjects, with all type of body skin, the test item was "Dermatologist-Tested" and did not induce skin irritation nor show any evidence of induced allergic contact dermatitis in human subjects.

L'élément d'essai SEBOCEA® code CT14/0001 peut être considéré comme « hypoallergénique ».
*The test item **SEBOCEA® code CT14/0001** can be considered "hypoallergenic".*

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 28, 2019

SUBJECT: Information on a Mixture Containing Water, and Sargassum Muticum Extract

Anonymous. 2019. Specification data sheet for a mixture containing Water, and Sargassum Muticum Extract.

Anonymous. 2019. Flow chart for a mixture containing Water, and Sargassum Muticum Extract.

Anonymous. 2019. Attestation on heavy metals for a mixture containing Water, and Sargassum Muticum Extract.

Eurofins ATS. 2006. Summary: Evaluation of the potential irritancy of a product through its application on the chorioallantoic membrane of a chicken eggshell: Het Cam Method (Water, and Sargassum Muticum Extract).

Eurofins ATS. 2006. Summary: Evaluation of the cutaneous tolerance of a cosmetic product after a single application under occlusive patch during 48 hours: patch test method (Water, and Sargassum Muticum Extract).

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Gelyma

SPECIFICATION DATA SHEET

Trade name:

Product: Version: 1.0 - 2019

Specification: Print date: 01 - 2019

is a patented aqueous and concentrated fraction prepared selectively from the symplasm of the brown algae *Sargassum muticum* collected exclusively from populations growing along farming sites.

Patent

1 – Identification and composition of the substance

Product	N° CAS	N°EINECS	Ingredients %
Water	7732-18-5	231-791-2	54
Sargassum muticum extract	-	-	46
Preservative	None		

2 – Characteristics (standard)

Appearance: limpid liquid.

Color: orange light to dark.

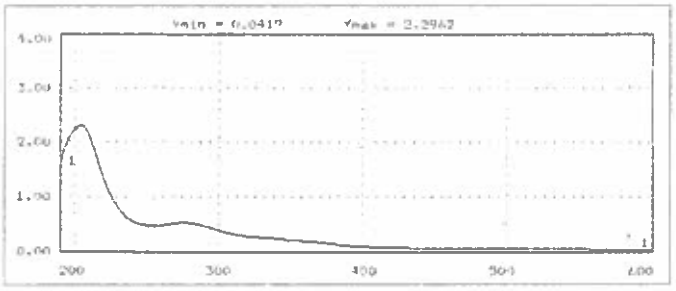
Odour: *sui generis.*

pH 5.5 ± 1.0.

Relative density: 1.013 ± 0.010.

Dry residuals (%): 2.3 ± 0.5.

UV spectrum (5% in water)



Microbiological quality:

Total germs (germs/ml): < 100.
Pathogens: absence.
Yeasts /moulds: < 100.

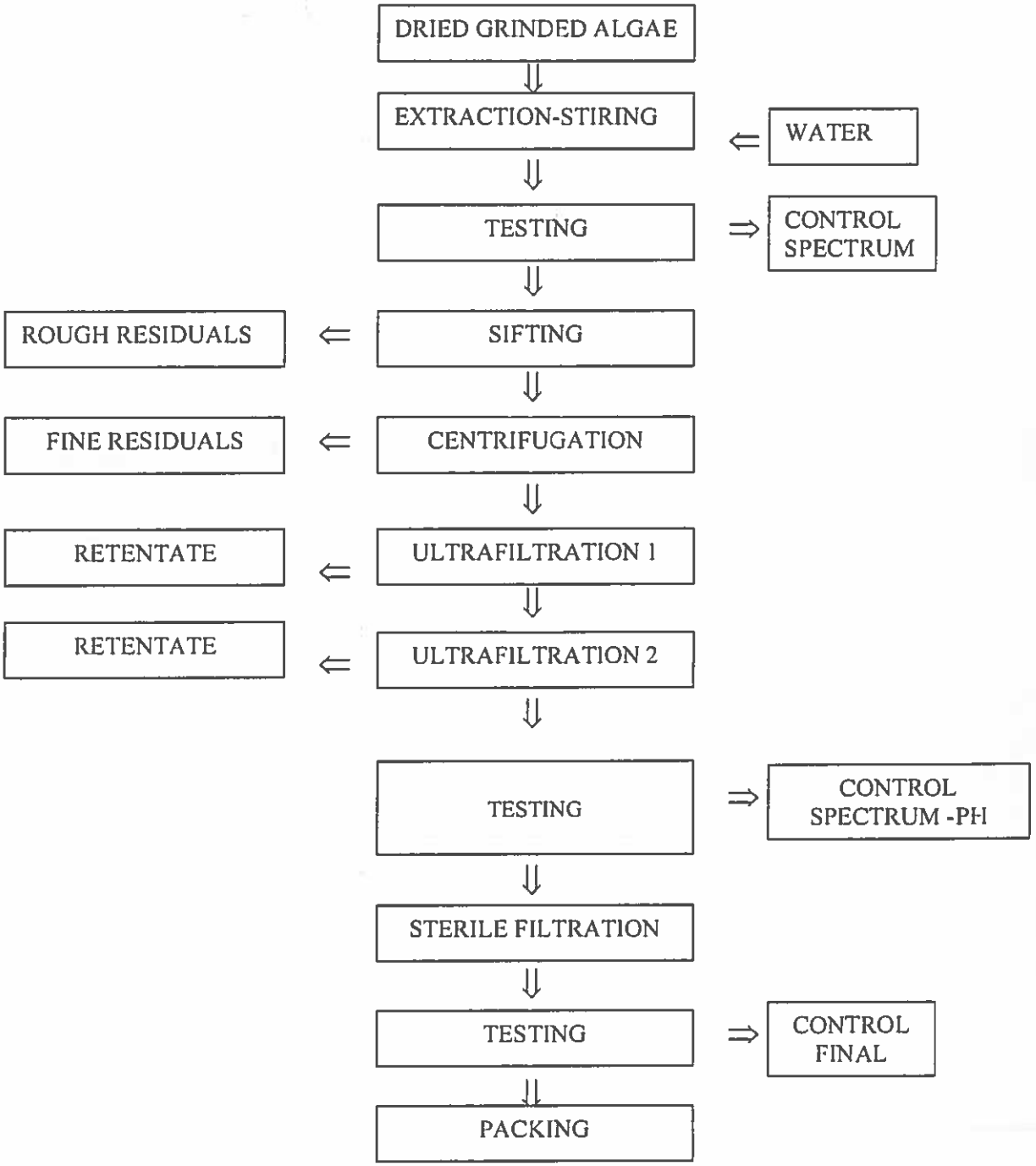
Storage: 15°C < store < 25°C.
Validity date: 6 months.

Remark: *No responsibility or liability for any consequences arising from the use of this technical data sheet can be accepted, including possible infringement of any patent.*

2019

FLOW CHART FOR

Water and Sargassum Muticum Extract



ATTESTATION ON HEAVY METALS

Product :

INCI names : Water CAS n° 7732-18-5 EINECS n° 231-791-2
Sargassum muticum extract

Some heavy metals in have been analysed. Based on these analysis, it is stated that the heavy metals content is below < 10 ppm in the above named product.

Arsenic : 1.562 ppm - Cadmium: < 0.010 ppm - Mercury: < 0.010 ppm - Lead : < 0.010 ppm

Date : 04/01/2019

STUDY SUMMARY

EVALUATION OF THE POTENTIAL IRRITANCY OF A PRODUCT THROUGH ITS APPLICATION ON THE CHORIOALLANTOIC MEMBRANE OF A CHICKEN EGGSHELL: *Het Cam Method*

- **Tested product :** Water Sargassum Muticum Extract 46 %
- **Promoter :**
- **Objective:** To assess the irritant potential of the tested product
- **Methodology:** The principle of this study is based on the visual observation, by a trained person, of the possible irritations (hyperaemia, haemorrhaging, coagulation / thrombosis) that may appear during the five minutes that follow the application of the said product on the chorioallantoic membrane of an embryonic chicken egg after eleven days of incubation.
- **Dates of study :** 12/12/2006
- **Place of study:** EUROFINS ATS, Pôle d'activité d'Aix en Provence
  Actimart, 1140, rue Ampère,
  13851 AIX EN PROVENCE cedex 3
- **Results :**

Denomination	ATS Reference	Initial concentration	Results	
			Score	Classification
	167110	100%	1.3	Slightly Irritant

- **Conclusion :**

According to the performed experimental conditions, the product : L tested by the HET CAM method, at 100 %, can be considered as slightly irritant regarding its ocular primary tolerance.

STUDY SUMMARY

EVALUATION OF THE CUTANEOUS TOLERANCE OF A COSMETIC PRODUCT AFTER A SINGLE APPLICATION UNDER OCCLUSIVE PATCH DURING 48 HOURS:
Patch test method

- **Product tested :** water Sargassum Muticum Extract 40%
- **Promoter :**
- **Monitor :**
- **Objective :** Assessment of the cutaneous local tolerance of the studied product after an epicutaneous test performed in occlusive conditions, during 48 hours.
- **Place of the study:** EUROFINS SCIENTIFIC TEST CENTER,
  3 allée des Ingénieurs
  1140 rue André Ampère
  13851 AIX EN PROVENCE cedex 3
- **Investigator :** Doctor Mary CREST
- **Date of study:** from 28/11/06 to 30/11/06 and from 12/12/06 to 14/12/06
- **Methodology:**
  - ✓ ***Application modes:***

Area of application : on the back
Quantity of product : 0.02 ml
Frequency and duration : only one application during 48 hours
Conditions of application : product applied pure under occlusive patch.

- ✓ ***Assessment method:***

A dermatologist makes the clinical observation, after the removal of the patches. The quantification of the cutaneous irritation is given according to a numeric scale (rash, oedema, dryness, blister). The average Irritant score of the product to be tested is measured with the average of the quotations obtained for the whole volunteers, allowing ranking the product from "not Irritant to very irritant". The assessment is always made by comparison with the "negative" control: patch alone.

- **Population:** 11 healthy adult volunteers.
- **Results:** The average irritant score of the product is 0,0.
- **Conclusion:**

According to the experimental conditions taken into account, after only one application of 0.02 ml of product, under occlusive patch and during 48 hours, on 11 healthy adult volunteers, and according to the scale used for the interpretation of the results, the raw material ' **can be considered as not irritant regarding its primary cutaneous tolerance.**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 28, 2019

SUBJECT: Information on a Mixture Containing Water and Pelvetia Canaliculata Extract

Anonymous. 2019. Specification data sheet for a mixture containing Water and Pelvetia Canaliculata Extract.

Anonymous. 2019. Flow chart for a mixture containing Water and Pelvetia Canaliculata Extract.

Anonymous. 2019. Attestation on heavy metals for a mixture containing Water and Pelvetia Canaliculata Extract.

Eurofins ATS. 2006. Summary: Evaluation of the potential irritancy of a product through its application on the chorioallantoic membrane of a chicken eggshell: Het Cam method (Water and Pelvetia Canaliculata Extract).

Eurofins ATS. 2006. Summary: Evaluation of the cutaneous tolerance of a cosmetic product after a single application under occlusive patch during 48 hours: patch test method (Water and Pelvetia Canaliculata Extract).

Roben Production Grup SRL. 2011. Assessment of sensitizing potential in the adult volunteer following the method of Marzulli-Maibach (Water and Pelvetia Canaliculata Extract).

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

SPECIFICATION DATA SHEET

Trade name:

Product: Version: 1.0 - 2019

Specification: Print date: 01 - 2019

is a patented cytoplasmic fraction prepared from the cytosol of the brown algae (*Phaeophyta*): *Pelvetia canaliculata.*

Patent GELYMA: FR 28 38 340.

1 – Identification and composition of the substance

Product	N° CAS	N°EINECS	Ingredients %
Water	7732-18-5	231-791-2	56
Pelvetia canaliculata extract	223751-75-5	-	44
Preservative	None		

2 – Characteristics (standard)

Appearance: limpid liquid.

Color: brown.

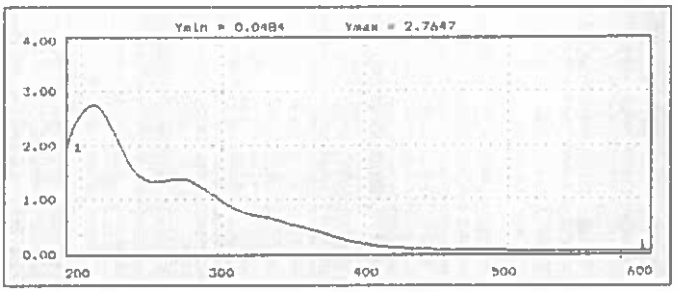
Odour: *sui generis.*

pH: 5.8 ± 1.0.

Relative density: 1.017 ± 0.015.

Dry residuals (%): 3.2 ± 0.5.

UV spectrum (5% in water):



Microbiological quality: Total germs (germs/ml): < 100.
Pathogens: absence.
Yeasts /moulds: < 100.

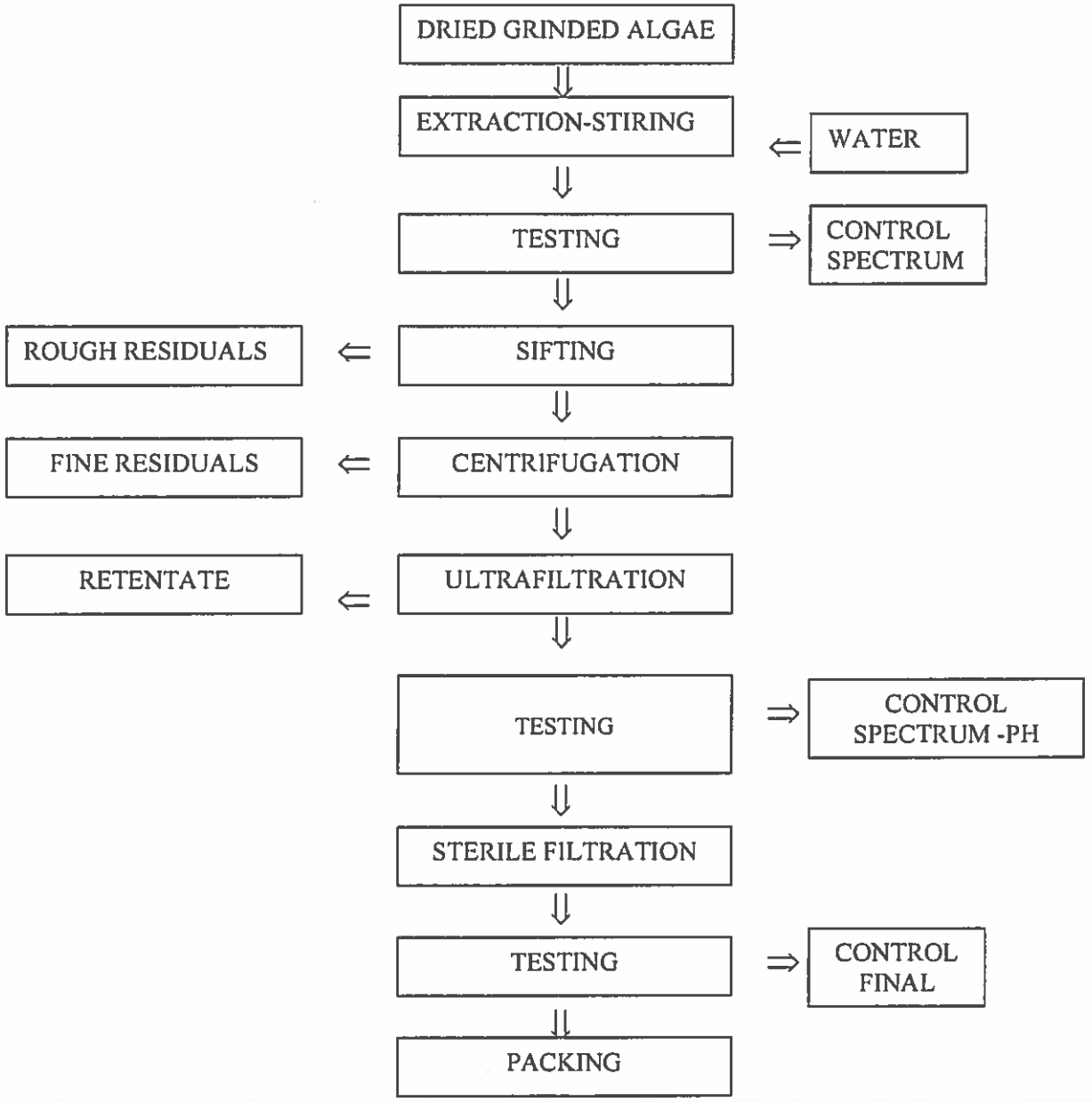
Storage: 15°C < store < 25°C.
Validity date: 6 months.

Remark: *No responsibility or liability for any consequences arising from the use of this technical data sheet can be accepted, including possible infringement of any patent.*

2019

FLOW CHART FOR

Water and
Pelvetia Canaliculata Extract



ATTESTATION ON HEAVY METALS

Product:

INCI names water CAS n° 7732-18-5 EINECS n° 231-791-2
Pelvetia canaliculata extract
CAS n° 223751-75-5

Some heavy metals in have been analysed. Based on these analysis, it is stated that the heavy metals content is below < 10 ppm in the above named product.

Arsenic : 2.383 ppm - Cadmium: < 0.010 ppm - Mercury: < 0.010 ppm - Lead : < 0.010 ppm

Date : 04/01/2019

STUDY SUMMARY

EVALUATION OF THE POTENTIAL IRRITANCY OF A PRODUCT THROUGH ITS APPLICATION ON THE CHORIOALLANTOIC MEMBRANE OF A CHICKEN EGGSHELL: *Het Cam Method*

- **Tested product :** Water and Pelvetia Canaliculata (44%)
- **Promoter :**
- **Objective:** To assess the irritant potential of the tested product
- **Methodology:** The principle of this study is based on the visual observation, by a trained person, of the possible irritations (hyperaemia, haemorrhaging, coagulation / thrombosis) that may appear during the five minutes that follow the application of the said product on the chorioallantoic membrane of an embryonic chicken egg after eleven days of incubation.
- **Dates of study :** 12/12/2006
- **Place of study:** EUROFINS ATS, Pôle d'activité d'Aix en Provence
  Actimart, 1140, rue Ampère,
  13851 AIX EN PROVENCE cedex 3
- **Results :**

Denomination	ATS Reference	Initial concentration	Results	
			Score	Classification
		100%	3.3	Slightly irritant

- **Conclusion :**

According to the performed experimental conditions, the product tested by the HET CAM method, at 100 %, can be considered as slightly irritant regarding its ocular primary tolerance.

STUDY SUMMARY

EVALUATION OF THE CUTANEOUS TOLERANCE OF A COSMETIC PRODUCT AFTER A SINGLE APPLICATION UNDER OCCLUSIVE PATCH DURING 48 HOURS:
Patch test method

- **Product tested :** Water and Pelvetia canaliculata Extract (44%)
- **Promoter :**
- **Monitor :**
- **Objective :** Assessment of the cutaneous local tolerance of the studied product after an epicutaneous test performed in occlusive conditions, during 48 hours.
- **Place of the study:** EUROFINS SCIENTIFIC TEST CENTER,
  3 allée des Ingénieurs
  1140 rue André Ampère
  13851 AIX EN PROVENCE cedex 3
- **Investigator :** Doctor Mary CREST
- **Date of study:** from 28/11/06 to 30/11/06 and from 12/12/06 to 14/12/06
- **Methodology:**
  ✓ ***Application modes:***

Area of application : on the back
Quantity of product : 0.02 ml
Frequency and duration : only one application during 48 hours
Conditions of application : product applied pure under occlusive patch.

✓ ***Assessment method:***

A dermatologist makes the clinical observation, after the removal of the patches. The quantification of the cutaneous irritation is given according to a numeric scale (rash, oedema, dryness, blister). The average irritant score of the product to be tested is measured with the average of the quotations obtained for the whole volunteers, allowing ranking the product from "not irritant to very irritant". The assessment is always made by comparison with the "negative" control: patch alone.

- **Population:** 11 healthy adult volunteers.
- **Results:** The average irritant score of the product is 0,0.
- **Conclusion:**

According to the experimental conditions taken into account, after only one application of 0.02 ml of product, under occlusive patch and during 48 hours, on 11 healthy adult volunteers, and according to the scale used for the interpretation of the results, the raw material ' :**an be considered as not irritant regarding its primary cutaneous tolerance.**

2011

ROBEN PRODUCTION GRUP SRL
CENTRUL DE CERCETARE A PLANTELOR
STRADA LUGOJ NR. 63 SECTOR 1, BUCURESTI, ROMANIA

EVALUATION DU POUVOIR SENSIBILISANT CHEZ LE VOLONTAIRE ADULTE SELON LA METHODE DE MARZULLI-MAIBACH

ASSESSMENT OF SENSITIZING POTENTIAL IN THE ADULT VOLUNTEER FOLLOWING THE METHOD OF MARZULLI-MAIBACH

Etude clinique sur 105 volontaires, tout type de peau
Clinical study on 105 volunteers, with all skin type

- Etude/ *Study*: 3.04
- Produit/ *Product*: RB10/0032

PRODUIT / *Product*	Water and Pelvetia Canaliculata Extrac 44%
CODE PRODUIT / *Code product*	:
DILUTION / *Dilution*	: PUR PURE
INVESTIGATEUR / *Investigator*	: DR. ANNE-MARIE MARINESCU

5. PANEL/ *TEST SUBJECTS*

111 volontaires, 93 femmes et 18 hommes âgés de 20 à 70 ans, ont été sélectionnés pour ce test.

111 subjects, 93 females and 18 males ranging in age from 20 to 70 years were empanelled for this test.

Les volontaires ont été choisis aptes à lire et comprendre les instructions. Les volontaires n'ont montré aucune pathologie ou lésion dermatologique pouvant perturber l'application du produit testé ou la lecture des réactions.

The subjects chosen were dependable and able to read and understand instructions. The subjects did not exhibit any physical or dermatological condition that would have precluded application of the test article or determination of potential effects of the test article.

6. DEROULEMENT DU TEST/ *TEST PROCEDURE*

Les 9 applications répétées (sous pansement occlusif) du patch-test (9-RIPT) ont été conduites comme suit/ *The 9 Repeated Insult (occlusive) Patch Test (9-RIPT) was conducted as follows:*

6.1. Phase d'induction/ *Induction phase*

Une quantité suffisante du produit testé pour couvrir la surface du patch a été placée sur le pansement occlusif type Haye's-Chambers et appliqué au niveau du dos de chaque volontaire entre l'omoplate et la taille, adjacente à la ligne médiane spinale. Cette procédure a été exécutée par l'investigateur et répétée chaque lundi, mercredi et vendredi jusqu'à 9 applications.

A sufficient amount of the tested product to cover the surface of the patch was placed into a Haye's chamber occlusive patch and applied to the back of each subject between the scapulae and waist, adjacent to the spinal mid-line. This procedure was performed by the investigator and repeated every Monday, Wednesday and Friday until 9 applications.

48 heures après la pose du patch, l'investigateur a procédé à la lecture du site, 20 minutes après l'enlèvement du patch. Les volontaires ont été formés pour enlever le patch le dimanche et la lecture est effectuée le lundi par l'investigateur.

48 hours after the pose of the patch, the investigator reads the site, 20 minutes after remove the patch. The subjects were formed to remove the patch on Sundays and the reading is made on Mondays by the investigator.

Si un volontaire a développé une réaction positive d'un érythème de niveau 2 ou plus important, pendant la phase d'induction, ou si, à l'appréciation de l'investigateur, la réponse de la peau a justifié un changement de site, le patch a été appliqué sur un site adjacent, qui n'avait pas été patché précédemment. Si un niveau 2 d'irritation ou plus a été observé au niveau du nouveau site, aucune nouvelle application n'a été faite. Cependant, n'importe quel volontaire ayant réagit sera par la suite évalué sur le patch du Challenge.

If subject developed a positive reaction of a level 2 erythema or greater during the Induction phase or if, at the discretion of the investigator, the skin response warranted a change in site, the patch was applied to a previously unpatched, adjacent site for the next application. If a level 2 reaction or greater occurred at the new site, no further applications were made. However, any reactive subjects were subsequently Challenge patch tested.

Les réponses dermatologiques pendant la phase d'induction de l'étude étaient notées selon l'échelle suivante/ *Dermal responses for the Induction phase of the study were scored according to the following scale :*

- = Aucune réaction mise en évidence/ *No evidence of any effect*
1 = Léger (érythème rose et uniforme couvrant la plupart du site de contact)/ *Mild (Pink, uniform erythema covering most of the contact site)*
2 = Modéré (érythème uniforme rose / rouge sur la totalité du site de contact)/ *Moderate (Pink-red erythema uniform in the entire contact site)*
3 = Marqué (érythème rouge vif avec ou sans pétéchies ou papules)/ *Marked (Bright red erythema with/ without petechiae or papules)*

4 = Sévère (érythème rouge foncé avec ou sans vésicules ou bulles)/ *Severe (Deep red erythema with/ without vesiculation or weeping)*

(L'ensemble des réactions dermatologiques observées (œdème, sécheresse, hypo pigmentation ou hyperpigmentation) a été convenablement enregistré sur le cahier d'observation et décrit comme léger, modéré ou sévère).

(All other observed dermal sequelae (eg, oedema, dryness, hypo- or hyperpigmentation) were appropriately recorded on the data sheet and described as mild, moderote or severe).

6.2. Phase de Challenge/ *Challenge Phase*

Après une période de repos de 2 semaines (aucune application du produit testé), le patch de Challenge a été appliqué durant 48 heures sur un site n'ayant pas été patché au préalable (vierge) et sur le site ayant été patché durant la phase d'induction (induit). La lecture a été effectuée 30 minutes, 24 heures et 48 heures après le retrait du patch. Tous les volontaires sont formés pour noter toutes les réactions tardives de la peau qui surviennent après la lecture finale du patch de Challenge.

After a rest period of 2 weeks (no applications of the test article), the Challenge patch was applied to a previously unpatched (virgin) and patched (inductal) test site. The site was scored 30 minutes, 24 and 48 hours after removal. All subjects were instructed to report any delayed skin reactivity that occurred after the final Challenge patch reading.

Les réponses dermatologiques pour la phase de Challenge de l'étude ont été notées selon les critères du I.C.D.R.G. (Groupe de Contact International de Recherche de Dermatite)/ *Dermal responses for the Challenge phase of the study were scored according to the following criteria of I.C.D.R.G. (the International Contact Dermatitis Research Group):*

Note / *Score*	**Interprétations** / *Interpretation*
-	Négatif/ *Negative*
+?	Réaction douteuse [a] (léger érythème) / *Doubtful reaction [a] (Slight erythema)*
+	Faible réaction (non vésiculaire) [b] / *Weak (non-vesicular) reaction [b]*
++	Forte réaction (oedème ou vésicules) / *Strong (oedematous or vesicular) reaction*
+++	Extrême (bulles ou ulcères) [c] / *Extreme (bullous or ulcerative) [c]*
NT	Non testé/ *Not tested*
IR	Réaction irritante de différent type / *Irritant reaction of different types*

[a] ?+ est un érythème douteux, faible, maculaire (non palpable) et qui n'est pas interprété comme étant une réaction allergique probante/ *is a questionable faint or macular (non-palpable) erythema and is not interpreted as proven allergic reaction*

[b] + est un érythème palpable, suggestif d'une légère réaction oedémique/ *is a palpable erythema, suggestive of a slight oedematous reaction*

[c] de vésicules/ *from coalescing vesicles*

7. RESULTATS ET INTERPRETATIONS/ *RESULTS AND DISCUSSION*

Voir la table 1 pour les caractéristiques des volontaires, la table 2 et la table 3 pour les scores individuels/ *See table 1 for volunteer characteristics, table 2 and table 3 for individual scores*

- 111 volontaires ont été sélectionnés pour ce test/ *111 subjects were empanelled for this test:*
  - Un total de 105 volontaires a terminé de façon satisfaisante la procédure de test sur le produit testé:

  A total of 105 subjects satisfactorily completed the test procedure on tested product:

- 6 volontaires ont été sortis de l'essai: n° 18, n° 27, n° 34, n° 81, n° 96 et n° 99, après la 1ère, 4ème, 5ème et 9ème applications, en raison d'une déviation au protocole.

-6 subjects were discontinued: n° 18, n°27, n° 34, n° 81, n° 96 and n° 99, after the 1 st, 4th, 5th and 9th applications due to a violation of the Protocol.

❖ Pendant la phase d'induction/ *During the induction phase*
- Il n'y a eu aucune réaction chez les volontaires.
- *There were no responses on any subject.*

❖ Pendant la phase de challenge/ *During the challenge phase*
- Il n'y a eu aucune réaction chez les volontaires.
- *There were no responses on any subject.*

8. CONCLUSIONS/ *CONCLUSIONS*

Dans les conditions d'une application répétée de la procédure de patch-test conduite auprès d'un panel de 105 volontaires présentant tout type de peau, le produit [redacted] a été «Testé dermatologiquement» et n'a pas présenté de risque d'irritation de la peau cliniquement significative ni montrer de réaction de type allergique au contact de la peau humaine.

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in a panel of 105 subjects, with all skin type, the product [redacted] was "Dermatologist-Tested" and did not induce clinically significant skin irritation nor show any evidence of induced allergic contact dermatitis in human subjects.

Le produit [redacted] peut être considéré comme «hypoallergénique».

The product [redacted] can be considered as "hypoallergenic".

TABLE DES MATIERES

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EVALUATION DU POUVOIR SENSIBILISANT CHEZ LE VOLONTAIRE ADULTE SELON LA METHODE DE MARZULLI-MAIBACH

ASSESSMENT OF SENSITIZING POTENTIAL IN THE ADULT VOLUNTEER FOLLOWING THE METHOD OF MARZULLI-MAIBACH

Produit/ *Product*: EFFICIENSEA
RB10/0032

ANNE-MARIE MARINESCU
Dermatologue
Investigateur médical
Directeur d'Etude
Dermatologist
Medical Investigator
Study Director

Date/ *Date*

MONICA ADY
Responsable Qualité
Quality Manager

Date/ *Date*

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 29, 2019

SUBJECT: Fucus Vesiculosus Extract

Consumer Product Testing Co. 2013. Repeated insult patch test of a trade name mixture containing 0.1% Fucus Vesiculosus Extract (tested undiluted).

Consumer Product Testing Co. 2016. Repeated insult patch test of a trade name mixture containing 0.1% Fucus Vesiculosus Extract (10% dilution tested).

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Consumer Product Testing Co.

EST. 1972

FINAL REPORT

CLIENT:

ATTENTION:

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

TEST MATERIAL: Trade name mixture containing 0.1% Fucus Vesiculosus Extract

EXPERIMENT REFERENCE NUMBER:

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

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

Approved by: Joy Frank, R.N.
Executive Vice President, Clinical Evaluations

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

Consumer Product Testing Co.

QUALITY ASSURANCE UNIT STATEMENT

Study Number: C13-4532.01

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.

Quality Assurance Representative

12/13/13
Date

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

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-six (56) qualified subjects, male and female, ranging in age from 18 to 69 years, were selected for this evaluation. Fifty-five (55) subjects completed this study. The remaining subject discontinued her participation for personal reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] and over.
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:

Study Schedule:

Panel #	Initiation Date	Completion Date
20130385	October 28, 2013	December 5, 2013

[a]With parental or guardian consent

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 twenty-four hours following each Tuesday and Thursday removal, and forty-eight hours 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 twenty-four and seventy-two hours post-application.

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, did not indicate a potential for dermal irritation or allergic contact sensitization.

Table 1
Panel #20130385

Individual Results

Subject Number	24*hr	Induction Phase									Virgin Challenge Site	
		1	2	3	4	5	6	7	8	9	24*hr	72 hr
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	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

24* = Supervised removal of 1st Induction and Challenge Patch
- = Subject not present for supervised removal

Table 1
(continued)
Panel #20130385

Individual Results

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
30	0	0	DID NOT COMPLETE STUDY									
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	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	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	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

24* = Supervised removal of 1st Induction and Challenge Patch

Table 2
Panel #20130385

Subject Demographics

Subject Number	Initials	Age	Sex
1	LAN	45	F
2	BMA	58	F
3	FPS	61	F
4	TDP	69	F
5	JMD	49	F
6	TAW	47	F
7	SBW	28	M
8	M-A	48	M
9	RHS	69	M
10	TDA	68	F
11	MAV	20	F
12	EMV	52	F
13	RRE	43	M
14	BNF	41	F
15	MJK	53	M
16	RMI	67	F
17	FMR	68	F
18	PLM	62	M
19	JBW	55	M
20	TYB	33	F
21	E-M	59	M
22	N-R	39	F
23	C-T	51	M
24	DFG	41	F
25	C-T	58	F
26	ZAA	25	F
27	JLS	63	M
28	LEC	33	M
29	MKP	40	F

Table 2
(continued)
Panel #20130385

Subject Demographics

Subject Number	Initials	Age	Sex
30	LLW	30	F
31	PJR	68	M
32	M-S	64	F
33	LMS	21	M
34	M-S	54	F
35	MBK	58	M
36	BAM	67	F
37	SNM	45	F
38	R-B	61	F
39	TWB	24	M
40	SDJ	55	F
41	J-D	27	F
42	A-R	49	F
43	ELR	53	F
44	AJB	26	M
45	JJM	18	F
46	LDD	18	F
47	M-G	48	F
48	JER	44	F
49	KWP	23	M
50	J-W	69	F
51	BAB	22	F
52	MAE	46	M
53	R-C	43	F
54	J-B	64	F
55	K-M	46	F
56	L-R	45	F

Consumer Product Testing Co.

EST 1973

FINAL REPORT

CLIENT:

ATTENTION:

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

TEST MATERIAL: Trade name mixture containing 0.1% Fucus Vesiculosus Extract

EXPERIMENT REFERENCE NUMBER:

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

Approved by: Michael Caswell, Ph.D., CCRA, CCRC
Vice President, Clinical Evaluations
16 Dec 2016

Approved by: Joy Frank, R.N.
Executive Vice President, Clinical Evaluations
12/16/16

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

Consumer Product Testing Co.

EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study Number: C16-5399.01

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 Cardiere
Quality Assurance Representative

12/28/2016
Date

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

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 76 years, were selected for this evaluation. Fifty-three (53) 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:

Study Schedule:

Panel #	Initiation Date	Completion Date
20160333	November 2, 2016	December 8, 2016

[a]With parental or guardian consent

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.

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:

On November 3, 2016, Subject #29, Panel 20160333, was examined at St. Joseph's Hospital, Paterson, New Jersey, after she suffered a fall. A diagnosis of a torn Achilles tendon of the left foot was made. On November 10, 2016, an orthopedist placed her foot in a soft cast for one week. It was the Principal Investigator's opinion that this occurrence was unlikely related to the test material.

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.

Table 1
Panel #20160333

Individual Results

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	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	----DID NOT COMPLETE STUDY----				
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	0	0	0	0	0	0	0	0
27	----------DID NOT COMPLETE STUDY----------											
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	----------DID NOT COMPLETE STUDY----------										

Day 1* = Supervised removal

Table 1
(continued)
Panel #20160333

Individual Results

Subject Number	Induction Phase									Virgin Challenge Site	
	Day1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
30	DID NOT COMPLETE STUDY											
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	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	DID NOT COMPLETE STUDY										
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	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
58	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal
† = Unsupervised removal

Table 2
Panel #20160333

Subject Demographics

Subject Number	Initials	Age	Gender
1	M-A	70	M
2	BDV	55	F
3	RAC	73	M
4	GAC	74	F
5	MAC	67	F
6	DMP	40	F
7	MLP	74	F
8	L-T	63	F
9	DNY	50	F
10	SKK	68	M
11	BCS	49	F
12	P-H	61	F
13	N-K	35	F
14	B-T	53	F
15	QST	33	M
16	CDR	42	M
17	JIR	52	M
18	WST	35	M
19	C-A	51	F
20	SAW	34	F
21	GGR	41	F
22	KAM	58	F
23	M-P	67	F
24	AEP	76	F
25	DJB	55	F
26	A-S	70	F
27	AHF	51	F
28	DAT	48	F
29	KUT	44	F

Table 2
(continued)
Panel #20160333

Subject Demographics

Subject Number	Initials	Age	Gender
30	MAM	37	F
31	K-C	25	F
32	NLM	28	F
33	MRM	23	F
34	S-I	22	F
35	D-I	20	M
36	M-T	57	F
37	K-C	23	F
38	JAP	75	F
39	GCL	66	F
40	S-B	42	F
41	JBS	60	F
42	S-J	69	F
43	SNM	48	F
44	ABC	40	M
45	SMS	61	F
46	DWB	67	M
47	JWB	39	M
48	SLB	66	F
49	DAF	53	F
50	FNA	40	M
51	GCL	70	F
52	KMG	22	F
53	EMS	62	F
54	D-P	49	F
55	GVC	18	F
56	INO	54	F
57	JRO	25	M
58	ONG	33	F

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: February 4, 2019

SUBJECT: Sargassum Filipendula Extract

Active Concepts. 2019. Compositional breakdown: AC Algae Blend Sorb (contains 1.3% Sargassum Filipendula Extract).

Active Concepts. 2018. OECD TG 442C: *In chemico* skin sensitization (AC Algae Blend sorb contains 1.3% Sargassum Filipendula Extract).

Active Concepts. 2018. OECD TG 442D: *In vitro* skin sensitization (AC Algae Blend sorb contains 1.3% Sargassum Filipendula Extract).

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

Active Concepts

info@activeconceptsllc.com • Phone: +1-704-276-7100 • Fax: +1-704-276-7101

Compositional Breakdown

AC Algae Blend Sorb
Code: 11037MK

Compositional Breakdown:

Ingredient	%
Water	81.775
Sorbitol	14.00
Hypnea Musciformis Extract	1.40
Gellidiela Acerosa Extract	1.30
Sargassum Filipendula Extract	1.30
Methylparaben	0.20
Propylparaben	0.025

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Compositional Breakdown

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This is to certify that AC Algae Blend Sorb does not contain, neither directly nor through cross contamination, any of the 26 allergenic flavors or fragrances (Gas Chromatography-Mass Spectrometer Coupled):

ALLERGENS listed in Annex III of EU Cosmetic Regulation(EC) No. 1223/2009 amending EU Directive 2003/15/EC		
INCI NAME	CAS NUMBER	Limit (ppm)
Alpha-IsoMethyl Ionone	127-51-5	< 0.02
Amyl Cinnamal	122-40-7	< 0.10
Anise Alcohol	105-13-5	< 0.00
Benzyl Alcohol	100-51-6	< 0.01
Benzyl Benzoate	120-51-4	< 0.09
Benzyl Cinnamate	103-41-3	< 0.30
Benzyl Salicylate	118-58-1	< 0.06
Butylphenyl Methylpropional	80-54-6	< 0.50
Cinnamal	104-55-2	< 0.01
Cinnamyl Alcohol	104-54-1	< 0.30
Citral	5392-40-5	< 1.00
Citronellol	106-22-9	< 1.00
Coumarin	91-64-5	< 0.00
Eugenol	97-53-0	< 0.70
Farnesol	4602-84-0	< 0.04
Geraniol	106-24-1	< 0.08
Hexyl Cinnamal	101-86-0	< 0.40
Hydroxycitronellal	107-75-5	< 1.00
Hydroxymethylpentyl 3-Cyclohexene carboxaldehyde	31906-04-4	< 0.00
Isoeugenol	97-54-1	< 0.06
Limonene	5989-27-5	< 0.05
Linalool	78-70-6	< 0.00
Methyl 2 Octynoate	111-12-6	< 0.20
Evernia prunastri	90028-68-5	< 0.00
Evernia furfuracea	90028-67-4	< 0.00
Amylcinnamyl Alcohol	101-85-9	< 1.00

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Compositional Breakdown

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This is to certify that AC Algae Blend Sorb does not contain pesticide levels exceeding the following (Reverse Phase High Performance Liquid Chromatography-Mass Spectrometer Coupled):

EPA Pesticide Levels	
INCI NAME	LIMIT (mg/kg)
Alachlor	< 0.02
Aldrin and Dieldrin	< 0 .05
Azinphos-methyl	< 1. 00
Bromopropylate	< 3.0 0
Chlordane(cis and trans)	< 0.05
Chlorfenvinphos	< 0.50
Chlorpyrifos	< 0.20
Chlorpyrifos-methyl	< 0.10
Cypermethrin	< 1.00
DDT	< 1.00
Deltamethrin	< 0.50
Diazinon	< 0.50
Dichlorvos	< 1.00
Dithiocarbamates	< 2.00
Endosulfan	< 3.00
Endrin	< 0.05
Ethion	< 2.00
Fenitrothion	< 0.50
Fenvalerate	< 1.50
Fonofos	< 0.05
Heptachlor	< 0.05
Hexachlorobenzene	< 0.10
Hexachlorocyclohexane	< 0.30
Lindane	< 0.60
Malathion	< 1.00
Methidathion	< 0.20
Parathion	< 0.50
Parathion-methyl	< 0.20

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Compositional Breakdown

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Permethrin	< 1.00
Phosalone	< 0.10
Piperonyl butoxide	< 3.00
Pirimiphos-methyl	< 4.00
Pyrethrins	< 3.00
Quintozene(sum of 3 items)	< 1.00

Active Concepts

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OECD TG 442C: *In Chemico* Skin Sensitization

Tradename: AC Algae Blend Sorb Contains 1.3% Sargassum Filipendula Extract

Code: 11037MK

CAS #: 92128-82-0 & 92128-82-0 & 92128-82-0

Test Request Form #: 3956

Lot #: 46737P

Sponsor: *Active Concepts, LLC; 107 Technology Drive Lincolnton, NC 28092*
Study Director: *Maureen Danaher*
Principle Investigator: *Jennifer Goodman*

Test Performed:
OECD TG 442C: *In Chemico* Skin Sensitization
Direct Peptide Reactivity Assay (DPRA)

Introduction

A skin sensitizer is a substance that will lead to an allergic response following skin contact[1]. Haptenation is the covalent binding of a hapten, or low-molecular weight substance or chemical, to proteins in the skin. This is considered the prominent mechanism which defines a chemical as a sensitizer. Haptenation is described as a "molecular initiating event" in the OECD Adverse Outcome Pathway (AOP) for skin sensitization which summarizes the key events known to be involved in chemically-induced allergic contact dermatitis[2]. The direct peptide reactivity assay (DPRA) is designed to mimic the covalent binding of electrophilic chemicals to nucleophilic centers in skin proteins by quantifying the reactivity of chemicals towards the model synthetic peptides containing cysteine and lysine. The DPRA is able to distinguish sensitizers from non-sensitizer with 82% accuracy (sensitivity of 76%; specificity of 92%)[3].

This assay was conducted to determine skin sensitization hazard of **AC Algae Blend Sorb** in accordance with European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) and OECD Test Guideline 442C.

Assay Principle

The DPRA is an *in chemico* method which addresses peptide reactivity by measuring depletion of synthetic heptapeptides containing either cysteine or lysine following 24 hours incubation with the test substance. The peptide is a custom material containing phenylalanine to aid in detection. Depletion of the peptide in the reaction mixture is measured by HPLC with gradient elution and UV detection at 220 nm. Cysteine and lysine peptide percent depletion values are then calculated and used in a prediction model which allows assigning the test chemical to one of four reactivity classes used to support the discrimination between sensitizers and non-sensitizers.

1. United Nations Economic Commission (UNECE) (2013) Global Harmonized System of Classification and Labelling of Chemicals (GHS) 5th Revised Edition
2. OECD (2012). The Adverse Outcome Pathway for Skin Sensitization Initiated by Covalent Binding to Proteins. Part 1: Scientific Evidence. Series on Testing and Assessment No. 168
3. EC EURL ECVAM (2012) Direct peptide reactivity assay (DPRA) validation study report; pp 1 -74.

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Materials

A. **Equipment:**	HPLC-UV (Waters Breeze - Waters 2998 Photodiode Array Detector); Pipettes; Analytical balance
B. **HPLC/Guard Columns:**	Agilent Zorbax SB-C18 2.1mm x 100mm x 3.5µm; Phenomenex Security Guard C18 4mm x 2mm
C. **Chemicals:**	Trifluoroacetic acid; Ammonium acetate; Ammonium hydroxide; Acetonitrile; Cysteine peptide (Ac-RFAACAA-COOH); Lysine peptide (Ac-RFAAKAA-COOH); Cinnamic aldehyde
D. **Reagents/Buffers:**	Sodium phosphate buffer (100mM); Ammonium acetate buffer (100mM)
E. **Other:**	Sterile disposable pipette tips

Methods

Solution Preparation:

- 0.667mM Cysteine Peptide in 100mM Phosphate Buffer (pH 7.5)
- 0.667mM Lysine Peptide in 100mM Ammonium Acetate Buffer (pH 10.2)
- 100mM Cinnamic Aldehyde in Acetonitrile
- 100mM* **AC Algae Blend Sorb** in Acetonitrile

  *For mixtures and multi-constituent substances of known composition such as **AC Algae Blend Sorb**, a single purity should be determined by the sum of the proportion of its constituents (excluding water), and a single apparent molecular weight determined by considering the individual molecular weights of each component in the mixture (excluding water) and their individual proportions. The resulting purity and apparent molecular weight can then be used to calculate the weight of test chemical necessary to prepare a 100 mM solution.

Reference Controls:

- Reference Control A: For calibration curve accuracy
- Reference Control B: For peptide stability over analysis time of experiment
- Reference Control C: For verification that the solvent does not impact percent peptide depletion

Sample, Reference Control, and Co-Elution Control Preparation:

- Once these solutions have been made they should be incubated at room temperature, protected from light, for 24±2 hours before running HPLC analysis.
- Each chemical should be analyzed in triplicate.

1:10 Ratio, Cysteine Peptide 0.5mM Peptide, 5mM Test Chemical	1:50 Ratio, Lysine Peptide 0.5mM Peptide, 25mM Test Chemical
• 750µL Cysteine Peptide Solution (or 100mM Phosphate Buffer, pH 7.5, for Co-Elutio Controls) • 200µL Acetonitrile • 50µL Test Chemical Solution (or Acetonitrile for Reference Controls)	• 750µL Lysine Peptide Solution (or 100mM Ammonium Acetate Buffer, pH 10.2, for Co-Elution Controls) • 250µL Test Chemical Solution (or Acetonitrile for Reference Controls)

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Calibration Curve:

- Standards are prepared in a solution of 20% Acetonitrile:Buffer
  - For the Cysteine peptide using the phosphate buffer, pH 7.5
  - For the Lysine peptide using the ammonium acetate buffer, pH 10.2

	Standard 1	Standard 2	Standard 3	Standard 4	Standard 5	Standard 6	Standard 7
mM Peptide	0.534	0.267	0.1335	0.0667	0.0334	0.0167	0.000

HPLC Analysis:

- HPLC-UV system should be equilibrated at 30°C with 50% Mobile Phase A (0.1% (v/v) trifluoroacetic acid in water) and 50% Mobile Phase B (0.085% (v/v) trifluoroacetic acid in acetonitrile) for 2 hours
- Absorbance is measured at 220nm
- Flow Conditions:

Time	Flow	%A	%B
0 minutes	0.35 mL/min	90	10
10 minutes	0.35 mL/min	75	25
11 minutes	0.35 mL/min	10	90
13 minutes	0.35 mL/min	10	90
13.5 minutes	0.35 mL/min	90	10
20 minutes	End Run		

Data and Reporting

Acceptance Criteria:

1. The following criteria must be met for a run to be considered valid:
   a. Standard calibration curve should have an $r^2 > 0.99$.
   b. Mean percent peptide depletion values of three replicates for the positive control cinnamic aldehyde should be between 60.8% and 100% for the cysteine peptide and between 40.2% and 69% for the lysine peptide and the maximum standard deviation should be <14.9 for the percent cysteine depletion and <11.6 for the percent lysine depletion.
   c. Mean peptide concentration of reference controls A should be 0.50±0.05mM and the coefficient of variable of the peptide peak areas for reference B and C in acetonitrile should be <15.0%.

2. The following criteria must be met for a test chemical's results to be considered valid:
   a. Maximum standard deviation should be <14.9 for percent cysteine depletion and <11.6 for percent lysine depletion.
   b. Mean peptide concentration of the three reference control C should be 0.50±0.05mM.

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Prediction Model:

Cysteine 1:10/Lysine 1:50 Prediction Model		
Mean of Cysteine and Lysine % Depletion	**Reactivity Class**	**Prediction**
0% < Mean % Depletion < 6.38%	Minimal Reactivity	Non-sensitizer
6.38% < Mean % Depletion < 22.62%	Low Reactivity	Sensitizer
22.62% < Mean % Depletion < 42.47%	Moderate Reactivity	Sensitizer
42.47% < Mean % Depletion < 100%	High Reactivity	Sensitizer

If co-elution occurs with the lysine peptide, than the cysteine 1:10 prediction model can be used:

Cysteine 1:10 Prediction Model		
Mean of Cysteine and Lysine % Depletion	**Reactivity Class**	**Prediction**
0% < Cys % Depletion < 13.89%	Minimal Reactivity	Non-sensitizer
13.89% < Cys % Depletion < 23.09%	Low Reactivity	Sensitizer
23.09% < Cys % Depletion < 98.24%	Moderate Reactivity	Sensitizer
98.24% < Cys % Depletion < 100%	High Reactivity	Sensitizer

Therefore the measured values of % depletion in the three separated runs for each peptide depletion assay include:

Cysteine 1:10/Lysine 1:50 Prediction Model		
Mean of Cysteine and Lysine % Depletion	**Reactivity Class**	**Prediction**
3.10	Minimal Reactivity	Non-sensitizer
2.98	Minimal Reactivity	Non-sensitizer
3.04	Minimal Reactivity	Non-sensitizer

Cysteine 1:10 Prediction Model		
Mean of Cysteine and Lysine % Depletion	**Reactivity Class**	**Prediction**
3.20	Minimal Reactivity	Non-sensitizer
3.19	Minimal Reactivity	Non-sensitizer
3.14	Minimal Reactivity	Non-sensitizer

Results and Discussion

The data obtained from this study met criteria for a valid assay and the controls performed as anticipated.

Percent peptide depletion is determined by the following equation:

$$Percent\ Peptide\ Depletion = \left[1 - \left(\frac{Peptide\ Peak\ Area\ in\ Replicate\ Injection}{Mean\ Peptide\ Peak\ Area\ in\ Reference\ Controls\ C}\right)\right] \times 100$$

Based on HPLC-UV analysis of **AC Algae Blend Sorb (11037MK)** we can determine this product is not classified as a sensitizer and is not predicted to cause allergic contact dermatitis. The Mean Percent Depletion of Cysteine and Lysine was 3.11% causing minimal reactivity in the assay giving us the prediction of a non-sensitizer.

Active Concepts

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OECD TG 442D: *In Vitro* Skin Sensitization

Tradename: AC Algae Blend Sorb Contains 1.3% Sargassum Filipendula Extract

Code: 11037MK

CAS #: 92128-82-0 & 92128-82-0 & 92128-82-0

Test Request Form #: 3955

Lot #: 46737P

Sponsor: *Active Concepts, LLC; 107 Technology Drive Lincolnton, NC 28092*
Study Director: *Maureen Danaher*
Principle Investigator: *Jennifer Goodman*

Test Performed:
OECD TG 442D: In Vitro Skin Sensitization *ARE-Nrf2 Luciferase Test Method*

Introduction

Skin sensitization refers to an allergic response following skin contact with the tested chemical, as defined by the United Nations Globally Harmonized System of Classification and Labelling of Chemicals[1]. Substances are classified as skin sensitizers if there is evidence in humans that the substance can lead to sensitization by skin contact or positive results from appropriate tests, both *in vivo* and *in vitro*. Utilization of the KeratinoSens™ cell line allows for valid *in vitro* testing for skin sensitization.

This assay was conducted to determine skin sensitization potential of **AC Algae Blend Sorb** in accordance with the UN GHS.

Assay Principle

The ARE-Nrf2 luciferase test method addresses the induction of genes that are regulated by antioxidant response elements (ARE) by skin sensitizers. The Keap1-Nrf2-ARE pathways have been shown to be major regulator of cytoprotective responses to oxidative stress or electrophilic compounds. These pathways are also known to be involved in the cellular processes in skin sensitization. Small electrophilic substances such as skin sensitizers can act on the sensor protein Keap1 (Kelch-like ECH-associated protein 1), by covalent modification of its cysteine residue, resulting in its dissociation from the transcription factor Nrf2 (nuclear factor-erythroid 2-related factor 2). The dissociated Nrf2 can then activate ARE-dependent genes such as those coding for phase II detoxifying enzymes.

The skin sensitization assay utilizes the KeratinoSens™ method which uses an immortalized adherent human keratinocyte cell line (HaCaT cell line) that has been transfected with a selectable plasmid to quantify luciferase gene induction as a measure of activation of Keap1-Nrf2-antioxidant/electrophile response element (ARE). This test method has been validated by independent peer review by the EURL-ECVAM. The addition of a luciferin containing reagent to the cells will react with the luciferase produced in the cell resulting in luminescence which can be quantified with a luminometer.

1. United Nations (UN) (2013). Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Fifth revised edition, UN New York and Geneva, 2013

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OECD TG 442D: *In Vitro* Skin Sensitization

Materials

A. Incubation Conditions:	37°C at 5% CO_2 and 95% relative humidity (RH)
B. Equipment:	Humidified incubator; Biosafety laminar flow hood; Microplate Reader; Pipettes
C. Cell Line:	KeratinoSens™ by Givaudan Schweiz AG
D. Media/Buffers:	Dulbecco's Modified Eagle Medium (DMEM); Fetal Bovine Serum (FBS); Phosphate Buffered Saline (PBS); Geneticin
E. Culture Plate:	Flat bottom 96-well tissue culture treated plates
F. Reagents:	Dimethyl Sulfoxide (DMSO); Cinnamic Aldehyde; ONE-Glo Reagent; 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT); sodium lauryl sulfate (SLS)
G. Other:	Sterile disposable pipette tips; wash bottles

Methods

KeratinoSens™ were into seeded four 96-well tissue culture plates and allowed to grow to 80 – 90% confluency in DMEM containing 10% FBS and 500µg/mL G418 geneticin. Twelve test concentrations of **AC Algae Blend Sorb** were prepared in DMSO with a concentration range from 0.98 - 2000 µM. These 12 concentrations were assayed in triplicate in 2 independently performed experiments. The positive control was cinnamic aldehyde for which a series of 5 concentrations prepared in DMSO had final test concentrations of 4 – 64 µM. The negative control was a 1% test concentration of DMSO.

24 hour post KeratinoSens™ seeding, the culture media was removed and replaced with fresh media containing 10% FBS without G418 geneticin. 50 µL of the above described test concentrations was added to the appropriate wells. The treated plates were then incubated for 48 hours at 37°C in the presence of 5% CO_2 and 95% relative humidity. After treatment incubation was complete the media was removed and the wells were washed with PBS 3 times.

One of the four plates was used for a cytotoxicity endpoint, where MTT was added to the wells and incubated for 4 hours at 37°C in the presence of 5% CO_2. SLS was then added to the wells and incubated overnight at room temperature. A spectrometer measured the absorbance at 570 nm. The absorbance values (optical density) were then used to determine the viability of each well by comparing the optical density of each test material treated well to that of the solvent control wells to determine the IC_{50} and IC_{30} values.

The remaining 3 plates were used in the luciferase induction endpoint of the assay. 100 µL of Promega's ONE-Glo Reagent was added to 100 µL of fresh media containing 10% FBS without geneticin. Cells were incubated for 5 minutes to induce cell lysis and release luciferin into the media. Plates were read with a luminometer and $EC_{1.5}$ and maximum response (I_{max}) values were obtained.

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Data and Reporting

Acceptance Criteria:

1. Gene induction obtained with the positive control, cinnamic aldehyde, should be statistically significant above the threshold of 1.5 in at least one of the tested concentrations (from 4 to 64 µM).
2. The EC1.5 value should be within two standard deviations of the historical mean and the average induction in the three replicates for cinnamic aldehyde at 64 µM should be between 2 and 8.
3. The average coefficient of variability of the luminescence reading for the negative (solvent) control DMSO should be below 20% in each experiment.

A KeratinoSens™ prediction is considered positive if the following conditions are met:

1. The Imax is higher than 1.5-fold and statistically significantly higher as compared to the solvent (negative) control
2. The cellular viability is higher than 70% at the lowest concentration with a gene induction above 1.5 fold (i.e., at the EC1.5 determining concentration)
3. The $EC_{1.5}$ value is less than 1000 µM (or < 200 µg/ml for test chemicals with no defined MW)
4. There is an apparent overall dose-response for luciferase induction

Results

Compound	Classification	$EC_{1.5}$ (µM)	IC_{50}	I_{max}
Cinnamic aldehyde	Sensitizer	19	289.19 µM	32.3
DMSO	Non-Sensitizer	No Induction	243.24 µM	0.17
AC Algae Blend Sorb	Non-Sensitizer	No Induction	> 1000 µM	0.31

Table 1: Overview of KeratinoSens™ Assay Results (I_{max} equals the average induction values Fg.1)

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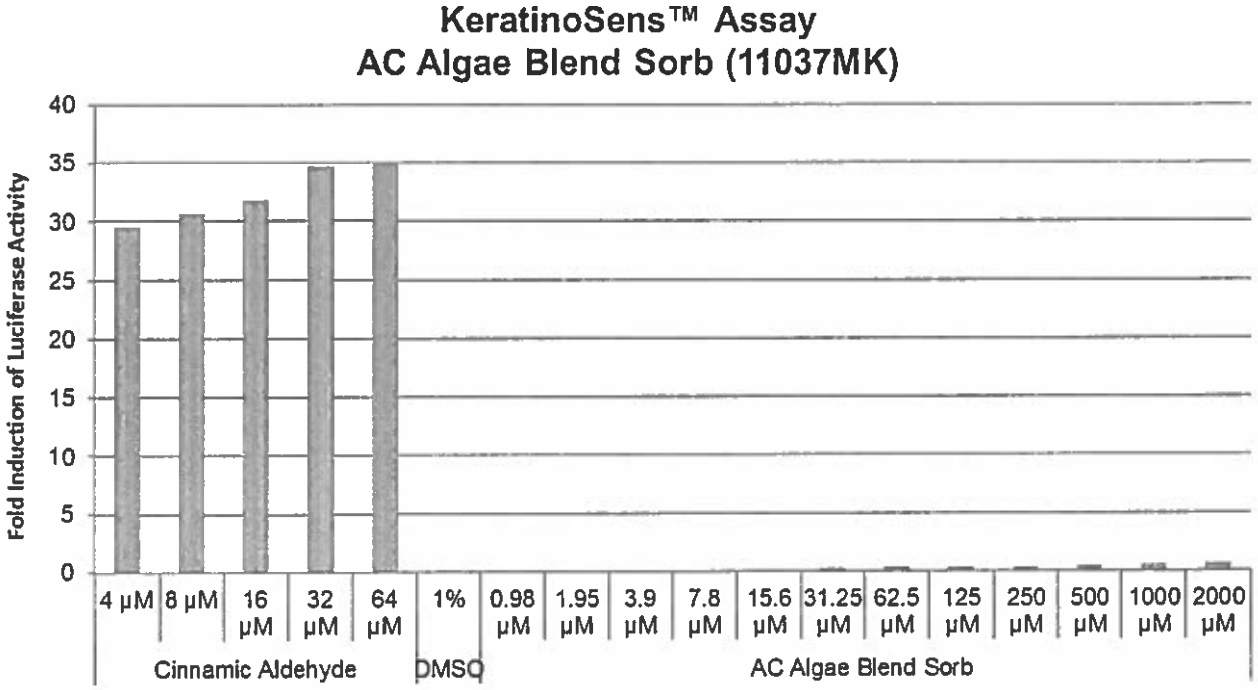

Figure 1: Fold Induction of Luciferase

Discussion

As shown in the results, **AC Algae Blend Sorb (11037MK)** was not predicted to be a skin sensitizer based on the KeratinoSens™ ARE-Nrf2 Luciferase Test Method as there was not a significant increase in luciferase expression. It can be concluded that **AC Algae Blend Sorb** can be safely used in cosmetics and personal care products at typical use levels.

Concentration of Use by FDA Product Category – Brown Algae

Additional Concentration of Use Information – Halidrys Siliquosa Extract

Product Category	Maximum Concentration of Use
Eye lotions	0.29%
Foundations	0.29%
Skin Cleansing (cold creams, cleansing lotions, liquids and pads)	0.029%
Face and neck products Not spray	0.29%
Night products Not spray	0.29%

Information provided in 2019

Table prepared February 19, 2019

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 14, 2019

SUBJECT: Brown Algae Summary Information from UNITIS - added dose volume information for some HRIPTs

UNITIS. 2019. UNITIS CIR Safety Reports on Brown Algae-Derived Ingredients as Used in Cosmetics (addition of some dose volume information for HRIPTs).

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

Please note that the % of brown algae contained in each below mentioned EXTRACT ranges between 0.5 and 10%

INCI name PCPC	chemical characterization data	dermal toxicity data	dermal irritation and sensitization data -% test	description of the method of manufacture	solvent used to extract algae	presence of arsenic	presence of iodine
Water (and) Cystoseira Baccata Extract	/	acute cutaneous tolerance on the adult volunteer : Patch-test 24 hours The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 10 volunteers, was found to be no irritating.	Evaluation of the allergenic potential after repeated cutaneous applications over 50 volunteers. Results obtained under experimental conditions showed that the product was found to be no irritant with regard to the cutaneous tolerance and did not induce any significant skin reaction of contact allergy. It can be thus qualified as hypoallergenic. Concentration test : 100 % (HRIPT: Dose 25ML Marzulli-Maibach Method Not irritating or sensitizing)	extraction with water	water	arsenic mineral : 8,8 mg/kg (FCC V method), arsenic : 20 ppm (ICP-OES method)	/
caprylic/Capric Triglycerides (and) Cystoseira Tamaricifolia Extract	/	acute cutaneous tolerance on the adult volunteer : Patch-test 24 hours The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 10 volunteers, was found to be no irritating.	/	extraction with supercritical CO2	CO2		<1 mg/kg (colorimetry method)
Water (and) Dipropylene glycol (and) Himanthalia elongata extract	/	acute cutaneous tolerance on the adult volunteer : Patch-test 24 hours The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 10 volunteers, was found to be no irritating.	/	extraction with water and dipropylene glycol	water/dipropylene glycol		<9 mg/kg (alcaline mineralisation and potentiometric method)

Water (and) Laminaria digitata extract (and) Sea salt	/	Evaluation of the primary cutaneous tolerance on the rabbit, the product was found to be no irritant.	/	extraction with water	water	1,5 mg/kg (ICP-MS method)	62 mg/kg (alcaline mineralisation and potentiometric method)
Water (and) Glycerin (and) Laminaria Digitata Extract	see phycojuvenine						
Water (and) Dipropylene glycol (and) Laminaria digitata extract	/	Evaluation of the acute skin tolerance on the rabbit, the product was found to be no irritant.	/	extraction with water and dipropylene glycol	water/Dipropylene glycol	2,37 mg/kg (ICP-MS method)	87 mg/kg (alcaline mineralisation and potentiometric method), average : 110 ppm
Water (and) Laminaria digitata extract	/	acute cutaneous tolerance on the adult volunteer : Patch-test 24 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 10 volunteers with sensitivie skin, was found to be non irritating.	Evaluation of the allergic potential after repeated epicutaneous applications on 50 volunteers. The results obtained in the experimental conditions retained permitted to conclude that the product was found to be very well tolerated at the cutaneous level, showing no significant reaction of a contact allergy. It can thus be qualified as hypoallergenic. Concentration test : 100 %	extraction with water	water	contains less than 10 ppm	contains approximately 550 +/- 150 ppm of iodine (mean of 12 analysis performed on 12 different industrial batches produced between 2003 and 2006). Maximum value : 700 ppm
Water (and) Laminaria digitata extract	/	Evaluation of the primary cutaneous tolerance on the rabbit : the product was found to be slightly irritant.	/	extraction with water	water	yes, 19,06 mg/kg (ICP-MS method)	192 mg/kg (alcaline mineralisation and potentiometric method), average : 300 ppm
water (and) phyllacantha fibrosa extract	/	/	/	extraction with water	water	yes, 11,35 ppm (ICP-M	yes, 97 mg/l (method ionic chromatography), average :140 ppm
Water (and) Dipropylene glycol (and) Sphacelaria scoparia extract	/	acute cutaneous tolerance on the adult volunteer : Patch-test 24 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 11 volunteers, was found to be non irritating.	Evaluation of the allergic potential after repeated epicutaneous applications on 50 volunteers. The results obtained in the experimental conditions retained permitted to conclude that the product was found to be very well tolerated at the cutaneous level, showing no significant irritative reaction of a contact allergy reaction. It can thus be qualified as hypoallergenic. Concentration test : 100 % (HRIPT dose 15µL Marzulli Maibach method	extraction with water and dipropylene glycol	Water / Dipropylene glycol	yes, 0,73 mg/kg (ICP-MS method)	15 mg/kg (alcaline mineralisation and potentiometric method)

non-irritating non-sensitizing)

Water (and) Dipropylene glycol (and) undaria pinnatifida extract	/	acute cutaneous tolerance on the adult volunteer : Patch-test 24 hours The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 10 volunteers, was found to be no irritating.	/	extraction with water and dipropylene glycol	water/dipropylene glycol	/	<9 mg/kg (alkaline mineralisation and potentiometric method)

UNITIS – CIR Safety Report on Brown Algae-Derived Ingredients as Used in Cosmetics – Additions January 2019

Please note that the % of brown algae contained in each below mentioned extract ranges between 0.5 and 10%

INCI Name	Dermal Toxicity Data	Dermal Irritation and Sensitization Data	Method of manufacture (solvent)	Arsenic	Iodine
Water (and) Ascophyllum Nodosum Extract	Acute cutaneous tolerance on the adult volunteer: patch test 24 hours. The results obtained under the experimental conditions showed that the product applied pure and locally under an occlusive dressing during 24 hours, on the skin of 10 volunteers, was found to be non-irritating.	Evaluation of the allergenic potential after repeated cutaneous application over 50 volunteers. Results obtained under experimental conditions showed that the product was found to be very well tolerated on cutaneous level. It can be considered as hypoallergenic. Concentration tested: 100% (of the extract in water) (HRIPT – Dose of the test substance: 25 µL Marzulli-Maibach method – not irritating; non-sensitizing)	Extraction with Water	2.69 mg/kg (ICP-MS method)	41 mg/kg (alkaline mineralization and potentiometric method)
Water (and) Phyllacantha Fibrosa Extract	Acute cutaneous tolerance on the adult volunteer: patch test 24 hours. The results obtained under the experimental conditions showed that the product applied pure and locally under	Evaluation of the allergenic potential after repeated cutaneous application over 50 volunteers. Results obtained under experimental conditions showed that the product was found to be non-	Extraction with Water	11.35 ppm (ICP-MS method)	97 mg/L (ionic chromatography method)

	an occlusive dressing during 24 hours, on the skin of 10 volunteers, with sensitive skin was found to be non-irritating.	irritant with regard to the cutaneous tolerance and did not induce any significant skin reaction of contact allergy. It can be thus qualified as hypoallergenic. Concentration tested: 100% (of the extract in water) (HRIPT – Dose of the test substance: 25 µL Marzulli-Maibach method – not irritating; non-sensitizing)			
Glycerin (and) Water (and) Undaria Pinnatifida Extract	Cytotoxicity assay on human fibroblasts by MTT method. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-cytotoxic.	Evaluation of the sensitizing potential with Marzulli-Maibach method on 100 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritant and no allergic reaction was observed. Concentration tested: 100% (of the extract in glycerin and water)	Extraction with Water and dilution with Glycerin	0.837 mg/kg (ICP-MS method)	<1 mg/kg (colorimetry method)
Caprylic/Capric Triglyceride (and) Undaria Pinnatifida Extract	Evaluation of the cutaneous compatibility with occlusive 24 hours patch test method. This study was completed on 10	Evaluation of the sensitizing potential with Marzulli-Maibach method on 50 volunteers. The results obtained in the reserved experimental	Extraction with supercritical CO_2 with Caprylic/Capric Triglyceride	<0.025 mg/kg (ICP-MS method)	1.2 mg/kg (ICP-MS method)

	volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritating.	conditions allowed to conclude that the product is non-irritant and no allergic reaction was observed. Concentration tested: 100% (of the extract in Caprylic/Capric Triglyceride)			
Water (and) Dipropylene Glycol (and) Halopteris Scoparia Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 24 hours. The results obtained under the experimental conditions showed that the product applied pure and locally under an occlusive dressing during 24 hours on the skin of 11 volunteers was found to be non-irritating.	Evaluation of the allergic potential after repeated epicutaneous application on 50 volunteers. The results obtained in the experimental conditions retained permitted to conclude that the product was found to be very well tolerated at the cutaneous level, showing no significant irritative reaction or a contact allergy reaction. It can thus be qualified as hypoallergenic. Concentration tested: 100% (of the extract in Water and Dipropylene Glycol) (HRIPT 40 days – Dose of the test substance: 15 µL Marzulli-Maibach method – not irritating; non-sensitizing)	Extraction with Water and Dipropylene Glycol	0.73 mg/kg (ICP-MS method)	15 mg/kg (alkaline mineralization and potentiometric method)

Glycerin (and) Water (and) Cystoseira Tamariscifolia Extract	Evaluation of the cutaneous compatibility with occlusive 48 hours patch test method – applied diluted at 20%. This study was completed on 11 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the skin compatibility is very good.	Evaluation of the sensitizing potential with Marzulli-Maibach method on 105 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritating and non-sensitizing. Concentration tested: 20% (of the extract in Glycerin and Water) (HRIPT – Dose of the test substance: 25 µL Marzulli-Maibach method – not irritating; non-sensitizing)	Extraction with water and depolymerization with enzyme and denaturation of the enzyme and addition of Glycerin	1.35 mg/kg (ICP-MS method)	1.4 mg/kg (ICP-MS method)
Glycerin (and) Water (and) Dictyopteris Polypodioides Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 48 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 48 hours, on the skin of 10 volunteers, was found to be non-irritating.	See below	Extraction with Water and dilution in Glycerin	0.809 mg/kg (ICP-MS method)	19 mg/kg

Water and Dictyopteris Polypodioides Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 48 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 48 hours, on the skin of 10 volunteers, was found to be non-irritating.	Evaluation of the allergic potential after repeated epicutaneous application on 50 volunteers. The results obtained in the experimental conditions retained permitted to conclude that the product was found non-irritant at the cutaneous level, showing no significant reaction of a contact allergy. Concentration tested: 100% (of the extract in water) (HRIPT – Dose of the test substance: 25 µL Marzulli-Maibach method – not irritating; non-sensitizing)	Extraction with water	0.602 mg/kg (ICP-MS method)	19 mg/kg
Water (and) Dipropylene Glycol (and) Fucus Vesiculosis Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 24 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 24 hours , on the skin of 10 volunteers		Extraction with Water and Dipropylene Glycol		<9 mg/kg (alkaline mineralization and potentiometric method)

	was found to be non-irritating.				
Caprylic/Capric Triglyceride (and) Dictyopteris Polypodioides Extract	Acute cutaneous tolerance on the adult volunteer: Patch test 48 hours. The results obtained under the experimental conditions retained showed that the product applied pure and locally under an occlusive dressing during 48 hours, on the skin of 10 volunteers, was found to be non-irritating.	Evaluation of the sensitizing potential with Marzulli-Maibach method. This study realized on 50 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non-irritant and non-sensitizer. Concentration test: 100% (of the extract in Caprylic/Capric Triglyceride) (HRIPT – Dose of the test substance: 25 µL Marzulli-Maibach method – not irritating; non-sensitizing)	Extraction with supercritical CO_2 with Caprylic/Capric Triglyceride	0.051 mg/kg (ICP-MS method)	<9 mg/kg (FCC V method)

Ingredient (37)	GRAS	Food	Tox	Sensitization data
Ascophyllum Nodosum Extract		✓	✓ - 4 week oral	✓
Fucus Vesiculosus Extract		✓	✓ - 4 week oral	✓
Himanthalia Elongata Extract		✓		✓
Undaria Pinnatifida Extract	✓	✓	✓ - 32 week oral	✓
Undaria Pinnatifida Cell Culture Extract	✓	✓		✓
Macrocystis Pyrifera (Kelp) Extract	✓	✓		✓
Alaria Esculenta Extract		✓		✓
Laminaria Digitata Extract	✓	✓		✓
Laminaria Saccharina Extract	✓	✓		✓
Undaria Pinnatifida Powder	✓	✓	✓ - 36 week oral	
Laminaria Diabolica Extract (synonymous with Laminaria Japonica Extract, Laminaria Ochroleuca Extract, and Saccharina Japonica Extract)	✓	✓	✓ - 6 week oral	
Laminaria Japonica Extract (synonymous with Laminaria Diabolica Extract, Laminaria Ochroleuca Extract, and Saccharina Japonica Extract)	✓	✓	✓ - 6 week oral	
Laminaria Ochroleuca Extract (synonymous with Laminaria Diabolica Extract, Laminaria Japonica Extract, and Saccharina Japonica Extract)	✓	✓	✓ - 6 week oral	
Saccharina Japonica Extract (synonymous with Laminaria Diabolica Extract, Laminaria Japonica Extract, and Laminaria Ochroleuca Extract)	✓	✓	✓ - 6 week oral	
Laminaria Japonica Powder	✓	✓	✓ - lifetime oral	
Cladosiphon Okamuranus Extract		✓	✓ - 3 month oral	
Ecklonia Cava Extract		✓	✓ - 13 week oral	
Macrocystis Pyrifera (Kelp)	✓	✓		
Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract	✓	✓		
Macrocystis Pyrifera (Kelp) Juice	✓	✓		
Macrocystis Pyrifera (Kelp) Protein	✓	✓		
Hizikia Fusiforme Extract (synonymous with Sargassum Fusiforme Extract)	✓	✓		
Sargassum Fusiforme Extract (synonymous with Hizikia Fusiforme Extract)	✓	✓		
Hizikia Fusiformis Water	✓	✓		
Hizikia Fusiformis Callus Culture Extract	✓	✓		

Laminaria Longissima Extract	✓	✓		
Undaria Pinnatifida Leaf/Stem Extract	✓	✓		
Undaria Pinnatifida Root Powder	✓	✓		
Ecklonia Cava Water		✓		
Ascophyllum Nodosum			✓ - 4 week oral	
Nereocystis Leutkeana Extract	✓			
Laminaria Cloustoni Extract (synonymous with Laminaria Hyperborea Extract)	✓			
Laminaria Hyperborea Extract (synonymous with Laminaria Cloustoni Extract)	✓			
Laminaria Digitata Powder	✓			
Ascophyllum Nodosum Powder		✓		
FucusVesiculosus		✓		
Fucus Vesiculosus Powder		✓		
Fucus Serratus Extract		✓		
Fucus Spiralis Extract				✓
Halidrys Siliquosa Extract				✓
Pelvetia Canaliculata Extract				✓
Sargassum Filipendula Extract				✓
Sargassum Muticum Extract				✓
Sphacelaria Scoparia Extract (synonymous with Halopteris Scoparia Extract)				✓
Halopteris Scoparia Extract (synonymous with Sphacelaria Scoparia Extract)				✓
Cystoseira Tamariscifolia Extract				✓
Dictyopteris Polypodiodes Extract				✓
Cystoseira Amentacea/Caespitosa/Branchycarpa Extract				✓
Cystoseira Baccata Extract (synonymous with Phyllacantha Fibrosa)				✓
Phyllacantha Fibrosa Extract (synonymous with Cystoseira Baccata Extract)				✓

For the GRAS and Food column, as seen in the report, specific ingredient types were not reported, however, larger ingredient groups were reported. For example, Laminaria digitata since considered GRAS, it was assumed that the related ingredients, Laminaria Digitata Extract and Laminaria Digitata Powder, would also be considered GRAS. Ingredients in green text are **not** among the 6 previously proposed safe ingredients.

Remaining Ingredients

Agarum Cribrosum Extract
Cladosiphon Novae-Caledoniae Extract
Cystoseira Balearica Extract (synonymous with Cystoseira Caespitosa Extract)
Cystoseira Caespitosa Extract (synonymous with Cystoseira Balearica Extract)
Cystoseira Compressa Extract
Cystoseira Compressa Powder
Dictyota Coriacea Extract
Durvillaea Antarctica Extract
Ecklonia Kurome Extract
Ecklonia Kurome Powder
Ecklonia/Laminaria Extract
Ecklonia Maxima Extract
Ecklonia Maxima Powder
Ecklonia Radiata Extract
Eisenia Arborea Extract
Himanthalia Elongata Extract
Himanthalia Elongata Powder
Hydrolyzed Ecklonia Cava Extract
Hydrolyzed Fucus Vesiculosus Extract
Hydrolyzed Fucus Vesiculosus Protein
Lessonia Nigrescens Extract
Lessonia Nigrescens Powder
Pelvetia Siliquosa Extract
Saccharina Angustata Extract
Saccharina Longicruris Extract
Sargassum Fulvellum Extract
Sargassum Glaucescens Extract
Sargassum Horneri Extract
Sargassum Pallidum Extract
Sargassum Siliquastrum Extract
Sargassum Thunbergii Extract
Sargassum Vulgare Extract
Undaria Peterseniana Extract

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: January 31, 2019

SUBJECT: Tentative Report: Safety Assessment of Brown Algae-Derived Ingredients as Used in Cosmetics (release date January 9, 2019)

The Council respectfully submits the following comments on the tentative report, Safety Assessment of Brown Algae-Derived Ingredients as Used in Cosmetics.

Key Issues

Throughout the report (including the Abstract and Introduction) it should be made clear that 82 is the number of INCI names included in the report. Based on the information in Table 2, two ingredients have two names: Phyllacantha Fibrosa Extract and Cystoseira Baccata Extract are two names for the same ingredient, and Sphacelaria Scoparia Extract and Halopterus Scoparia Extract are two names for the same ingredient. Therefore, the report actually concerns 80 ingredients.

Since Sphacelaria Scoparia Extract has sensitization data (it is blue in the conclusion) and it is another name for Halopteris Scoparia Extract, the sensitization data on Sphacelaria Scoparia Extract should be applicable to Halopteris Scoparia Extract and Halopteris Scoparia Extract should also be blue in the Conclusion.

See comments submitted by the Council on January 3, 2018 for a discussion on why information in the report and provided by industry should also support the safety of Ascophyllum Nodosum Extract and Fucus Vesiculosus Extract. In addition, an HRIPT on Laminaria Ochroleuca Extract (in French) provided by industry with Council memo 21 still needs to be added to the CIR report. This should be sufficient to move Laminaria Ochroleuca Extract to the list of safe ingredients.

Rather than stating specific concentrations for each extract, the submissions from UNITIS (associated with memo 25 [reference 49] and memo 36 [not in the tentative report]) indicated that the concentration of the algae portion of the ingredients ranged from 0.5% to 10%. Rather than stating that concentrations were not reported, either the range should be stated or the 0.5% concentrations should be assumed for all ingredients for which

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This report should focus only on brown algae. The algae identification section and Table 3 should be deleted. Although this information may help the CIR Expert Panel gain perspective on brown algae compared to other algae and could be useful as a background document, it is not useful information for assessing the safety of brown algae. Algae taxonomy is changing. If this information is left in the report, it should be based on recent information. For example, brown algae are now in the Kingdom Chromista not Stramenopila (as stated in Table 3). It is also inappropriate to include "Class/Phylum" as a column heading. Each group of algae is associated with a phylum and at least one class. For example brown algae are in the phylum Phaeophyceae and the class Ochrophyta. In contrast green algae are in the phylum Chlorophyta, but are found in multiple classes including Trebouxiophyceae and Ulvophyceae.

Discussion - The CIR Expert Panel did not require "chronic" oral exposure data to cover systemic toxicity concerns; shorter-term studies were considered sufficient. Please delete the word "chronic".

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The Definition of Ecklonia Cava Water has been corrected (plant deleted) in the Dictionary database.

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Table 7 - Please correct "Unidaria"

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Table 28 - Please correct: "performed in according"

Table 29 - Please change "autopsy" to "necropsy" - the use of the word "autopsy" is only appropriate for a post mortem examination of humans. Please correct: "rats were dived between 3 treatment groups".

Table 30 - Please correct the spelling of "Tamaricifolia"

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Reference 61 - Please correct "myagenicity" and "cast" (should be mutagenicity and coast)

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

CIR Expert Panel

Liaisons to the CIR Expert Panel

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

DATE: February 22, 2019

SUBJECT: CIR Tentative Report on Brown Algae-Derived Ingredients

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to comment on the tentative report on brown algae-derived ingredients.

Currently, six brown algae-derived ingredients in the CIR tentative report are considered safe based on history of use as food (or food GRAS determination) and/or systemic toxicity data, and sensitization data. We suggest that knowing the major constituents of an ingredient should also be a route to a safe conclusion.

There are three ingredients (Laminaria Japonica Extract, Ecklonia Cava Extract, Undaria Pinnatifida Powder) in the report on brown algae-derived ingredients for which only sensitization data are needed, and for which we believe have sufficient composition information to support safety. The composition information is found in the tentative report in Table 13 (Laminaria Japonica Extract), Table 14 (Ecklonia Cava Extract) and Table 15 (Undaria Pinnatifida Powder) (tables attached).

The reference[1] from which the information in Table 13 was obtained indicates that a low molecular weight fucoidan (<667 Da) from enzyme hydrolysis of Laminaria Japonica Extract is 85.9% fucose. The Ecklonia Cava Extract (used as a food supplement) in Table 14 is about 90% phlorotannins and the Undaria Pinnatifida Powder is primarily (532 mg/g) dietary fiber.

[1] Hwang P-A, Yan M-D, Lin H-T V et al. 2016. Toxicological evaluation of low molecular weight fucoidan in vitro and in vivo. *Mar Drugs* 14: 121.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4962011/pdf/marinedrugs-14-00121.pdf

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Although there are other compounds that are not accounted for in these tables, we believe that they are at low concentrations that will be even lower in finished products (among these three ingredients the maximum use concentration is 5% for Laminaria Japonica Extract in skin fresheners). For example, using a distillation method[2], the essential oil obtained from dried *Undaria pinnatifida* accounted for only 0.08% of the algae (one compound proposed as 1,6,9,12,15,18-henicosahexaene accounted for >40% of the essential oil). Although the amount of essential oil obtained from dry *Laminaria japonica* was not stated, the composition of the essential oil was given as fatty acids (89.66%), ketones (3.34%), alcohols (2.68%), aldehydes (2.38%), monoterpenes (0.95%) and benzypyridine (0.66%)[3].

Sensitization data on other preparations derived from *Undaria pinnatifida* can also be used as read-across to support the safety of Undaria Pinnatifida Powder. The safety of Undaria Pinnatifida Cell Culture Extract is supported by 2 negative *in vitro* sensitization assays, and the safety of Undaria Pinnatifida Extract is supported by a 100-person HRIPT of an extract (<5%) in caprylic/capric triglycerides.

When safety is based on composition, the CIR report should make it clear that the conclusion is for the material for which the composition is stated. We believe that having examples of ingredients found safe for use in cosmetics based in part on composition would be helpful to suppliers as examples of the composition detail that is necessary to support safety.

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[2] Lu SJ, Yosemoto S, Takayama S, et al. 2018. Characteristic aroma components from dried "Wakame" *Undaria pinnatifida*. *J Oleo Science* 67(10): 1201-1207. https://www.jstage.jst.go.jp/article/jos/67/10/67_ess17227/_pdf/-char/en

[3] Patra JK, Das G and Baek K-H. 2015. Chemical composition and antioxidant and antibacterial activities of an essential oil extracted from an edible seaweed, *Laminaria japonica* L. *Molecules* 20: 12093-12113. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6332342/pdf/molecules-20-12093.pdf

Table 13. Composition of enzyme hydrolysis extracts of *Laminaria japonica*[43]

Constituent	Concentration (% w/w)
	Laminaria japonica extract[43]
Ash	4.1 ± 0.1
Fat	0.6 ± 0.1
Fucose	85.9
Moisture	3.9 ± 0.8
Monosaccharides (neutral)	NR
Protein	4.3 ± 0.3%
Sulfate	28.4 ± 2.1

NR = not reported

Table 14. Specifications of an alcohol extract of *Ecklonia cava* for use as a food supplement[9]

Parameter	Specification
Phlorotannin	90 ± 5.0%
Dieckol	6.6% – 9.9%
Moisture content	< 5%
Ash	< 5%
Insoluble substances	Negative
Substances not originating from *E. cava*	Negative
Viable cell count	< 3000 CFU/g
Staphylococcus aureus	Negative
Molds and yeasts	< 300 CFU/g
Salmonella spp.	Negative
Coliforms	Negative
Lead	< 3 mg/kg
Mercury	< 0.1 mg/kg
Cadmium	< 3 mg/kg
Arsenic	< 25 mg/kg
Iodine	150.0 – 650.0 mg/kg
Sieving size	> 60 (0.250 mm)

CFU = colony-forming unit

Table 15. Constituents of desalinated Undaria pinnatifida powder[44]

Constituent	Amount (mg/g)
Ash	147
Calcium	13.6
Copper	0.00130
Dietary fiber	532
Iron	0.107
Lipid	14
Magnesium	13.4
Protein	209
Sodium	25.4
Zinc	0.02

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Memorandum

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

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

DATE: January 3, 2019

SUBJECT: Brown Algae: Comments on Potentially Safe Ingredients and Additional Publications Regarding Composition

Please review the available information on *Ascophyllum nodosum* -derived ingredients and Fucus Vesiculosus Extract.

There is a 4 week oral study on Ascophyllum Nodosum and an HRIPT on Ascophyllum Nodosum Extract included in the CIR report. Based on the approach taken by the CIR Expert Panel at the December 3-4, 2018 meeting, Ascophyllum Nodosum Extract should be considered safe for use in cosmetics.

Memo 16 provided by the Council on September 11, 2018 includes an HRIPT on Fucus Vesiculosus Extract that was not included in the draft CIR report on brown algae-derived ingredients prepared for the December 3-4, 2018 CIR Expert Panel meeting. The addition of this study, with the 4 week oral study on Fucus Vesiculosus Extract already in the report should provide sufficient information to support the safety of Fucus Vesiculosus Extract as used in cosmetic products.

The following papers (open-access; links provided) may help address concerns of the CIR Expert Panel regarding composition.

Li Y, Fu X, Duan D, et al. 2017. Extraction and identification of phlorotannins from the brown alga, *Sargassum fusiforme* (Harvey) Setchell. *Mar Drugs* 15: 49. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5334629/pdf/marinedrugs-15-00049.pdf

Lu SJ, Yosemoto S, Takayama S, et al. 2018. Characteristic aroma components from dried "wakame" *Undaria pinnatifida*. *J Oleo Sci* 67(10): 1201-1207. https://www.jstage.jst.go.jp/article/jos/67/10/67_ess17227/_pdf/-char/en

Máximo P, Ferreira LM, Branco P, et al. 2018. Secondary metabolites and biological activity of invasive macroalgae of southern Europe. *Mar Drugs* 16:265. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6117733/pdf/marinedrugs-16-00265.pdf

Patra JK, Das G, Baek K-H. 2015. Chemical composition and antioxidant and antibacterial activities of an essential oil extracted from an edible seaweed, *Laminaria japonica* L. *Molecules* 20: 12093-12113. https://www.mdpi.com/1420-3049/20/7/12093

The following articles concerning composition were obtained through ResearchGate (scanned copies provided):

Gaysinski M, Ortalo-Magné A, Thomas OP, Culioli G. 2015. Extraction, purification, and NMR analysis of terpenes from brown algae. In: Natural Products From Marine Algae: Methods in Molecular Biology, vol 1308. Springer Science+Business Media, New York.

Mišurcová L. 2012. Chemical composition of seaweeds. In: Handbook of Marine Macroalgae: Biotechnology and Applied Phycology, First Edition. John Wiley & Sons, Ltd.

Yoshie-Stark Y, Hsieh Y-P, Suzuki T. 2003. Distribution of flavonoids and related compounds from seaweeds in Japan. *J of Tokyo University of Fisheries* 89:1-6.

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Memorandum

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Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: January 31, 2019

SUBJECT: Tentative Report: Safety Assessment of Brown Algae-Derived Ingredients as Used in Cosmetics (release date January 9, 2019)

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