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

Status:	Draft Tentative Report for Panel Review
Release Date:	February 16, 2021
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer, CIR.

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Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer, CIR
Date: February 16, 2021
Subject: Safety Assessment of Red Algae-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Tentative Report of the Safety Assessment of Red Algae-Derived Ingredients as Used in Cosmetics (*redalg032021rep*). At the September 2020 meeting, the Panel issued an Insufficient Data Announcement for this ingredient group, and the following data were requested:

- composition/impurities data for ingredients without a GRAS designation;
- a 28-day dermal toxicity assay of Corallina Officinalis Extract at the current maximum concentration of use (2%); if positive, systemic toxicity data such as DART and genotoxicity may be needed; and
- dermal sensitization data on all ingredients

It should be noted that, as suggested by the Council and agreed upon by the Panel at the September meeting, Kappaphycus Alvarezii Extract has been added to this ingredient group, as it is derived from a red algae species. Concentration of use for this ingredient have been received and incorporated into the report (*redalg032021data1*).

Since the review of the Draft Report, the Council has provided considerable additional information regarding the red-algae derived ingredients. These data are summarized below and have been marked in the report with yellow highlight.

Data Point/Test Substance	Data	Data Source
Asparagopsis Armata Extract		
Acute oral toxicity of a dry extract Asparagopsis Armata Extract (100 %)	rat; tested undiluted; summary data; LD_{50} > 2000 mg/kg	*redalg032021data5*
Genotoxicity assay on a mixture consisting of 80% Asparagopsis Armata Extract and 20% methylpropanediol	OECD TG 471 Ames assay; summary data; tested undiluted; non-mutagenic	*redalg032021data5*
In vitro dermal irritation on a mixture consisting of 80% Asparagopsis Armata Extract and 20% methylpropanediol	OECD TG 439; reconstructed human epidermis; summary data; tested undiluted; non-irritating	*redalg032021data5*
In vitro eye irritation assay on a mixture containing 98.6% Asparagopsis Armata Extract, 1% butylene glycol, 0.2% chlorphenesin, and 0.2% parabens/phenoxyethanol	HET-CAM; tested undiluted; summary data; non-irritating	*redalg032021data5*
Betaphycus Gelatinum Extract		
Specifications of a Betaphycus Gelatinum Extract	less than 20 ppm heavy metals; less than 2 ppm arsenic	*redalg032021data6*
Human dermal sensitization data on a mixture containing 7% Betaphycus Gelatinum Extract	HRIPT; semi-occlusive conditions; tested undiluted; 56 subjects; non-irritating and non-sensitizing	*redalg032021data6*
Ceramium Kondoi Extract		
Specifications of a mixture containing Ceramium Kondoi Extract	not more than 20 ppm heavy metals; not more than 5 ppm arsenic	*redalg032021data7*
Corallina Officinalis Extract		
Composition and impurities data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae) and water	summary data; minerals such as chlorides, nitrogen, calcium, magnesium, phosphorous, zinc, and potassium can be found in this mixture; contains less than 9 mg/kg iodine	*redalg032021data9*
Impurities data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae), sea water, propylene glycol, and calcium chloride	summary data; mixture contains less than 1 mg/kg iodine	*redalg032021data9*

Acute oral toxicity data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae) and water	summary data; rats; tested at 100%; LD_{50} > 5 g/kg	*redalg032021data9*
Genotoxicity data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae) and water	summary data; Ames assay OECD TG 471; with and without metabolic activation; non-genotoxic	*redalg032021data9*
Genotoxicity data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae), sea water, calcium carbonate, and calcium chloride	summary data; Ames assay OECD TG 471; with and without metabolic activation; non-genotoxic	*redalg032021data9*
In vitro dermal irritation data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae), sea water, propylene glycol, and calcium chloride	summary data; reconstructed skinethic epidermis; tested at 100%; non-irritating	*redalg032021data9*
Animal dermal irritation data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4%) and water	summary data; microcirculation assay; tested at 5%; 30 subjects; well-tolerated	*redalg032021data9*
Animal dermal irritation data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae) and water	summary data; rabbit; tested at 100%; non-irritating	*redalg032021data9*
Human dermal sensitization data on a blush powder containing 2% Corallina Officinalis Extract	HRIPT; 102 subjects; test concentration not reported; occlusive patch; non-irritating and non-sensitizing	*redalg032021data4*
Human dermal sensitization data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae), sea water, calcium carbonate, and calcium chloride	summary data; 103 subjects; tested at 100%; non-irritating and non-sensitizing	*redalg032021data9*
Phototoxicity data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae) and water	summary data; 3T3NRU method; OECD 432; test concentration not reported; non-phototoxic	*redalg032021data9*
Phototoxicity data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae), sea water, calcium carbonate, and calcium chloride	summary data; 3T3NRU method; OECD 432; test concentration not reported; non-phototoxic	*redalg032021data9*
In vitro ocular irritation data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae), sea water, propylene glycol, and calcium chloride	summary data; PREDISAFE assay; slightly irritating	*redalg032021data9*
Animal ocular irritation data on a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae) and water	summary data; rabbit; tested at 100%; slightly irritating	*redal032021data9*
Delesseria Sanguinea Extract		
Composition/impurities data on a mixture consisting of Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol	summary data; algae contains cholesterol, 22-dehydrocholésterol, 7-dehydrocholésterol, and nor-24-cholestadiene-5,22-ol-3B; contains < 9 mg/kg iodine; 0.064 ppm arsenic, 0.168 ppm chromium	*redalg032021data9*
Acute oral toxicity assay on a mixture consisting of Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol	summary data; rat; tested undiluted; LD_{50} > 2000 mg/kg	*redalg032021data9*
Animal dermal irritation assay on a mixture consisting of Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol	summary data; rabbit; test concentration not reported; non-irritating	*redalg032021data9*
Human dermal irritation assay on a mixture consisting of Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol	summary data; 12 human subjects; 48-hr patch test; occlusive conditions; tested undiluted; non-irritating	*redalg032021data9*
Human dermal sensitization assay on a mixture consisting of Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol	summary data; HRIPT; 104 subjects; tested at 100%; non-sensitizing	*redalg032021data9*
In vitro ocular irritation assay on a mixture consisting of Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol	summary data; neutral red release assay; tested at 100%; non-irritating	*redalg032021data9*
Animal ocular irritation assay on a mixture consisting of Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol	summary data; rabbit; test concentration not reported; slightly irritating	*redalg032021data9*

Furcellaria Lumbricalis Extract		
Composition/impurities data on a mixture consisting of Furcellaria Lumbricalis Extract (0.2 – 4%) and water	summary data; total galactose: 1.6 – 2.4 g/l; contains < 0.025 mg/kg arsenic, mercury, lead, cadmium; < 0.125 mg/kg nickel, chromium, cobalt, silver, antimony; < 1 mg/kg iodine	*redalg032021data9*
Human dermal irritation assay on a mixture consisting of Furcellaria Lumbricalis Extract (0.2 – 4%) and water	summary data; 48-hr patch test; 10 subjects; tested at 100%; occlusive conditions; non-irritating	*redalg032021data9*
Human dermal irritation assay on a mixture consisting of Furcellaria Lumbricalis Extract (0.2 – 4%) and water	summary data; 48-hr patch test; 11 subjects; tested at 100%; occlusive conditions; non-irritating	*redalg032021data9*
Human dermal sensitization assay on a mixture consisting of Furcellaria Lumbricalis Extract (0.2 – 4%) and water	summary data; HRIPT; 50 subjects; tested at 100%; non-irritating and non-sensitizing	*redalg032021data9*
Human dermal sensitization assay on a mixture consisting of Furcellaria Lumbricalis Extract (0.2 – 4%) and water	summary data; HRIPT; 105 subjects; tested at 100%; non-irritating and non-sensitizing	*redalg032021data9ss*
In vitro ocular irritation assay on a mixture consisting of Furcellaria Lumbricalis Extract (0.2 – 4%) and water	summary data; agarose diffusion assay; tested at 100%; non-irritating	*redalg032021data9*
Kappaphycus Alvarezii Extract		
Human dermal sensitization data on a trade name mixture consisting of 0.8% Kappaphycus Alvarezii Extract, 79.2% water, and 20% 1,3-butylene glycol	HRIPT; 50 subjects; tested undiluted; occlusive conditions; non-irritating and non-sensitizing	*redalg032021data8*

As it may help the Panel decide on a conclusion of safety for several of these red-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 *redalg032021data2*.

In addition, updated 2021 FDA VCRP data has been received and incorporated into the report (*redalg032021fda*). Number of uses decreased for the majority of ingredients, compared to 2020 FDA VCRP data. It should be noted that uses are now reported for Cyanidium Caldarium Extract, Gelidium Amansii Extract, Hydrolyzed Chondrus Crispus Extract, and Porphyridium Purpureum Extract. These ingredients were not previously reported to be in use.

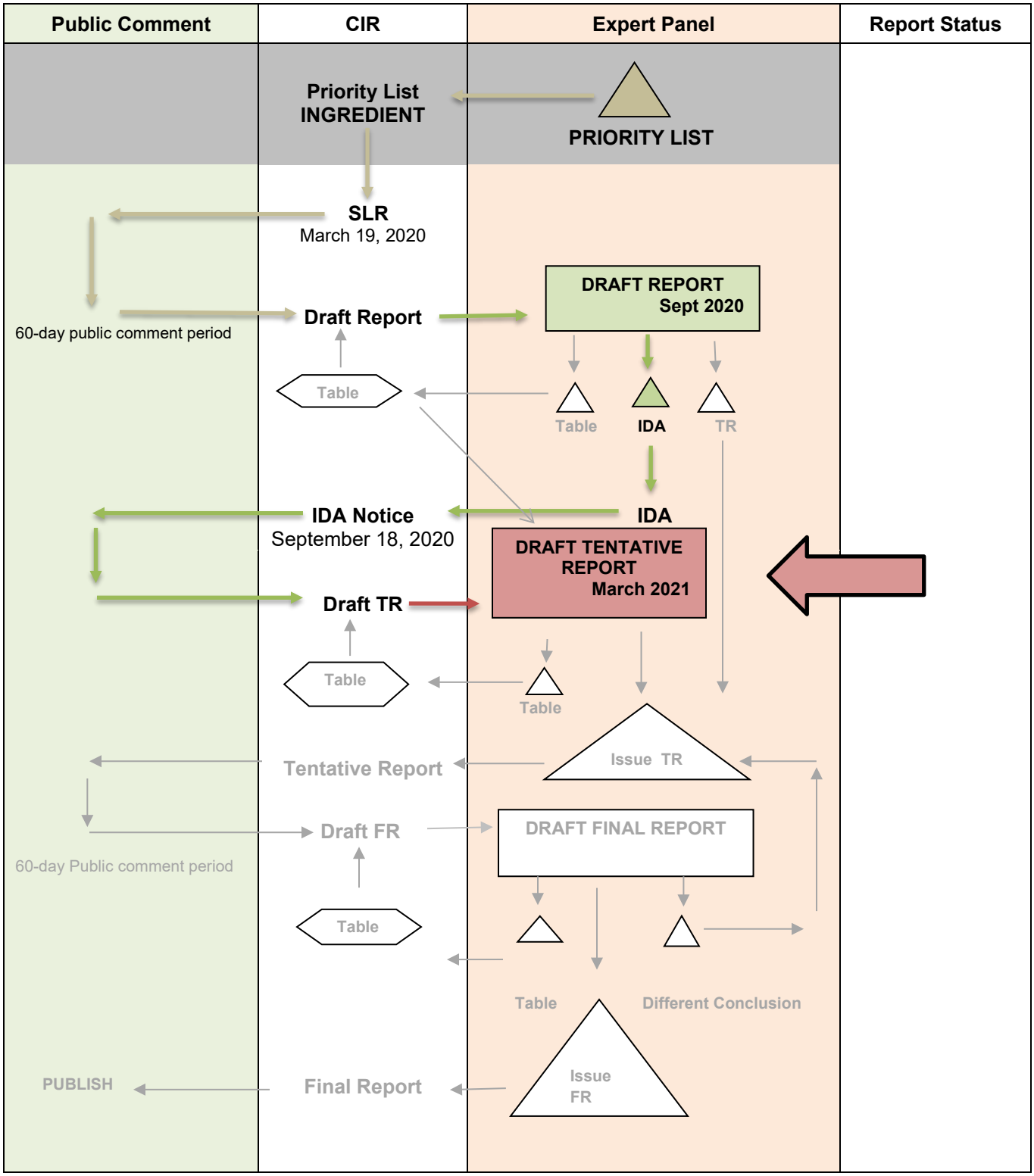
The flow chart (*redalg032021flow*), history (*redalg032021hist*), search strategy (*redalg032021strat*), and the presentation created for the Panel on Algal diversity and application given by Rex L. Lowe (*redalg032021data3*), have been included in this packet. Also included in this packet is an updated date profile (*redalg032021prof*). New data have been indicated by a highlighted "**x**" in this document.

A draft Discussion has been incorporated into the report, based on the proceedings and comments from the September meeting. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Red-Algae Derived Ingredients

MEETING March 2021



Red Algae-Derived Ingredients History

March 2020

-SLR posted

April 2020

-concentration of use received

-Council comments on SLR received

-data received on the following:

-Chondrus Crispus Powder (manufacturing data)

-Asparagopsis Armata Extract (manufacturing data, sensitization data)

-*Corallina officinalis* (general information on the species)

-*Gelidium sesquipidale* (general information on the species)

-*Gigartina stellata* (general information on the species)

-*Kappaphycus alvarezii* (general information on the species)

-*Porphyra umbilicalis* (general information on the species)

-Gelidium Sesquipidale Extract (composition, physical and chemical properties, impurities, human dermal irritation)

-*Gigartina stellata*, Kappaphycus Alvarezii Extract, Corallina Officinalis Extract (physical and chemical properties, manufacturing, impurities, genotoxicity, human dermal irritation, in vitro ocular irritation)

-Porphyra Umbilicalis Extract (composition, physical and chemical properties, manufacturing, impurities, phototoxicity, photosensitization, genotoxicity, human sensitization, in vitro ocular irritation)

-Corallina Officinalis Extract and Undaria Pinnatifida Extract (composition, physical and chemical properties, method of manufacturing, impurities, human dermal irritation, in vitro ocular irritation)

-Polysiphonia Lanosa Extract (composition, physical and chemical properties, human dermal irritation

-Gelidiella Acerosa Extract (human sensitization)

-Chondrus Christpus Extract (human sensitization)

-Rhodymenia Palmata Extract (in vitro ocular irritation, human dermal irritation)

-Chondrus Crispus (in vitro ocular irritation, human dermal irritation

-Hypnea Musciformis Extract and Palmaria Palmata Extract (physical and chemical properties, manufacturing, impurities, human dermal irritation, human sensitization, use in food)

June 2020

-data received on the following:

-Chondrus Crispus Powder (manufacturing, human dermal irritation)

-Chondrus Crispus Extract and Gigartina Stellata Extract (manufacturing, composition, human dermal irritation)

-Gelidium Cartilagineum Extract (manufacturing, composition, human dermal irritation, human sensitization)

-Asparagopsis Armata Extract (manufacturing, composition, human dermal irritation, human sensitization)

-Hydrolyzed Corallina Officinalis Extract (manufacturing, composition, human irritation, human sensitization)

-Hypnea Musciformis Extract (manufacturing, composition, human dermal irritation, in vitro ocular irritation)

-Lithothamnion Calcareum Powder (manufacturing, composition, human dermal irritation, in vitro ocular irritation)

-Ahnfeltiopsis Concinna Extract (specifications, human dermal irritation, in vitro ocular irritation)

-Chondrus Crispus Extract (composition, specifications, human dermal irritation, in vitro ocular irritation)

September 2020

-Panel reviews Draft Report and issues an IDA

-comments on Draft Report received from Council

October 2020

-use information on Kappaphycus Alvarezii Extract received

November 2020

-Data received on the following:

-Corallina Officinalis Extract (composition, impurities, oral toxicity, genotoxicity, dermal irritation, dermal sensitization, phototoxicity, ocular irritation)

-Asparagopsis Armata Extract (acute oral toxicity, genotoxicity, dermal irritation, eye irritation)

-Betaphycus Gelatinum Extract (specifications and HRIPT)

-Ceramium Kondoi Extract (specifications)

-Kappaphycus Alvarezii Extract (HRIPT)

-Delesseria Sanguinea Extract (composition, impurities, oral acute toxicity, dermal irritation, dermal sensitization, ocular irritation)

-Furcellaria Lumbricalis Extract (composition, impurities, oral acute toxicity, dermal irritation, dermal sensitization, ocular irritation)

January 2021

-updated 2021 FDA VCRP data received

March 2021

-Panel reviews the Draft Tentative Report

Red Algae Profile – March 2021 – Writer, Priya Cherian

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Ahnfeltiopsis Concinna Extract	x		x																x							x			
Asparagopsis Armata Extract	x	x						x							x				x		x			x		x			
Hydrolyzed Asparagopsis Armata Extract																													
Betaphycus Gelatinum Extract			x																					x					
Botryocladia Occidentalis Extract																													
Calliblepharis Ciliata Extract																													
Ceramium Kondoi Extract			x																										
Ceramium Rubrum Extract																													
Chondracanthus Teedei Powder																													
Chondrus Crispus	x		x																		x					x			
Chondrus Crispus Extract	x	x																	x		x			x		x			
Chondrus Crispus Powder	x	x																			x								
Hydrolyzed Chondrus Crispus Extract	x																												
Corallina Officinalis Extract	x	x	x					x							x				x	x	x			x	x	x	x		
Corallina Officinalis Powder																													
Corallina Officinalis Thallus Extract																													
Hydrolyzed Corallina Officinalis																								x					
Hydrolyzed Corallina Officinalis Extract	x	x																			x								
Cyanidium Caldarium Extract	x																												
Delesseria Sanguinea Extract	x		x					x												x				x		x	x		
Digenea Simplex Extract	x	x																											
Dilsea Carnosa Extract																													
Furcellaria Lumbricalis Extract	x		x																					x		x			
Gelidiella Acerosa Extract	x	x												x	x									x					
Gelidium Amansii Extract	x	x																											
Gelidium Amansii Oligosaccharides																													
Gelidium Cartilagineum Extract	x	x																			x			x					
Gelidium Pulchrum Protein																													
Gelidium Sesquipedale Extract			x																		x								
Gigartina Skottsbergii Extract																													
Gigartina Stellata Extract	x	x													x						x								
Gloiopeltis Tenax Extract			x																										

Gloiopeltis Tenax Powder																													
Gracilaria Verrucosa Extract																													
Gracilariopsis Chorda Extract		x																											
Grateloupia Livida Powder								x																					
Hypnea Musciformis Extract	x	x	x																	x			x						
Kappaphycus Alvarezii Extract	x		x												x								x		x				
Lithothamnion Calcareum Extract	x							x			x																		
Lithothamnion Calcareum Powder	x	x																			x					x			
Lithothamnion Corallioides Powder																													
Mesophyllum Lichenoides Extract																													
Palmaria Palmata Extract	x	x	x																		x			x					
Palmaria Palmata Powder																													
Phymatolithon Calcareum Extract	x																												
Pikea Robusta Extract																													
Polysiphonia Lanosa Extract																					x								
Porphyra Linearis Powder																													
Porphyra Tenera Extract																													
Porphyra Tenera Sporophyte Extract																													
Porphyra Umbilicalis Extract	x	x	x												x									x	x	x			
Porphyra Umbilicalis Powder																													
Hydrolyzed Porphyra Yezoensis																													
Porphyra Yezoensis Extract	x																												
Porphyra Yezoensis Powder																													
Porphyridium Cruentum Culture Conditioned Media																													
Porphyridium Cruentum Extract	x																												
Porphyridium Purpureum Extract	x																												
Rhodymenia Palmata Extract	x																				x					x			
Sarcodiotheca Gaudichaudii Extract																													

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

Red Algae Search Strategy

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Ahnfeltiopsis Concinna Extract		x				x													x
Asparagopsis Armata Extract		x	x			x													x
Hydrolyzed Asparagopsis Armata Extract		x				x													
Betaphycus Gelatinum Extract		x	x			x													x
Botryocladia Occidentalis Extract		x				x													x
Calliblepharis Ciliata Extract		x				x													x
Ceramium Kondoi Extract		x				x													x
Ceramium Rubrum Extract		x	x			x													x
Chondracanthus Teedei Powder		x	x			x													x
Chondrus Crispus		x	x			x													x
Chondrus Crispus Extract		x	x			x													x
Chondrus Crispus Powder		x				x													x
Hydrolyzed Chondrus Crispus Extract		x				x													x
Corallina Officinalis Extract		x	x			x													x
Corallina Officinalis Powder		x				x													
Corallina Officinalis Thallus Extract		x				x													
Hydrolyzed Corallina Officinalis		x				x													
Hydrolyzed Corallina Officinalis Extract		x				x													
Cyanidium Caldarium Extract		x	x			x													x
Delesseria Sanguinea Extract		x	x			x													x
Digenea Simplex Extract		x	x			x													x
Dilsea Carnosa Extract		x				x													x
Furcellaria Lumbricalis Extract		x				x													x

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Gelidiella Acerosa Extract		x	x			x													x
Gelidium Amansii Extract		x	x			x													x
Gelidium Amansii Oligosaccharides		x				x													
Gelidium Cartilagineum Extract	9495-01-4	x				x	x												x
Gelidium Pulchrum Protein		x				x													x
Gelidium Sesquipedale Extract		x	x			x													x
Gigartina Skottsbergii Extract		x	x			x													x
Gigartina Stellata Extract		x			x	x													x
Gloiopeltis Tenax Extract		x	x			x													x
Gloiopeltis Tenax Powder		x				x													
Gracilaria Verrucosa Extract		x	x			x													x
Gracilariopsis Chorda Extract		x	x			x													x
Grateloupia Livida Powder		x	x			x													x
Hypnea Musciformis Extract		x	x			x													x
Lithothamnion Calcareum Extract		x	x			x													x
Lithothamnion Calcareum Powder		x				x													
Lithothamnion Corallioides Powder		x				x													x
Mesophyllum Lichenoides Extract		x				x													x
Palmaria Palmata Extract		x	x			x													x
Palmaria Palmata Powder		x				x													
Phymatolithon Calcareum Extract		x				x													x
Pikea Robusta Extract		x				x													x
Polysiphonia Lanosa Extract		x				x													x
Porphyra Linearis Powder		x				x													x
Porphyra Tenera Extract		x	x		x	x													x

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Porphyra Tenera Sporophyte Extract		x																	
Porphyra Umbilicalis Extract		x	x																x
Porphyra Umbilicalis Powder		x																	
Hydrolyzed Porphyra Yezoensis		x																	
Porphyra Yezoensis Extract		x	x																x
Porphyra Yezoensis Powder		x																	
Porphyridium Cruentum Culture Conditioned Media		x																	
Porphyridium Cruentum Extract		x	x																x
Porphyridium Purpureum Extratc		x	x																x
Rhodymenia Palmata Extract		x	x		x														x
Sarcodiotheca Gaudichaudii Extract		x																	x

Typical Search Terms

- INCI names
- chemical/technical names
- genus names
- species names
- dermal
- irritation
- sensitization
- ocular
- metabolism
- ingestion
- food
- dietary
- cancer
- carcinogenicity
- genotoxicity
- mutagenicity
- synonymous genus/species names – accepted genus/species names

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org

- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

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
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

SEPTEMBER 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 14, 2020

DR. BELSITO: I guess, Red Algae. First, just draw your attention to the presentation that we had on algae which is the Part 2 data that it seems to be cellulose with mucopolysaccharides. Then it's the source of carrageenan and an agar is what we were told in the presentation. There didn't seem to be anything terribly toxic in red algae at least based upon the fact that they talked about other kinds being toxic.

Then, I guess the best place to start probably with all this data is Table 1 that Priya put together for us. And it has a list of those algae that are reported to be used in food. They're not GRAS per se. A lot of them just are reported in Asian foods. There was a list from France of red algae that were approved for food use or condiments. I forget what the phrase was. Some are used in jellies, probably for their carrageenan or agar. But we have a list of those that are used in food in Table 1.

So my assumption is, if they're used in food, then our systemic tox needs sort of go away. Are you comfortable with that?

DR. LIEBLER: Yeah, you're referring to Table 12 of the document, Don? PDF 42.

DR. BELSITO: For some reason -- which page number?

DR. LIEBLER: Forty-two.

MS. CHERIAN: I think he's referring to page 53.

DR. BELSITO: Yeah, I just printed it out and for some reason -- yes, I'm referring to page 53. It's labeled Table 1 for some reason.

DR. LIEBLER: Oh, I see. Your data profile. I'm sorry. I see what you're saying. Yeah. This is good. There is also a Table 12 with just the food information.

DR. BELSITO: Right. Yeah. So this has food versus sensitization data.

DR. LIEBLER: Yeah.

DR. BELSITO: So my assumption was that if we have food use, we're not worried about tox data; we're worried about sensitization data, and the sensitization data is negative in all cases.

DR. KLAASSEN: I guess I would say, in regard to toxicity, you know, there are a couple of real known poisons in this group. This so-called red tide is due to kainic acid. That's produced by these compounds so, I think, you know, in general I agree with you.

DR. BELSITO: But I thought that was because that acid reduced oxygen levels in the water. Is it directly toxic or is it an effect on oxygen?

DR. KLAASSEN: No, it affects humans.

DR. BELSITO: Okay.

DR. KLAASSEN: It's a neurotoxicant.

DR. BELSITO: Okay.

DR. KLAASSEN: So we just need to be a little bit aware of that.

DR. BELSITO: But, if it's used as a food, if it has a reported food use, you're then concerned about it.

DR. KLAASSEN: Well, you know, maybe in food, they make sure there isn't -- it is on a certain amount. I don't argue. I'm not an expert on its content, but, you know, red tide is a bad -- you know, can be a bad thing.

DR. BELSITO: Right.

DR. EISENMANN: But red tide is not caused by a red species of algae though; I think it's caused by certain dinoflagellates instead.

MS. CHERIAN: Right.

DR. LIEBLER: Yeah.

MS. CHERIAN: So when I was doing research on red tide --

DR. KLAASSEN: Okay.

MS. CHERIAN: I found that it was caused by a dinoflagellate called Karenia brevis, which is not one of the ingredients we review in the report.

DR. KLAASSEN: So the so-called red tide is not due to any of these? To red algae? Is that what you're saying?

DR. BELSITO: Yes.

DR. HELDRETH: Yeah, the stuff that creates red tide is protozoan in nature; whereas, these genus and species of red algae that we have here are more on the plant side -- although, they're not plants because they're not terrestrial -- but they're certainly not these protozoans, and they're just not associated with it. Unfortunately, algae is this non-class of things. It can mean so many things, and, unfortunately, while those dinoflagellates are technically algae, they're not something we considered to include in this report.

DR. SNYDER: Yeah, Rex's thing covered that pretty nicely when he talked about the toxic algae being a cyanobacteria and then dinoflagellates.

DR. KLAASSEN: Okay.

DR. BELSITO: Okay. So, back to my question, if we have food data and we have sensitization data, can we at least say those are safe?

DR. LIEBLER: Yeah, that was our strategy with brown algae as well.

DR. BELSITO: Right.

DR. LIEBLER: I agree with that approach.

DR. BELSITO: So we have Chondrus Cripsus and all its forms as safe. We would have Gelidiella as safe. And we would have Palmaria Palmata, which is synonymous with Rhodymenia Palmata Extract as safe. So the Palmaria Palmata and Rhodymenia -- this type is so small -- that we can off the back say safe so where we have both a food use and sensitization, which brings us back to those where we have sensitization but nothing else or those in which we have some tox data but no sensitization.

DR. KLAASSEN: Well, on most of them we have very little tox data.

DR. BELSITO: Right.

DR. SNYDER: There's only two that are not food: Armata and Corallina, right? Those are the only two that are not foods.

MS. CHERIAN: There are ingredients on page 54 that don't have any of the data, so those are (audio skip).

DR. SNYDER: Oh, okay. So that's not inclusive on the table, okay. Sorry. Oh my. I mean, the Corallina that we don't have any data on, on that first part of the table, is the abstract used.

DR. BELSITO: Has the greatest number, yeah.

DR. SNYDER: Yeah. That's the greatest number and the highest at two percent. All the rest of them are less than 0.25 percent.

DR. BELSITO: So the most important one, we have no data.

DR. SNYDER: Yeah.

DR. LIEBLER: So I think we need tox data on Corallina and on Corallina Officinalis. There's no getting around it. If it's not food, do we need tox?

DR. BELSITO: Mm-hmm.

DR. LIEBLER: And one of them -- I would say that one of them could clear the rest.

DR. BELSITO: So the hydrolyzed could clear the extract or do you want it on the extract?

DR. LIEBLER: Yeah. Only the extracts. Actually, yeah.

DR. SNYDER: We, actually, want 28-day dermal. If it is absorbed, then we want other systemic tox data. Otherwise, we just need data and sensitization.

DR. BELSITO: Well, we have sensitization.

DR. LIEBLER: Yeah.

DR. SNYDER: Oh, you're right. We have it. So we don't even need that. Yep.

DR. BELSITO: What about the others for which we have no data?

DR. LIEBLER: For which we have no true data or tox data?

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah.

DR. SNYDER: Well, we've got to have composition and see where there's any similarities in a composition across all these different algae.

DR. BELSITO: Well, we have broad composition.

DR. LIEBLER: The composition data are just really not very much help here because we have such dissimilar types of data for different ingredients that we just can't look at trends. Some compositions just, you know, talks about protein and carbohydrates and lipids, and others actually measures specific chemical species of potential interest. So it really just -- it's not very helpful.

DR. EISENMANN: I think there is a range of composition of these materials because the one is essentially minerals, the Lithothamnion Calcareum. It is a mixture of minerals rather than being anything but of an organic nature. That's my understanding of that one.

DR. LIEBLER: Well, if it's a living thing, it's got plenty of organic stuff in it.

DR. EISENMANN: But what they'd make from it is it's kind of like more of a coral-type structure rather than what you usually think of a red algae is my understanding.

DR. LIEBLER: Ah.

DR. EISENMANN: So all they have left is the minerals, and that's what they're selling for that one. That's my understanding.

DR. LIEBLER: Right.

DR. EISENMANN: It was 12 percent calcium, I think, and then other minerals. So composition might be sufficient instead of tox data if it's something like that.

DR. SNYDER: Yeah, I prefer to start with composition and impurities, and then we'll go from there and compare it to what we have.

DR. BELSITO: So all of the ones that are non-food or they're food and sensitization are safe. All the ones where we don't have one or the other or both are insufficient for composition and impurities. And, particularly, on the one that's most frequently used -- the Corallina -- we want are 28-day dermal on the Officinalis Extract at concentration of use?

DR. SNYDER: Correct.

DR. LIEBLER: Yeah.

DR. SNYDER: And, if it's absorbed, then we want reproduction data, et cetera, like always.

DR. BELSITO: And, for all of the others, we simply at this point want composition and impurities.

DR. SNYDER: I think so. If they're all 0.25 percent or less, so that may clear them.

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah, I think that's a reasonable strategy.

DR. BELSITO: I would just like to point out a couple of things then -- this is going more quickly than I thought -- so, in the introduction, we talk about skin bleaching agents, so this is coming up again. So we'll have to point that out that that would be an non-cosmetic use. Of course, in our discussion we have a heavy metal and botanical boilerplates for these as we did.

The other important thing is on PDF page 21, Gracilariopsis Chorda Extract apparently contains arachidonic acid which is not -- which we found to be insufficient and never got data on before. So, I guess, it went off of safety, not -- what is that called, Bart, when we claimed insufficient and never got data?

DR. HELDRETH: Use not supported.

DR. BELSITO: Safety not supported?

DR. HELDRETH: Use not supported.

DR. BELSITO: Now, we probably can get around that by the very low concentration of use, but I just point that out. The arachidonic acid content was calculated to be 0.64 percent, and I'm not even sure that we got a concentration of use level for that one. But it's something we would have to mention in our discussion if we go forward with a safety on that one.

MS. CHERIAN: I don't think that ingredient is currently in use.

DR. BELSITO: Okay. And, Paul, what did you think of the DART data there with the absorption of all the embryos?

DR. SNYDER: Yeah, that was a study done out of Sri Lanka, and it was a crude extract. And I was very bothered by it because I had a hundred percent post-implantation reabsorptions, but they were actually looking at it as a post-coital contraceptive. So I don't know what to make of that. I think if this is absorbed, then we're going to have to ask for repro data anyway.

DR. BELSITO: Okay.

DR. SNYDER: But it was a crude extract. I mean, the methodologies there were very limited, and, basically, they just made an extract of the algae and then distilled it down and treated them.

DR. BELSITO: Right.

DR. SNYDER: It wasn't a -- it calls for concern, but we would verify if we had dermal absorption.

DR. BELSITO: Okay. And the same thing with the lack of mammalian mutagenicity?

DR. SNYDER: Yes. Okay.

DR. SNYDER: I mean, that one that was in that study too is a food, so that Gelidiella Acerosa.

DR. BELSITO: Mm-hmm. Okay. Priya, so you can go through that table you provided us, and, if it's a food use and sensitization data, those are all safe as used. For the Corallina Officinalis, we want 28-day dermal at use concentration and, if absorbed, other data may be needed. And for all of the other ingredients that either do not have -- are not used in food or we don't have sensitization data, we would like composition and impurities. You're muted, Priya, but I think you said okay.

MS. CHERIAN: I did. Sorry. Okay. I thank you. Yeah.

DR. BELSITO: Any other points to be made on this? So I'm not going to read out the entire list of what we said safe and what we said insufficient. You can figure it out.

DR. SNYDER: Until tomorrow.

DR. BELSITO: Until tomorrow, when Jim Marks reports on it, I believe.

DR. SNYDER: Oh, he does. He does report on that.

DR. BELSITO: For once, I get not all the difficult ones.

DR. SNYDER: Well, he might as well go out in flames, huh?

DR. LIEBLER: Yeah.

DR. BELSITO: Bart was kind to me after my complaints at the June meeting.

DR. HELDRETH: That's right. I tried to spread it out.

DR. BELSITO: Yeah. Thank you.

DR. SNYDER: I didn't know we could file complaints.

DR. HELDRETH: You can't.

DR. BELSITO: Okay. Quaternium-18 then would be the next one.

Marks Team – September 14, 2020

DR. MARKS: So let me see where I --

DR. SLAGA: Bring on the red tide.

DR. MARKS: Well, I put that in because I wanted to get Ron Shank's response because I didn't see the saxitoxin, the ichthyotoxins, and the brevotoxins mentioned in the report, but maybe I missed it. But at any rate, let's --

DR. SLAGA: I didn't see it either.

DR. MARKS: And I don't know if it's relevant or not. I mean, presumably they're red algae, so somehow you would think that toxicologic effect needs to be mentioned or at least addressed in the report. But David, you'll be sinking your teeth into this, and I'll be glad to hand it off to you. Hopefully, it won't be an incomplete pass from me.

But at any rate, first time reviewing this group of ingredients, and immediately we have some issues in terms of nomenclature because are there 59 ingredients or are there 56 ingredients, since it seems like there're some synonyms here? And these are

derived from multiple species of red algae, which is a functional group when we look at our presentation in the past on algae. So there're plants. There're protozoa, and then there are unique organisms that make up red algae.

So we'll get the read across, but that to me creates problems. How the hell can you read across when you have different organisms, whether it be plant, protozoa, or something that's unique? We mentioned the red tide, and then I was glad to see red algae part 2. Priya, I was concerned you were going to give me more data in that second -- that there was so much on red algae -- but part 2 was Rex Lowe's presentation on algal diversity and application. And red algae is specifically addressed on page 35 and 30 -- to 38 at part 2. David, very important. I'm really glad Priya included that because you need that perspective when you look at these ingredients.

DR. SLAGA: I guess we're --

DR. MARKS: Previous --

DR. SLAGA: It's Tom. The presentation in part 2, there was nothing mentioned about red tide in there either other than blue-green algae had a lot of toxins.

DR. MARKS: Yeah. So you know we --

DR. SHANK: The red tide is caused by dinoflagellates, which I don't think come into the red algae family.

DR. ANSELL: Yeah. Red tide and red algae are only related by the word "red."

DR. SHANK: Yes.

DR. MARKS: It's interesting. When I looked up red tide, they used the word, as I recall -- let me pull it -- "algae" in it. So I would say that would be part of the insufficient data announcement is what is the relationship --

DR. SLAGA: Clarify that.

DR. MARKS: Yeah. Clarify it.

DR. HELDRETH: Yeah. Unfortunately, as we've seen even in the brown algae report before, the word "algae" is really not a classification. It doesn't tell you what family or anything about these groups. You can have anything from a protozoan to a very plant-like creature. And what we're looking at in these red algae ingredients are those more plant-like species, not the dinoflagellates or other protozoans or things like that. Even though they share the algae name, it's really not applicable to these ingredients to be associated with the red tide, like Jay had mentioned.

DR. MARKS: Well, this is from the number one encyclopedia that we all go to now: Wikipedia. Their definition is "Red tide is a common name for algal blooms, which are large concentrations of aquatic microorganisms, such as protozoans and unicellular algae. For example, dinoflagellates and diatoms." So I still think we need to reconcile whether red tide really falls under the category of red algae or not since it --

DR. HELDRETH: Would it be helpful if we simply made a statement in the introduction stating something to the effect that this report only focuses on non-unicellular algae and protozoans and the like? Would that calm concerns if we put that kind of information in the introduction saying that we're not commenting on those types of algae that can result in these red tides or those associated toxicities?

DR. SHANK: That's a good suggestion.

DR. PETERSON: I agree with that.

DR. MARKS: Yeah. I agree, Bart. I would also -- and then I think probably somewhere in this report before the final one's issued -- and maybe start reengaging Dr. Rex Lowe. And I might put that question directly to him since he was our outside expert consultant.

DR. HELDRETH: We can certainly do that. We also have -- some updated information have come from the biologist that works for the nomenclature committee.

DR. MARKS: Oh, okay.

DR. HELDRETH: So she's weighed in on some of these ingredients, whether or not they're really red algae in the since of these types of cosmetic ingredients. And in fact, that's why we have this addition from the council that we should potentially add this one because she has weighed in and said, yes, this fits the plant-like red algae definition that the ingredients in this report share.

DR. MARKS: Yeah. What you're talking about -- I'll get to that -- Alex's memo where it had Kappaphycus Alvarezii extract. I think that's the one you're talking about from Alex's 9/4 memo.

DR. HELDRETH: That's correct.

DR. MARKS: So that's why I said the numbers -- besides some synonyms, the suggestion of adding another ingredient. And then there was previous CIR reports referred to as polysaccharide gums. And it's interesting. When I looked up polysaccharide gums, it didn't exist. But then when I looked up algae, I found algae exopolysaccharides. That's how it's in the CIR database.

So if you look up polysaccharide gums, you won't find anything. You have to look it up under algae exopolysaccharides, and it says it was retired. So Bart, I'll defer that to you -- how you want to cross-reference things because, Priya, you referred to it in the report as polysaccharide gums, didn't you? Those previous CIR reports.

DR. HELDRETH: Yeah. I think we added some additional language, and I think some of the names may have been retired or changed because there was concern that maybe we were talking about some of these phosphorylated versions of the saccharides when that's not the kind of polysaccharides that were in that report.

DR. MARKS: Yeah. There were 106 ingredients, so lot of ingredients. All of them we felt were safe except for hydrolyzed carrageenan. Okay. Continue on my sort of thing, so when I looked at these, my first question for Lisa, Ron, and Tom was what approach do we take in tackling this large number and diverse group of ingredients? Can we read across when they're clearly different organisms? There're plants. There're protozoa. There're unique organisms.

Do we have to have each individual safety data or composition? And then we get into powder versus extract. If you look at use concentration, porphyra umbilicalis extract in a leave on is 0.0035 percent. In my mind, it seems like that's such a low percentage that's probably not toxic, but I'll defer that to the toxicologist on the team. And then do we use GRAS? We've had multiple discussions about that for systemic toxicity. Then we need method of manufacture, impurities, skin/eye tox. So Lisa, Ron, Tom, what do you think about the ingredients? That's the first thing.

DR. SHANK: Well, seven of them are foods, and we have skin sensitization data. And they're not sensitizers, so I think those could be put into the category of safe as used. All of the others, like 27 of them, are insufficient, and we need 28-day dermal tox. We need genotox. We need skin irritation and sensitization at least. I don't think you can read across.

DR. PETERSON: Yeah. I agree with that. They're so different, and they could have very different compositions. The methods of manufacturing for the ones that we have seem quite similar across the board, but we don't have method of manufacturing on quite a few of them. But this is my inexperience how you do the read across.

If you have so many that are basically the same, do you assume that the others are the same? But since we're asking for more information, I would include a request for method of manufacturing for those that we do not have method of manufacturing for and impurities because -- it would be useful to know -- and I guess if any of these have any potential for making anything that's toxic, but my guess is not. But it'd be nice to be able to say something to the affirmative that, based on the literature, all of these species are not known to produce toxins.

To basically clarify that it's really different than the red tide and how people are going to associate in their head these different things, you know, making a -- if it's possible, based on the biology, to say the expectation is this. You know, that there's -- unlikely to produce anything that's toxic.

DR. SLAGA: I agree both with Ron and Lisa that the ones that are in foods with the sensitization data would be safe, and the 17 remaining, as Ron pointed out, would be insufficient. And we should include in what Ron wanted also, the method of manufacturing impurities. It's the first time. Let's see what we get. We have a lot of time to massage this.

DR. MARKS: Ron, repeat that again. So for the insufficient data, method of manufacture, impurities, 28-day tox?

DR. SHANK: There are seven ingredients that are foods and have been tested for sensitivity and were negative as sensitizers.

DR. MARKS: Yeah. I have --

DR. SHANK: I have those listed here. The others -- yes?

DR. MARKS: I'm sorry, Ron. Go ahead.

DR. SHANK: The others, I think we need 28 dermal toxicity data, genotoxicity data, skin irritation and skin sensitization. If the dermal toxicity data are of concern, we may need reproductive and developmental toxicity as well. And then as Dr. Peterson says, methods of manufacture and impurities.

DR. MARKS: And you had mentioned seven are safe. I think I had one, two, three, four, five. I had the safe for Chondrus Crispus as is -- the extract and hydrolyzed. That's three ingredient. The Gelidiella Acerosa extract and then the prophyra umbilicalis extract -- the powder -- using GRAS and irritation/sensitization. Did I miss -- I think you said seven. I think I have here five or six. Which one did I miss, Ron, that you have? And I based it on both what you said, either -- am I using that term correctly, Ron? We always get into this what is GRAS. Is it -- should I use that or put food?

DR. SHANK: That's mainly for food additives.

DR. MARKS: Okay. So --

DR. SHANK: And these are not additives. They're foods.

DR. MARKS: Okay. Gotcha.

DR. SHANK: I'm still having trouble with the sound.

DR. MARKS: Huh. Can you hear me, Lisa?

DR. COHEN: Jim, one question. When you have such a big group and you have just a few further down the field and others way up field, do you ever split them out, or is the whole group have to go through together?

DR. MARKS: You'll see with silicates later on --

DR. SHANK: We split them out.

DR. MARKS: -- what we did, David. We did split them out, so it varies with the ingredients. Like red algae is a subset of the whole algae group. And as Bart said earlier, we did brown algae. So we do split out ingredients from groups. Usually, it's determined by the chemistry. That's one of the reasons Lisa is part of the team, but it can be other reasons. This one, obviously, because these ingredients are all characterized under the red algae nomenclature.

DR. HELDRETH: That's right. If there are -- it's the Panel's prerogative to either split the conclusion and have possibly five to seven ingredients marked as safe and the other ones marked as insufficient, or if the differences are so different that it doesn't make sense to review the ingredients together, the Panel may choose to redirect a portion of the ingredients to a separate report. So yes, to your question, the Panel does have the prerogative to split out the report if need be.

DR. ANSELL: And this is Jay. This is an issue that's of great concern. Of course, in this particular case this is the first review, so we just kind of listen to what the Panel's questions are. But overall, the formation of families is critical, and the data on one member of a family should inform the safety assessment of all members of the family. And when we find that one substance -- one ingredient is thrown in and its insufficient but is unrelated to the other ingredients, we get into this conundrum. And so we very much want to see that the families are all related and all rely on -- it's able to rely on the same dataset. We think specific to the red algae there's some members which should be split out from this group.

DR. BERGFELD: Was that the CRISPR one?

DR. ANSELL: It's in our letter.

DR. BERGFELD: Yes. I thought it was CRISPR.

DR. ANSELL: The ones that are not marine -- there's four that are found in other environments, but we'll provide -- we have provided these comments. And we'll comment later as well, but the issue of forming families which are appropriate and reliant is critical -- a critical issue for us.

DR. MARKS: So Ron Shank, can you hear me? Ron? Ron Shank?

DR. SHANK: Yes. I only heard a small part of that. Sorry. I don't know what's wrong.

DR. MARKS: So I have safe for the Chondrus Crispus, the Gelidiella Acerosa extract, the porphyra umbilicalis extract. Was there anything else you had as safe? When I look down -- so David, this is where I -- it's very important. I go down this table and put in the use and concentration. This is titled the -- this is the profile, which is always done in the beginning of the reports. And this is very helpful. It's a spreadsheet which I actually update with every time we look at the ingredient.

I only had -- as I said earlier, Ron, I only had like about five ingredients that had both were used as a food and we had irritation/sensitization. Again, this can be reconciled in the future because we're going to move that an insufficient data announcement be put forward. And the needs for almost all the ingredients are going to be method of manufacture, impurities, 28-day tox, genotox, irritation, and sensitization and, if there's dermal tox, then DART.

So we're going to be seeing this again, but I don't know if we need a preview of which ones are safe. I have it in my notes. So Priya, you'll get to see that, and Ron Shank, you can put in your notes. And I'll probably just do a summary as what we really are looking for, for each individual ingredient is, is it a food? And then we can -- and do we have irritation and sensitization? If yes, then it would be safe. If not, then we need all those toxicologic endpoints. Does that sound good, Lisa, Tom, Ron?

DR. SLAGA: Sounds good to me.

DR. PETERSON: Yes.

DR. SHANK: Okay.

MS. CHERIAN: There should be ten safe ingredients. According to table 1, if you go to page 53 on the PDF, there's a table with GRAS ingredients, use in food, toxicity and sensitization. And so there's ten ingredients in that table that are technically

safe, but that's assuming that the genus and species -- if the genus and species are the same for the ingredient, they would be safe for any ingredient with the same genus and species.

DR. MARKS: I'll need to review that, Priya. So I didn't have -- so you -- the first one you have, yeah, I have the extract of the Chondrus. I had all the Chondrus.

DR. CHERIAN: Mm-hmm.

DR. MARKS: Oh, okay. I see. You have the hydrolyzed. There's four. Okay. That's page 53, table 1. And you said there're ten of them?

MS. CHERIAN: Yes.

DR. MARKS: Okay. I'll refer to that, and you can put in the specifics of that. And obviously, we're going to take a look at this again. Or you guys are going to take a look at it again in the future. Let me go back to -- need tox, need ten ingredients as safe, food, and irritation/sensitization, page 53. Okay. Thank you, Priya.

MS. CHERIAN: You're welcome.

DR. MARKS: David, you'll find the writers are invaluable. You're shaking your head, Ron. I see that nonverbal.

DR. SHANK: Yeah. I lost your sound. Okay. In the introduction, it says that these ingredients also function as exfoliants, abrasives, skin bleaching agents. Is that true? Because that's very -- that changes the profile for toxicity testing a great deal if they're exfoliants.

DR. HELDRETH: Yeah. Unfortunately, those functions are not vetted. Whenever a raw material supplier submits to the nomenclature committee to get a name for their ingredient, they forward along what they think the function of the ingredient is, and that's just accepted as is. So whether or not it's actually being used for those functions is information we would have to receive directly from the supplier.

DR. SHANK: Okay. We could handle that in the discussion, I think.

DR. MARKS: And you could hear Bart okay, Ron?

DR. SHANK: Most of it.

DR. MARKS: It sounds like it's something with your California connection. Have they maintained the wiring or cable out there in Tahoe? Are you in California?

DR. SHANK: Maybe that's it, but why it's selective, I don't know.

DR. MARKS: Well, I won't take it personally, Ron.

DR. SHANK: Yeah. Good.

DR. MARKS: Okay. So tomorrow, I'm going to move an insufficient data announcement for our team. We want method of manufacture, impurities, 28-day tox, genotox, irritation, and sensitization and, if there's dermal absorption, DART. David, DART is development and reproductive toxicology. And ten of the ingredients, just as a preview, we feel are safe because we have both their use as a food and then we have irritation and sensitization data. That's listed on page 53 in the table. Any other comments? Well, red algae wasn't as toxic as I thought it was going to be.

DR. SLAGA: Well, it's in a lot of foods, so…

DR. MARKS: Yeah. I noticed that. Ice cream, the whole business.

DR. SLAGA: On table 12, it lists all of the -- you look at that. It's quite impressive.

DR. MARKS: Okay. Let me save. This must be a big file because it's taking my computer a while to save the changes I've made. Okay.

Full Panel – September 15, 2020

DR. MARKS: The best for last is that what this is? Holy mackerel. Well, this is pretty easy; it's going to end up with an insufficient data announcement, but. So this is the first time reviewing this group of ingredients. And depending on which ones are synonyms it's either 59 or 56 ingredients. That'll be clarified in the future. And, it's derived from multiple species of Red Algae, which is a heterogeneous group or a functional group made up of plants and some Red Algae, protozoa and others, and then this category unique organism. That was Part I, and I'll come back to that.

Part 2 of the Red Algae was Dr. Rex Lowe's presentation, in the previous -- entitled "Algal diversity and application". And I will refer you to Page 35 to 38 in that document discussing Red Algae.

There was a reference to a previous CIR report on Polysaccharide Gums. And it's actually found -- when you look for it, it's Algae Exopolysaccharide. That is retired, but in that document and Panel assessment we found 106 ingredients that were review; all of them were safe except for the Hydrolyzed Carrageenan.

Let me see, this is probably the longest notes I've had. So, I refer you to Page 53, and that table in which there are 10 ingredients that the approach, if we're going to use for safety, and I don't think we can do much read-across different species. But within the same species we can read across.

So, like, Chondrus Crispus has data for both food -- it's a food product and it's also we had sensitization/irritation. As is Powder Extract and Hydrolyzed. So there are 10 of them that have both uses of food and irritation/sensitization. Ultimately, those ingredients I think we're going to move that's safe.

But for the rest of the ingredients, I have an insufficient data announcement for method of manufacture, impurities, 28-day tox, genotox, irritation and sensitization, and possibly DART. So, the motion is that an insufficient data announcement be put forth by our team for those needs in the ingredients other than the 10 that have both food and irritation/sensitization.

DR. BERGFELD: Nicely done. Big, big job. Don?

DR. BERGFELD: Yeah, so we did the same thing with the table that Jim is referring to on PDF Page 53. Those with food use and sensitization data are safe as used.

We took a slightly different tact. Most of these are used in very low amounts, except for Corallina Officinalis Extract. And, so, we asked for a 28-day dermal on that, and if absorbed other endpoints. For all of the others, which are used in very low concentrations, rather than asking for all the data that you asked for at this point we were just asking for composition and impurities. And if there were any significant differences, then additional data points may be needed.

But pretty much the same thing except we're not asking for 28-day dermal and sensitization/ irritation on all the others. Because when you look at them their concentrations are low. The only one with -- I mean, the greatest uses and the highest concentration are the Corallina.

DR. MARKS: Yeah, Don, I think that's fine. We can focus on those with a higher concentration and if we don't get the others we'll put those aside if the concentration is felt to be so low that the issue of toxicity should be moot. Yeah, that sounds fine, Don.

I would just bring up also, I brought up yesterday the issue of red tide and that wasn't mentioned in the report. And we just wanted more information about that. It is --

DR. BELSITO: We brought up that too Jim. Red tide is not due to Red Algae, it's due to a protozoa.

DR. MARKS: Well, Red Algae can be protozoa, correct?

DR. BELSITO: Yeah, but the protozoa that causes red tide is not among the ones we're looking at. Carol, I think you discussed that?

DR. MARKS: Because when I looked up red tide, I didn't see where it identified a species, which was not in this report. So, if that's the case, yeah, Carol, we can eliminate red tide as an issue.

MS. EISENMANN: Red tide should not be an issue. It's a dinoflagellate, it's a different type of organism that causes red tide. Most of the ingredients in this report are macro marine algae; they are large plants. There are just a handful that are not macro marine.

MS. CHERIAN: If it's helpful, I can add a sentence somewhere in the report stating that the algae that contributes to red tide wouldn't be of issue in this report.

DR. BERGFELD: I think that's important, so please do that.

DR. KLAASSEN: Yeah, in that regard, make sure that statement is correct. And, for example, the Digenea simplex, make sure about that and the Palmaria palmate, that there is no kainic acid in those two. Because I kind of think they might could be a problem, but I might be wrong.

DR. BELSITO: Well, we would get that, Curt, from composition and impurities.

DR. KLAASSEN: Well, our composition and impurities isn't too great on these.

DR. BELSITO: Well, we're asking for that data.

DR. BERGFELD: Bart, did you have a comment?

DR. HELDRETH: Yeah, I was just talking with Priya about this yesterday. I think a really great place to explain how these ingredients are different from those that produce these red tidal blooms is in the algae identification section, it's the second section under "Chemistry". And therein we have the algae classifications that Dr. Lowe provided for us. The ingredients in

this report that we're calling Red Algae fall under the Rhodophyta family. Whereas, if you read further on in that sentence, the family of algae that produce this tidal blooms are called dinoflagellates, of the family name is Pyrrhophyta.

So, I think they are two distinct families and that the red tide producing one is not a family that we're looking at here. Those are not even technically classified as Red Algae, per se.

DR. BERGFELD: Thank you. Curt, did you want to say something?

DR. KLAASSEN: No, as long as we're absolutely sure about this. In our textbook it says, Red Algae Digenea simplex under certain conditions can produce rapidly leading to the notorious beach, red tide, producing kainic acid. So, that's why I'm bringing it up. I'm not an expert on red tide. We don't have too much of it in Kansas.

DR. LIEBLER: It doesn't come up that far?

DR. KLAASSEN: But, it's pretty black and white according to our textbook but I didn't write this chapter.

DR. SNYDER: Come to Florida and I'll buy you a speedo and you can swim amongst it. I think what Priya said about the wording to say that we're only considering macro marine algae, and not the micro. That pretty much takes care of what Curt's concerned about.

DR. KLAASSEN: But this one that I just mentioned, guys, is on our list.

DR. BELSITO: Right. Not all of them are macro marine, Paul, the majority are.

DR. KLAASSEN: So if you look on the first -- well, on the page that I'm looking at the one that's spelled D-I-G-E-N-E-A simplex.

DR. BELSITO: Which page are you on, Curt, 53?

DR. KLAASSEN: This is a table up in the front where it gives them all. But, it's the one that's spelled D-I-G-E-N-E-A. And that's the exact one that's in the textbook that causes red tides. So I'm just saying let's look this up, make sure that this is -- that's all I'm asking. I'm not saying that it's a problem; I'm just saying that we need to look this up in great detail.

DR. BELSITO: Okay, so which one is this, Pikea Robusta? Is that the one you're talking about?

DR. KLAASSEN: It starts with a "D" like a dog, Digenea simplex.

DR. BELSITO: Okay.

DR. MARKS: Would it help to have Rex Lowe also review the ingredients and see if he sees any red flags? Dr. Rex Lowe was the one who gave the presentation.

DR. KLAASSEN: It sure wouldn't hurt.

DR. SLAGA: Well, in his presentation he didn't bring red tide up at all under Red Algae. He did bring up the green that there were toxins, but nothing related to the Red Algae. But it still would be worthwhile to ask him again, for sure.

DR. BELSITO: Yeah, the toxins were not in Red Algae, they were in blue-green.

DR. SLAGA: Yeah, blue-green.

DR. MARKS: Well, the red tide has toxins, saxitoxins, the ichthyotoxins and the brevetoxins. We haven't even mentioned those, and they have both neuro and respiratory harm.

DR. BELSITO: No, we understand that. But when, you know, obviously if that were the case I'm assuming, although it wouldn't hurt to have him come back, that he would have particularly pointed out those algae as being toxic. And, if you look at his presentation, basically he was saying there, you know, it's carrageenan, and agar.

DR. MARKS: Yeah, I wouldn't have him come back. I would just send the list to him and ask him is there any concerns.

DR. BELSITO: With red tide among these.

DR. MARKS: Yeah, and not only red tide but perhaps --

DR. BELSITO: Or a toxin.

DR. MARKS: Yeah. And maybe he can clarify what red tide is too, based on his classification of these functional groups. I know we have some reference in the paper already to this, but he could help clarify it perhaps, just a suggestion.

DR. BERGFELD: Well, Bart, is that something we can do? Is that something you can do from the office, Bart?

DR. HELDRETH: Yes, I'll send a message to Dr. Lowe. I'll also send the same message to the Nomenclature Committee, because they also have a very good biologist botanist that they reference for these ingredients, especially botanical ones. So, I'll send the message to both of them, and maybe we can get input from one or more.

DR. SNYDER: I have a reference up called "SeaLifeBase", and it talks about Digenea simplex. And they have a specific category; it's a useful category that I looked at for all of these when I was reviewing them. But, they have a category it says threat to humans and it's classified green, harmless. So, I'm doubting that it produces a toxin.

DR. BERGFELD: Okay. Any other discussion points? We need to have a motion restated regarding Red Algae. It's been somewhat modified by the Belsito team. Bart and Marks?

DR. MARKS: Yeah, so an insufficient data announcement for method of manufacture, impurities, a 28-day tox and geno, irritation/sensitization. And, as Don said, he would limit it initially to the ones with the highest concentration of use. We can send it out for all of them, but focus on those that Don identified.

DR. BERGFELD: Okay, so you're not going to include the 10 food ingredients?

DR. MARKS: That's correct. The preview is that we're going to use that tact of if they're a food and we have the irritation/sensitization, they're going to be safe, unless we have the other tox data, obviously, to support the safety. So, that's just a preview that would -- yes, those 10 we don't need the IDA for.

DR. BERGFELD: Okay. Don, are you approving or seconding that motion, or approving what has been stated?

DR. BELSITO: Yeah, those with food use and sensitization are safe as used. The only one that's used in higher amounts are Corallina Officinalis and that we asked for a 28-day dermal, and if absorbed other endpoints. And for the remaining ones we asked for composition and impurities and go from there. But if the other team wants to ask for, you know, composition, impurities, 28-day dermal, I mean at this point it's going to be insufficient. I don't have an issue with their requests. I doubt we'll get them; the concentrations are quite low.

DR. BERGFELD: Jim, what are you going to ask for? Are you going to include the 28-day dermal so that our scientific writers know?

DR. MARKS: Yeah, just as Don has stated. Let's ask for all, but we focus on the one with the highest concentrations. Let's see what we get.

DR. BERGFELD: Okay. Any other --

DR. KLAASSEN: I want to ask Paul, what did you just state that you read? What, and where? In your last comment, Paul?

DR. SNYDER: There's a website call "SeaLifeBase" and they list all of the protozoans, plankton, everything there. And I looked up Digenea simplex, and it talks about all of the characteristics, the distribution, the description, the biology. And then they have a category where it says -- it's all referenced -- and it says threat to humans, harmless. And there's a reference provided for that, so I can forward that to Priya.

DR. KLAASSEN: Okay, let me just give a little support to my statement. I also looked up on the internet the Digenea simplex and it says that it contains kainic acid. Now most of you know that we have kainic acid receptors, and they cause convulsions. And, in fact, in the movie "The Birds" to get the birds to fly and be crazy they gave them kainic acid. And where did the kainic acid come from? The Digenea simplex, so, therefore, I think we need to know if the Digenea simplex contains kainic acid, and if it does how much is there.

MS. CHERIAN: So, on Page 27 of the report there's a sentence in that first paragraph under Palmaria Palmata. And it says, "The results indicated that the contents are fairly low (in the range of 2 - 7 µg/g). In addition, kainic acid has been reported to be present in Palmaria Palmata and Digenea simplex." I don't think I have -- well, it's just in Iceland it ranged from 1 - 21 µg/g.

DR. KLAASSEN: Okay, as long as it says that that is low and would not cause a problem, then it's fine. But that is a very toxic substance.

DR. BERGFELD: Well, our minutes are going to reflect that. And, the addition to the text is adequate I understand by what you said.

DR. KLAASSEN: Yeah.

DR. BERGFELD: We have a motion; it's been seconded to go forward with an IDA on the Red Algae, with the knowledge that 10 others are foods and are safe. So I'm going to say all those that disagree with this or voting against it, to give me your name at this point and time. We're moving forward with the vote.

MS. CHERIAN: Oh, I actually had one more question.

DR. BERGFELD: Yeah.

MS. CHERIAN: The Council comments, they say that they wanted to include an ingredient called (inaudible) [02:22:29]. I just wanted to make sure that that's definitely something that we need to do.

DR. MARKS: That was fine with our team.

MS. CHERIAN: Okay. Thank you.

DR. BERGFELD: All right, I'm going to call the question, it's in reverse. All those against the IDA, please indicate by giving me your name. Hearing none, I'll assume a unanimous support for an IDA on the Red Algae.

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

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer, CIR.

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DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of red algae-derived ingredients; 60 red algae-derived ingredients were found 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. These ingredients are mostly reported to function as skin-conditioning agents. Impurities, particularly arsenic, heavy metals, and pesticides may be present in these ingredients; industry should continue to use good manufacturing practices to monitor and limit these possible impurities. The Panel considered the available data and concluded that…[to be determined].

INTRODUCTION

The safety of the following 60 red algae ingredients, as used in cosmetics, is reviewed in this assessment.

Ahnfeltiopsis Concinna Extract
Asparagopsis Armata Extract
Betaphycus Gelatinum Extract
Botryocladia Occidentalis Extract
Calliblepharis Ciliata Extract
Ceramium Kondoi Extract
Ceramium Rubrum Extract
Chondracanthus Teedei Powder
Chondrus Crispus
Chondrus Crispus Extract
Chondrus Crispus Powder
Corallina Officinalis Extract
Corallina Officinalis Powder
Corallina Officinalis Thallus Extract
Cyanidium Caldarium Extract
Delesseria Sanguinea Extract
Digenea Simplex Extract
Dilsea Carnosa Extract
Furcellaria Lumbricalis Extract
Gelidiella Acerosa Extract
Gelidium Amansii Extract
Gelidium Amansii Oligosaccharides
Gelidium Cartilagineum Extract
Gelidium Pulchrum Protein
Gelidium Sesquipedale Extract
Gigartina Skottsbergii Extract
Gigartina Stellata Extract
Gloiopeltis Tenax Extract
Gloiopeltis Tenax Powder
Gracilaria Verrucosa Extract
Gracilariopsis Chorda Extract
Grateloupia Livida Powder
Hydrolyzed Asparagopsis Armata Extract
Hydrolyzed Chondrus Crispus Extract
Hydrolyzed Corallina Officinalis
Hydrolyzed Corallina Officinalis Extract
Hydrolyzed Porphyra Yezoensis
Hypnea Musciformis Extract
Kappaphycus Alvarezii Extract
Lithothamnion Calcareum Extract
Lithothamnion Calcareum Powder
Lithothamnion Corallioides Powder
Mesophyllum Lichenoides Extract
Palmaria Palmata Extract
Palmaria Palmata Powder
Phymatolithon Calcareum Extract
Pikea Robusta Extract
Polysiphonia Lanosa Extract
Porphyra Linearis Powder
Porphyra Tenera Extract
Porphyra Tenera Sporophyte Extract
Porphyra Umbilicalis Extract
Porphyra Umbilicalis Powder
Porphyra Yezoensis Extract
Porphyra Yezoensis Powder
Porphyridium Cruentum Culture Conditioned Media
Porphyridium Cruentum Extract
Porphyridium Purpureum Extract
Rhodymenia Palmata Extract
Sarcodiotheca Gaudichaudii Extract

The majority of the ingredients in this review are extracts and powders derived from different species of red algae. Although a total of 60 International Nomenclature Cosmetic Ingredient (INCI) names identifying red-algae derived ingredients were found in the web-based *International Cosmetic Ingredient Dictionary and Handbook (*wINCI *Dictionary*) several ingredients appear to be equivalent based on the accepted scientific name, as given in the definition.[1] Accordingly, the total number of distinct cosmetic ingredients is 56.

According to the *Dictionary*, these red-algae derived ingredients are mostly reported to function as skin-conditioning agents (Table 1).[1] These ingredients are also reported to function as abrasives, antioxidants, exfoliants, skin protectants, skin bleaching agents, viscosity increasing agents, and anti-microbial agents.

Several ingredients that are obtained from red algae, such as agar, carrageenan, hydrolyzed carrageenan, and hydrolyzed furcellaran, have been previously reviewed by the Expert Panel for Cosmetic Ingredient Safety (Panel).[2] In 2015, it was concluded that these ingredients were considered safe in the present practices of use and concentration as described in that safety assessment; however, available data were insufficient in determining the safety of hydrolyzed carrageenan in cosmetic products. The full report on these ingredients can be accessed on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

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 the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://ewww.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

These red algae-derived ingredients may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, the Panel will review the potential toxicity of each of the red algae ingredients as a whole, complex mixture.

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 ingredients are derived, the standard taxonomic practice of using italics is followed (e.g., *Ahnfeltiopsis concinna*). It is often not known how the substance being tested in a study compares to the cosmetic ingredient. In the report text, if it is known that the material being tested is a cosmetic ingredient, the INCI naming convention will be used (e.g., Asparagopsis Armata Extract). However, if it is not known that the test substance is the same as the cosmetic ingredient, the taxonomic naming conventions (e.g., an *Asparagopsis armata* extract) will be used.

CHEMISTRY

Definition

The ingredients in this safety assessment are derived from various species of red algae. "Algae" is not a taxonomic group, but a functional group of convenience.[3] 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, commonly referred to as red algae (*Rhodophyta*), brown algae (*Phaeophyceae*), green algae (*Chlorophyta*), diatoms (*Bacillariophyceae*), chrysophytes (*Chrysophyta*), blue-green algae (*Cyanophyta*), dinoflagellates (*Pyrrhophyta*), and euglenoids (*Euglenophyta*). It should be noted that the red algae-derived ingredients reviewed in this report are a part of the *Rhodophyta* family, and does not include the dinoflagellate algae that produce the red tidal blooms known as "red tide". The various types of algae are arranged by storage products, pigmentation, and cell wall composition.[3] The corresponding subclass, order, family, and genus for each of the red-algae ingredients are presented in Table 2.

Red algae are of the kingdom Plantae, and are comprised of approximately 6100 species.[4] These algae lack flagella, and range in size from thin films to filamentous membranous forms of 1 m. The color of red algae results from the presence of the pigments phycoerythrin and phycocyanin. Red algae store floridean starch and floridoside, and the cells walls are made up of long-chain polysaccharide agars, carrageenans, and cellulose. General characteristics and the geographic distribution of several specific species of red algae that are included in this report are presented in Table 3.

Chemical Properties

No chemical properties of these red algae-derived ingredients were found in the published literature, and unpublished data were not submitted.

Method of Manufacture

Numerous methods of manufacture are provided in Table 4. General production of a red algae extract includes harvesting, washing to remove epiphytes/sand, drying, grinding, addition of a solvent and preservative, filtration, quality control, and packaging.[5-7] Typical solvents include water, caprylic/capric triglycerides, and butylene glycol.

Composition and Impurities

Red algae constituents comprise of approximately 50 - 75% carbohydrates, based on dry weight (DW), and the majority of such constituents are cellulose, xylan, mannan, or agar.[8] Red algae also contain proteins, polyphenols, polysaccharides, minerals, and amino acids. In addition, red algae may accumulate compounds like arsenic and antimony, and toxic metals such as cadmium, lead, mercury, tin, and aluminum.[9] The accumulation of these contaminants is influenced by environmental factors and structural features of the algae.

Ahnfeltiopsis Concinna Extract

A trade name mixture containing 0.75% Ahnfeltiopsis Concinna Extract was reported to have less than 20 ppm heavy metals and less than 2 ppm arsenic.[10]

Betaphycus Gelatinum Extract

A trade name mixture containing 1.5% Betaphycus Gelatinum Extract was reported to have less than 20 ppm heavy metals and not more than 2 ppm arsenic.[11]

Ceramium Kondoi Extract

A mixture containing 0.17% Ceramium Kondoi Extract and 0.83% saccharina angustata extract was reported to have less than 20 ppm heavy metals and not more than 5 ppm arsenic.[12]

Chondrus Crispus Extract

The composition of dried *Chondrus crispus* was reported to be 76.8% moisture, 27.7% ash, 4.58% potassium, 0.0736% iodine, 2.16% crude fiber, and 1.65% nitrogen.[13] two trade name mixture containing Chondrus Crispus Extract (20% and 3.5%) was reported to have < 20 ppm heavy metals, < 10 ppm lead, < 2 ppm arsenic, and < 1 ppm cadmium.[14]

Corallina Officinalis Extract

A mixture of water and Corallina Officinalis Extract (0.2 – 4%) was reported to contain vitamin C (140 µg/100 mL), vitamin B1 (35 µg/100 mL), vitamin B2 (75 µg/100 mL), vitamin B3 (386 µg/100 mL), vitamin B6 (26 µg/100 mL) and vitamin PP (2.61 µg/100 mL).[15] This mixture also contains chlorides (2500 mg/l), nitrogen (431 mg/l), calcium (50 - 250 mg/l), magnesium (50 – 250 mg/l), phosphorus (17 mg/l), zinc (6.2 mg/l), iron (2.1 mg/l), potassium (1.1 mg/l), and iodine (< 9 mg/kg). The amount of iodine in a mixture of Corallina Officinalis Extract (0.2 – 4% algae), propylene glycol, and calcium chloride was determined to be < 1 mg/kg via a colorimetry assay.[15] A mixture containing Corallina Officinalis Extract (0.2 – 4% algae), calcium carbonate, sea water, and calcium chloride, was reported to contain 10 – 25 g/L magnesium.

A mineral and heavy metal analysis was performed on a trade name mixture consisting of 50% glycerin, 30% water, 18.5% undaria pinnatifida extract (a brown algae), and 1.5% Corallina Officinalis Extract; Table 5.[16] Iodine, arsenic, cadmium, mercury, and lead were present in amounts of 1.9 mg/l, 1383 µg/kg, 29 µg/kg, < 10 µg/kg, and 86 µg/kg, respectively.

Cyanidium Caldarium Extract

The major lipids in algae samples of *Cyanidium caldarium* include monogalactosyl diglyceride, digalactosyl diglyceride, plant sulfolipid, lecithin, phosphatidyl glycerol, phosphatidyl inositol, and phosphatidyl ethanolamine.[17] The fatty acid composition is variable, but major fatty acids include palmitic acid, oleic acid, linoleic acid, and stearic acid.

Delesseria Sanguinea Extract

The chemical composition of *Delesseria sanguinea* is characterized by two non-halogenated phenolic compounds of original structure: cyclohexadienone and delesserin.[18] Sterols such as cholesterol, 22-dehydrochelesterol, 7-dehydro-cholesterol, and nor-24-cholestadiene-5, 22-ol-3β may be found in this species. A mixture consisting of Delesseria Sanguinea Extract (0.2 – 4% algae), water, and dipropylene glycol was reported to contain < 9 ppm iodine, 0.064 ppm arsenic, 0.168 ppm chromium, and no antimony, nickel, cobalt, silver, cadmium, lead, or mercury.

Furcellaria Lumbricalis Extract

A mixture of Furcellaria Lumbricalis Extract (0.2 – 4% algae), water, and sea salt, was reported to contain 1.6 – 2.4 g/l galactose.[19] The amount of arsenic, cadmium, mercury, and lead in this mixture were below 0.025 mg/kg. In addition, the mixture contained <1 mg/kg iodine, and < 0.125 mg/kg nickel, chromium, cobalt, silver, and antimony.

Gelidiella Acerosa Extract

A phytochemical analysis was performed on several *Gelidiella acerosa* extracts extracted with solvents of varying polarity (hexane, dichloromethane, ethyl acetate, ethanol, and methanol).[20] Total polyphenols (61.2 µg/100 mg) and flavonoids (13 µg/100 mg) were highest in the ethyl acetate *Gelidiella acerosa* extract.

Gelidium Amansii Extract

The total polyphenolic and flavonoid content of a methanolic *Gelidium amansii* extract was reported to be 0.26 ± 0.08 mg/ml and 1.55 ± 0.16 mg/ml, respectively.[21]

Gelidium Sesquipedale Extract

A heavy metal and mineral analysis was performed on a trade name mixture containing 4% Gelidium Sesquipedale Extract; Table 6.[22] Ashes and iodine were detected in amounts of 0.4 g/100 g and 1.02 mg/kg, respectively. All other evaluated minerals and metals were present at 98.3 mg/100g or less.

Gloiopeltis Tenax Extract

The essential constituents of *Gloiopeltis tenax* were extracted by supercritical carbon dioxide extraction, and the constituents were identified and analyzed by gas chromatography-mass spectroscopy (GC/MS).[23] The identified constituents included six sesquiterpenes (14.39%), three ketones (5.02%), seven fatty acids and their esters (29.1%), two phenols (1.71%) and three sterols (12.81%). A list of 23 of the constituents identified is provided in Table 7.

Gracilaria Verrucosa Extract

Mycosporine-like amino acids (MAAs) were detected in a crude aqueous *Gracilariopsis longissima* extract (equivalent to *Gracilaria verrucosa* extract) via a high performance chromatography-photodiode array detector and electrospray ionization mass spectrometry.[24] The five MAAs detected include palythine (0.3 ± 0.1%), asterina-330 (42.9 ± 1.1%), shinorine (41.2 ± 2%), porphyra-334 (1.7 ± 0.1%), and palythinol (13.9 ± 0.5%) (percentages are in terms of the total amount of MAAs).

Gracilariopsis Chorda Extract

The amount of arachidonic acid in an ethanolic *Gracilariopsis chorda* extract and *Gracilariopsis chorda* powder was determined via reverse-phase high-pressure liquid chromatography.[25] The arachidonic acid content was calculated as 0.64% of the *Gracilariopsis chorda* extract, and 1.5 mg/100 DW of the *Gracilariopsis chorda* powder.

Grateloupia Livida Extract

The chemical composition of a petroleum ether fraction of *Grateloupia livida* was evaluated by GC/MS.[26] The primary constituents detected were n-hexadecanoic acid (20.68%), mono-(2-ethylhexyl) phthalate (11.08%), cholesterol (9.16%), methyl eicosapentaenoate (6.98%), and heptadecane (6.68%).

Hypnea Musciformis Extract

The total phenolic content of a methanolic *Hypnea musciformis* extract was reported to be 6.9 mg gallic acid equivalent (GAE)/g.[27] According to a supplier, Hypnea Musciformis Extract is reported to be composed of 75% sugars (mainly polysaccharides which average molecular weight is below 700 kDa), 22% mineral ashes, and 3% proteins.[28] A heavy metal analysis performed on a Hypnea Musciformis Extract detected the following impurities: 0.082 ppm arsenic, < 0.020 ppm cadmium, < 0.020 ppm cobalt, 0.052 ppm chromium, < 0.020 ppm mercury, 0.185 ppm nickel, < 0.020 ppm lead, < 0.020 ppm antimony, 0.031 ppm selenium, and 0.053 ppm vanadium.[28] In addition, the sum of aflatoxins B1, B2, G1, and G2 in the Hypnea Musciformis Extract did not exceed 0.4 µg/kg.

Lithothamnion Calcareum Extract

A *Lithothamnion calcareum* extract was reported to contain 12% calcium, 1% magnesium, and measurable levels of 72 other trace minerals, including manganese, selenium, copper, and zinc.[29]

Palmaria Palmata Extract

The total protein content in *Palmaria palmata* has been reported to be in the range of 8 - 35%, and is variable based on geographical and seasonal variations.[30] The most abundant amino acids in this red algae species are alanine, aspartic acid, glutamic acid, and glycine. Samples of newly dried fresh, as well as stored dry, *Palmaria palmata* were analyzed for their contents of phylloquinone (vitamin K_1). The results indicated that the contents are fairly low (in the range of 2 - 7 µg/g). In addition, kainic acid has been reported to be present in *Palmaria palmata* and *Digenea simplex*. In the same study, levels of kainic acid in *Palmaria palmata* samples from Iceland ranged from 1 - 21 µg/g. The phenolic content in algae extracts are variable depending on extraction methods. The total phenolic content in *Palmaria palmata* extracted with distilled water, 80% methanol, 70% acetone, and 100% methanol was reported to be 31.8, 26.5, 25, and 10.7 mg GAE/g, respectively.[31] According to a manufacturer, Palmaria Palmata Extract is reported to be composed of 73% sugars (mainly oligosaccharides, which average molecular weight is between 540 and 2000 Da), 24% mineral ashes, and 3% proteins.[28]

Levels of iodine in *Palmaria palmata* can exhibit a wide range of value (10 - 100 µg/g) depending on location and time of harvest.[30] In one study, iodine levels from *Palmaria palmata* samples from several sources were reported to contain iodine in amounts of 5 µg/g or less. In a different study, the total iodine content of *Palmaria palmata* from Maine was reported to be 72 µg/g.[32] Arsenic content also varies widely based on location and age of the specimen. For example, *Palmaria palmata* (young, whole broad-leaf material) from Maine contained < 0.02 µg/g inorganic arsenic, whereas a granular product produced from older *Palmaria palmata* was found to contain 0.3 µg/g. In the same study, the total amounts of arsenic in *Palmaria palmata* specimens from several locations range from 1 - 10 µg/g. Levels of cadmium and lead in *Palmaria palmata* from different sources are generally found to be below 1 µg/g.

According to a heavy metal analysis performed by a supplier, antimony, arsenic, chromium, nickel, and vanadium, were detected in a Palmaria Palmata Extract in amounts of 0.069, 1.480, 0.046, 0.433, and 2.29 ppm, respectively.[28] Approximately 3.8 ppm iodine was detected in the same extract. No aflatoxins were detected in this Palmaria Palmata Extract.

Porphyra Umbilicalis Extract

The heavy metal impurities of trade name mixture containing Porphyra Umbilicalis Extract was reported to be < 3.0 ppm arsenic, < 0.1 ppm cadmium, < 1.0 ppm lead, < 0.1 ppm mercury, < 0.5 antimony, < 1.0 chromium, < 1.0 nickel, and < 0.5 cobalt.[33] Due to manufacturing processes, traces of residual phenol (< 0.1 ppm) and ethylene oxide (< 0.02 ppm) may be present in this Porphyra Umbilicalis Extract. Heavy metals detected in a different Porphyra Umbilicalis Extract include 3679 µg/kg arsenic, < 10 µg/kg cadmium, < 10 µg/kg mercury, and < 10 µg/kg lead.[34]

Porphyra Tenera Extract, Porphyra Umbilicalis Extract, and Porphyra Yezoensis Extract

Dried *Porphyra* sp. contains numerous nutrients, including proteins, dietary fibers, polyunsaturated fatty acids, minerals, and vitamins.[35] The dried, raw *Porphyra* sp. contains approximately 40% proteins and 40% carbohydrates, which are mostly derived from the soluble dietary fiber, porphyran. Dried *Porphyra* sp. contains a small amount of lipids (approximately 4%), with eicosapentanoic acid (1200 mg/100 g) and palmitic acid (500 mg/100 g) being the predominant fatty acids. Vitamins and minerals, such as vitamin K (2600 µg/100 g), vitamin C (160 mg/100 g), folate (1200 µg/100 g), vitamin B_{12} (78 µg/100 g), potassium (3100 mg/100 g), and iodine (1400 µg/100 g) are found in dried *Porphyra* sp. A large amount of iron (11 mg/100 g) is also found in these species. *Porphyra* sp. also contain compounds such as polysaccharides (porphyrans; > 40% DW), phycobiliproteins (phycoerythrin and phycocyanin), peptides, MAAs, and phenolic compounds (phlorotannin and taurine).

Dried nori (*Porphyra* sp.) samples contained none or trace amounts of inorganic arsenic and total arsenic content.[35] However, dried and toasted nori contain 2.1 – 21.6 mg of total arsenic/kg DW. In addition, cadmium was reported to be present in dried *Porphyra* sp. products in amounts varying from 0.58 – 11 mg/kg of DW.

Porphyra Tenera Extract, Porphyra Umbilicalis Extract, Porphyra Yezoensis Extract, Chondrus Crispus, Palmaria Palmata Extract, Gelidium Amansii Extract, Gelidium Cartilagineum Extract, Gelidium Sesquipedale, Lithothamnion Calcareum Extract and Gracilaria Verrucosa Extract

Heavy metal and metalloid contents in several edible red algae species (*Porphyra* sp., *Chondrus crispus*, *Palmaria Palmata*, *Gracilaria* sp.) based on geographical location was evaluated.[36] Aluminum was present in *Gracilaria* species from Italy, *Palmaria palmata* from Spain, and *Porphyra* species from Spain in amounts of 19-149 mg/kg, 62 mg/kg DW, and 15-890 mg/kg DW, respectively. The concentration levels of 20 metals were analyzed by inductively coupled plasma atomic emission spectroscopy in various dehydrated red seaweed genera (*Chondrus, Gelidium, Palmaria, Porphyra,* and *Gracilaria*), from two origins (Asia and Europe).[37] The mean metal content in seaweed samples for the different genera of red algae is presented in Table 8. The highest levels of aluminum (32 mg/kg DW) was detected in Palmaria, and the highest content of lead (0.15 mg/kg DW) was detected in Porphyra.

Palmaria palmata, *Porphyra umbilicalis*, *Porphyra tenera*, *Porphyra yezoensis*, *Chondrus crispus*, *Gracilaria verrucosa*, and *Lithothamnion calcareum* are authorized as vegetables and condiments in France, with certain specifications.[9] Maximum allowed minerals and metals have been established by French legislature for these species when used in foods (inorganic arsenic, < 3 mg/kg DW; cadmium, < 0.5 mg/kg DW; mercury, < 0.1 mg/kg DW; lead, < 5 mg/kg DW; tin, < 5 mg/kg DW; and iodine, < 2000 mg/kg DW).

Gigartina Stellata Extract and Corallina Officinalis Extract

A mineral and heavy metal analysis was performed on a trade name mixture containing water (45.7%), glycerin (40%), *Gigartina stellata* (4.43%), Kappaphycus Alvarezii Extract (5.9%), and Corallina Officinalis Extract; Table 9.[38] Sodium, chlorides, and potassium were detected at levels of 419.9 mg/100 g, 391 mg/100 g, and 109.4 mg/100 g, respectively. All other minerals and metals were detected in an amount of 11.9 mg/100 g or less.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics 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 a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

Collectively, based on VCRP and Council survey data, 26 of the red algae-dervied ingredients are reported to be inuse. According to 2021 VCRP survey data, Chondrus Crispus Extract is reported to be used in 268 formulations (222 leave-on formulations, 45 rinse-off formulations, and 1 formulation diluted for bath; Table 10).[39] Chondrus Crispus is reported to be used in 94 formulations, Corallina Officinalis Extract is reported to be used in 66 formulations, and Chondrus Crispus Powder is reported to be used in 63 formulations. All other in-use ingredients are reported to be used in 52 formulations or less. The results of the concentration of use survey conducted by Council in 2020 indicate Corallina Officinalis Extract has the highest reported maximum concentration of use; it is used at up to 2% in blushers, other makeup preparations, and face and neck products.[40]

In some cases, reports of uses were received in the VCRP, but concentration of use data were not provided. For example, Ahnfeltiopsis Concinna Extract is reported to be used in 16 formulations, but no concentration of use data were reported. In other cases, no uses were reported in the VCRP, but concentration of use data were reported in the industry survey; e.g., Rhodymenia Palmata Extract had no reported uses in the VCRP, but a use concentration in eye lotions and face and neck products 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 34 ingredients not in use, according to the VCRP and concentration of use survey data, are listed in Table 11.

Several of these ingredients are used in formulations that are near the eye. For example, Chondrus Crispus Extract is reported to be used in eyeshadows at up to 0.14%. Incidental ingestion and/or contact with mucous membranes may also occur (e.g., Chondrus Crispus is reported to be used at up to 1.4% in dentifrices).

Additionally, some red algae-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Chondrus Crispus is reported to be used at up to 0.08% in aerosol suntan 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.[41,42] 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.[43,44] Red-algae derived ingredients have also been reported to be used in face powders that could possibly be inhaled (e.g., Chondrus Crispus Extract is reported to be used in face powders at up to 0.15%). Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[45-47]

None of the red algae-derived ingredients named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[48]

Non-Cosmetic

Several species of red algae (e.g., *Palmaria palmata*) have become established as part of popular international cuisine.[49] According to the US FDA, several red algae species (*Gloiopeltis furcata*, *Porphyra crispata*, *Porphyra deutata*, *Porphyra perforata*, *Porphyra suborbiculata*, *Porphyra tenera*, and *Rhodymenia palmata*) are direct food substances that are generally recognized as safe (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). [21CFR184.1121] Of these red algae species, two are relevant for the purposes of this report (*Porphyra tenera* and *Rhodymenia palmata*). Some red algae species are used in Hawaiian, Irish, or Asian cuisine (e.g., *Ahnfeltiopsis concinna*, *Chondrus crispus*, *Gracilaria verrucosa*, *Palmaria palmata*, *Porphyra* sp.) Other red algae species are used in jellies and as thickeners in food products (e.g., *Gelidiella* and *Gracilaria* sp).[50] A listing of red algae species that are frequently ingested by humans as foods is provided in Table 12.

In addition, red algae species have been used in historical folk medicine. Chinese and Japanese monks used preparations containing *Gelidium amansii* to treat sun stroke and fevers.[50] *Gloiopeltis tenax* has also been reported to be used in China to treat diarrhea and colitis.[23] In Japan and the Mediterranean area, *Gelidium cartilagineum* and *Chondrus Crispus* were used in diarrhea and urinary tract irritation treatment.[50] Extracts of the dried red algae, *Digenea simplex*, was sold by Asian apothecaries by the name of "helminol" to treat ascariasis and oxyuriasis.

Red algae species are still used in present-day holistic medicine for treatment and prevention of various ailments. Some red algae species (e.g., *Gigartina*) have been reported to be used in dietary supplements for immunity-boosting effects.[51] The red algae species*, Lithothamnion calcareum,* is marketed as a nutritional supplement for calcium and minerals in Brazil and other countries due to presence of calcium and magnesium carbonate precipitates in the cell wall.[52] This algae is also used in implants for bone surgery, animal nutrition, fertilizers, and soil treatments. *Gracilariopsis chorda* may be used as a medicinal food to prevent neurological disorders.[25] *Grateloupia livida* is also an edible and medicinal seaweed used to treat sore throat, stomachache, ascariasis, and dysentery.[53] Red algae species such as *Gelidium amansii*, *Gelidium cartilagineum*, and *Gigartina stellata* have been reported to be used in pharmaceutical and industrial preparations due to gelling, water-retention, emulsifying, and other physical properties.[27,50] *Corallina officinalis* extract is a popular ingredient in traditional Asian medicine used for the treatment of various ailments.[54] Several red algae species (e.g. *Chondrus crispus* (Irish moss) and *Gelidiella acerosa*) are widely used for the preparation of carrageenan, agar and for other industrial uses.[20,55]

TOXICOKINETIC STUDIES

No toxicokinetic studies on these ingredients were found in the published literature, and unpublished data were not submitted. In general, toxicokinetics data are not expected to be found on algal ingredients because each natural sourced ingredient is a complex mixture of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Animal

Oral

Asparagopsis Armata Extract

An acute oral toxicity assay was performed according to Organisation for Economic Co-operation and Development Test Guidelines (OECD TG) 423.[56] The test substance (100% dry extract Asparagopsis Armata Extract; up to 2000 mg/kg) was administered to rats (strain not reported) via an oral route (method of oral administration and dose not stated). No other details regarding this study were provided. The median lethal dose (LD_{50}) was reported to be > 2000 mg/kg.

Corallina Officinalis Extract

The acute oral toxicity of a mixture containing water and Corallina Officinalis Extract (0.2 – 4% algae) was evaluated in 10 rats (strain not reported).[15] Animals (number of animals not reported) received the test substance, undiluted, via ingestion. The LD_{50} was reported to be > 5000 mg/kg. No other details regarding this study were provided.

Delesseria Sanguinea Extract

Acute oral toxicity of a mixture consisting of Delesseria Sanguinea Extract (0.2 – 4 % algae), water, and dipropylene glycol, was evaluated in 10 rats (strain not reported).[18] The test substance was given undiluted. The method of oral administration was not stated. The LD_{50} was reported to be > 2000 mg/kg.

Grateloupia Livida Extract

The acute oral toxicity of several *Grateloupia livida* extracts (petroleum ether, ethyl acetate, n-butyl alcohol, and aqueous) was evaluated in female Kumming mice (20/group).[26] Animals were dosed with 5, 30, 300, or 2000 mg/kg of the extracts. No mortality or severe toxic effects were seen with any extract or dose level. The LD_{50} values were expected to be > 2000 mg/kg.

Lithothamnion Calcareum Extract

A *Lithothamnion calcareum* aqueous suspension was evaluated for acute oral toxicity in groups of 5 female Wistar rats.[52] One group was treated with the aqueous vehicle and the other was treated with a single 2000 mg/kg dose of the *Lithothamnion calcareum* suspension. The method of oral administration was not stated. Clinical observation of the rats was conducted 5, 15, and 30 min, and each hour for 12 h. The rats were also examined twice a day for an additional 13 d. After 14 d, rats were euthanized and subjected to macroscopic and microscopic necropsy. No signs of toxicity were observed in any of the treated rats.

Short-Term Toxicity Studies

Human

Dermal

Corallina Officinalis Extract

A microcirculation assay was performed on 30 subjects using a mixture containing Corallina Officinalis Extract (0.2 – 4% algae) and water.[15] A 5% dilution of the mixture was placed on the skin for 27 consecutive days. The test substance was considered to be well-tolerated. No other details regarding this study was provided.

Subchronic Toxicity Studies

Animal

Oral

Lithothamnion Calcareum Extract

A *Lithothamnion calcareum* aqueous suspension was evaluated for oral toxicity in Wistar rats.[52] Rats were divided into five groups: a control group (10 rats/sex/group), two experimental groups (10 rats/sex/group), and two satellite test groups (5 rats/sex/group). The satellite control group received the aqueous vehicle alone while the satellite high-dose group received a dose of 2000 mg/kg (specific use of satellite groups not specified). A constant volume of *Lithothamnion calcareum* suspension (1000 or 2000 mg/kg) was administered to all test groups (including satellite groups), daily, via gavage, for 90 d. Following treatment, blood was collected and animals were euthanized. No significant abnormalities in mortality, feces, hair, or behavior were identified in any group. Food intake of groups receiving the test substance was statistically higher than in the control group. Serum creatine levels were increased in female rats treated with 1000 mg/kg of the test substance, and in male and female rats treated with 2000 mg/kg of the test substance. Total serum protein levels decreased in rats treated with 2000 mg/kg of the test substance, and an even greater decrease occurred in the high-dose

satellite group. Decreased serum albumin levels were observed in male rats treated with 1000 mg/kg of the test substance and in high-dose male and female rats, with a greater decrease observed in the high-dose satellite group. Some differences were observed in the organ weights (body weight/organ weight ratio) of the rats, although gross necropsy and histopathologic evaluation of the same organs revealed no abnormality or significant changes between treated and control groups.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Gelidiella Acerosa Extract

The potential reproductive toxicity of a crude extract of *Gelidiella acerosa* was evaluated in albino rats.[57] In order to prepare the crude extract, *Gelidiella acerosa* was collected and extracted into a 1:1 methanol:methylene chloride solvent system and co-precipitated with polyvinylpyrrolidone (PVP). The co-precipitate was dissolved in distilled water to obtain the 1000 mg/kg dose in 1 ml aliquots. Pregnant rats (5/group) were orally administered (via gavage) either 1 ml vehicle (PVP in distilled water) or 1 ml of the crude extract (PVP co-precipitate) in distilled water, daily, at different stages of gestation (on day 1 only, days 1 - 3, days 4 - 6, or days 7 - 8). On day 14 of gestation, animals were laparotomized, and the number of implantation sites, resorption sites, number of viable embryos, and the gross appearance and number of corpora lutea were observed. Administration of the crude extract did not cause significant ($p > 0.05$) change in any of the parameters evaluated in the animals treated during day 1, days 1 - 3, or days 4 - 6 of gestation. Administration of the crude extract on day 7 - 8 of gestation significantly ($p < 0.01$) reduced the total number of viable implantation sites (by 72%), and significantly ($p < 0.01$) increased the number of resorption sites and post-implantation loss (by 89%).

Within the same study, 12 rats were divided into two equal groups, and one received 1 ml of the vehicle/day, and the other 1 ml of the crude extract/day. Administration occurred on days 1 - 7 of gestation. On day 8 of pregnancy, animals were laparotomized and evaluated. After examination of the number of implantation sites, resorption sites, and viable embryos, animals were sutured, treated locally and subcutaneously with antibiotics, and allowed to recover. Apparent size and distribution of the embryos in the uterine horns were also noted. These animals were re-laparotomized on day 14 of gestation, and the above parameters were recorded. At first laparotomy, the size, appearance, and color of the implants in treated animals were similar to those of the control; however, a clumping of embryos towards the cervical end of the uterine horns was evident in crude extract-treated rats. At second laparotomy, control animals had the same number of viable implants on day 14 as on day 8 of pregnancy. All embryos in the treated group on day 14 of gestation were non-viable and resorbing. There was a 100% post-implantation loss in the treated group ($p < 0.001$).

GENOTOXICITY STUDIES

Summaries of the in vitro genotoxicity studies summarized below are provided in Table 13.

Ames assays performed on an Asparagopsis Armata Extract (containing 8% dry algal matter; up to 5000 µg/plate), a mixture containing Asparagopsis Armata Extract (80%) and methylpropanediol (20%) (test concentration not reported), a mixture consisting of Corallina Officinalis Extract (0.2 – 4%) and water (test concentration not reported), a mixture containing Corallina Officinalis Extract (0.2 – 4% algae), sea water, calcium carbonate, and calcium chloride (test concentration not reported), a trade name mixture containing Corallina Officinalis Extract (3.97%), Kappaphycus Alvarezii Extract (5.9%), and *Gigartina stellata* (4.43%) (up to 5000 µg/plate), and a *Gelidiella acerosa* extract (up to 4000 µg/plate), yielded negative results.[15,56,58-60] A chemiluminescent 3D genotoxicity assay performed on a test substance containing 48% Porphyra Umbilicalis Extract also yielded negative results.[61]

CARCINOGENICITY STUDIES

No carcinogenicity studies on these red algae-derived ingredients were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

Hypnea Musciformis Extract

The effect of an ethanolic *Hypnea musciformis* extract on anthracene-induced mammary carcinogenesis was evaluated in female Sprague-Dawley rats (8/group).[62] Rats in group 1 served as a control. Rats in group 2 and 3 received a single subcutaneous injection of 7,12-dimethylbenz[a]anthracene (DMBA) (25 mg/kg bw) in the mammary gland to develop a mammary carcinoma. Rats in group 3 were also orally administered 200 mg/kg bw/d of *Hypnea musciformis* extract for 16 wk. Rats in group 4 received 200 mg/kg bw *Hypnea musciformis* extract alone, each day, orally, for 16 wk. (The method of oral administration was not stated.) At the end of the treatment, animals in group 2 showed decreased weight gain compared to control rats ($p < 0.05$). This effect was not seen in animals in any other group. One hundred percent of animals treated with DMBA alone displayed tumors, however in animals treated with DMBA and *Hypnea musciformis* extract, the incidence of mammary tumors was significantly lower (25%). No tumors were observed in control rats or rats treated with *Hypnea musciformis* extract alone.

Anti-Tumorigenicity

In Vitro

Asparagopsis Armata Extract and Gelidium Cartilagineum Extract

The antitumor potential of methanolic and dichloromethane extracts of *Asparagopsis armata* and *Plocamium cartilagineum* (equivalent to *Gelidium cartilagineum*) was evaluated in human liver cancer (HepG-2) cells via cell viability and cell proliferation studies.[63] For the cell viability and proliferation studies, extracts (1000 µg/ml) were incubated with HepG-2 cells for 24 h. Both methanolic and dichloromethane extracts of *Asparagopsis armata* presented high cytotoxicity with 11 ± 2.98 and 1.51 ± 0.38 % of HepG-2 live cells, respectively. Potent anti-proliferative activity was also induced by the dichloromethane extracts of *Asparagopsis armata* and *Plocamium cartilagineum*, with 98.56 ± 0.81 and 85.13 ± 1.04 % of cell's proliferation reduction, respectively.

Animal

Porphyra Tenera Powder

The effect of *Porphyra tenera* powder on intestinal tumor incidence was evaluated in Sprague-Dawley rats (10/group).[64] Tumors were induced in all experimental animals via a weekly subcutaneous injection of 1,2-dimethylhydrazine (DMH) for 12 wk. Experimental animals were fed a dietary seaweed preparation containing 2% *Porphyra tenera* powder, and controls were fed a basic diet. Animals were necropsied 8 wk after the cessation of the diet and DMH administrations. There was a significant decrease ($p < 0.01$) in the incidence of tumors in rats fed *Porphyra tenera* powder (2/10) versus control animals (8/10).

OTHER RELEVANT STUDIES

Cytotoxicity

Ceramium Virgatum Extract, Corallina Officinalis Extract, Furcellaria Lumbricalis Extract, Gelidium Cartilagineum Extract, Porphyra Linearis Extract, and Gelidium Cartilagineum Extract

The cytotoxic potential of *Ceramium virgatum* extract (equivalent to *Ceramium rubrum* extract), *Corallina officinalis* extract, *Furcellaria lumbricalis* extract, *Plocamium cartilagineum* extract (equivalent to *Gelidium cartilagineum* extract), *Porphyra linearis* extract, and *Mastocarpus stellata* extract (equivalent to *Gigartina stellata* extract), was evaluated using rat skeletal myoblasts (L6-cells).[65] Concentrations used were not reported. Among all extracts tested, only Corallina officinalis showed some weak cytotoxic potential towards the mammalian cells (half maximal inhibitory concentration (IC_{50}) value of 88.6 µg/ml). The remaining extracts had no toxicity at the highest concentration.

Gracilariopsis Longissima Extract

The potential cytotoxicity of a crude aqueous *Gracilariopsis longissima* extract (equivalent to *Gracilaria verrucosa* extract) was evaluated by a 3-(4,5-dimethylthiazol-2yl)-diphenyl tetrazolium bromide (MTT) assay.[24] This assay was carried out in vitro in three cell lines: murine macrophages of the immune system (RAW264.7), gingival fibroblasts (HGF), and immortalized human keratinocytes (HaCaT). All cell lines were exposed to the extract at concentrations ranging from 0 - 10 mg/ml for 72 h. No cytotoxicity was observed in either human cell line (HGF or HaCaT) at any concentration; however, cytotoxicity was observed in murine tumor cells.

Photoprotective Effects

Porphyra Umbilicalis Extract

A study was performed to assess the photoprotective effects of cosmetic formulations containing *Porphyra umbilicalis*.[66] Four groups of four hairless mice were treated with topical formulations on the dorsum for 5 d as follows: group 1 – control (no treatment); group 2 – application of sunscreen formulation containing only ultraviolet light (UV) filters; group 3 – application of sunscreen formulation with 5% *Porphyra umbilicalis* extract; group 4 – application of the sunscreen formulation with 5% *Porphyra umbilicalis*, 1.5% *Ginkgo biloba*, and vitamins A, E, and C. After application, mice were immobilized and exposed to long-wavelength ultraviolet A (UVA)/ultraviolet B (UVB) radiation for 28 min, which resulted in a cumulative UVB dose of approximately 0.67 J/cm^2. Apoptosis and erythema were evaluated in each group. Immunohistochemical analysis showed that UV radiation caused an increase in the expression of tumor antigen p53 and apoptosis mediator caspase-3, confirming that the damage caused by UV radiation exposure led to apoptosis. Applications of the test material in groups 2, 3, and 4 resulted in a statistically significant reduction in the expression of p53 and caspase-3, with a more pronounced effect following treatment in group 3 (treatment of sunscreen formulation with *Porphyra umbilicalis* extract). Groups 3 and 4 displayed a statistically significant decrease in erythema values compared with the irradiated control ($p < 0.05$) group.

Anti-Allergic Activity of Porphyran

The effect of porphyran (a major component of *Porphyra tenera* and *Porphyra yezoensis*) on the contact hypersensitivity reaction in female Balb/c mice (10/group) was evaluated.[67] Control and treated groups were given a regular

diet for 7 d. On day 7 and 8, mice were administered 2 topical applications of 50 µl of a 5% 2,4,6-trinitrochlorobenzene (TNCB) solution in acetone on shaved abdominal skin. The control and treated groups resumed regular diets, however, the porphyran-treated groups were administered either 0.5, 1, or 2% porphyran in drinking water for the remainder of the test period. The control group was given plain water only. Three days after administration of the TNCB solution, 20 µl of a 1% TNCB solution in acetone was applied to the right ear lobe of each mouse. Twenty-four h later, the thickness of the ear lobe was measured. Oral administration of porphyran at 2% significantly suppressed ear edema induced by TNCB. In addition, it was found that porphyran suppressed the serum level of immunoglobin E and the production of interferon-γ in the challenged ear lobe.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below are presented in Table 14.

Irritation

In vitro dermal irritation assays were performed on a trade name mixture containing 0.75% Ahnfeltiopsis Concinna Extract (tested at 100%; other components of mixture not reported), an Asparagopsis Armata Extract containing 4% dry algal matter (tested at 10%; other components of extract not reported), a mixture containing 80% Asparagopsis Armata Extract and 20% methylpropanediol (tested at 100%), a trade name mixture containing 3.5% Chondrus Crispus Extract (tested at 100%; other component of mixture not reported), and a mixture consisting of Corallina Officinalis Extract (0.2 – 4% algae), propylene glycol, calcium chloride, and sea water (tested at 100%).[15,56,58,68,69] All test substances were predicted to be non-irritating.

No irritation was reported in animal dermal irritation assay in which rabbits (strain not reported) were dermally exposed to an undiluted mixture containing Corallina Officinalis Extract (0.2 – 4% algae) and water.[15] Similarly, no irritation was reported when a mixture consisting of Delesseria Sanguinea (0.2 – 4% algae), water, and dipropylene glycol, was applied to the skin of 3 rabbits (strain not reported).[18] The test concentration was not provided.

Many human dermal irritation studies were conducted using test substances containing a red algae-derived ingredient, or combination of ingredients, along with other substances such as water, propanediol, glycerin, and butylene glycol. The majority of these studies yielded negative results; however, slight irritation was noted (at 30 min after patch removal) in a 24-h patch test assay in which the undiluted test substance (trade name mixture consisting of 72 - 77% water; 20 - 70% butylene glycol; 1 - 3% Hypnea Musciformis Extract; ≤ 1% potassium gluconate; 0.16 - 0.2% methylparaben) was applied to the skin of 12 subjects under occlusive conditions.[70]

Sensitization

Numerous sensitization studies were performed on human subjects. All studies evaluating various red algae-derived ingredients (Asparagopsis Armata Extract (0.325% and 0.5 – 2%), Betaphycus Gelatinum Extract (7%), Chondrus Crispus Extract (0.49%), Corallina Officinalis Extract (0.2 – 4% algae), Corallina Officinalis Extract (2%), Delesseria Sanguinea Extract (0.2 – 4% algae), Furcellaria Lumbricalis Extract (0.2 – 4% algae), Gelidiella Acerosa Extract (0.0028%), Gelidium Cartilagineum Extract (< 2%), Hydrolyzed Corallina Officinalis Extract (0.5 – 3%), Hypnea Musciformis Extract (15% (0.36% dry matter)), Kappaphycus Alvarezii Extract (0.8%), Palmaria Palmata Extract (25% (1.87% dry matter)), and Porphyra Umbilicalis Extract (0.0004%)) were negative.[15,18,19,28,71-80]

Phototoxicity

In Vitro

Corallina Officinalis Extract

The potential phototoxicity of a mixture containing Corallina Officinalis Extract (0.2 – 4% algae) and water was evaluated in a 3T3 neutral red uptake (NRU) phototoxicity assay performed according to OECD TG 432.[15] Cytotoxicity was evaluated in a cell monolayer (fibroblast Balb/c3Tc clone) after incubation with the test substance at 7 concentrations (concentrations not specified), and irradiation with UVA. The test substance was considered to be non-cytotoxic. The same procedure was performed using a test substance consisting of Corallina Officinalis Extract (0.2 – 4% algae), sea water, calcium carbonate, and calcium chloride. No signs of phototoxicity were observed.

Porphyra Umbilicalis Extract

The phototoxic potential of a test substance consisting of 52% water and 48% Porphyra Umbilicalis Extract was evaluated according to the same procedure as above.[61] The test substance was considered to be non-cytotoxic.

OCULAR IRRITATION STUDIES

The ocular irritation studies summarized below are presented in Table 15.

In Vitro

An in vitro ocular irritation assay performed on reconstructed cornea epithelium using a trade name mixture containing 0.75% Ahnfeltiopsis Concinna Extract yielded negative results.[68] MatTek EpiOcular™ MTT viability assays were performed to evaluate the ocular irritation potential of three different test substances containing red algae-derived ingredients (an after-shave balm containing 0.8% Chondrus Crispus, a trade name mixture containing 3.5% Chondrus Crispus Extract, or an eye cream containing 0.0375% Rhodymenia Palmata Extract).[69,81,82] All test substances were considered to be non-irritating.

Slight irritation was noted in an in vitro ocular irritation assay performed using the PREDISAFE method on an Asparagopsis Armata Extract (4% dry algal matter).[58] According to summary data, a mixture containing Corallina Officinalis Extract (0.2 – 4% algae) sea water, calcium chloride, and propylene glycol was slightly irritating in a PREDISAFE assay.[15] A mixture containing Delesseria Sanguinea Extract (0.2 – 4% algae), water, and dipropylene glycol, was not considered to be a ocular irritant in a neutral red release assay.[18] No other details regarding this study were provided.

Several hen's egg test chorioallantoic membrane (HET-CAM) assays were performed on various red algae-derived ingredients (Asparagopsis Armata Extract (98.6%), Corallina Officinalis Extract (0.15%, 0.397%), Kappaphycus Alvarezii Extract (5.9%), Lithothamnion Calcareum Powder (up to 5.7 – 6.1%), and Porphyra Umbilicalis Extract (48%)). Most assays reported slight or no irritation.[56,61,82-85] However, moderate irritation was noted when a trade name mixture consisting of 57 - 61% Lithothamnion Calcareum Powder, 26 - 31% mannitol, 9 - 11% diatomaceous earth, 0.7 - 1.5% zinc sulfate was used in a HET-CAM assay tested at 10%, but not at 2 and 5%.

An agar diffusion cytotoxicity assay was performed in order to determine the ocular irritation potential of a mixture consisting of Furcellaria Lumbricalis Extract (0.2 – 4%), water, and sea salt.[19] Cytotoxicity was reported to be low, supporting a lack of ocular irritation. No other details regarding this study were provided.

Animal

According to summary data, Corallina Officinalis Extract (0.2 – 4% algae) in water was slightly irritating when applied undiluted to the eyes of 3 rabbits (strain not reported).[15] Similarly, slight irritation was observed in an ocular irritation study in which Delesseria Sanguinea Extract (0.2 – 4% algae) in dipropylene glycol and water was applied to the eyes of three rabbits (strain not reported). Details regarding these studies were not reported.[18]

SUMMARY

This is a safety assessment of 60 red algae-derived ingredients. However, several of these ingredients are equivalent according to accepted scientific names; accordingly, the number of distinct cosmetic ingredients is 56. The ingredients reviewed in this report are primarily extracts and powders derived from red algae species, and may be derived from the whole plant or a defined part of the plant. These ingredients are mostly reported to function in cosmetics as skin-conditioning agents.

According to 2021 VCRP survey data, Chondrus Crispus Extract is reported to be used in 268 formulations (222 leave-on formulations, 45 rinse-off formulations, and 1 formulation diluted for bath). Chondrus Crispus is reported to be used in 94 formulations, Corallina Officinalis Extract is reported to be used in 66 formulations, and Chondrus Crispus Powder is reported to be used in 63 formulations. All other in-use ingredients are reported to be used in 52 formulations or less. The results of the 2020 concentration of use survey conducted by Council indicate that Corallina Officinalis Extract has the highest reported maximum concentration of use; it is used at up to 2% in leave-on dermal products. All other in-use ingredients are reported to be used at 1.4% or less.

Several species of red algae have become established as part of popular international cuisine (e.g., *Ahnfeltiopsis concinna*, *Chondrus crispus*, *Gracilaria verrucosa*, *Palmaria palmata*, *Porphyra* sp.). According to the US FDA, *Porphyra tenera* and *Rhodymenia palmata* 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. [21CFR184.1121] Several red algae species have historical and present-day use in holistic medicine. Red algae also have industrial uses due to their gelling and emulsifying properties.

No toxicity was observed in an acute oral toxicity study involving rats given up to 2000 mg/kg of a 100% dry extract Asparagopsis Armata Extract. The oral LD_{50} was reported to be > 5000 mg/kg in an acute toxicity assay using a mixture containing Corallina Officinalis Extract (0.2 – 4% algae) in rats. In an acute oral toxicity assay performed on rats, using a test substance containing Delesseria Sanguinea Extract (0.2 – 4% algae), the LD_{50} was reported to be > 2000 mg/kg. The acute oral toxicity potential of multiple *Grateloupia livida* extracts were evaluated in female mice at up to 2000 mg/kg. No toxicity was observed with any extract or dose level. Similarly, no acute oral toxicity was observed in Wistar rats given a single 2000 mg/kg dose of an aqueous *Lithothamnion calcareum* suspension.

A 27-d microcirculation assay was performed on 30 subjects. The test substance (Corallina Officinalis Extract (0.2 – 4% algae in water) was considered to be well-tolerated. A 90-d oral toxicity study was performed in which Wistar rats were given either 1000 or 2000 mg/kg/d of a Lithothamnion Calcareum suspension. Serum creatine levels were increased in female rats given 1000 mg/kg of the test substance and in males and females treated with 2000 mg/kg of the test substance.

Some differences were observed in the organ weights of the rats, although gross necropsy and histopathologic evaluation of the same organs revealed no abnormality or significant changes between treated and control groups.

The potential reproductive toxicity of a crude extract of *Gelidiella acerosa* (1000 mg/kg/d) was evaluated in female albino rats at different stages of gestation. Administration of the crude extract did not cause significant ($p > 0.05$) change in any of the parameters evaluated in the animals treated during most gestation periods. However, administration of the crude extract on day 7 - 8 of gestation significantly ($p < 0.01$) reduced the total number of viable implantation sites (by 72%), and significantly ($p < 0.01$) increased the number of resorption sites and post-implantation loss (by 89%). Within the same study, 12 rats were divided into two equal groups, and one received 1 ml of the vehicle/day, and the other 1 ml of the crude extract/day. Administration occurred on days 1 - 7 of gestation. Animals were first laparotomized on day 8 of gestation, and allowed to recover. Animals were then re-laparotomized and evaluated on day 14 of gestation. At first laparotomy, the size, appearance, and color of the implants in treated animals were similar to those of the control, however, a clumping of embryos towards the cervical end of uterine horns was evident in crude extract-treated rats. When rats were observed on day 14 of gestation, control animals had the same number of viable implants as on day 8 of pregnancy. All embryos in the treated group on day 14 of pregnancy were non-viable and resorbing. There was a 100% post-implantation loss in the treated group ($p < 0.001$).

Ames assays performed on an Asparagopsis Armata Extract (containing 8% dry algal matter), a mixture containing Asparagopsis Armata Extract (80%) and methylpropanediol (20%), a mixture consisting of Corallina Officinalis Extract (0.2 – 4%) and water, a mixture containing Corallina Officinalis Extract (0.2 – 4% algae), sea water, calcium carbonate, and calcium chloride, a trade name mixture containing Corallina Officinalis Extract (3.97%), Kappaphycus Alvarezii Extract (5.9%), and *Gigartina stellata* (4.43%), and a *Gelidiella acerosa* extract, yielded negative results. A chemiluminescent 3D genotoxicity assay performed on a test substance containing 48% Porphyra Umbilicalis Extract also yielded negative results.

The effect of an ethanolic *Hypnea musciformis* extract on anthracene-induced mammary carcinogenesis was evaluated in female Sprague-Dawley rats. The test groups were given a subcutaneous injection of DMBA to induce carcinomas, along with 200 mg/kg bw/d of the algae extract, orally, for 16 wk. One hundred percent of animals treated with DMBA alone displayed tumors, however in animals treated with DMBA and *Hypnea musciformis* extract, the incidence of mammary tumors was significantly lower (25%). No tumors were observed in control rats or rats treated with *Hypnea musciformis* extract alone.

The anti-tumorigenic potential of methanolic and dichloromethane extracts of *Asparagopsis armata* and *Plocamium cartilagineum* (equivalent to *Gelidium cartilagineum*) was evaluated in HepG-2 cells. Cells were incubated with 1000 µg/ml of the extracts and evaluated for cell viability and proliferation. Both methanolic and dichloromethane extracts of *Asparagopsis armata* presented high cytotoxicity with 11 ± 2.98 and 1.51 ± 0.38 % of HepG-2 live cells, respectively. Anti-proliferative activity of HepG-2 cells was observed in cells treated with dichloromethane extracts of both algae species. The effect of *Porphyra tenera* powder on intestinal tumor incidence was evaluated in Sprague-Dawley rats. Tumors were induced in animals via a weekly injection of DMH for 12 wk, and algae-treated animals received a dietary seaweed preparation containing 2% *Porphyra tenera* powder. Control animals were fed a regular diet. There was a significant decrease ($p < 0.01$) in the incidence of tumors in rats fed *Porphyra tenera* powder (2/10) versus control animals (8/10).

The cytotoxic potential of *Ceramium virgatum* extract (equivalent to *Ceramium rubrum* extract), *Corallina officinalis* extract, *Furcellaria lumbricalis* extract, *Plocamium cartilagineum* extract (equivalent to *Gelidium cartilagineum* extract), *Porphyra linearis* extract, and *Mastocarpus stellata* extract (equivalent to *Gigartina stellata* extract), was evaluated using L6-cells.[65] Among all extracts tested, only *Corallina officinalis* showed some weak cytotoxic potential towards the mammalian cells (half maximal inhibitory concentration (IC_{50}) value of 88.6 µg/ml). The remaining extracts had no toxicity at the highest concentration. An MTT assay was performed using human and tumor cells on a crude aqueous extract of *Gracilariopsis longissima* (equivalent to *Gracilaria verrucosa* extract) at up to 10 mg/ml for 72 h. No cytotoxicity was observed in either human cell line (HGF or HaCaT) at any concentration, however, significant cytotoxicity was observed in murine tumor cells.

The potential photoprotective effects of cosmetic formulations containing 5% *Porphyra umbilicalis* was evaluated in hairless mice (4 animals/group). After administration of the test substance, animals were exposed to UV radiation. A more pronounced reduction in the expression of p53 and caspase-3 and decreased erythema values were observed in groups treated with Porphyra umbilicalis compared to the control groups.

The effect of porphyran on the contact hypersensitivity reaction in female Balb/c mice was evaluated. Induced ear edema was evaluated after treatment with porphyran in the diet at up to 2%, for 7 d. Oral administration of porphyran at 2% significantly suppressed ear edema induced by TNCB. In addition, it was found that porphyran suppressed the serum level of immunoglobin E and the production of interferon-γ in the challenged ear lobe.

In vitro dermal irritation assays were performed on trade name mixture containing 0.75% Ahnfeltiopsis Concinna Extract (tested at 100%; other components of mixture not reported), an Asparagopsis Armata Extract containing 4% dry algal matter (tested at 10%; other components of extract not reported), a mixture containing 80% Asparagopsis Armata Extract and 20% methylpropanediol (tested at 100%), a trade name mixture containing 3.5% Chondrus Crispus Extract (tested at 100%;

other component of mixture not reported), and a mixture consisting of Corallina Officinalis Extract (0.2 – 4%), propylene glycol, calcium chloride, and sea water (tested at 100%). All test substances were considered to be non-irritating.

No irritation as reported in animal dermal irritation assays in which rabbits were dermally exposed to a mixture containing Corallina Officinalis Extract (0.2 – 4% algae) and water (tested at 100%), or a mixture containing Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol (test concentration not reported). Many human dermal irritation studies were conducted using test substances containing a red algae ingredient, or combination of ingredients, along with other substances such as water, propanediol, glycerin, and butylene glycol. The majority of these studies yielded negative results; however, slight irritation was noted (at 30 min after patch removal) in a 24-h patch test assay on a trade name mixture containing 72 - 77% water; 20 - 70% butylene glycol; 1 - 3% Hypnea Musciformis Extract; ≤ 1% potassium gluconate; 0.16 - 0.2% methylparaben. All sensitization studies performed on humans, evaluating various red algae-derived ingredients (Asparagopsis Armata Extract (0.325% and 0.5 – 2%), Betaphycus Gelatinum Extract (7%), Chondrus Crispus Extract (0.49%), Corallina Officinalis Extract (0.2 – 4% algae), Corallina Officinalis Extract (2% (dilution not reported), Delesseria Sanguinea Extract (0.2 – 4% algae), Furcellaria Lumbricalis Extract (0.2 – 4% algae), Gelidiella Acerosa Extract (0.0028%), Gelidium Cartilagineum Extract (< 2%), Hydrolyzed Corallina Officinalis Extract (0.5 – 3%), Hypnea Musciformis Extract (15% (0.36% dry matter)), Kappaphycus Alvarezii Extract (0.8%), Palmaria Palmata Extract (25% (1.87% dry matter)), and Porphyra Umbilicalis Extract (0.0004%)), were negative.

3T3 NRU phototoxicity assays were performed on two different mixtures containing Corallina Officinalis Extract (0.2 – 4% algae), and a mixture of Porphyra Umbilicalis Extract (48%) and water. These test substances were considered to be non-cytotoxic.

No irritation was observed in in vitro ocular assays performed on a trade name mixture containing 0.75% Ahnfeltiopsis Concinna Extract, a mixture containing 98.6% Asparagopsis Armata Extract, an after-shave balm containing 0.8% Chondrus Crispus, a trade name mixture containing 3.5% Chondrus Crispus Extract, a trade name mixture containing 1.5% Corallina Officinalis Extract, a mixture containing 0.2 – 4% Delesseria Sanuginea Extract, and a mixture containing 0.2 – 4% Furcellaria Lumbricalis Extract. Slight irritation was observed in a PREDISAFE assay evaluating an Asparagopsis Armata Extract (4% dry algal matter). Slight irritation was also observed in a HET-CAM assay using a test substance containing *Gigartina stellata* (4.43%), Kappaphycus Alvarezii Extract (5.9%), and Corallina Officinalis Extract (3.97%). Moderate irritation was noted when a trade name mixture containing 57 - 61% Lithothamnion Calcareum Powder was used in a HET-CAM assay and tested at 10%, but not when tested at 2 and 5%. In vivo Ocular irritation assays performed in rabbits revealed slight irritation when exposed to Corallina Officinalis Extract (0.2 – 4% algae) in water and Delesseria Sanguinea Extract (0.2 – 4% algae) in water and dipropylene glycol.

DRAFT DISCUSSION

[**Note**: This Discussion is in draft form, and changes may be made following the Panel meeting.]

The majority of the ingredients in this review are extracts and powders derived from different species of red algae. The Panel noted that elevated levels of heavy metals, arsenic, and pesticide residues may be present in these red algae-derived ingredients. The cosmetics industry should continue to use cGMPs to limit these impurities. The Panel also noted the presence of kainic and arachidonic acid (which was previously found by the Panel to have insufficient data to determine safety) in several of these red algae ingredients, and determined that the concern can be mitigated as the final concentration of this material would be minimal in cosmetic formulations.

In addition, it was noted that several ingredients evaluated in this report are GRAS or used in foods. Because exposure via ingestion would be far greater than exposure via cosmetics, the Panel deferred the need for systemic toxicity data.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., up to 0.08% Chondrus Crispus in aerosol suntan products and 0.15% Chondrus Crispus Extract in face powders). Inhalation toxicity data were not available. However, 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.

CONCLUSION

To be determined.

TABLES

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

Ingredient	Definition	Function
Ahnfeltiopsis Concinna Extract	Ahnfeltiopsis Concinna Extract is the extract of the alga, *Ahnfeltiopsis concinna*. The accepted scientific name for *Ahnfeltiopsis concinna* is *Gymnogongrus durvillei*.	Skin-Conditioning Agents - Emollient; Skin-Conditioning Agents - Miscellaneous
Asparagopsis Armata Extract	Asparagopsis Armata Extract is the extract of the red alga, *Asparagopsis armata*.	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Asparagopsis Armata Extract	Hydrolyzed Asparagopsis Armata Extract is the hydrolysate of Asparagopsis Armata Extract derived by acid, enzyme, or other method of hydrolysis.	Skin Protectants
Betaphycus Gelatinum Extract	Betaphycus Gelatinum Extract is the extract of the alga, *Betaphycus gelatinum.*	Skin Bleaching Agents
Botryocladia Occidentalis Extract	Botryocladia Occidentalis Extract is the extract of the alga, *Botryocladia occidentalis*.	Skin-Conditioning Agents - Miscellaneous
Calliblepharis Ciliata Extract	Calliblepharis Ciliata Extract is the extract of the algae, *Calliblepharis ciliate.*	Skin-Conditioning Agents - Miscellaneous
Ceramium Kondoi Extract	Ceramium Kondoi Extract is the extract of the algae, *Ceramium kondoi.*	Skin-Conditioning Agents - Humectant
Ceramium Rubrum Extract	Ceramium Rubrum Extract is the extract of the algae, *Ceramium rubrum*. The accepted scientific name for *Ceramium rubrum* is *Ceramium virgatum*.	Skin-Conditioning Agents – Emollient; Skin-Conditioning Agents - Humectant
Chondracanthus Teedei Powder	Chondracanthus Teedei Powder is the powder obtained from the dried, ground alga, *Chondracanthus teedei.*	Skin-Conditioning Agents - Miscellaneous
Chondrus Crispus	Chondrus Crispus is the material obtained from the whole alga, *Chondrus crispus*.	Exfoliants
Chondrus Crispus Extract	Chondrus Crispus Extract is the extract of the red alga, *Chondrus crispus.*	Humectants; Skin-Conditioning Agents - Miscellaneous
Chondrus Crispus Powder	Chondrus Crispus Powder is the powder obtained from the dried, ground alga, *Chondrus crispus.*	Abrasives
Hydrolyzed Chondrus Crispus Extract	Hydrolyzed Chondrus Crispus Extract is the hydrolysate of Chondrus Crispus Extract derived by acid, enzyme, or other method of hydrolysis	Skin-Conditioning Agents - Miscellaneous
Corallina Officinalis Extract	Corallina Officinalis Extract is the extract of the alga, *Corallina officinalis.*	Skin-Conditioning Agents - Miscellaneous
Corallina Officinalis Powder	Corallina Officinalis Powder is the powder obtained from the dried, ground alga, *Corallina officinalis*	Binders; Dispersing Agents – Nonsurfactant; Viscosity Increasing Agents - Nonaqeuous
Corallina Officinalis Thallus Extract	Corallina Officinalis Thallus Extract is the extract of the thallus of *Corallina officinalis.*	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Corallina Officinalis	Hydrolyzed Corallina Officinalis is the hydrolysate of the whole plant, *Corallina officinalis* derived by acid, enzyme, or other method of hydrolysis.	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Corallina Officinalis Extract	Hydrolyzed Corallina Officinalis Extract is the hydrolysate of the extract of the alga, *Corallina officinalis,* obtained by acid, enzyme, or other method of hydrolysis.	Not Reported
Cyanidium Caldarium Extract	Cyanidium Caldarium Extract is the extract of the alga, *Cyanidium caldarium.*	Skin-Conditioning Agents - Miscellaneous
Delesseria Sanguinea Extract	Delesseria Sanguinea Extract is the extract of the alga, *Delesseria sanguinea.*	Skin-Conditioning Agents - Miscellaneous
Digenea Simplex Extract	Digenea Simplex Extract is the extract of the alga, *Digenea simplex.*	Not Reported
Dilsea Carnosa Extract	Dilsea Carnosa Extract is the extract of the alga, *Dilsea carnosa.*	Skin Protectants
Furcellaria Lumbricalis Extract	Furcellaria Lumbricalis Extract is the extract of the alga, *Furcellaria lumbricalis.*	Skin-Conditioning Agents - Miscellaneous
Gelidiella Acerosa Extract	Gelidiella Acerosa Extract is the extract of the red alga, *Gelidiella acerosa.*	Skin-Conditioning Agents - Miscellaneous
Gelidium Amansii Extract	Gelidium Amansii Extract is the extract of the alga, *Gelidium amansii.*	Skin-Conditioning Agents - Miscellaneous
Gelidium Amansii Oligosaccharides	Gelidium Amansii Oligosaccharides are oligosaccharides produced by the enzymatic degradation of Agar that is obtained from *Gelidium amansii.*	Skin-Conditioning Agents - Humectant
Gelidium Cartilagineum Extract	Gelidium Cartilagineum Extract is the extract of the alga, *Gelidium cartilagineum.* The accepted scientific name for *Gelidium cartilagineum* is *Plocamium cartilagineum.*	Skin-Conditioning Agents - Miscellaneous
Gelidium Pulchrum Protein	Gelidium Pulchrum Protein is the protein fraction isolated from the alga, *Gelidium pulchrum.*	Skin-Conditioning Agents - Miscellaneous
Gelidium Sesquipedale Extract	Gelidium Sesquipedale Extract is the extract of the alga, *Gelidium sesquipedale.* The accepted scientific name for *Gelidium sesquipedale* is *Gelidium corneum.*	Skin Protectants
Gigartina Skottsbergii Extract	Gigartina Skottsbergii Extract is the extract of the alga, *Gigartina skottsbergii.*	Skin-Conditioning Agents - Miscellaneous
Gigartina Stellata Extract	Gigartina Stellata Extract is the extract of the thallus of the alga, *Gigartina stellata.* The accepted scientific name for *Gigartina stellata* is *Mastocarpus stellatus*	Humectants; Skin-Conditioning Agents - Miscellaneous
Gloiopeltis Tenax Extract	Gloiopeltis Tenax Extract is the extract of the alga, *Gloiopeltis tenax.*	Antifungal Agents; Antimicrobial Agents; Antioxidants
Gloiopeltis Tenax Powder	Gloiopeltis Tenax Powder is the powder obtained from the dried, ground alga, *Gloiopeltis tenax*.	Skin-Conditioning Agents - Miscellaneous

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

Ingredient	Definition	Function
Gracilaria Verrucosa Extract	Gracilaria Verrucosa Extract is the extract of the alga, *Gracilaria verrucosa.* The accepted scientific name for *Gracilaria verrucosa* is *Gracilariopsis longissima.*	Humectants; Skin-Protectants; Skin-Conditioning Agents - Humectant
Gracilariopsis Chorda Extract	Gracilariopsis Chorda Extract is the extract of the alga, *Gracilariopsis chorda.*	Skin-Conditioning Agents - Miscellaneous
Grateloupia Livida Powder	Grateloupia Livida Powder is the powder obtained from the dried, ground alga, *Grateloupia livida.*	Viscosity Increasing Agents - Aqueous
Hypnea Musciformis Extract	Hypnea Musciformis Extract is the extract of the red alga, *Hypnea musciformis*.	Skin-Conditioning Agents - Miscellaneous
Kappaphycus Alvarezii Extract	Kappaphycus Alvarezii Extract is the extract of the alga, *Kappaphycus alvarezii*	Skin-Conditioning Agents – Emollient; Skin-Conditioning Agents – Miscellaneous
Lithothamnion Calcareum Extract	Lithothamnion Calcareum Extract is the extract of the red alga, *Lithothamnion calcareum.* The accepted scientific name for *Lithothamnion calcareum* is *Phymatolithon calcareum.*	Skin-Conditioning Agents - Miscellaneous
Lithothamnion Calcareum Powder	*See Phymatolithon Calcareum Extract*	
Lithothamnion Corallioides Powder	Lithothamnion Corallioides Powder is the powder obtained from the dried, ground alga, *Lithothamnion corallioides.*	Abrasives
Mesophyllum Lichenoides Extract	Mesophyllum Lichenoides Extract is the extract of the alga, *Mesophyllum lichenoides.*	Skin-Conditioning Agents - Miscellaneous
Palmaria Palmata Extract	Palmaria Palmata Extract is the extract of the alga, *Palmaria palmata.*	Skin-Conditioning Agents - Miscellaneous
Rhodymenia Palmata Extract	Rhodymenia Palmata Extract is the extract of the alga, *Rhodymenia palmata.* The accepted scientific name for *Rhodymenia palmata* is *Palmaria palmata*	Antioxidants; Binders; Skin-Conditioning Agents - Emollient
Palmaria Palmata Powder	Palmaria Palmata Powder is the powder obtained from the dried, ground alga, *Palmaria palmata.*	Viscosity Increasing Agents - Aqueous
Phymatolithon Calcareum Extract	Phymatolithon Calcareum Extract is the extract of the alga, *Phymatolithon calcareum.*	Skin-Conditioning Agents - Miscellaneous
Lithothamnion Calcareum Powder	Lithothamnion Calcareum Powder is the powder obtained from the dried, ground red alga, *Lithothamnion calcareum.* The accepted scientific name for *Lithothamnion calcareum* is *Phymatolithon calcareum.*	Abrasives
Pikea Robusta Extract	Pikea Robusta Extract is the extract of the alga, *Pikea robusta.* The accepted scientific name for *Pikea robusta* is *Pikea pinnata.*	Antioxidants; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Polysiphonia Lanosa Extract	Polysiphonia Lanosa Extract is the extract of the alga, *Polysiphonia lanosa.* The accepted scientific name for *Polysiphonia lanosa* is *Vertebrata lanosa.*	Skin-Conditioning Agents - Miscellaneous
Porphyra Linearis Powder	Porphyra Linearis Powder is the powder obtained from the dried, ground alga, *Porphyra linearis.*	Exfoliants
Porphyra Tenera Extract	Porphyra Tenera Extract is the extract of the alga, *Porphyra tenera.* The accepted scientific name for *Porphyra tenera* is *Pyropia tenera.*	Skin-Conditioning Agents - Humectant
Porphyra Tenera Sporophyte Extract	Porphyra Tenera Sporophyte Extract is the extract of the sporophyte of the alga, *Porphyra tenera.* The accepted scientific name for *Porphyra tenera* is *Pyropia tenera.*	Antioxidants; Skin Protectants
Porphyra Umbilicalis Extract	Porphyra Umbilicalis Extract is the extract of the alga, *Porphyra umbilicalis.*	Skin-Conditioning Agents - Miscellaneous
Porphyra Umbilicalis Powder	Porphyra Umbilicalis Powder is the powder obtained from the dried, ground alga, *Porphyra umbilicalis.*	Abrasives; Absorbents; Binders; Colorants; Exfoliants; Viscosity Increasing Agents - Nonaqueous
Hydrolyzed Porphyra Yezoensis	Hydrolyzed Porphyra Yezoensis is the hydrolysate of the alga, *Porphyra yezoensis* derived by acid, enzyme, or other method of hydrolysis.	Hair Conditioning Agents; Skin-Conditioning Agents - Humectant
Porphyra Yezoensis Extract	Porphyra Yezoensis Extract is the extract of the alga, *Porphyra yezoensis.* The accepted scientific name for *Porphyra yezoensis* is *Pyropia yezoensis.*	Skin-Conditioning Agents - Miscellaneous
Porphyra Yezoensis Powder	Porphyra Yezoensis Extract is the extract of the alga, *Porphyra yezoensis.* The accepted scientific name for *Porphyra yezoensis* is *Pyropia yezoensis.*	Viscosity Increasing Agents - Aqueous
Porphyridium Cruentum Culture Conditioned Media	Porphyridium Cruentum Culture Conditioned Media is the growth media removed from cultures of the algae, *Porphyridium cruentum*, after several days of growth.	Antioxidants
Porphyridium Cruentum Extract	*See Porphyridium Purpureum Extract*	
Porphyridium Purpureum Extract	Porphyridium Purpureum Extract is the extract of the alga, *Porphyridium purpureum.*	Skin-Conditioning Agents – Miscellaneous
Porphyridium Cruentum Extract	Porphyridium Cruentum Extract is the extract of the alga, *Porphyridium cruentum.* The accepted scientific name for *Porphyridium cruentum* is *Porphyridium purpureum.*	Skin-Conditioning Agents - Miscellaneous
Rhodymenia Palmata Extract	*See Palmaria Palmata Extract*	
Sarcodiotheca Gaudichaudii Extract	Sarcodiotheca Gaudichaudii Extract is the extract of the alga, *Sarcodiotheca gaudichaudii.*	Antioxidants

Table 2. Taxonomy of red-algae derived ingredients based on currently accepted scientific name[86]

Subclass	Order	Family	Genus	Ingredient (INCI name)
Rhodymeniophycidae	Bonnemaisoniales	Bonnemaisoniaceae	Asparagopsis	Asparagopsis Armata Extract
Rhodymeniophycidae	Bonnemaisoniales	Bonnemaisoniaceae	Asparagopsis	Hydrolyzed Asparagopsis Armata Extract
Rhodymeniophycidae	Gigartinales	Solieriaceae	Betaphycus	Betaphycus Gelatinum Extract
Rhodymeniophycidae	Rhodymeniales	Rhodymeniaceae	Botryocladia	Botryocladia Occidentalis Extract
Rhodymeniophycidae	Gigartinales	Cystocloniaceae	Calliblepharis	Calliblepharis Ciliata Extract
Rhodymeniophycidae	Ceramiales	Ceramiaceae	Ceramium	Ceramium Kondoi Extract
Rhodymeniophycidae	Ceramiales	Ceramiaceae	Ceramium	Ceramium Rubrum Extract
Rhodymeniophycidae	Gigartinales	Gigartinaceae	Chondracanthus	Chondracanthus Teedei Powder
Rhodymeniophycidae	Gigartinales	Gigartinaceae	Chondrus	Chondrus Crispus
Rhodymeniophycidae	Gigartinales	Gigartinaceae	Chondrus	Chondrus Crispus Extract
Rhodymeniophycidae	Gigartinales	Gigartinaceae	Chondrus	Chondrus Crispus Powder
Rhodymeniophycidae	Gigartinales	Gigartinaceae	Chondrus	Hydrolyzed Chondrus Crispus Extract
Rhodymeniophycidae	Corallinales	Corallinaceae	Corallina	Corallina Officinalis Extract
Rhodymeniophycidae	Corallinales	Corallinaceae	Corallina	Corallina Officinalis Powder
Rhodymeniophycidae	Corallinales	Corallinaceae	Corallina	Corallina Officinalis Thallus Extract
Rhodymeniophycidae	Corallinales	Corallinaceae	Corallina	Hydrolyzed Corallina Officinalis Extract
Rhodymeniophycidae	Corallinales	Corallinaceae	Corallina	Hydrolyzed Corallina Officinalis Thallus Extract
Rhodymeniophycidae	Cyanidiales	Cyanidiaceae	Cyanidium	Cyanidium Caldarium Extract
Rhodymeniophycidae	Ceramiales	Delesseriaceae	Delesseria	Delesseria Sanguinea Extract
Rhodymeniophycidae	Ceramiales	Rhodomelaceae	Digenea	Digenea Simplex Extract
Rhodymeniophycidae	Gigartinales	Dumontiaceae	Dilsea	Dilsea Carnosa Extract
Rhodymeniophycidae	Gigartinales	Furcellariaceae	Furcellaria	Furcellaria Lumbricalis Extract
Rhodymeniophycidae	Gigartinales	Solieriaceae	Kappaphycus	Kappaphycus Alvarezii Extract
Rhodymeniophycidae	Gelidiales	Gelidiellaceae	Gelidiella	Gelidiella Acerosa Extract
Rhodymeniophycidae	Gelidiales	Gelidiaceae	Gelidium	Gelidium Amansii Extract
Rhodymeniophycidae	Gelidiales	Gelidiaceae	Gelidium	Gelidium Amansii Oligosaccharides
Rhodymeniophycidae	Gelidiales	Gelidiaceae	Gelidium	Gelidium Cartilagineum Extract
Rhodymeniophycidae	Gelidiales	Gelidiaceae	Gelidium	Gelidium Pulchrum Protein
Rhodymeniophycidae	Gelidiales	Gelidiaceae	Gelidium	Gelidium Sesquipedale Extract
Rhodymeniophycidae	Gigartinales	Gigartinaceae	Gigartina	Gigartina Skottsbergii Extract
Rhodymeniophycidae	Gigartinales	Gigartinaceae	Gigartina	Gigartina Stellata Extract
Rhodymeniophycidae	Gigartinales	Endocladiaceae	Gloiopeltis	Gloiopeltis Tenax Extract
Rhodymeniophycidae	Gigartinales	Endocladiaceae	Gloiopeltis	Gloiopeltis Tenax Powder
Rhodymeniophycidae	Gracilariales	Gracilariaceae	Gracilaria	Gracilaria Verrucosa Extract
Rhodymeniophycidae	Gracilariales	Gracilariaceae	Gracilariopsis	Gracilariopsis Chorda Extract
Rhodymeniophycidae	Halymeniales	Halymeniaceae	Grateloupia	Grateloupia Livida Powder
Rhodymeniophycidae	Gigartinales	Phyllophoraceae	Gymnogongrus	Ahnfeltiopsis Concinna Extract
Rhodymeniophycidae	Gigartinales	Cystocloniaceae	Hypnea	Hypnea Musciformis Extract
Corallinophycidae	Corallinales	Lithothamniaceae	Lithothamnion	Lithothamnion Corallioides Powder
Corallinophycidae	Hapalidiales	Mesophyllumaceae	Mesophyllum	Mesophyllum Lichenoides Extract
Nemaliophycidae	Palmariales	Palmariaceae	Palmaria	Palmaria Palmata Extract
Nemaliophycidae	Palmariales	Palmariaceae	Palmaria	Palmaria Palmata Powder
Corallinophycidae	Corallinales	Lithothamniaceae	Phymatolithon	Lithothamnion Calcareum Extract
Corallinophycidae	Corallinales	Lithothamniaceae	Phymatolithon	Lithothamnion Calcareum Powder
Corallinophycidae	Corallinales	Lithothamniaceae	Phymatolithon	Phymatolithon Calcareum Extract
Rhodymeniophycidae	Gigartinales	Dumontiaceae	Pikea	Pikea Robusta Extract
Rhodymeniophycidae	Ceramiales	Rhodomelaceae	Polysiphonia	Polysiphonia Lanosa Extract
Bangiophycidae	Bangiales	Bangiaceae	Porphyra	Porphyra Linearis Powder
Bangiophycidae	Bangiales	Bangiaceae	Porphyra	Porphyra Tenera Extract
Bangiophycidae	Bangiales	Bangiaceae	Porphyra	Porphyra Tenera Sporophyte Extract
Bangiophycidae	Bangiales	Bangiaceae	Porphyra	Porphyra Umbilicalis Extract
Bangiophycidae	Bangiales	Bangiaceae	Porphyra	Porphyra Umbilicalis Powder
Bangiophycidae	Bangiales	Bangiaceae	Porphyra	Hydrolyzed Porphyra Yezoensis
Bangiophycidae	Bangiales	Bangiaceae	Porphyra	Porphyra Yezoensis Extract
Bangiophycidae	Bangiales	Bangiaceae	Porphyra	Porphyra Yezoensis Powder
Porphyridiophyceae	Porphyridiales	Porphyridiaceae	Porphyridium	Porphyridium Cruentum Culture Conditioned Media
Porphyridiophyceae	Porphyridiales	Porphyridiaceae	Porphyridium	Porphyridium Cruentum Extract
Porphyridiophyceae	Porphyridiales	Porphyridiaceae	Porphyridium	Porphyridium Purpureum Extract
Rhodymeniophycidae	Rhodymeniales	Rhodymeniaceae	Rhodymenia	Rhodymenia Palmata Extract
Rhodymeniophycidae	Gigartinales	Solieriaceae	Sarcodiotheca	Sarcodiotheca Gaudichaudii Extract

Table 3. General characteristics and geographic distribution of several red algae species

Species	Description	Distribution/Habitat/Ecology	References
Asparagopsis armata	-pale purplish-red gametophytes, quickly degenerating when removed from water -fronds bushy with cylindrical axis (1mm wide and 200 mm long) -irregularly branched -harpoon-like barbs	-native to southern Australia and New Zealand; now found from the British Isles, the Canary, and Salvage Islands, to Senegal	86,87
Calliblepharis ciliata	-flattened, subcartilaginous, purple-red fronds -300 mm long and 20 -70 mm wide -irregularly pinnate -short, cylindrical stipe arises from creeping, branched holdfast	-common in South and West -larger lower intertidal pools and subtidal on stones, maerl, and shells -occasionally abundant on bedrock	86
Chondrus crispus	-thallus of cartilaginous consistency, perennial, erect, expanding gradually onto a flat, fan-like or curled -variable in form -blade is dichotomously branched in tufts from a discoid holdfast -color of fronds vary depending on time of year and depth of water (white to yellowing green in the summer and in shallow water; dark purplish-red in autumn and deeper water)	-mainly distributed on Atlantic coasts of Europe, East Africa, and North America -found in lower intertidal and shallow subtidal stages -on rocks and stones and also in tide pools	88
Corallina officinalis	-calcified or calcareous red marine algae reaching 5-12 cm in height -erect articulated thallus arising from a firmly attached crustose base up to 70 mm in diameter and bearing tufts of branches and articulated fronds up to 120 mm long -varied in color; thallus appears to be dull purple when growing in deep water, becoming red yellow and finally white on exposure	-widely distributed in temperate areas on rocks, mid tidal pools and drainage runnels	54
Delesseria sanguinea	-membranous, bright crimson fronds, with cartilaginous, cylindrical, branched stipe, from thickened discoid holdfast -up to 300 mm long -branches bear spirally arranged, leaf-like, ovate-lanceolate blades, each with short stipe and pinnately branched midrib	-on rocks, in deep shady lower intertidal pools and in the subtidal -generally distributed, common	86
Dilsea carnosa	-dark red, frequently becoming yellow -thickest of the foliose red algae in the North Atlantic -flattened cartilaginous fronds, arising in groups of small, medium, and large from a thick, discoid holdfast -up to 500 mm long, 250 mm wide	-on rocks in shady pools, lower intertidal on rock and shallow subtidal up to 25 m -usually on rock in kelp forests	86
Furcellaria lumbricalis	-cartilaginous, cylindrical, brownish-black fronds -repeatedly dichotomously branched -up to 2 mm diameter, 300 mm long, with acute apices	-on rocks, lower intertidal and shallow subtidal -in pools and runnels -in open situations, often on sandy and muddy shores -common, widespread	86
Gelidiella acerosa	-thallus yellow to dark red -cartilaginous with decumbent and erect terete axes up to 2 mm diameter -lateral branches, 1-3 mm long	-widespread in most warm seas, just below intertidal zone -attached to rock reefs at depths of 0-1 m	86
Gelidium sesquipedale	-composed of several erect axes, compressed and branched -axes bear secondary aces with ramuli short and pinnate -the thallus appears robust with a cartilaginous consistency, dark red in color -can reach up to 25-30 cm long	-develops on rocks in semi-exposed to exposed locations in the lower intertidal and shallow subtidal level	89
Gigartina stellata	-thallus bears dichotomously branches blades which arise form a basal discoid crust -stiff and cartilaginous -purplish-brown in color -10-20 cm high -stipe is narrow and compressed, expanding into strap-like blade, usually inrolled to form a channel	-found in large continuous mats on rocks, on exposed and semi-exposed sites in the low intertidal zone with some extension into the upper sublittoral	90

Table 3. General characteristics and geographic distribution of several red algae species

Species	Description	Distribution/Habitat/Ecology	References
Kappaphycus alvarezii	-thallus shows a simple discoid hold-fast from which arises a main axis with irregular branches -morphology changes with habitat; thalli range from terete to foiliose -thalli can reach up to 2 m tall; their color is green or yellow	-origin is from Malaysia; the species occurs naturally in the Sulu Sea and the Sulu Archipelago -it has been naturalized in several western and central Pacific localities for farming purposes	[91]
Phymatolithon calcareum	-fragile, reddish-violet, branched, calcareous fronds -branches are 2-3 mm in diameter -variable in form	-free-living in clear, clean water, forming extensive beds of live and dead material, particularly where there are subtidal currents -widely distributed	[86]
Palmaria palmata	-reddish-brown, membranous or leathery, flattened fronds (50-300 mm long) -blade variable in shape, having broadly ovate to narrowly linear segments -palmate branching with finger-like extensions	-North Atlantic -on rock and mussels, intertidal and shallow subtidal -widely distributed	[86]
Polysiphonia lanosa	-cartilaginous, cylindrical, densely tufted, dark brown fronds up to 75 mm long -repeatedly pseudo dichotomous branches, apices pointed, widely forked	-hemiparasitic on *Ascophyllum nodosum*, more rarely on *Fucus vesiculosus* -never directly on rock -sheltered mid-tidal -generally distributed	[86]
Porphyra linearis	-delicate, linear, membranous, purple-brown fronds, 20-40 mm long and 5-10 mm broad -usually simple with short stipe with basal holdfast -orange patches when reproductive	-zone-forming on rock in the intertidal and splash zone of semi-exposed and exposed shores -generally distributed -winter occurrence	[86]
Porphyra umbilicalis	-blades appear reddish brown, brownish, grey brown, or olive green in the field; in a dried state they are very thin and violet in color -blades constituted by a single cell layer can reach 60 cm in height	-common and abundant everywhere on the rocky parts of coasts or on beach pebbles on the Atlantic coasts of Europe (from Scandinavia to Morocco) and North America -appears in the upper littoral zone singly or in dense colonies	[92]
Sarcodiotheca Gaudichaudii	-medium to large species with cylindrical, brittle fronds -color varies from straw yellow to deep red or reddish brown	-lower intertidal pools to upper subtidal -mainly on small stones and shells	[86]

Table 4. Methods of manufacture for brown algae-derived ingredients

Ingredient (characterization)	Method of Manufacture	Reference
Asparagopsis armata extract	fresh seaweed → wash → freeze → grind → extraction with 1:4 biomass:solvent ratio with methanol and dichloromethane	[93]
Asparagopsis Armata Extract	algae → grinding → extraction with water → stabilization with vegetable glycerin →filtration	[94]
Asparagopsis Armata Extract	fresh seaweed → grinding → cold cellular extraction → filtration → concentration → freeze-drying under neutral atmosphere	[95]
Asparagopsis Armata Extract	harvesting/identification → washing → grinding → extraction with solvents (propanediol and water) → filtration → quality control → packaging → quality control	[96]
Chondrus Crispus Extract and Gigartina Stellata Extract	harvesting/identification → washing → condensation of cellular water by soft drying → filtration and UV treatment → quality control → addition of preservatives and pH adjustment → quality control → packaging → quality control	[97]
Chondrus Crispus Powder	harvesting → naturally dried via sun exposure → grinding/sieving → packaging → sterilized via gamma ray treatment	[98]
Chondrus Crispus Powder	harvesting/identification → drying → cutting → ionization → quality control → packaging → quality control	[99]
Corallina Officinalis Extract, Gigartina Stellata Extract, and Kappaphycus Alvarezii Extract	dried grounded algae → extraction with water → testing → sifting → centrifugation → ultrafiltration → testing → homogenization → testing → sterile filtration → testing → packing	[100]
Corallina Officinalis Extract	dried grounded algae → extraction with water → testing → sifting → centrifugation → ultrafiltration → testing → homogenization → testing → sterile filtration → testing → packing	[101]
Digenea simplex extract	Dried algal powder (200 mg) extracted with 6 ml 80% methanol → ultrasonic bath → vortex → centrifuge → filtration → drying	[102]
Gelidiella acerosa extract	100 g seaweed packed in Soxhlet apparatus → addition of solvent (petroleum ether, hexane, benzene, dichloromethane, chloroform, ethyl acetate, acetone, methanol, or water) → re-distillation → filtration→ placed in desiccator	[60]
Gelidium amansii extract	algae collection → washing → dried at room temperature → grinding → powder extracted with 80% ethanol for 24 h → freeze-drying	[21]

Table 4. Methods of manufacture for brown algae-derived ingredients

Ingredient (characterization)	Method of Manufacture	Reference
Gelidium Cartilagineum Extract	harvesting/identification → drying → grinding → extraction with solvent (caprylic/capric triglyceride) → addition of sterol → filtration → quality control → packaging → quality control	6
Gracilariopsis chorda extract	seaweed collection → mechanical washing → drying in room temperature → pulverization → extraction with 95% ethanol→ mixture placed in orbital shaker at 200 rpm → centrifugation → filtration → concentration → drying under steam of nitrogen gas	25
Hydrolyzed Corallina Officinalis Extract	harvesting/identification → extraction with water → addition of sodium methylparaben or 2-phenoxyethanol → filtration →quality control → packaging →quality control	5,103
Hypnea Musciformis Extract	harvesting/identification → drying → grinding → extraction with the solvent (water and butylene glycol) → addition of potassium gluconate and methylparaben → filtration →quality control → packaging → quality control	7
Hypnea Musciformis Extract	solubilization of *Hypnea musciformis* in water → separation of soluble and insoluble phases → filtration → membrane sterilization	28
Lithothamnion Calcareum Powder	harvesting → drying → grinding → micronisation → ionization → mixture → addition of mannitol, zinc sulfate, and diatomaceous earth → packaging → quality control	104
Palmaria Palmata Extract	solubilization of powder of *Palmaria palmata* in water → separation of soluble and insoluble phases → concentration of soluble phase → membrane sterilization	28
Porphyra Umbilicalis Extract	circular flow extraction of 7.8% dry algae on dry algae → in-process control → maturation at room temperature → filtration of the supernatant → cationic exchange → filtration → cross flow filtration → encapsulation of the extract into liposomes → packaging → quality control	33
Porphyra Umbilicalis Extract	dried grounded algae → extraction with water → testing → centrifugation → ultrafiltration → testing → sterile filtration → testing → packaging	105

Table 5. Mineral and metal analysis of a trade name mixture consisting of 50% glycerin; 30% water; 18.5 % undaria pinnatifida extract; 1.5% Corallina officinalis Extract[16]

Determination	Results/Units
Sodium	420.4 mg/100 ml
Calcium	142.9 mg/100 ml
Phosphorus	8.9 mg/100 ml
Magnesium	60.7 mg/100 ml
Potassium	530.3 mg/100 ml
Copper	<0.5 mg/100 ml
Iron	<0.5 mg/100 ml
Manganese	0.0 mg/100 ml
Zinc	<0.5 mg/100 ml
Iodine	1.9 mg/l
Arsenic	1383 µg/kg
Cadmium	29 µg/kg
Mercury	<10 µg/kg
Lead	86 µg/kg
Selenium	<50 µg/kg
Silicon	0 mg/kg

Table 6. Mineral and metal analysis of a trade name mixture containing 4% Gelidium Sesquipedale Extract[22]

Analysis	Results ± Uncertainties	Units
Ashes	0.4 ± 0.2	g/100 g
Calcium	<4.0	mg/100 g
Magnesium	14.0 ± 1.4	mg/100 g
Phosphorus	<2.0	mg/100 g
Potassium	82 ± 8.2	mg/100 g
Sodium	98.3 ± 9.8	mg/100 g
Copper	<0.3	mg/100 g
Iron	<0.2	mg/100 g

Manganese	<0.3	mg/100 g
Zinc	<0.3	mg/100 g
Arsenic	72	µg/kg
Cadmium	<10	µg/kg
Mercury	<5	µg/kg
Molybdenum	<51	µg/kg
Lead	<10	µg/kg
Selenium	<811	µg/kg
Iodine	1.02	mg/kg

Table 7. Chemical composition of a supercritical carbon dioxide extract of Gloiopeltis tenax[23]

Constituents	***%****
p-hydroxybenzaldehyde	0.57
(-) – thujopsene	4.68
α-curcumene	1.54
α-zingiberene	2.98
(+)-cuparene	0.28
(−)-β-bisabolene	1.00
cedrol	3.91
vanillylacetone	1.92
n-heptadecane	10.30
myristic acid	2.85
fitone	2.53
methhyl hexadecanoate	1.32
palmitic acid	21.21
linoleic acid	0.23
hexadeca-1,4-lactone	0.57
cis-9-octadecenoic acid	0.73
stearic acid	0.93
oleamide	0.24
2,2′-methylenebis(6-*tert*-butyl-4-methylphenol)	1.14
2-monopalmitin	1.83
cholesta-4,6-dien-3β-ol	6.62
cholesterol	5.74
cholesta-3,5-dien-7-one	0.45

*percentage of relative amount to total

Table 8. Mean metal content ± standard deviation in seaweed samples for different genera of red algae (mg/kg DW)[37]

	***Chondrus* (n = 2)**	***Gelidium* (n = 2)**	***Palmaria* (n = 4)**	***Porphyra* (n = 10)**	***Gracilaria (*n = 2*)***
Sodium	6799 ± 84.6	1279 ± 0	3803 ± 463	2274 ± 675	-
Arsenic	-	-	-	-	15
Potassium	9901 ± 270	543 ± 53.2	8044 ± 0	6563 ± 854	-
Calcium	2028 ± 153	908 ± 7.01	459 ± 0.00	1793 ± 1211	-
Cadmium	-	-	-	-	0.04 – 0.4
Magnesium	3134 ± 45.7	452 ± 4.68	787 ± 87.6	3732 ± 5070	-
Boron	43.3 ± 6.60	4.50 ± 0.98	31.5 ± 6.45	5.10 ± 0.00	-
Barium	0.35 ± 0.08	0.30 ± 0.10	0.62 ± 0.28	3.19 ± 2.88	-
Cobalt	0.13 ± 0.01	0.008 ± 0.00	0.03 ± 0.01	0.12 ± 0.18	-
Chromium	0.15 ± 0.00	0.16 ± 0.001	0.15 ± 0.02	0.33 ± 0.14	-
Copper	0.79 ± 0.21	0.54 ± 0.02	1.03 ± 0.09	2.99 ± 0.68	-
Iron	22.3 ± 3.79	9.86 ± 0.24	34.7 ± 8.10	156 ± 239	-
Lithium	0.85 ± 0.01	0.93 ± 0.58	1.16 ± 0.45	1.41 ± 0.00	-
Manganese	9.78 ± 0.56	1.66 ± 0.01	1.62 ± 0.45	36.5 ± 56.9	-
Molybdenum	0.12 ± 0.01	0.008 ± 0.00	0.09 ± 0.01	0.22 ± 0.09	-
Nickel	5.08 ± 0.10	0.11 ± 0.001	0.05 ± 0.13	0.50 ± 0.87	-
Strontium	-	-	3.44 ± 0.36	2.22 ± 2.92	-
Vanadium	0.58 ± 0.47	-	25.5 ± 0.00	0.48 ± 0.41	-
Zinc	9.33 ± 2.57	2.21 ± 0.25	5.03 ± 1.06	13.6 ± 3.72	-
Aluminum	8.41 ± 2.85	8.21 ± 0.61	32 ± 5.18	28.9 ± 27.3	19 - 149
Cadmium	0.29 ± 0.03	0.008 ± 0.00	0.16 ± 0.11	0.58 ± 0.30	-
Lead	0.07 ± 0.00	0.05 ± 0.01	0.05 ± 0.02	0.15 ± 0.21	0.8 – 7

- = None reported

Table 9. Mineral and metal analysis of a trade name mixture containing water (45.7%), glycerin (40%), *Gigartina stellata* (4.43%), Kappaphycus Alvarezii Extract (5.9%), Corallina Officinalis Extract (3.97%)[38]

Determination	Results/Units
Sodium	419.9 mg/100 g
Calcium	4.8 mg/100 g
Phosphorus	<2 mg/100 g
Chlorides	391 mg/100 g
Magnesium	11.9 mg/100 g
Potassium	109.4 mg/100 g
Copper	<0.5 mg/100 g
Iron	<0.5 mg/100 g
Manganese	<0.5 mg/100 g
Zinc	<0.5 mg/100 g
Iodine	1.2 mg/kg
Arsenic, inorganic	<0.15 mg/kg
Arsenic	116 µg/kg
Cadmium	<10 µg/kg
Mercury	<10 µg/kg
Lead	<10 µg/kg
Selenium	<10 µg/kg

Table 10. Frequency (2021) and concentration of use (2020) of red algae-derived ingredients[39,40,106]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Ahnfeltiopsis Concinna Extract		Asparagopsis Armata Extract		Chondrus Crispus	
Totals*	**5**	**NR**	**18**	**0.031 – 0.33**	**94**	**0.00004 – 1.4**
Duration of Use						
Leave-On	*4*	*NR*	*16*	*0.031 – 0.33*	70	*0.00004 – 0.8*
Rinse-Off	*1*	*NR*	*2*	*0.1*	17	*0.005 – 1.4*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	7	*NR*
Exposure Type						
Eye Area	0	NR	8	0.031	12	0.12
Incidental Ingestion	NR	NR	NR	NR	5	1.4
Incidental Inhalation-Spray	2[a]; 1[b]	NR	4[a]; 3[b]	NR	18[a]; 27[b]	0.08; 0.005[b]
Incidental Inhalation-Powder	2[a]	NR	4[a]	0.063[c]	5; 18[a]	0.13; 0.51[c]
Dermal Contact	5	NR	18	0.031 – 0.063	86	0.08 - 0.8
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.1 – 0.33	3	0.00004 – 0.005
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	NR	20	0.3 – 1.4
Baby Products	NR	NR	NR	NR	NR	NR

	Chondrus Crispus Extract		Chondrus Crispus Powder		Corallina Officinalis Extract	
Totals*	**268**	**0.000003 – 0.5**	**63**	**0.1**	**66**	**0.00013 – 2**
Duration of Use						
Leave-On	*222*	*0.000003 – 0.49*	52	*0.1*	56	*0.000013 – 2*
Rinse Off	*45*	*0.0018 – 0.5*	11	*NR*	10	*0.00014 – 0.11*
Diluted for (Bath) Use	*1*	*NR*	NR	*NR*	NR	*NR*
Exposure Type						
Eye Area	37	0.14 – 0.3	12	0.1	2	0.0004 – 0.01
Incidental Ingestion	9	NR	6	NR	NR	NR
Incidental Inhalation-Spray	71[a]; 57[b]	0.001[b]	24[a]; 8[b]	NR	7[a]; 37[b]	NR
Incidental Inhalation-Powder	17; 71[a]	0.15; 0.0005 – 0.29[c]	24[a]	NR	1; 7[a]	2[c]
Dermal Contact	243	0.000003 – 0.5	56	0.1	61	0.00013 – 2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	14	0.001 – 0.0018	1	NR	1	NR
Hair-Coloring	NR	0.01	NR	NR	NR	NR
Nail	NR	NR	NR	NR	4	0.099
Mucous Membrane	13	NR	8	NR	NR	NR
Baby Products	NR	0.000003	NR	NR	NR	NR

Table 10. Frequency (2021) and concentration of use (2020) of red algae-derived ingredients[39,40,106]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Cyanidium Caldarium Extract		**Delesseria Sanguinea Extract**		**Furcellaria Lumbricalis Extract**	
Totals*	**3**	**NR**	**2**	**NR**	**44**	**NR**
Duration of Use						
Leave-On	*3*	*NR*	*2*	*NR*	*44*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	3	NR
Incidental Ingestion	NR	NR	NR	NR	2	NR
Incidental Inhalation-Spray	3[b]	NR	1[a]; 1[b]	NR	10[a]; 16[b]	NR
Incidental Inhalation-Powder	NR	NR	1[a]	NR	10[a]	NR
Dermal Contact	3	NR	2	NR	42	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	2	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Gelidium Amansii Extract		**Gelidium Cartilagineum Extract**		**Gelidiella Acerosa Extract**	
Totals*	**1**	**NR**	**36**	**NR**	**29**	**0.0001 – 0.028**
Duration of Use						
Leave-On	*1*	*NR*	*33*	*NR*	*14*	*0.00065 - 0.028*
Rinse-Off	*NR*	*NR*	*3*	*NR*	*15*	*0.0001 – 0.015*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	2	NR	3	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[b]	NR	7[a]; 18[b]	NR	9[b]	NR
Incidental Inhalation-Powder	NR	NR	7[a]; 1[c]	NR	NR	0.007 – 0.028[c]
Dermal Contact	1	NR	36	NR	16	0.0001 – 0.028
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	9	0.0008
Hair-Coloring	NR	NR	NR	NR	4	0.0045
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	0.015
Baby Products	NR	NR	1	NR	NR	NR

	Gigartina Stellata Extract		**Hydrolyzed Chondrus Crispus Extract**		**Hydrolyzed Corallina Officinalis Extract**	
Totals*	**7**	**NR**	**1**	**0.012 – 0.017**	**4**	**NR**
Duration of Use						
Leave-On	*2*	*NR*	*1*	*0.012 – 0.017*	*4*	*NR*
Rinse-Off	*5*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	0.012 – 0.017	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]; 1[b]	NR	1[a]	NR	1[a]; 2[b]	NR
Incidental Inhalation-Powder	1[a]	NR	1[a]	NR	1[a]	NR
Dermal Contact	1	NR	1	0.012 – 0.017	4	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	6	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 10. Frequency (2021) and concentration of use (2020) of red algae-derived ingredients[39,40,106]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Hypnea Musciformis Extract		**Kappaphycus Alvarezii Extract**		**Lithothamnion Calcareum Extract**	
Totals*	**52**	**0.0003 – 0.13**	**24**	**0.019 – 0.19**	**19**	**0.0059 – 0.037**
Duration of Use						
Leave-On	*18*	*0.0003 – 0.08*	*15*	*0.019 – 0.19*	*19*	*0.0059 – 0.037*
Rinse-Off	*34*	*0.0004 – 0.13*	*9*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	3	NR	1	NR	4	0.012
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1; 8[b]	0.03	8[a]; 4[b]	NR	1[a]; 2[b]	NR
Incidental Inhalation-Powder	NR	0.02 – 0.08[c]	8[a]	0.019 – 0.19[a]	1[a]	0.0059[c]
Dermal Contact	16	0.0003 – 0.13	16	0.019 – 0.19	1	0.0059 – 0.012
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	20	0.0045	8	NR	NR	NR
Hair-Coloring	15	NR	NR	NR	NR	NS
Nail	1	NR	NR	NR	12	0.037
Mucous Membrane	NR	0.13	1	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Lithothamnion Calcareum Powder		**Palmaria Palmata Extract**		**Phymatolithon Calcareum Extract**	
Totals*	**8**	**NR**	**52**	**0.0005 – 0.075**	**2**	**NR**
Duration of Use						
Leave-On	*3*	*NR*	*48*	*0.0005 – 0.075*	*2*	*NR*
Rinse-Off	*5*	*NR*	*4*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	3	NR	1	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2[a]	NR	21[a]; 12[b]	0.0006	NR	NR
Incidental Inhalation-Powder	2[a]	NR	21[a]	0.075[c]	NR	NR
Dermal Contact	8	NR	50	0.0005 – 0.075	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	2	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	0.0005	1	NR
Mucous Membrane	NR	NR	1	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Porphyra Umbilicalis Extract		**Porphyra Yezoensis Extract**		**Porphyridium Cruentum Extract**	
Totals*	**21**	**0.0004 – 0.0035**	**3**	**NR**	**35**	**0.00055 – 0.03**
Duration of Use						
Leave-On	*15*	*0.0004*	*3*	*NR*	*28*	*0.00055 – 0.03*
Rinse-Off	*5*	*0.0035*	*NR*	*NR*	*7*	*0.00055 – 0.017*
Diluted for (Bath) Use	*1*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	1	*NR*	7	0.00055
Incidental Ingestion	NR	NR	NR	*NR*	NR	0.00055
Incidental Inhalation-Spray	7[a]; 7[b]	NR	1[a]; 1[b]	*NR*	7[a]; 9[b]	0.00055[b]
Incidental Inhalation-Powder	7[a]	NR	1[a]	*NR*	7[a]	0.03[c]
Dermal Contact	19	0.0004 – 0.0035	3	*NR*	35	0.00055 – 0.03
Deodorant (underarm)	NR	NR	NR	*NR*	NR	NR
Hair - Non-Coloring	2	NR	NR	*NR*	NR	0.00055
Hair-Coloring	NR	NR	NR	*NR*	NR	NR
Nail	NR	NR	NR	*NR*	NR	NR
Mucous Membrane	3	NR	NR	*NR*	NR	0.00055
Baby Products	NR	NR	NR	*NR*	NR	NR

Table 10. Frequency (2021) and concentration of use (2020) of red algae-derived ingredients[39,40,106]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Porphyridium Purpureum Extract		Rhodymenia Palmata Extract			
Totals*	**5**	**NR**	**NR**	**0.038**		
Duration of Use						
Leave-On	*5*	*NR*	*NR*	*0.038*		
Rinse-Off	*NR*	*NR*	*NR*	*NR*		
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*		
Exposure Type						
Eye Area	NR	NR	NR	*0.038*		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation-Spray	2[a]; 3[b]	NR	NR	NR		
Incidental Inhalation-Powder	2[a]	NR	NR	0.038[c]		
Dermal Contact	5	NR	NR	0.038		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	NR	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	NR	NR	NR	NR		
Baby Products	NR	NR	NR	NR		

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – no reported use

Table 11. Red algae-derived ingredients with no reported uses in the VCRP

Hydrolyzed Asparagopsis Armata Extract	Gracilaria Verrucosa Extract
Betaphycus Gelatinum Extract	Gracilariopsis Chorda Extract
Botryocladia Occidentalis Extract	Grateloupia Livida Powder
Calliblepharis Ciliata Extract	Lithothamnion Corallioides Powder
Ceramium Kondoi Extract	Mesophyllum Lichenoides Extract
Ceramium Rubrum Extract	Palmaria Palmata Powder
Chondracanthus Teedei Powder	Pikea Robusta Extract
Corallina Officinalis Powder	Polysiphonia Lanosa Extract
Corallina Officinalis Thallus Extract	Porphyra Linearis Powder
Digenea Simplex Extract	Porphyra Tenera Extract
Hydrolyzed Corallina Officinalis	Porphyra Tenera Sporophyte Extract
Dilsea Carnosa Extract	Porphyra Umbilicalis Powder
Gelidium Amansii Oligosaccharides	Hydrolyzed Porphyra Yezoensis
Gelidium Pulchrum Protein	Porphyra Yezoensis Powder
Gelidium Sesquipedale Extract	Porphyridium Cruentum Culture Conditioned Media
Gigartina Skottsbergii Extract	Sarcodiotheca Gaudichaudii Extract
Gloiopeltis Tenax Extract	
Gloiopeltis Tenax Powder	

Table 12. Red algae species ingested by humans as foods

Species	Methods of consumption	Reference
Ahnfeltiopsis concinna	Hawaiian cuisine; Eaten raw with limpets or baked with other foods	107
Chondrus crispus	Used as thickener/gelling agent; used in drinks; also known as Irish moss; eaten whole	108
Gelidiella sp.	Used in jellies	50
Gelidium amansii	Used in jellies	21
Gigartina stellata	Used interchangeably with Chondrus crispus; thickener/gelling agent	50,86
Gracilaria sp.	Used in jellies	50
Gracilaria verrucosa	Eaten whole, with salads	108
Hypnea musciformis	Eaten whole, dried	109
Lithothamnion calcareum	Used as vegetables and condiments in France	9
Palmaria palmata	Eaten fresh or dry; used in breads and cakes	28,49
Porphyra tenera	Typically, dried and used to make sushi; nori, spices, seasoning, flavoring (GRAS)	21CFR184.1121, [35]
Porphyra umbilicalis	Typically, dried and used to make sushi	92,108
Porphyra yezoensis	Typically, dried and used to make sushi, nori	35,110
Rhodymenia palmata	Spices, seasoning, flavoring (GRAS)	21CFR184.1121

Table 13. In Vitro Genotoxicity studies

Ingredient	Test Substance	Concentration	Test System/Species/Conditions	Results	Reference
Asparagopsis Armata Extract	Asparagopsis Armata Extract (8% dry algal matter)	52, 164, 512, 1600, 5000 µg/plate	Ames test; *S. typhimurium* (strains TA98, TA100, TA1537, TA102); with and without metabolic activation	Negative	[58]
Asparagopsis Armata Extract	Mixture containing 80% Asparagopsis Armata Extract and 20% methylpropanediol	NR	Ames test; OECD TG 471; strains and use of metabolic activation not reported	Negative	[56]
Corallina Officinalis Extract	Corallina Officinalis Extract (0.2 – 4% algae) and water	NR	Ames test; OECD TG 471; performed using 4 strains of *S. typhimurium* and 1 strain of *E. coli* (strains not specified; with and without metabolic activation	Negative	[15]
Corallina Officinalis Extract	Corallina Officinalis Extract (0.2 – 4% algae), sea water, calcium carbonate, and calcium chloride	NR	Ames test; OECD TG 471; performed using 5 strains of *S. typhimurium* (strains not specified; with and without metabolic activation	Negative	[15]
Corallina Officinalis Extract, Gigartina Stellata Extract, and Kappaphycus Alvarezii Extract	Trade name mixture consisting of water (45.7%), glycerin (40%), *Gigartina stellata* (4.43%), Kappaphycus Alvarezii Extract (5.9%), and Corallina Officinalis Extract (3.97%)	50, 160, 500, 1600, 5000 µg/plate	Ames test; *S. typhimurium* (strains TA98, TA100, TA1535, TA1537, TA102); with and without metabolic activation	Negative	[59]
Gelidiella Acerosa Extract	Benzene extract of *Gelidiella acerosa*	250, 500, 1000, 2000, 4000 µg/plate	Ames test; *S. typhimurium* (strains TA98, TA100, TA1535); with and without metabolic activation	Negative	[60]
Porphyra Umbilicalis Extract	48% Porphyra Umbilicalis Extract and 52% water	2, 10, 25, 50, 100%	Chemiluminescent 3D assay; with and without UVB irradiation; positive control of chlorpromazine	Negative	[61]

Table 14. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population/# of test samples	Procedure	Results	Reference
IRRITATION						
In Vitro						
Ahnfeltiopsis Concinna Extract	Trade name mixture containing 0.75% Ahnfeltiopsis Concinna Extract (other components not reported)	100%; 30 µl (liquid) or 25 mg (solid)	3	Reconstructed human epidermal model; 3 tissues treated with test substance and incubated for 60 min	Non-irritating	[68]
Asparagopsis Armata Extract	An Asparagopsis Armata Extract containing 4% dry algal matter (other components not reported)	10%; 200 µl	2	Local tolerance evaluated in EPISKIN reconstructed human epidermis model; 18-h incubation	Non-irritating	[58]
Asparagopsis Armata Extract	A mixture containing 80% Asparagopsis Armata Extract (4 % dry algal matter) and 20% methylpropanediol	100%; dose not reported	NR	Reconstructed human epidermis model; OECD TG 439	Non-irritating	[56]
Chondrus Crispus Extract	Trade name mixture containing 3.5% Chondrus Crispus Extract (other components not reported)	100%; 20 µl	3	MatTek EpiDerm™ MTT Assay; 3 tissues treated	Non-irritating	[69]
Corallina Officinalis Extract	Mixture containing Corallina Officinalis (0.2 – 4% algae), sea water, calcium chloride, and propylene glycol	100%	NR	Reconstructed human epidermis model	Non-irritating	[15]
Animal						
Corallina Officinalis Extract	Mixture containing Corallina Officinalis Extract (0.2 – 4% algae) and water	100%; dose not reported	3 rabbits (strain not reported)	primary cutaneous tolerance assay	Non-irritating	[15]
Delesseria Sanguinea Extract	Mixture containing Delesseria Sanguinea Extract (0.2 – 4% algae), dipropylene glycol, and water	NR	3 rabbits (strain not reported)	primary cutaneous tolerance assay	Non-irritating	[18]
Human						
Asparagopsis Armata Extract	An Asparagopsis Armata Extract containing 4% dry algal matter in water	10%; 20 µl	10	48-h patch test under occlusive conditions	Non-irritating	[58]
Asparagopsis Armata Extract	Trade name mixture containing 0.5 –2% Asparagopsis Armata Extract, 56 – 62% water, and 38 – 42% propanediol	3%; 20 µl	22	48-h patch test under occlusive conditions	Non-irritating	[111]
Chondrus Crispus	After-shave balm containing 0.8% Chondrus Crispus	100%; 0.2 ml	30	23-h exposure per day for 14 d; occlusive conditions	Non-irritating	[112]
Chondrus Crispus Extract and Gigartina Stellata Extract	Trade name mixture containing Chondrus Crispus Extract and Gigartina Stellata Extract (98.10 – 98.95% extract, 0.80 – 1.10% sodium benzoate; 0.25 – 0.35% potassium sorbate; 0 -0.30% lactic acid)	100%; 25 µl	22	48-h patch test; occlusive conditions	Non-irritating	[113]
Chondrus Crispus Powder	Chondrus Crispus Powder (100%)	100%; 0.02 ml	12	24-h patch test; occlusive conditions	Non-irritating	[114]
Corallina Officinalis Extract, Gigartina Stellata Extract, Kappaphycus Alvarezii Extract	Trade name mixture containing water (45.7%), glycerin (40%), *Gigartina stellata* (4.43%), Kappaphycus Alvarezii Extract (5.9%), Corallina Officinalis Extract (3.97%)	10%; 0.02 ml	25	48-h patch test; occlusive conditions	Non-irritating	[115]
Corallina Officinalis Extract	Trade name mixture containing 50% glycerin; 30% water; 18.5 % undaria pinnatifida extract; 1.5% Corallina Officinalis Extract	10%; 160 µl	10	48-h patch test; semi-occlusive conditions	Non-irritating	[116]
Delesseria Sanguinea Extract	Mixture containing Delesseria Sanguinea Extract (0.2 – 4% algae), water, and dipropylene glycol	100%; dose not reported	12	48-h patch test; occlusive conditions	Non-irritating	[18]

Table 14. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population/# of test samples	Procedure	Results	Reference
Furcellaria Lumbricalis Extract	Mixture containing Furcellaria Lumbricalis Extract (0.2 – 4% algae) and water	100%: dose not reported	10	48-h patch test; occlusive conditions	Non-irritating	19
Gelidium Cartilagineum Extract	Trade name mixture containing >96% glycerides, mixed decanoyl and octanoyl; <2 % Gelidium Cartilagineum Extract; 1.5-2% 4-cholesten-3-one	10% dilution; 20 µl	10	24-h patch test; occlusive conditions	Non-irritating	117
Gelidium Sesquipedale Extract	Trade name mixture containing 48% water; 48% butylene glycol; 4% Gelidium Sesquipedale Extract	5% dilution; 0.02 ml	10	48-h patch test; occlusive conditions	Non-irritating	118
Hydrolyzed Corallina Officinalis Extract	Trade name mixture containing >96% water; 0.5-3% Hydrolyzed Corallina Officinalis Extract; 0.16-0.20% sodium methylparaben	100%; 0.02 ml	11	24-h patch test; occlusive conditions	Non-irritating	119
Hydrolyzed Corallina Officinalis Extract	Trade name mixture containing >96% water; 0.5-3% Hydrolyzed Corallina Officinalis Extract; 0.8-1.2% phenoxyethanol	100%; 20 µl	11	24-h patch test; occlusive conditions	Non-irritating	120
Hypnea Musciformis Extract	Trade name mixture consisting of 72-77% water; 20-70% butylene glycol; 1-3% Hypnea Musciformis Extract; ≤1% potassium gluconate; 0.16-0.2% methylparaben	100%; 0.02 ml	12	24-h patch test; occlusive conditions	Slightly irritating at the 30-min reading (in 7/12 subjects) and non-irritating at the 24-h reading	70
Hypnea Musciformis Extract	Hypnea Musciformis Extract in water (specific composition not reported)	15% (0.36% dry matter); dose not reported	11	48-h patch test; occlusive conditions	Non-irritating	28
Lithothamnion Calcareum Powder	Trade name mixture consisting of 57-61% Lithothamnion Calcareum Powder. 26-31% mannitol, 9-11% diatomaceous earth, 0.7-1.5% zinc sulfate	100%; 0.02 ml	11	24-h patch test; occlusive conditions	Non-irritating	121
Palmaria Palmata Extract	Palmaria Palmata Extract in water (specific composition not reported)	10% (0.75% dry matter); dose not reported	11	48-h patch test; occlusive conditions	Non-irritating	28
Polysiphonia Lanosa Extract	Trade name mixture consisting of 67.5% water, 32% Polysiphonia Lanosa Extract	5%; 0.02 ml	11	48-h patch test; occlusive conditions	Non-irritating	122
Rhodymenia Palmata Extract	Eye cream containing 0.0375% Rhodymenia Palmata Extract	100%; 0.2 g	38	7-d exposure; semi-occlusive conditions	Non-irritating	123
SENSITIZATION						
Human						
Asparagopsis Armata Extract	Product containing 0.325% Asparagopsis Armata Extract	100%; dose not reported	108	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	124
Asparagopsis Armata Extract	Trade name mixture containing 0.5 –2% Asparagopsis Armata Extract, 56 – 62% water, and 38 – 42% propanediol	3%; 40 µl	104	HRIPT under semi-occlusive conditions	Non-irritating; Non-sensitizing	71
Betaphycus Gelatinum Extract	Mixture containing 7% Betaphycus Gelatinum Extract	100%; dose not reported	56	HRIPT under semi-occlusive conditions	Non-irritating; Non-sensitizing	78
Chondrus Crispus Extract	Product containing 0.49% Chondrus Crispus Extract	100%; dose not reported	113	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	72
Corallina Officinalis Extract	Mixture containing Corallina Officinalis Extract (0.2 – 4%), sea water, calcium carbonate, and calcium chloride	100%; dose not reported	103	HRIPT (occlusivity not reported)	Non-irritating; Non-sensitizing	15

Table 14. Dermal irritation and sensitization

Ingredient	Test Substance	Concentration/Dose of the test substance	Test Population/# of test samples	Procedure	Results	Reference
Corallina Officinalis Extract	Blush powder containing 2% Corallina Officinalis Extract mixed with distilled water	dilution not reported; 0.1 – 0.15 g	102	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	77
Delesseria Sanguinea Extract	Mixture containing Delesseria Sanguinea Extract (0.2 – 4% algae), water, and dipropylene glycol	100%; dose not reported	104	HRIPT (occlusivity not reported)	Non-irritating; Non-sensitizing	18
Furcellaria Lumbricalis Extract	Mixture containing Furcellaria Lumbricalis Extract (0.2 – 4% algae) and water	100%; dose not reported	50	HRIPT (occlusivity not reported)	Non-irritating; Non-sensitizing	19
Furcellaria Lumbricalis Extract	Mixture containing Furcellaria Lumbricalis (0.2 – 4% algae), sea salt, and water	100%; dose not reported	105	HRIPT (occlusivity not reported)	Non-irritating; Non-sensitizing	19
Gelidiella Acerosa Extract	Product containing 0.0028% Gelidiella Acerosa Extract	100%; dose not reported	105	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	73
Gelidium Cartilagineum Extract	Trade name mixture consisting of >96% glycerides, mixed decanoyl and octanoyl; < 2 % Gelidium Cartilagineum Extract; 1.5-2% 4-cholesten-3-one	100%; 25 µl	50	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	74
Hydrolyzed Corallina Officinalis Extract	>96% water; 0.5-3% Hydrolyzed Corallina Officinalis Extract; 0.16-0.20% sodium methylparaben	100%; 0.2 ml	51	HRIPT under occlusive conditions	Non-sensitizing	75
Hypnea Musciformis Extract	Hypnea Musciformis Extract (specific composition not reported)	15% (0.36% dry matter); dose not reported	100	HRIPT (use of occlusion not reported)	Non-irritating; Non-sensitizing	28
Kappaphycus Alvarezii Extract	Trade name mixture consisting of 0.8% Kappaphycus Alvarezii Extract, 79.2% water, and 20% 1,3-butylene glycol	100%; 50 µl	50	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	80
Palmaria Palmata Extract	Palmaria Palmata Extract in water (specific composition not reported)	25% (1.87% dry matter); dose not reported	58	HRIPT (use of occlusion not reported)	Non-sensitizing	28
Porphyra Umbilicalis Extract	Product containing 0.0004% Porphyra Umbilicalis Extract	100%; dose not reported	103	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	76

HRIPT = Human Repeat Insult Patch Test; MTT = 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide; NR = Not Reported

Table 15. Ocular Irritation Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IN VITRO					
Trade name mixture containing 0.75% Ahnfeltiopsis Concinna Extract (other components not specified)	100%; 50 µl (liquid) or 50 mg (solid)	2	Test substance was applied to reconstructed cornea epithelium; after application, epithelia was incubated for 90 min	Non-irritating	[68]
An Asparagopsis Armata Extract containing 4% dry algal matter (other components not specified)	100%; dose not reported	NR	Cell viability assessed by using neutral red release assay (PREDISAFE) method	Slightly-irritating	[58]
Mixture containing 98.6% Asparagopsis Armata Extract (4% dry extract), 1% butylene glycol, 0.2% chlorphenesin, and 0.2% parabens/ phenoxyethanol	100%; dose not reported	NR	HET-CAM assay	Non-irritating	[56]
After-shave balm containing 0.8% Chondrus Crispus (other components not specified)	100%; 100 µl	3	MatTek EpiOcular™ MTT assay	Non-irritating	[81]
Trade name mixture containing 3.5% Chondrus Crispus Extract (other components not specified)	100%; 50 µl (liquid) or 50mg (solid)	2	MatTek EpiOcular™ MTT assay	Non-irritating	[69]
Corallina Officinalis Extract (0.2 – 4% algae) in seawater, calcium chloride, and propylene glycol	NR	NR	PREDISAFE assay	Slightly-irritating	[15]
Trade name mixture consisting of 50% glycerin; 30% water; 18.5 % undaria pinnatifida extract; 1.5% Corallina Officinalis Extract	10%; 5 ml	4	HET-CAM assay	Non-irritating	[84]
Mixture containing Delesseria Sanguinea Extract (0.2 – 4%), water, and dipropylene glycol	100%; dose not reported	NR	Neutral red release assay	Non-irritating	[18]
Mixture consisting of Furcellaria Lumbricalis Extract (0.2 – 4%), water, and sea salt	100%; dose not reported	NR	Agar diffusion cytotoxicity assay	Non-irritating	[19]
Trade name mixture consisting of water (45.7%), glycerin (40%), *Gigartina stellata* (4.43%), Kappaphycus Alvarezii Extract (5.9%), Corallina Officinalis Extract (3.97%)	10%; 5 ml	4	HET-CAM assay	Slightly-irritating	[83]
Trade name mixture consisting of 57-61% Lithothamnion Calcareum Powder, 26-31% mannitol, 9-11% diatomaceous earth, 0.7-1.5% zinc sulfate in water	2%, 5%, and 10%; 0.3 ml	4	HET-CAM assay	Moderately irritating at the 10% concentration; non-irritating at the 2 and 5% concentrations	[85]
Trade name mixture consisting of 52% water, 48% Porphyra Umbilicalis Extract	100%; dose not reported	6	HET-CAM assay	Weakly irritating	[61]
Eye cream containing 0.0375% Rhodymenia Palmata Extract	100%; 100 µl	8	MatTek EpiOcular™ MTT assay	Non-irritating	[82]
ANIMAL					
Corallina Officinalis Extract (0.2 – 4% algae) in water	100%; dose not reported	3 rabbits (strain not reported)	Primary ocular tolerance assay	Slightly irritating	[15]
Delesseria Sanguinea Extract (0.2 – 4% algae) in water and dipropylene glycol	NR	3 rabbits (strain not reported)	Primary ocular tolerance assay	Slightly irritating	[18]

HET-CAM = hen's egg test chorioallantoic membrane; MTT = 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide; NR = not reported

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Red Algae Ingredients FDA VCRP 2021

Ahnfeltia Concinna Extract – 5 total uses

Cleansing	1
Face and Neck (exc shave)	2
Moisturizing	1
Other Skin Care Preps	1

Asparagopsis Armata Extract – 18 total uses

Eye Lotion	5
Other Eye Makeup Preparations	3
Makeup Bases	1
Other Personal Cleanliness Products	1
Cleansing	1
Face and Neck (exc shave)	3
Body and Hand (exc shave)	1
Moisturizing	3

Betaphycus Gelatinum Extract – No reported uses

Botryocladia Occidentalis Extract – No reported uses

Calliblepharis Ciliata Extract – No reported uses

Ceramium Kondoi Extract – No reported uses

Ceramium Rubrum – No reported uses

Chondrocathus Teedii Powder – No reported uses

Chondrus Crispus – 94 total uses

Bath Oils, Tablets, and Salts	2
Other Bath Preparations	5
Eye Shadow	7
Other Eye Makeup Preparations	5
Shampoos (non-coloring)	1
Tonics, Dressings, and Other Hair Grooming Aids	2
Blushers (all types)	1
Face Powders	5
Foundations	1
Other Makeup Preparations	1
Dentifrices	5
Bath Soaps and Detergents	3
Other Personal Cleanliness Products	5

Aftershave Lotion	1
Cleansing	2
Face and Neck (exc shave)	11
Body and Hand (exc shave)	7
Moisturizing	22
Night	2
Paste Masks (mud packs)	1
Other Skin Care Preps	4
Other Suntan Preparations	1

Chondrus Crispus Extract – 268 total uses

Bubble Baths	1
Eyeliner	1
Eye Shadow	25
Eye Lotion	4
Mascara	1
Other Eye Makeup Preparations	6
Hair Conditioner	3
Shampoos (non-coloring)	5
Tonics, Dressings, and Other Hair Grooming Aids	4
Other Hair Preparations	2
Blushers (all types)	7
Face Powders	17
Makeup Bases	2
Rouges	2
Other Makeup Preparations	4
Dentifrices	9
Bath Soaps and Detergents	1
Douches	1
Other Personal Cleanliness Products	1
Aftershave Lotion	1
Shaving Cream	1
Cleansing	12
Face and Neck (exc shave)	52
Body and Hand (exc shave)	19
Moisturizing	46
Night	4
Paste Masks (mud packs)	12
Skin Fresheners	3
Other Skin Care Preps	22

Chondrus Crispus Powder – 63 total uses

Eye Shadow	1
Other Eye Makeup Preparations	11

Tonics, Dressings, and Other Hair Grooming Aids	1
Dentifrices	6
Bath Soaps and Detergents	1
Other Personal Cleanliness Products	1
Aftershave Lotion	2
Cleansing	2
Face and Neck (exc shave)	24
Moisturizing	7
Paste Masks (mud packs)	1
Other Skin Care Preps	6

Corallina Officinalis Extract – 66 total uses

Eye Lotion	1
Other Eye Makeup Preparations	1
Rinses (non-coloring)	1
Face Powders	1
Basecoats and Undercoats	1
Nail Polish and Enamel	2
Other Manicuring Preparations	1
Cleansing	7
Face and Neck (exc shave)	6
Body and Hand (exc shave)	1
Moisturizing	34
Night	1
Paste Masks (mud packs)	2
Skin Fresheners	2
Other Skin Care Preps	5

Corallina Officinalis Powder – No reported uses

Cyanidium Caldarium Extract – 3 total uses

Moisturizing	1
Night	1
Skin Fresheners	1

Delesseria Sanguinea Extract – 2 total uses

Face and Neck (exc shave)	1
Night	1

Digenea Simplex Extract – No reported uses

Dilsea Carnosa Extract – No reported uses

Furcellaria Lumbricalis Extract – 44 total uses

Other Eye Makeup Preparations	3
Foundations	3
Lipstick	2
Makeup Bases	8
Other Makeup Preparations	1
Face and Neck (exc shave)	10
Moisturizing	10
Night	5
Skin Fresheners	1
Other Skin Care Preps	1

Gelidium Amansii Extract – 1 reported use

Moisturizing	1

Gelidium Cartilagineum Extract – 36 total uses

Baby Lotions, Oils, Powders, and Creams	1
Eye Lotion	1
Other Eye Makeup Preparations	1
Cleansing	1
Face and Neck (exc shave)	6
Body and Hand (exc shave)	1
Moisturizing	16
Paste Masks (mud packs)	2
Skin Fresheners	2
Other Skin Care Preps	5

Gelidium Pulchrum Protein – No reported uses

Gelidium Sesquipedale Extract – No reported uses

Gelidiella Acerosa Extract – 29 total uses

Eye Lotion	1
Other Eye Makeup Preparations	2
Hair Conditioner	3
Hair Straighteners	1
Shampoos (non-coloring)	4
Tonics, Dressings, and Other Hair Grooming Aids	1
Hair Shampoos (coloring)	4
Makeup Bases	1
Other Shaving Preparation Products	1
Cleansing	2

Moisturizing	5
Night	3
Other Skin Care Preps	1

Gigartina Skottsbergii Extract – No reported uses

Gigartina Stellata Extract – 7 total uses

Hair Conditioner	1
Rinses (non-coloring)	1
Shampoos (non-coloring)	3
Tonics, Dressings, and Other Hair Grooming Aids	1
Face and Neck (exc shave)	1

Gloiopeltis Aenax Powder – No reported uses

Gracilaria Verrucosa Extract – No reported uses

Gracialiopsis Chorda Extract – No reported uses

Grateloupia Livida Powder – No reported uses

Hydrolyzed Asparagopsis Armata Extact – No reported uses

Hydrolyzed Chondrus Crispus Extract – 1 total use

Face and Neck (exc shave)	1

Hydrolyzed Corallina Officinalis Extract – 4 total uses

Face and Neck (exc shave)	1
Moisturizing	2
Other Skin Care Preps	1

Hydrolyzed Chondrus Crispus Extract -

Hydrolyzed Porphyra Yezoensis – No reported uses

Hydrolyzed Rhodophycea Extract – 33 total uses

Eye Makeup Remover	1
Mascara	1
Hair Conditioner	8
Hair Spray (aerosol fixatives)	1
Shampoos (non-coloring)	4
Other Hair Preparations	1
Other Makeup Preparations	1
Nail Polish and Enamel	6
Cleansing	5
Face and Neck (exc shave)	2
Body and Hand (exc shave)	1

Moisturizing	2

Hypnea Musciformis Extract – 52 total uses

Eye Lotion	1
Other Eye Makeup Preparations	2
Hair Conditioner	8
Hair Spray (aerosol fixatives)	1
Hair Straighteners	2
Shampoos (non-coloring)	6
Tonics, Dressings, and Other Hair Grooming Aids	1
Other Hair Preparations	2
Hair Dyes and Colors (all types requiring caution statements and patch tests)	11
Hair Shampoos (coloring)	4
Makeup Bases	1
Other Makeup Preparations	1
Cuticle Softeners	1
Other Shaving Preparation Products	1
Cleansing	2
Moisturizing	4
Night	3
Other Skin Care Preps	1

Kappaphycus Alvarezii Extract – 24 total uses

Other Eye Makeup Preparations	1
Hair Conditioner	4
Shampoos (non-coloring)	3
Other Hair Preparations	1
Makeup Bases	1
Bath Soaps and Detergents	1
Cleansing	1
Face and Neck (exc shave)	8
Moisturizing	2
Night	1
Skin Fresheners	1

Lithothamnium Calcareum Extract – 19 total uses

Eye Shadow	3
Other Eye Makeup Preparations	1
Nail Polish and Enamel	12

Face and Neck (exc shave)	1
Night	2

Lithothamnium Calcareum Powder – 8 total uses

Body and Hand (exc shave)	2
Paste Masks (mud packs)	5
Other Skin Care Preps	1

Lithothamnium Corallioides Powder – No reported uses

Mesophyllum Lichenoides Extract – No reported uses

Palmaria Palmata Extract – 52 total uses

Eye Lotion	1
Other Eye Makeup Preparations	2
Face Powders	1
Leg and Body Paints	1
Other Makeup Preparations	2
Bath Soaps and Detergents	1
Other Personal Cleanliness Products	1
Cleansing	1
Face and Neck (exc shave)	18
Body and Hand (exc shave)	3
Moisturizing	10
Night	1
Skin Fresheners	1
Other Skin Care Preps	9

Palmaria Palmata Powder – No Reported Uses

Phymatolithon Calcareum Extract – 2 total uses

Eye Shadow	1
Nail Polish and Enamel	1

Pikea Robusta Extract – No reported uses

Polysiphonia Lanosa Extract – No reported uses

Porphyra Linearis Powder – No reported uses

Porphyra Tenera Extract – No reported uses

Porphyra Umbilicalis Extract – 20 total uses

Other Bath Preparations	1

Hair Conditioner	2
Bath Soaps and Detergents	2
Cleansing	1
Face and Neck (exc shave)	4
Body and Hand (exc shave)	3
Moisturizing	7

Porphyra Umbilicalis Powder – No reported uses

Porphyra Yezoensis Extract – 3 total uses

Other Eye Makeup Preparations	1
Body and Hand (exc shave)	1
Moisturizing	1

Porphyra Yezoensis Powder – No reported uses

Porphyridium Cruentum Extract – 35 total uses

Eye Lotion	6
Other Eye Makeup Preparations	1
Face and Neck (exc shave)	7
Moisturizing	9
Paste Masks (mud packs)	7
Other Skin Care Preps	5

Porphyridium Purpureum Extract – 5 total uses

Face and Neck (exc shave)	2
Moisturizing	2
Night	1

Porphyridium Purpureum Extract – No reported uses

Rhodymenia Palmata Extract – No reported uses

Sarcodiotheca Gaudichaudii Extract – No reported use

Concentration of Use by FDA Product Category - Kappaphycus Alvarezii Extract

FDA Product Category	Maximum Concentration of Use
Makeup bases	0.1%
Face and neck products Not spray	0.019-0.19%
Moisturizing products Not spray	0.19%

Information collected in 2020

Table prepared October 5, 2020

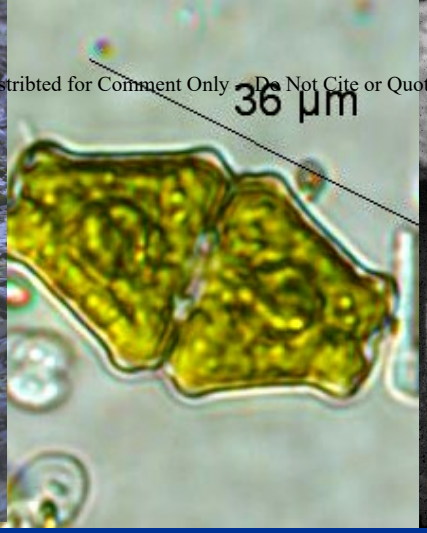
Table 1. Data profile of red algae-derived ingredients

Ingredient	GRAS	Food	Tox	Sensitization data
Ahnfeltiopsis Concinna Extract		✓		
Asparagopsis Armata Extract				✓
Hydrolyzed Asparagopsis Armata Extract				✓
Betaphycus Gelatinum Extract				✓
Chondrus Crispus		✓		✓
Chondrus Crispus Extract		✓		✓
Chondrus Crispus Powder		✓		✓
Hydrolyzed Chondrus Crispus Extract		✓		✓
Corallina Officinalis Extract				✓
Corallina Officinalis Powder				✓
Corallina Officinalis Thallus Extract				✓
Hydrolyzed Corallina Officinalis				✓
Hydrolyzed Corallina Officinalis Extract				✓
Delesseria Sanguinea Extract				✓
Furcellaria Lumbricalis Extract				✓
Gelidiella Acerosa Extract		✓		✓
Gelidium Amansii Extract		✓		
Gelidium Amansii Oligosaccharides		✓		
Gelidium Cartilagineum Extract				✓
Gigartina Stellata Extract		✓		
Gracilaria Verrucosa Extract		✓		
Hypnea Musciformis Extract		✓		✓
Kappaphycus Alvarezii Extract				✓
Lithothamnion Calcareum Extract (synonymous with Phymatolithon Calcareum Extract)		✓	✓	
Lithothamnion Calcareum Powder		✓	✓	
Palmaria Palmata Extract (synonymous with Rhodymenia Palmata Extract)	✓	✓		✓
Palmaria Palmata Powder	✓	✓		✓
Phymatolithon Calcareum Extract (synonymous with Lithothamnion Calcareum Extract)		✓	✓	
Porphyra Tenera Extract	✓	✓		
Porphyra Tenera Sporophyte Extract	✓	✓		
Porphyra Umbilicalis Extract		✓		✓
Porphyra Umbilicalis Powder		✓		✓
Hydrolyzed Porphyra Yezoensis		✓		
Porphyra Yezoensis Extract		✓		
Porphyra Yezoensis Powder		✓		
Rhodymenia Palmata Extract (synonymous with Palmaria Palmata Extract)	✓	✓		✓

It should be noted that if data points were available for an ingredient of a given genus and species, then the same data points would be checked off for all other ingredient forms with the same genus and species. For example, since sensitization data was provided for Chondrus Crispus Extract, the sensitization data point is also checked off for Chondrus Crispus, Chondrus Crispus Extract, Chondrus Crispus Powder, and Hydrolyzed Chondrus Crispus Powder.

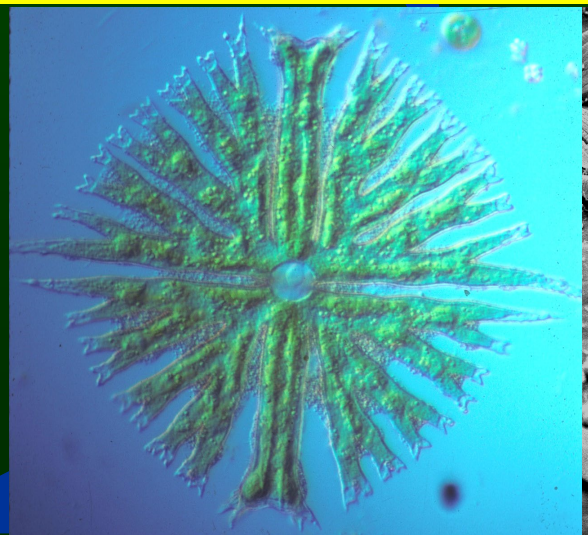
Ingredients with no GRAS/food data, systemic toxicity data, or sensitization data (24 ingredients)

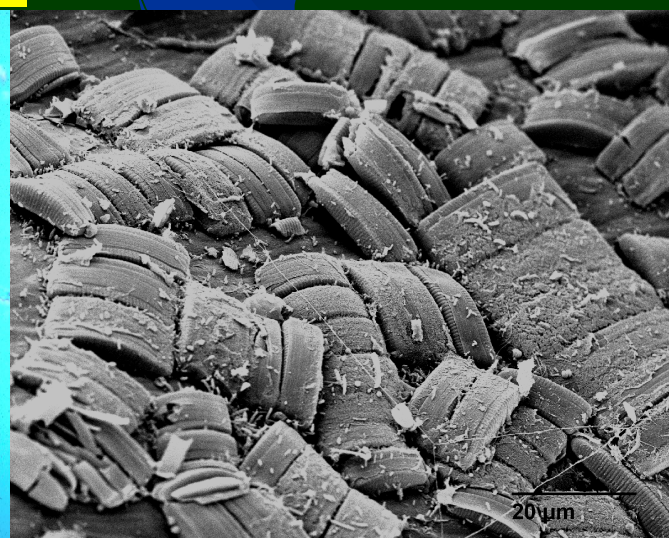
Botryocladia Occidentalis Extract
Calliblepharis Ciliata Extract
Ceramium Kondoi Extract
Ceramium Rubrum Extract
Chondracanthus Teedei Powder
Cyanidium Caldarium Extract
Digenea Simplex Extract
Dilsea Carnosa Extract
Gelidium Pulchrum Protein
Gelidium Sesquipedale Extract
Gigartina Skottsbergii Extract
Gloiopeltis Tenax Extract
Gloiopeltis Tenax Powder
Gracilariopsis Chorda Extract
Grateloupia Livida Powder
Lithothamnion Corraloides Powder
Mesophyllum Lichenoides Extract
Pikea Robust Extract
Polysiphonia Lanosa Extract
Porphyra Linearis Powder
Porphyridium Cruentum Culture Conditioned Media
Porphyridium Cruentum Extract
(synonymous with Porphyridium Purpureum Extract)
Porphyridium Purpureum Extract
(synonymous with Porphyridium Cruentum Extract)
Sardiotheca Gaudichaudii Extract



Algal diversity and application.

Rex L. Lowe
Bowling Green State University





Presentation Roadmap

What are these things called algae?

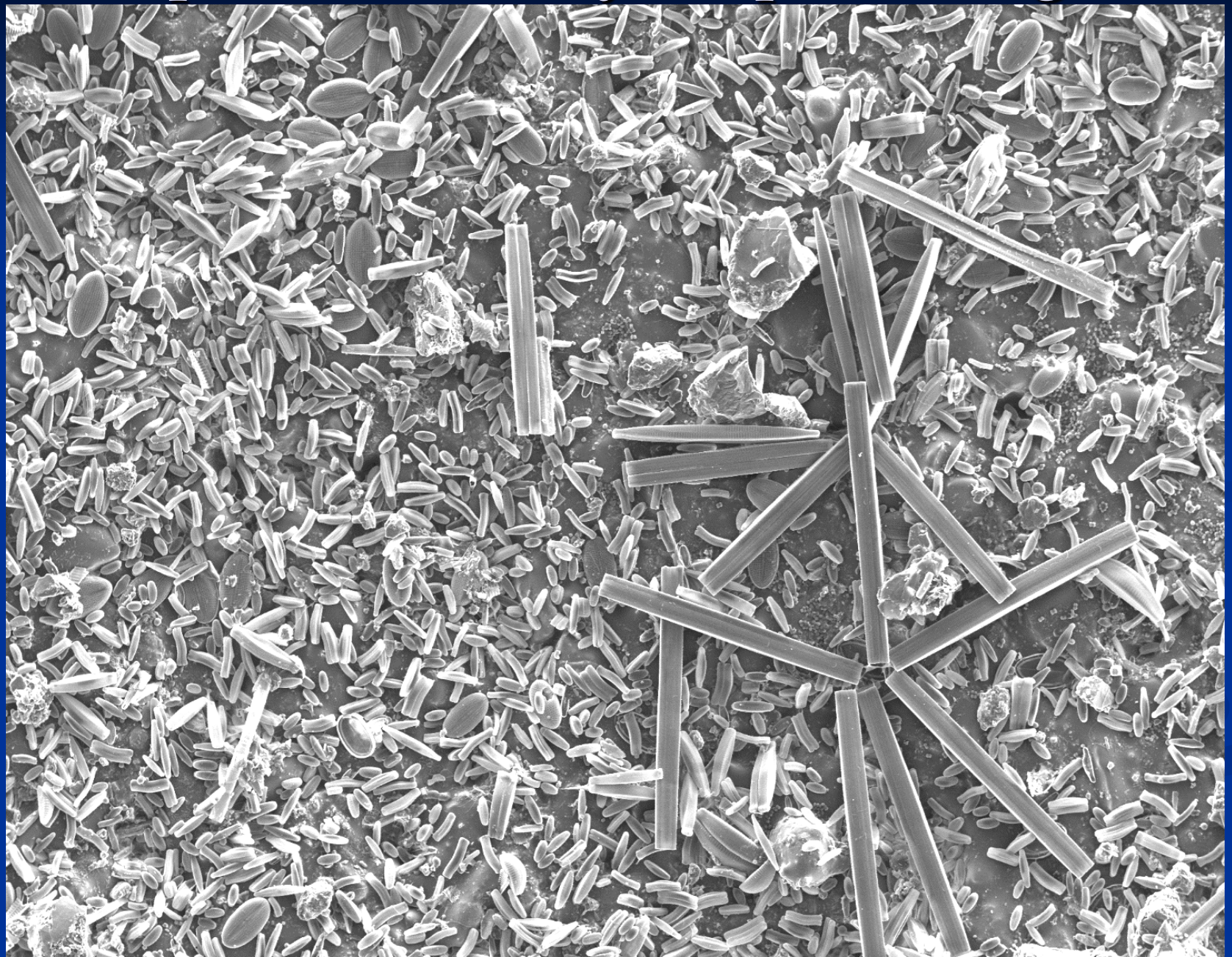
Species diversity & properties

Ecosystem services, Ecosystem hazards

Algal communities might look homogeneous but are very complex

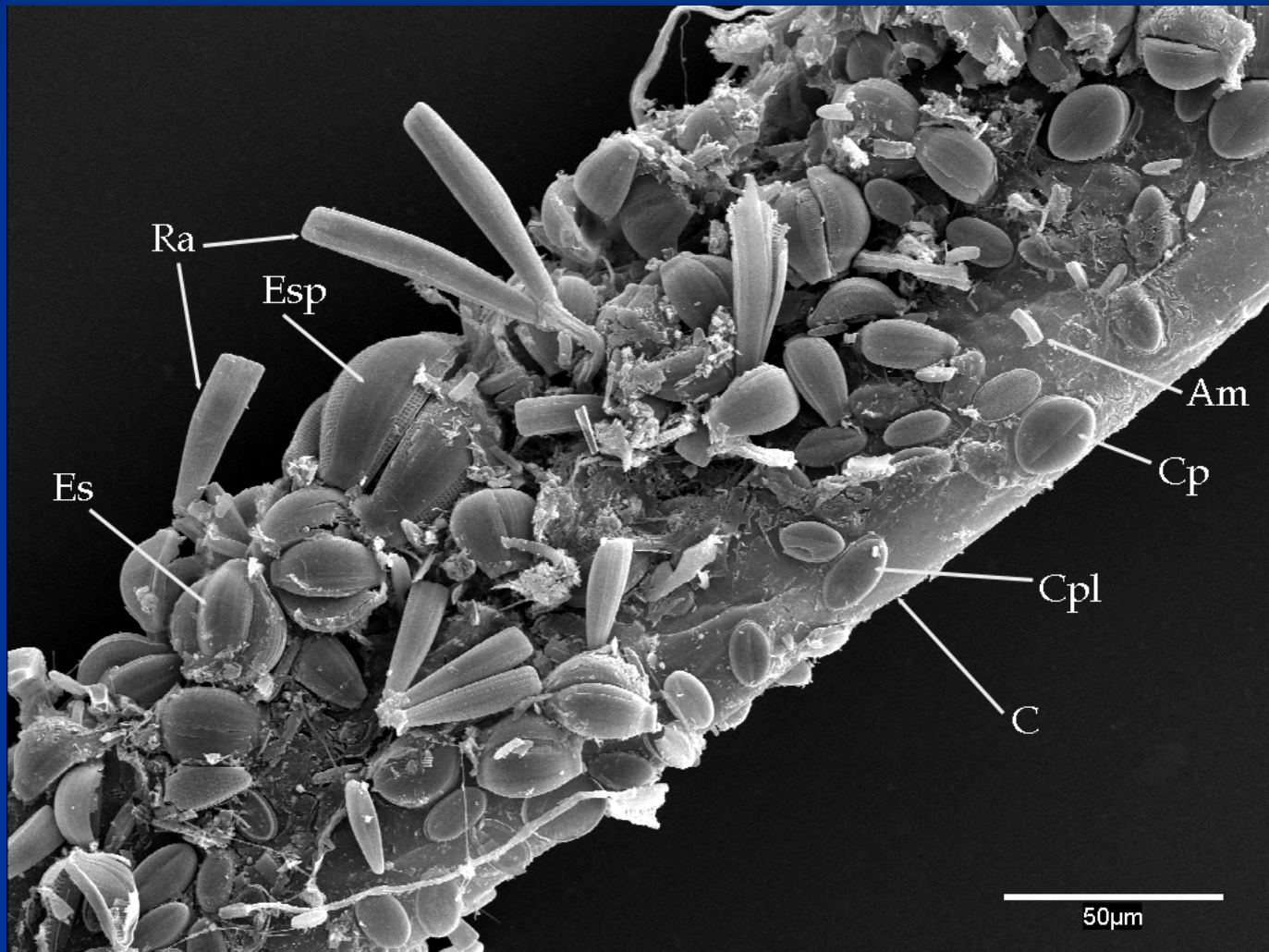
- A stone this size may contain hundreds of species in a very complex community.

A complex community of epilithic algae



A complex community of epiphytic algae on *Cladophora*

- Ra = *Rhoicosphenia abbreviata*
- Esp = *Epithemia* sp.
- Es = *Epithemia sorex*
- Am = *Achnanthidium minutissimum*
- Cp = *Cocconeis pediculus*
- Cpl = *Cocconeis placentula*
- C = *Cladophora*



What are algae?

Algos = Latin seaweed

Phycos = Greek seaweed

- Thalloid organisms bearing **chlorophyll a**, lacking multicellular **gametangia** and their **colorless relatives**.

- Morphologically diverse:
  - Prokaryotes, mesokaryotes, eukaryotes
  - Largest to smallest phototrophs (0.5µm-220 m)

- Physiologically diverse: autotrophs, facultative heterotrophs, obligate heterotrophs (molecules or particles), parasites).

"Algae" is not a "taxonomic" group but a functional group of convenience

Algae should not all be considered plants, some are, some are also protozoa, many are unique and belong in other kingdoms. But they are all part of the eclectic group called algae that are aquatic and oxygenic.

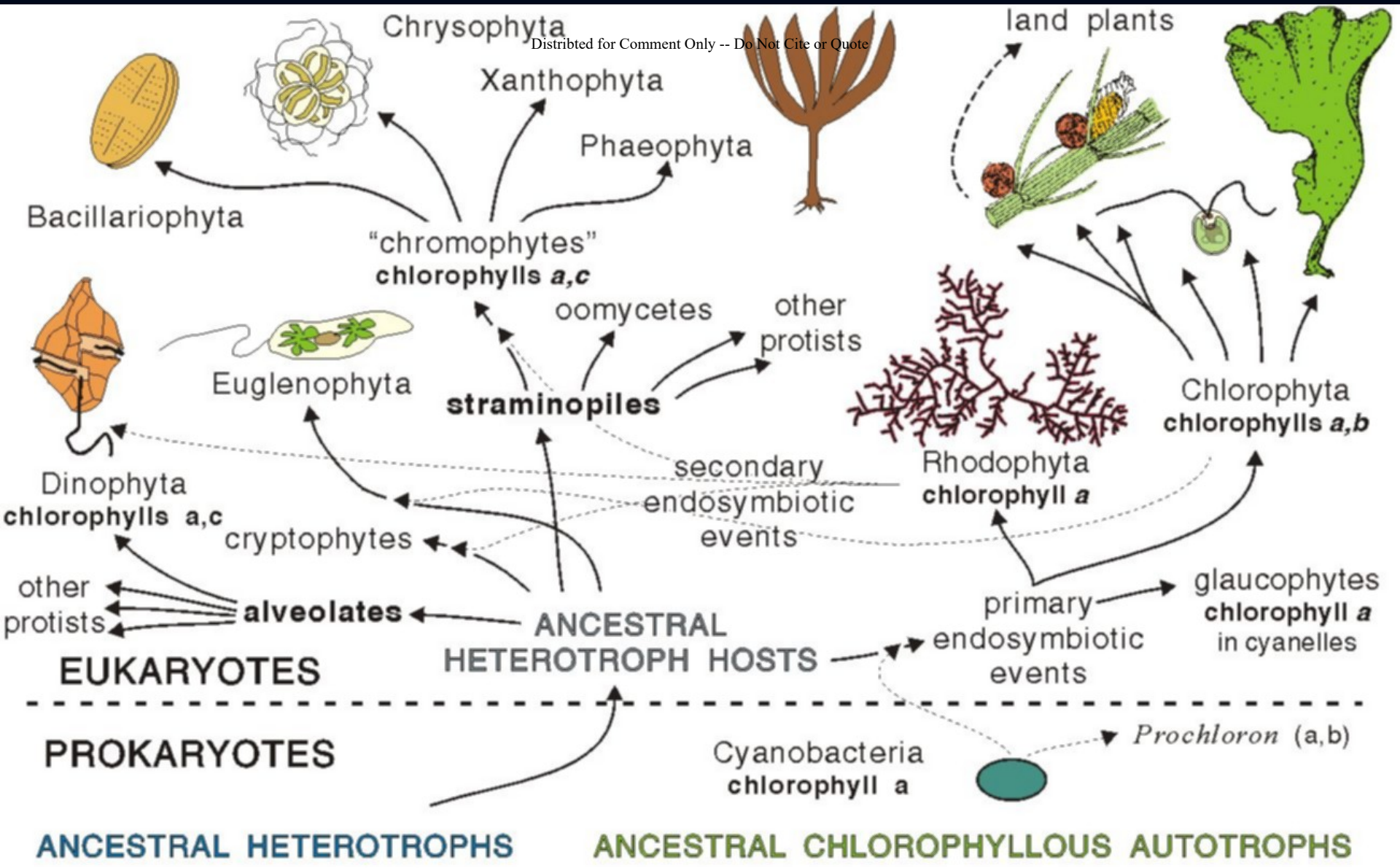


FIG. 9.1 HYPOTHETICAL ENDOSYMBIOTIC ORIGINS OF PLASTIDS IN ALGAE AND PLANTS. This figure should be compared with the phylogeny of the host cells shown in Fig. 1.1. Cavalier-Smith (2000) hypothesizes a single primary capture event and a number of secondary capture events along with losses of pigments and membranes.

Major groups of algae

Common Name	Phylum	Kingdom
Green Algae	Chlorophyta	Plantae
Diatoms	Bacillariophyta	Stramenopila
Chrysophytes	Chrysophyta	Stramenopila
Brown Algae	Phaeophyta	Stramenopila
Blue Green Algae	Cyanophyta	Monera
Red Algae	Rhodophyta	Rhodophyta
Dinoflagellates	Pyrrhophyta	Alveolata
Euglenoids	Euglenophyta	Euglenozoa

Algal Divisions (Phyla)

How do the phyla differ from each other?

We employ 4 main criteria

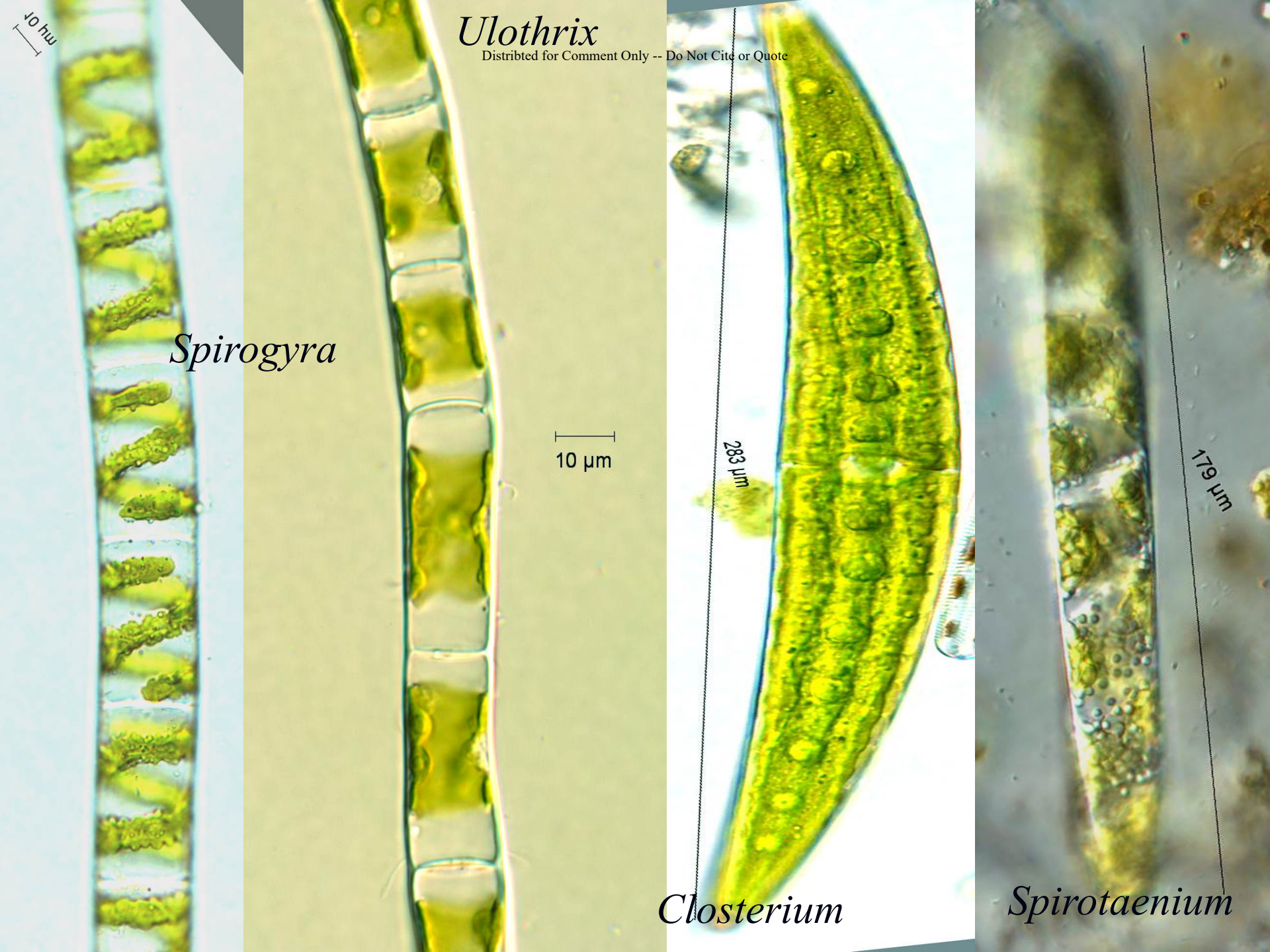
Pigmentation, storage products, cell wall, flagella

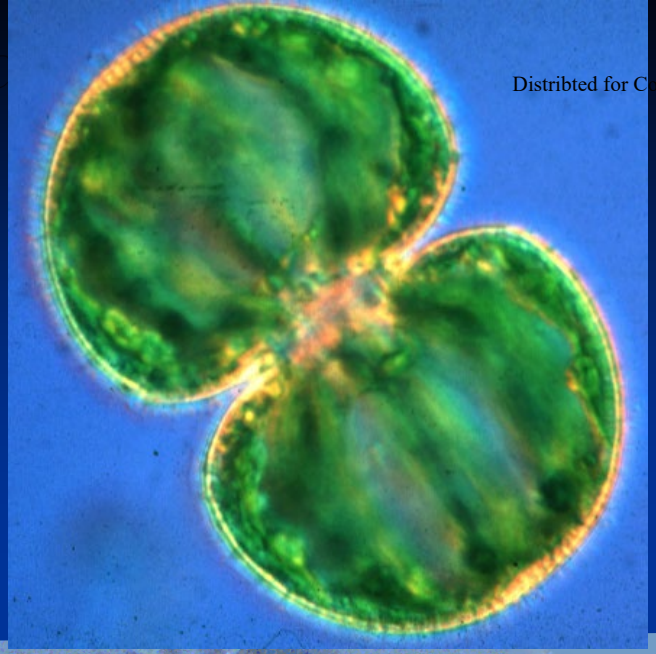
Overview of common phyla

- Green Algae
- Diatoms
- Cyanobacteria
- Brown Algae
- Red Algae

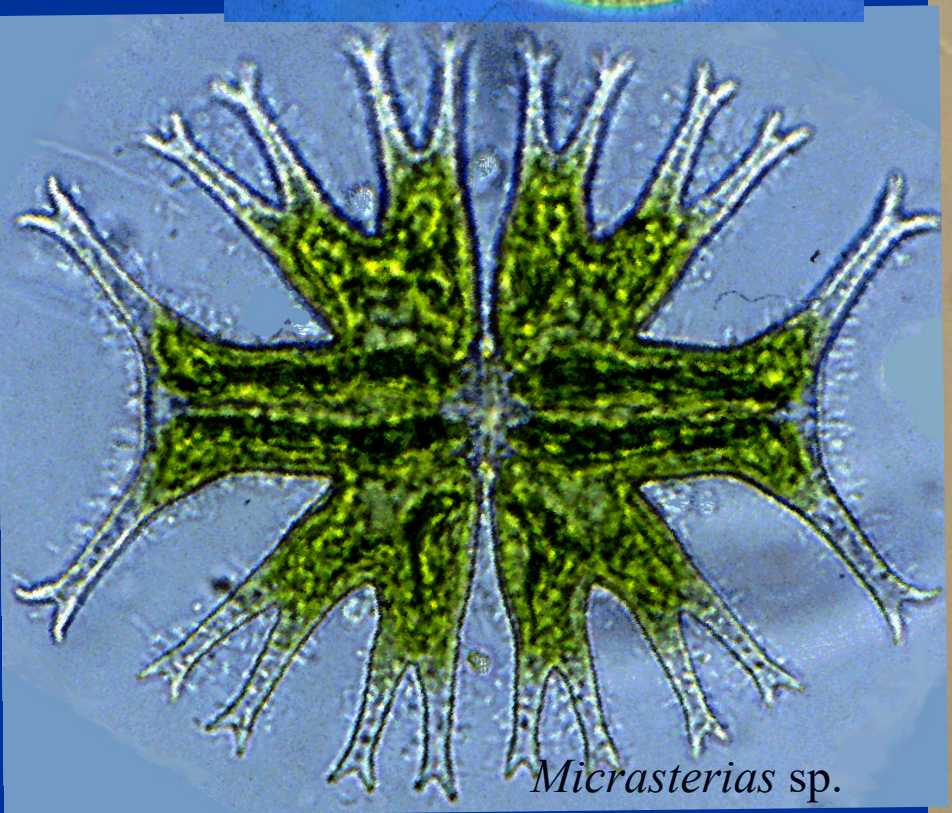
GREEN ALGAE

- Usually green in color
- Cellulose cell walls
- Store starch
- Ancestors of plants
  - Chlorophylls a & b dominate
  - Also rich in beta carotene


Ulothrix
Distribted for Comment Only -- Do Not Cite or Quote
Spirogyra
10 µm
283 µm
Closterium
179 µm
Spirotaenium



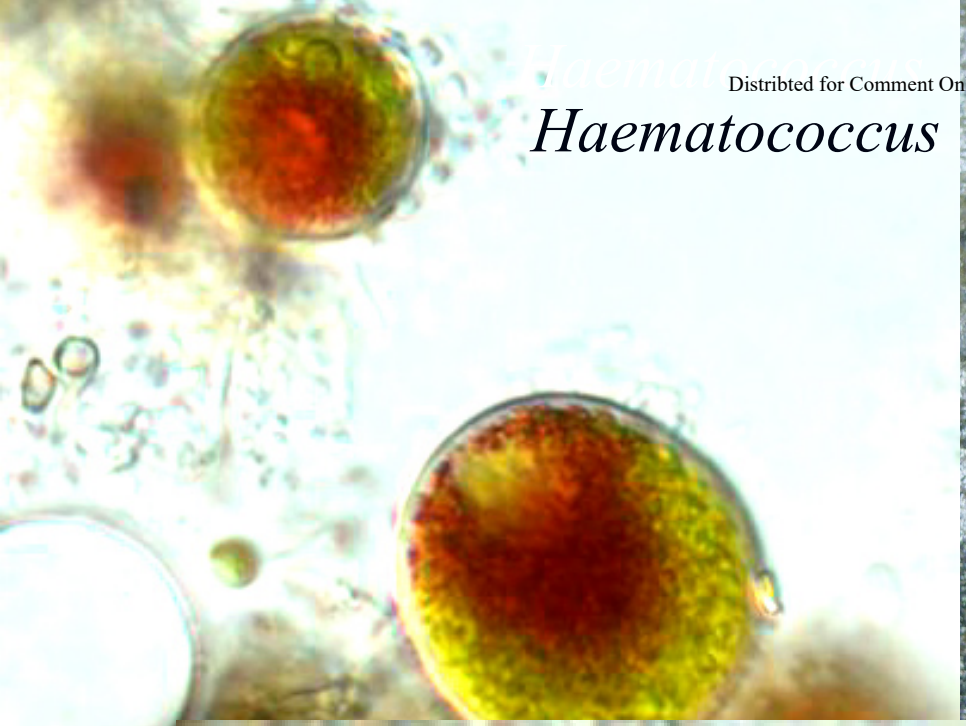
Ulothrix zonata



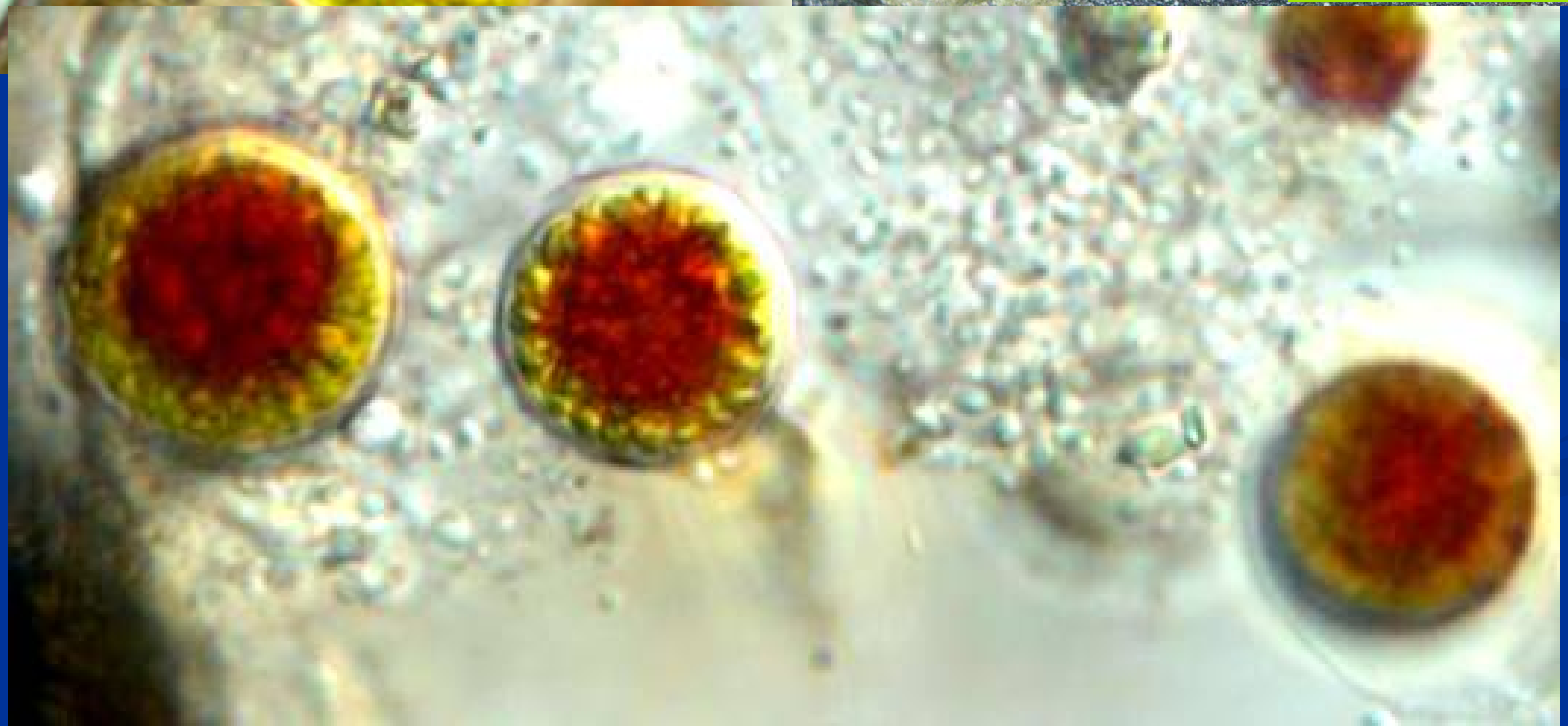
Micrasterias sp.

Staurastrum sp.

Haematococcus



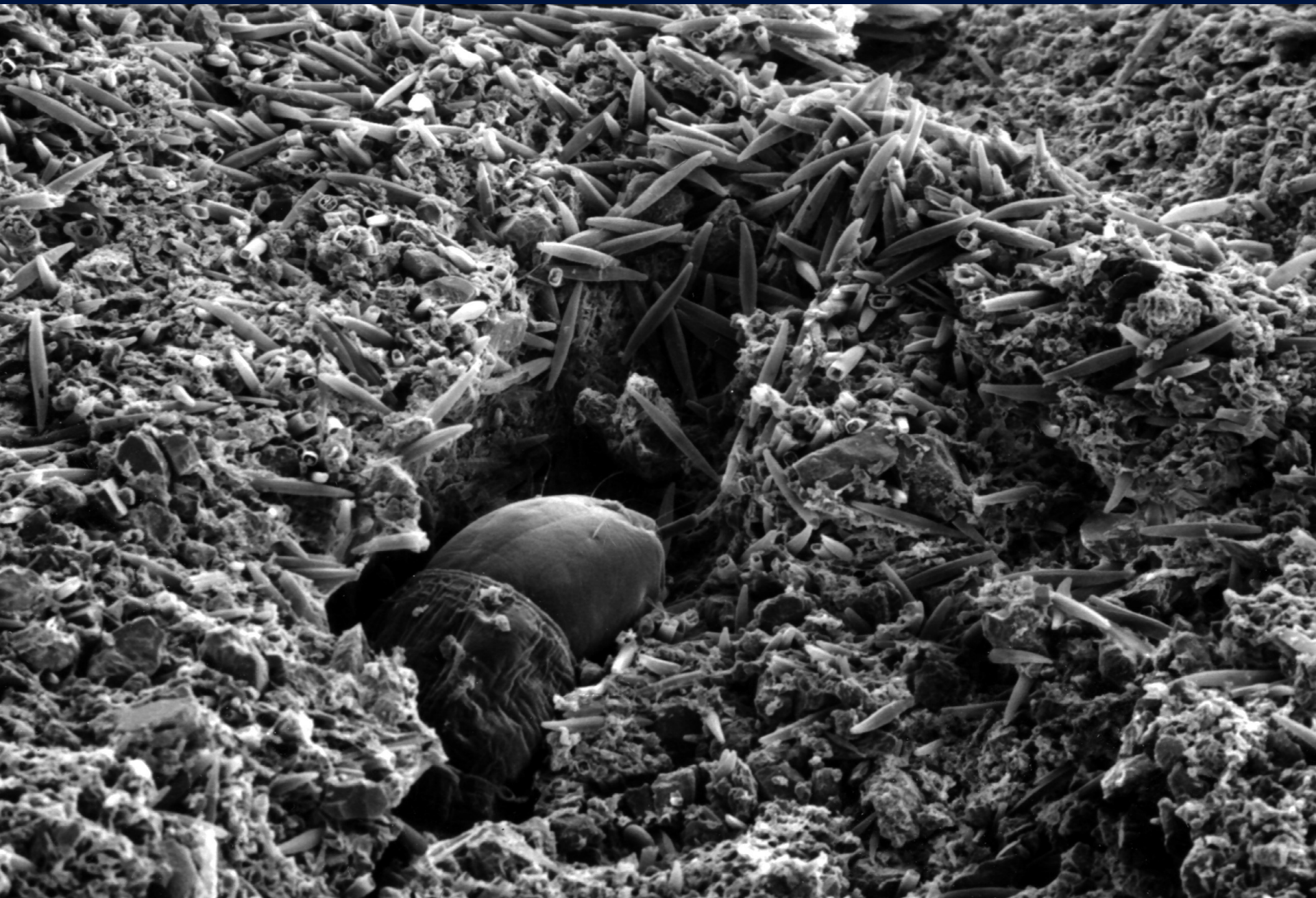
Not all green Algae are Green in color



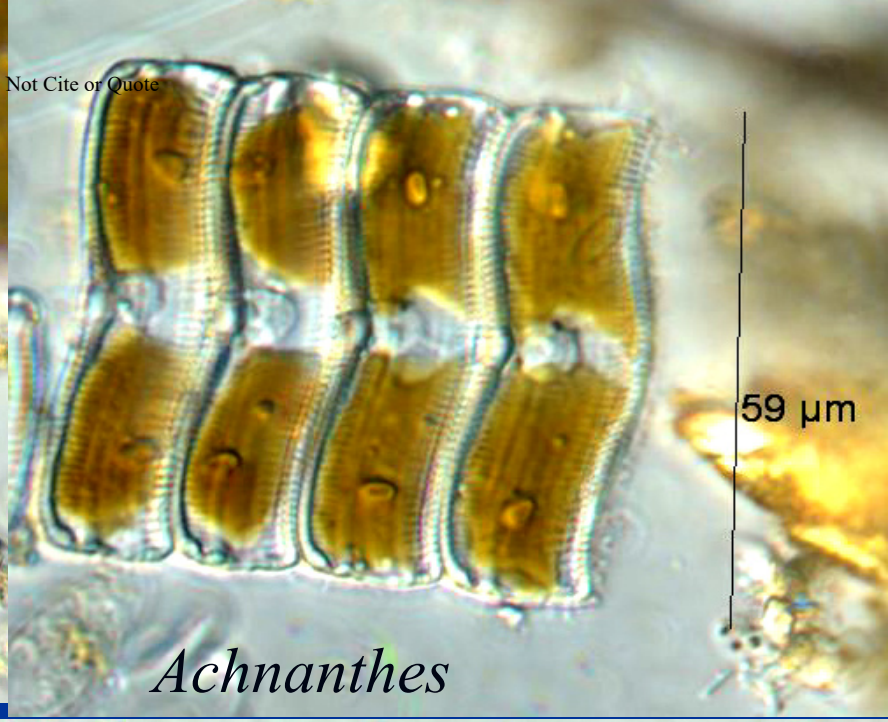
Bacillariophyta Diatoms

- Chlorophylls a & c but carotenoids dominate
- Golden-brown in color
- Silica cell walls
- Store oil as food reserve
- Very nutritious for grazers
- Rich in omega-3 oils

Chironomid consuming "french fry-like" diatoms, *Gyrosigma*

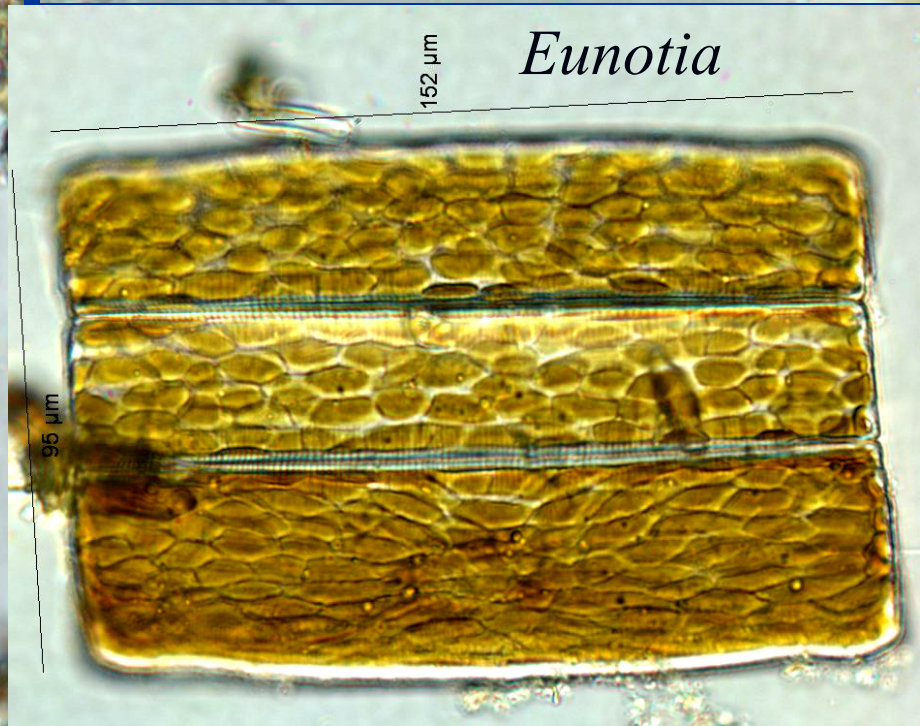


Orthosira



Achnanthes

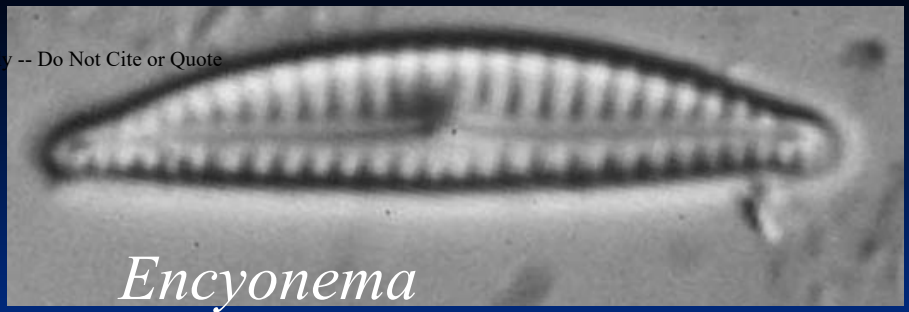
Melosira

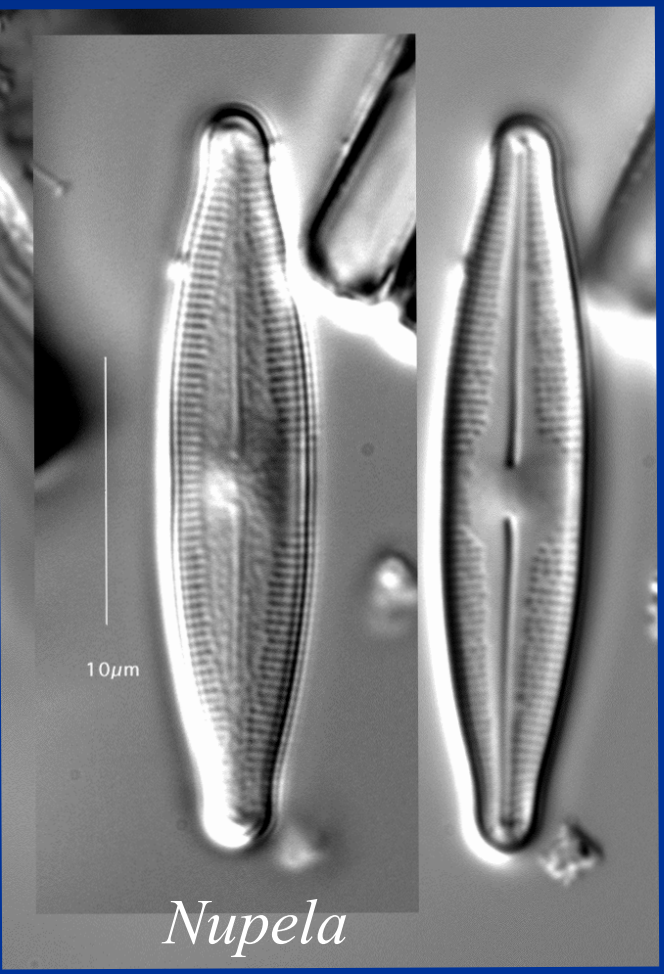


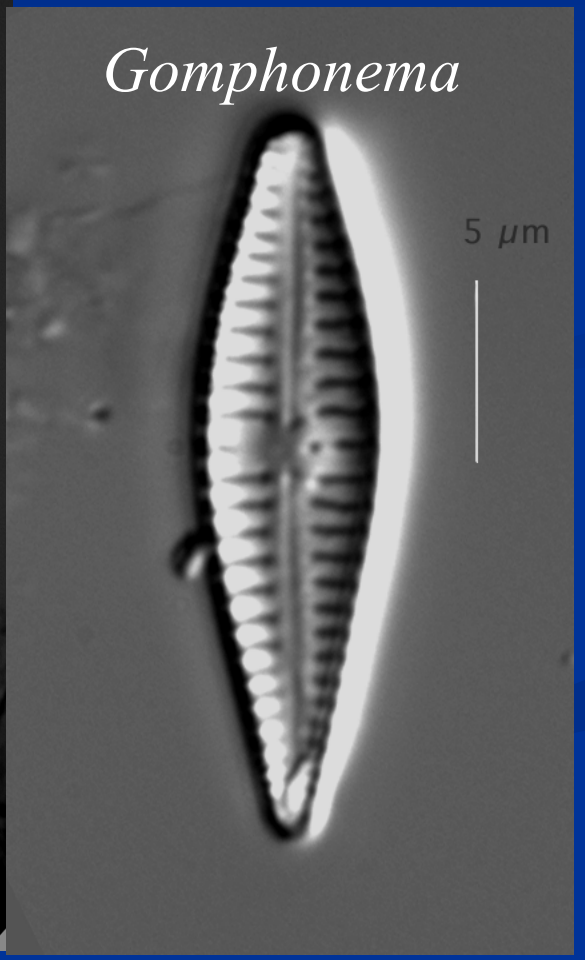
Eunotia

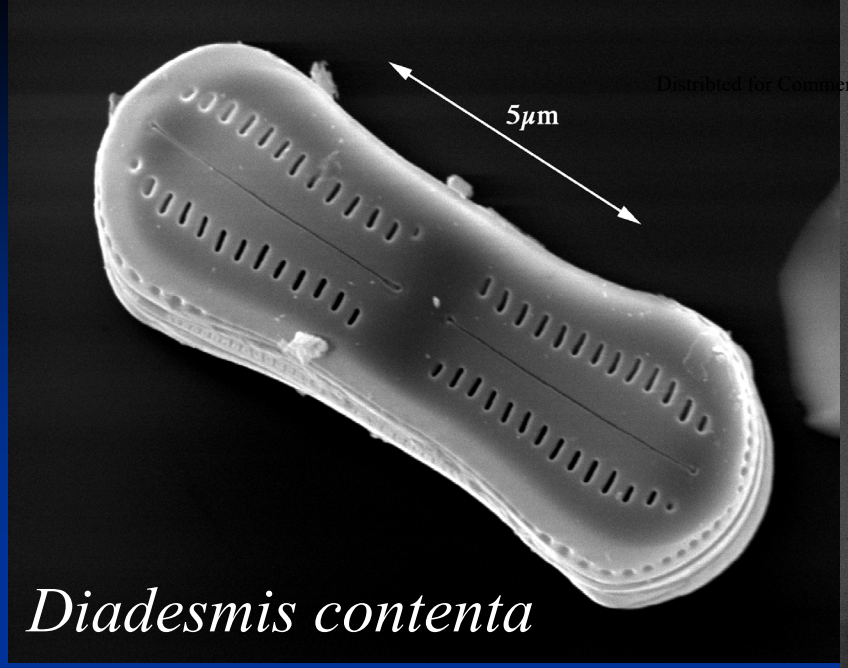
Diatoms normally need to be "cleaned" to identify them to species

- Boiled in nitric acid
- Mounted in Naphrax (a mounting medium of high refractive index)
  - For LM (light microscopy)
- Cleaned specimens are mounted onto specimen stubs for SEM (scanning electron microscopy)

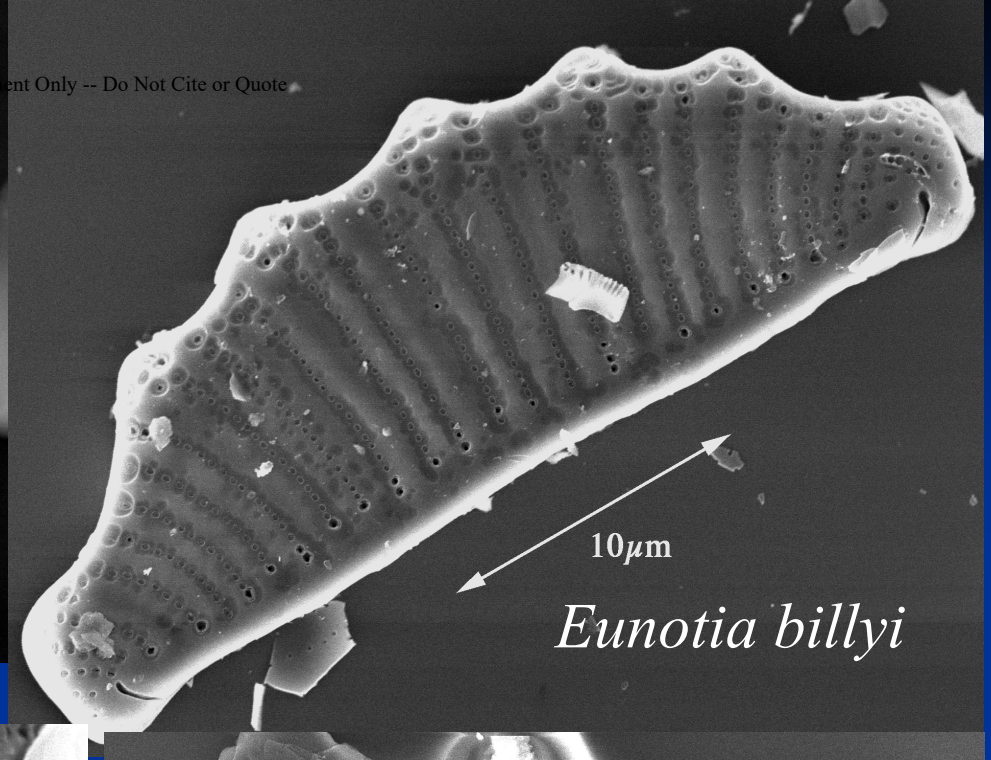




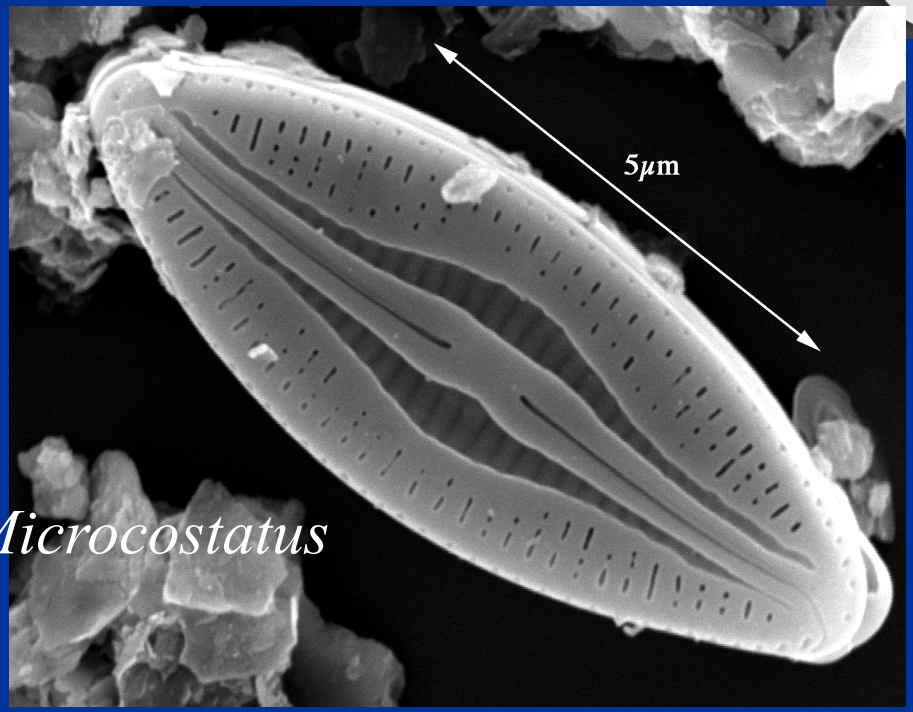




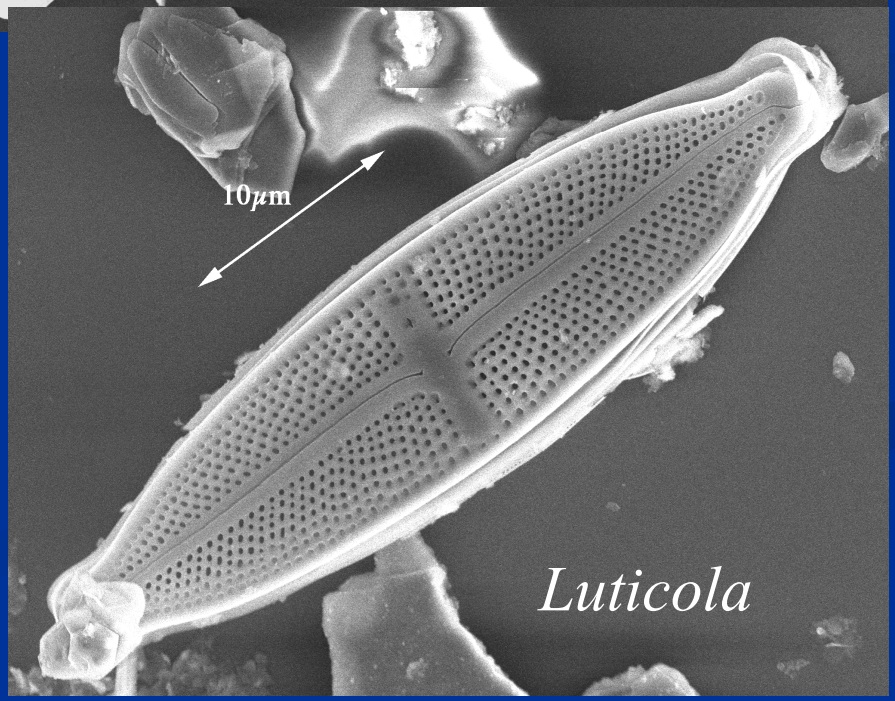
Diadesmis contenta



Eunotia billyi



Microcostatus



Luticola

Ecosystem services, Ecosystem hazards

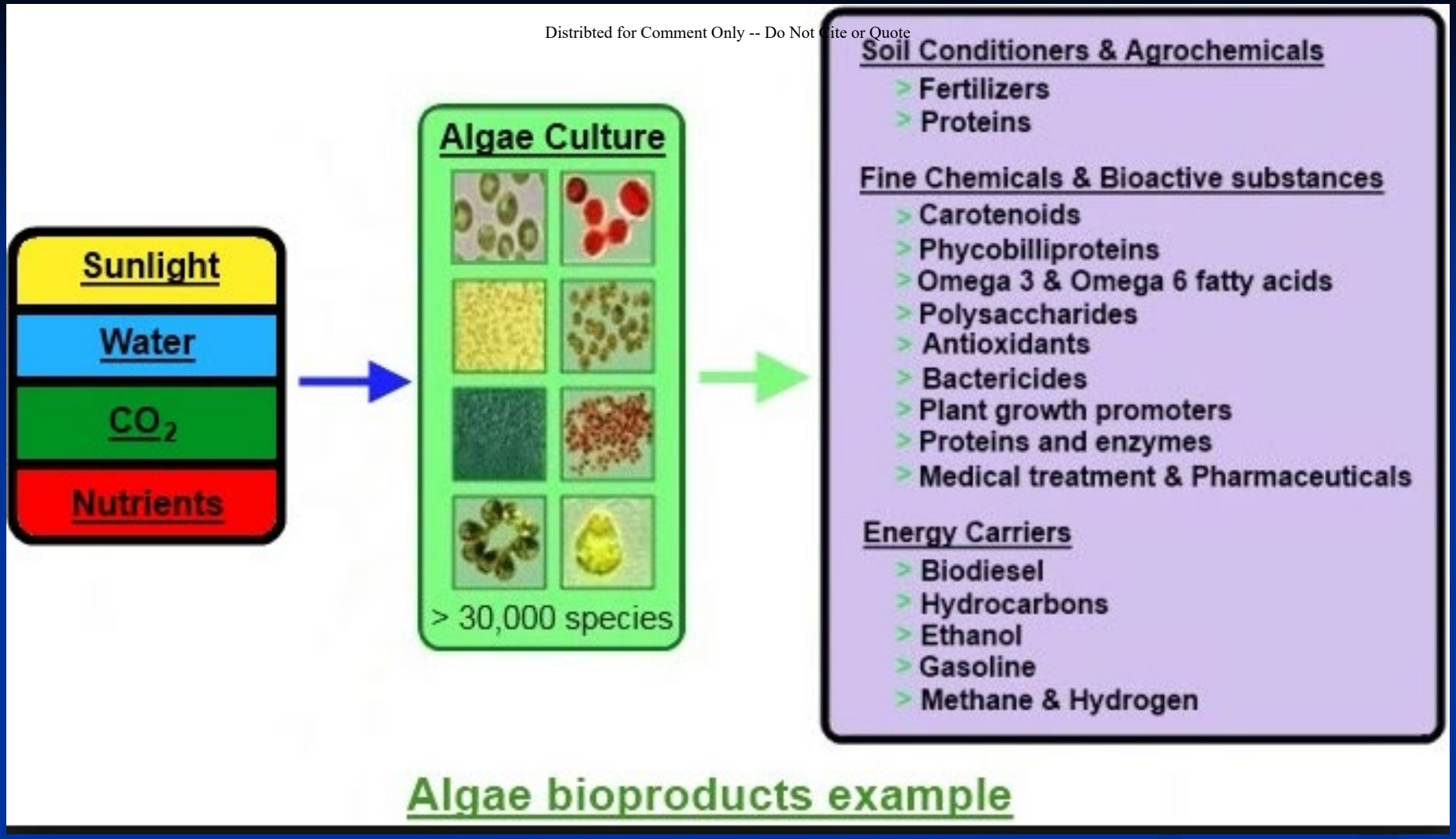
Services

Carbon fixation, about ½ is from algae

Oxygen!

Aquatic food webs

Useful Products



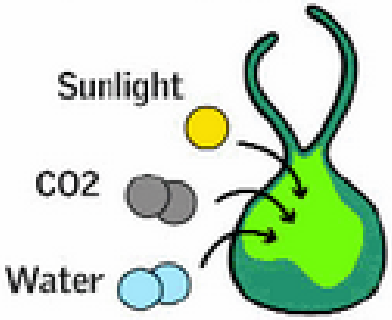
Algae bioproducts example

Biodiesel from algae

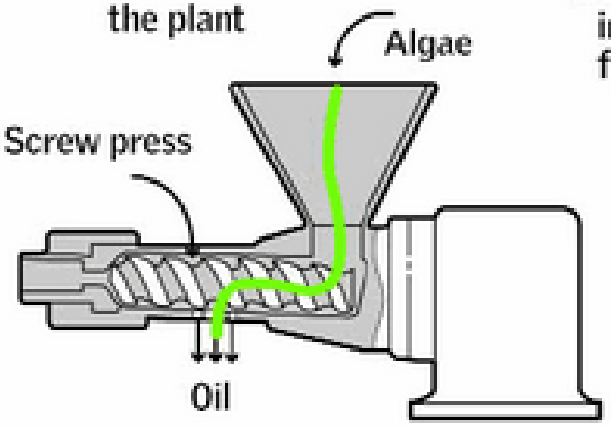
High oil prices and advances in biotech over the past decade have refueled the algae biofuel race.

The process

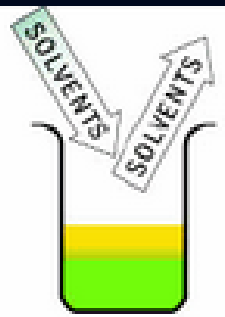
1 After initial growth, algae is deprived of nutrients to produce a greater oil yield



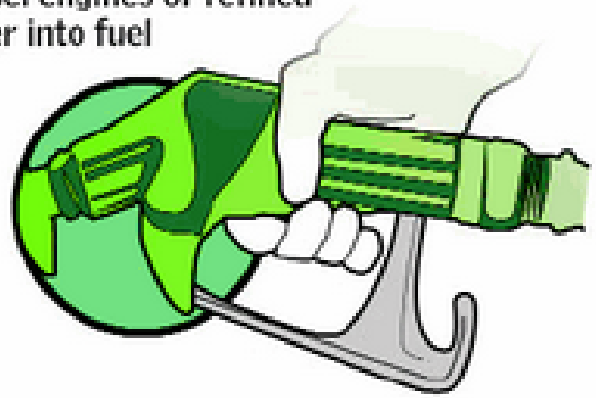
2 Extraction of oil
A press produces 70-75% of the oils from the plant



3 Solvents used to separate sugar from oil; solvents then evaporate

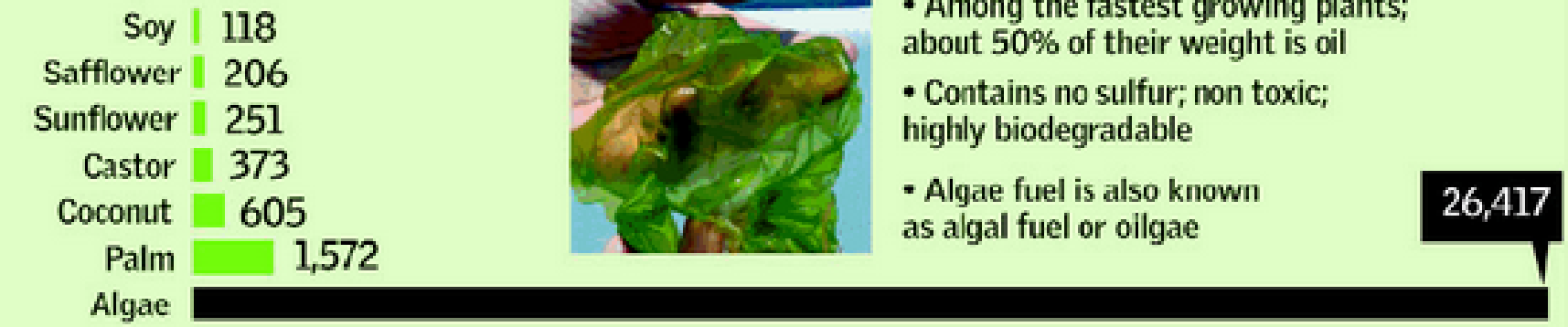


4 Oil is ready
Can be used as oil directly in diesel engines or refined further into fuel



Yield of various plant oils

(Gallons per hectare)



About algae

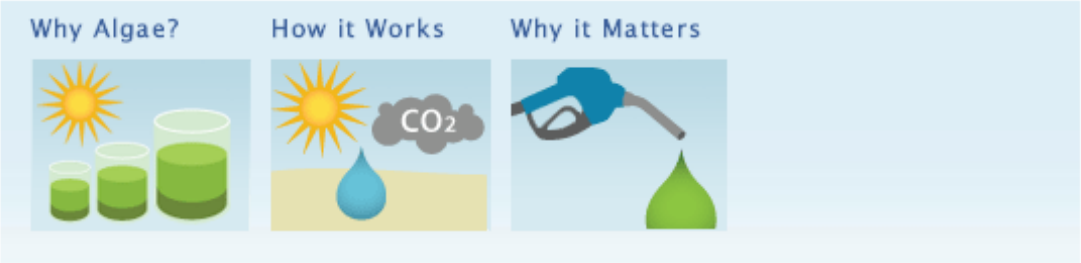
- Among the fastest growing plants; about 50% of their weight is oil
- Contains no sulfur; non toxic; highly biodegradable
- Algae fuel is also known as algal fuel or oilgae

Source: oilgae.com, MCT Photo Service
Graphic: Scott Bell

What is Green Crude

Green Crude is renewable crude oil that is a result of our proprietary process of turning sunlight, CO2, and algae into green oils to be refined into fuel. Our approach leverages the same industrial refining processes as current crude oil, yielding "drop-in" replacement transportation fuels that meet ASTM standards for gasoline, jet fuel, and diesel and that are environmentally sound, cost effective, and scalable.

First- and second-generation biofuels are not compatible with the petroleum infrastructure while Green Crude fits within the existing infrastructure – from refinement through distribution, including the retail supply chain for cars, trucks, and airplanes.



"The process for making algae into fuel at a very base level is this: Sunlight and CO2 are the source of energy and carbon dioxide, rather than sugar or other organic material."

Want more information? Try the tabs in the column to your left or visit allaboutalgae.com

RESOURCES

Fast Facts

Sapphire FAQ

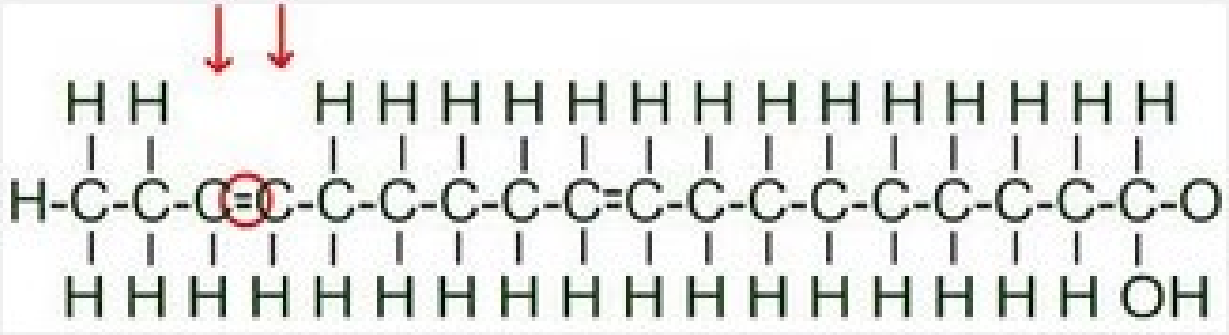
CONTACT SAPPHIRE

For media and analyst inquiries, please click:

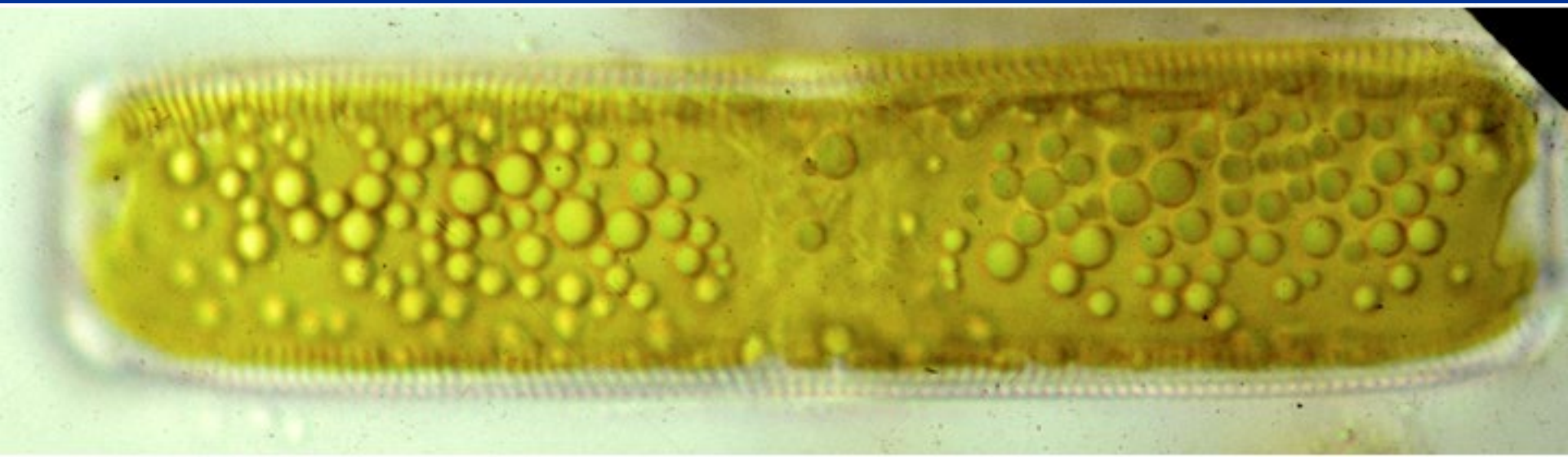
Media and analyst inquiry

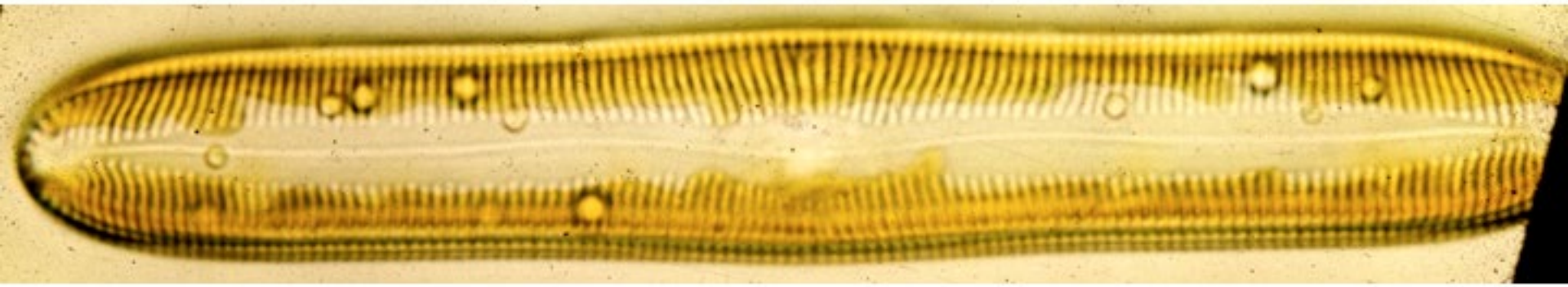
For general corporate inquiries contact Sapphire Energy by:

email:
info@sapphireenergy.com



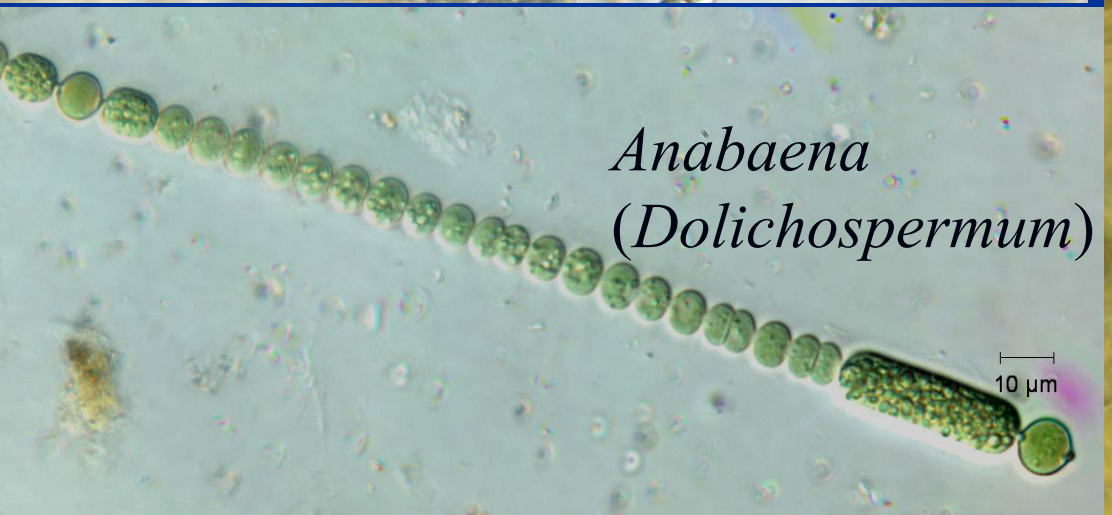
More diatoms Please.

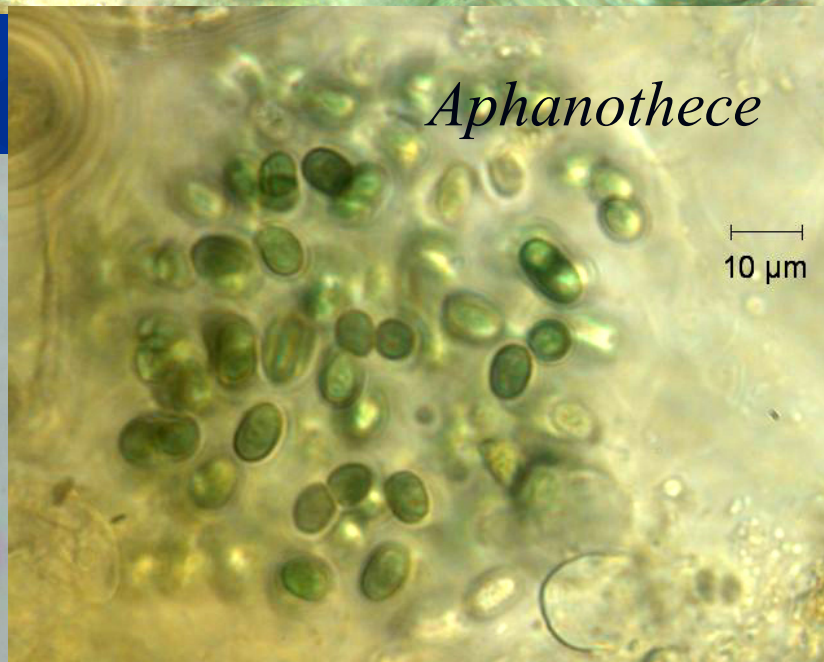




Blue Green Algae

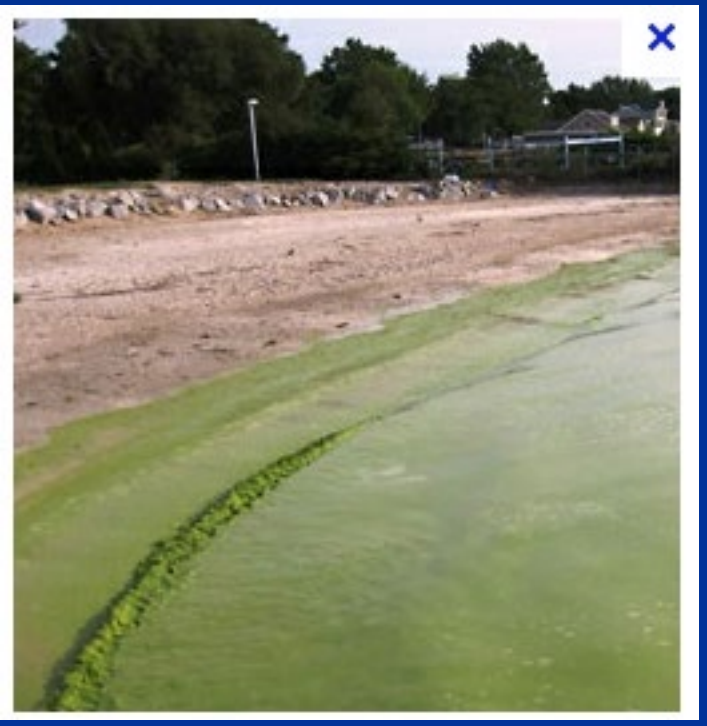
- Cyanobacteria
- Prokaryotic
- Chlorophyll a
- Phycobilins present
- Store glycogen
- Heterocytes on some species (N-fixation)
- Some species are toxic

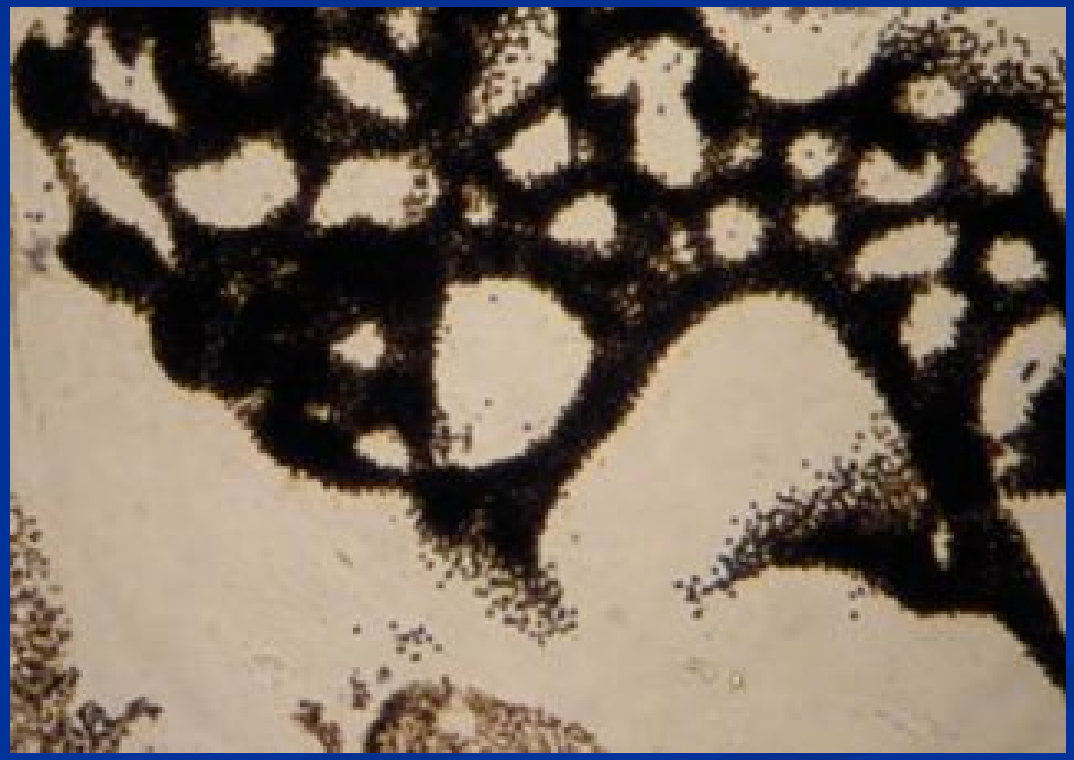




Hazards

Toxic Algae (Cyanobacteria, Dinoflagellates)





Microcystis

Toxins

- Blue-green algae produce two toxins, each with different symptoms. Signs of neurotoxin poisoning usually appear within 15 to 20 minutes after ingestion. In animals, symptoms include weakness, staggering, difficulty in breathing, convulsions and ultimately death. In humans, symptoms may include numbness of the lips, tingling in fingers and toes, and dizziness.
- Signs of liver poisoning may take hours or days to appear. Liver toxins can cause abdominal pain, diarrhea and vomiting in humans and death in animals.

Toxin and Taste-and-Odor Producing Cyanobacteria (list is not exhaustive)

(LYN, lyngbyatoxin-a; APL, aplysiatoxins; LPS, lipopolysaccharides; CYL, cylindrospermopsins; MC, m anatoxins; BMAA, β-N-methylamino-L-alanine; NEO, neosaxitoxins; SAX, saxitoxins; GEOS, geosmin;

	Dermatoxins			Hepatotoxins			Neurotoxins				Tastes and Odors	
	LYN	APL	LPS	CYL	MC	NOD	ANA	BMAA	NEO	SAX	GEOS	MIB
Cyanobacterial Genera												
Colonial/Filamentous												
Anabaena			X	X	X		X	X	X	X	X	
Anabaenopsis			X		X							
Aphanizomenon			X	X			X	X	X	X	X	
Aphanocapsa			X		X							
Cylindrospermopsis			X	X				X		X		
Fischerella			X					X			X	
Haplosiphon			X		X							
Hyella			X								X	X
Lyngbya (Plectonema)	X	X	X	X				X		X	X	X
Microcystis			X		X			X				
Nodularia			X			X		X				
Nostoc			X		X			X			X	X
Oscillatoria (Planktothrix)	X	X	X		X		X	X		X	X	X
Phormidium			X				X	X			X	X
Pseudanabaena			X		X							X
Raphidiopsis			X	X			X					
Schizothrix	X	X	X									
Umezakia			X	X								
Unicellular												
Synechococcus			X		X			X			X	X
Synechocystis			X		X			X				

Table courtesy of Jennifer Graham, USGS

Red Algae/Rhodophyta

- Chlorophylls a, d; phycobilins (phycoerythrin)
- Store Floridean Starch
- Flagella: ABSENT. Only major eukaryotic division without flagella in some stage
- Cell Wall: Cellulose w/mucopolysaccharides
- The source of agar

Red Algae Products

- Most are from the complex cell wall
- Carrageenan (stabilizer and thickener)
  - Salad dressing, soft serve ice cream, puddings, icings, sauces, creamed soups, laxatives, lotions, creams, etc.

Red Algae Products

- Most are from the complex cell wall
- Agar (suspending agent, stabilizer and thickener)
  - Frozen foods, dessert gels, candies, cheeses, electophoretic media, castings and impressions, radiology suspending agents, etc.

Carrageenan is a generic term for compounds extracted from species of red algae. Carrageenans are used in stabilizing and gelling foods, cosmetics, pharmaceuticals, and industrial products.

Brownie mix, Chocolate milk, Coffee creamer, Cottage cheese, Evaporated milk, Frozen yogurt, Ice cream, Infant formula, Pet food, Pudding, Relishes, Salad dressing, Sauces and gravies, Sour cream, Toothpaste, Whipped topping, Whipping cream, Yogurt

Brown Algae

- Mostly large leathery seaweeds
- Cellulose wall with alginic acid and the polysaccharide fucoidan

Brown Algae

Brown Algae Products

- Most are from the complex cell wall
- Alginic acid (alginate) (suspending agent, emulsifying, gel-forming and film-forming)
  - Frozen foods, dessert gels, candies, cheeses, electophoretic media, castings and impressions, radiology suspending agents, etc.

Algal species to consider

- This the list provided to me partitioned into major algal divisions.
- Mostly Red Green and Brown algae which are widely used as food and for other useful products. I would guess all are safe.

Agarum Cribrosum Extract
2. Ahnfeltia Concinna Extract
3. Alaria Esculenta Extract
4. Algae Extract (this ingredient name is slated to be retired due to the vagueness of the name and definition)
5. Aphanizomenon Flos-Aquae Powder
6. Ascophyllum Nodosum Extract
7. Ascophyllum Nodosum Powder
8. Asparagopsis Armata Extract
9. Betaphycus Gelatinum Extract
10. Botryocladia Occidentalis Extract
11. Calliblepharis Ciliata Extract
12. Capsosiphon Fulvescens Extract
13. Caulerpa Lentillifera Extract
14. Caulerpa Okamurai Extract
15. Caulerpa Racemosa Extract
16. Caulerpa Taxifolia Extract
17. Ceramium Kondoi Extract
18. Ceramium Rubrum
19. Chlamydocapsa Extract
20. Chlamydomonas

Algal Groups
Unknown
Blue Green
Brown
Red
Green
Euglenoid
Diatom
Haptophyte

21. **Chlorella Ellipsoidea Extract**
22. **Chlorella Emersonii Extract**
23. **Chlorella Minutissima Extract**
24. **Chlorella Pyrenoidosa Extract**
25. **Chlorella Pyrenoidosa Powder**
26. **Chlorella Variabilis Extract**
27. **Chlorella Vulgaris Extract**
28. **Chlorella Vulgaris Powder**
29. **Chondracanthus Teedii Powder**
30. **Chondrus Crispus**
31. **Chondrus Crispus Extract**
32. **Chondrus Crispus Powder**
33. **Cistus Monspeliensis Extract** (Cistus monspeliensis is a species of rockrose
34. **Cladosiphon Novae-Caledoniae Extract**
35. **Cladosiphon Okamuranus Extract**
36. **Codium Fragile Extract**
37. **Codium Tomentosum Extract**
38. **Codium Tomentosum Powder**
39. **Corallina Officinalis Extract**
40. **Corallina Officinalis Powder**

Algal Groups

Unknown

Blue Green

Brown

Red

Green

Euglenoid

Diatom

Haptophyte

41. Cyanidium Caldarium Extract
42. Cystoseira Amentacea/Caespitosa Branchycarpa Extract
43. Cystoseira Baccata Extract
44. Cystoseira Compressa Extract
45. Cystoseira Compressa Powder
46. Cystoseira Tamariscifolia Extract
47. Delesseria Sanguinea Extract
48. Dictyopteris Membranacea Extract
49. Dictyota Coriacea Extract
50. Digenea Simplex Extract
51. Dilsea Carnosa Extract
52. Dunaliella Bardawil Extract
53. Dunaliella Bardawil Powder
54. Dunaliella Salina Extract
55. Durvillea Antartica Extract bull kelp
56. Ecklonia Cava Extract
57. Ecklonia Kurome Extract
58. Ecklonia Kurome Powder
59. Ecklonia Laminaria Extract
60. Ecklonia Maxima Extract

Algal Groups
Unknown
Blue Green
Brown
Red
Green
Euglenoid
Diatom
Haptophyte

61. Ecklonia Maxima Powder
62. Ecklonia Radiata Extract
63. Eisenia Arborea Extract
64. Emiliania Huxleyi Extract (haptophyte)
65. Enteromorpha Compressa Extract
66. Enteromorpha Compressa Powder
67. Enteromorpha Flexuosa Extract
68. Euglena Gracilis Extract
69. Fucoxanthin
70. Fucus Serratus Extract
71. Fucus Vesiculosus Extract
72. Fucus Vesiculosus Powder
73. Furcellaria Lumbricalis Extract
74. Gelidium Amansii Extract
75. Gelidium Cartilagineum Extract
76. Gelidium Pulchrum Protein
77. Gelidium Sesquipedale Extract
78. Gellidiela Acerosa Extract
79. Gigartina Skottsbergii Extract
80. Gigartina Stellata Extract

Algal Groups
Unknown
Blue Green
Brown
Red
Green
Euglenoid
Diatom
Haptophyte

81. Gloiopeltis Aenax Powder
82. Gracilaria Verrucosa Extract
83. Gracilariopsis Chorda Extract
84. Grateloupia Livida Powder
85. Haematococcus Pluvialis Extract
86. Haematococcus Pluvialis Powder
87. Halimeda Opuntia Extract
88. Halopteris Scoparia Extract
89. Haslea Ostrearia Extract
90. Himanthalia Elongata Extract
91. Himanthalia Elongata Powder
92. Hizikia Fusiforme Extract
93. Hydrolyzed Algae Extract
94. Hydrolyzed Asparagopsis Armata Extract
95. Hydrolyzed Chlorella Vulgaris Extract
96. Hydrolyzed Chlorella Vulgaris Protein
97. Hydrolyzed Chondrus Crispus Extract
98. Hydrolyzed Corallina Officinalis Extract
99. Hydrolyzed Ecklonia Cava Extract
100. Hydrolyzed Enteromorpha Compressa

Algal Groups
Unknown
Blue Green
Brown
Red
Green
Euglenoid
Diatom
Haptophyte

101. Hydrolyzed Euglena Gracilis Extract
102. Hydrolyzed Fucus Vesiculosus Extract
103. Hydrolyzed Fucus Vesiculosus Protein
104. Hydrolyzed Porphyra Yezoensis
105. Hydrolyzed Rhodophycea Extract
106. Hypnea Musciformis Extract
107. Kappaphycus Alvarezii Extract
108. Kassou Genaric Japanese name for brown algae
109. Kousou
110. Kousou Ekisu brown algal extract
111. Laminaria Angustata Extract
112. Laminaria Cloustoni Extract
113. Laminaria Digitata Extract
114. Laminaria Hyperborea Extract
115. Laminaria Japonica Extract
116. Laminaria Longissima Extract
117. Laminaria Ochotensis Extract
118. Laminaria Ochroleuca Extract
119. Laminaria Saccharina Extract
120. Lessonia Nigrescens Extract

Algal Groups
Unknown
Blue Green
Brown
Red
Green
Euglenoid
Diatom
Haptophyte

121. Lessonia Nigrescens Powder
122. Lithothamnium Calcarum Extract
123. Lithothamnium Calcarum Powder
124. Lithothamnium Corallioides Powder
125. Macrocystis Pyrifera (Kelp)
126. Mesophyllum Lichenoides Extract
127. Monostroma Obscurum Extract
128. Nereocystis Leutkeana Extract
129. Odontella Aurita Oil
130. Palmaria Palmata Extract
131. Palmaria Palmata Powder
132. Pelvetia Canaliculata Extract
133. Pelvetia Siliquosa Extract
134. Phaeodactylum Tricornutum Extract
135. Phyllacantha Fibrosa Extract
136. Phymatolithon Calcareum Extract
137. Pikea Robusta Extract
138. Pleurochrysis Carterae Extract haptophyte
139. Polysiphonia Lanosa Extract
140. Porphyra Linearis Powder

Algal Groups
Unknown
Blue Green
Brown
Red
Green
Euglenoid
Diatom
Haptophyte

141. Porphyra Tenera Extract
142. Porphyra Umbilicalis Extract
143. Porphyra Umbilicalis Powder
144. Porphyra Yezoensis Extract
145. Porphyra Yezoensis Powder
146. Porphyridium Cruentum Extract
147. Porphyridium Purpureum Extract
148. Pyrocystis Noctiluca Extract dinoflagellate
149. Pytocystis Noctiluca Lysate
150. Ransou Ekisu blue green algae skin conditioner
151. Rhodymenia Palmata Extract
152. Rissoella Verruculosa Extract
153. Sahel Scenedesmus Extract
154. Sarcodiotheca Gaudichaudii Extract
155. Sargachromanol D
156. Sargachromanol E
157. Sargachromanol F
158. Sargassum Filipendula Extract
159. Sargassum Fulvellum Extract
160. Sargassum Fusiforme Extract

Algal Groups
Unknown
Blue Green
Brown
Red
Green
Euglenoid
Diatom
Haptophyte

161. Sargassum Horneri Extract
162. Sargassum Muticum Extract
163. Sargassum Vulgare Extract
164. Sphacelaria Scoparia Extract
165. Spirulina Maxima Powder
166. Spirulina Platensis Extract
167. Spirulina Platensis Powder
168. Spirulina Subsalsa Extract
169. Thalassiosira Pseudonana Extract
170. Ulva Lactuca Extract
171. Ulva Lactuca Powder
172. Ulva Pertusa Extract
173. Undaria Pinnatifida Extract

Algal Groups
Unknown
Blue Green
Brown
Red
Green
Euglenoid
Diatom
Haptophyte

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 3, 2020

SUBJECT: Corallina Officinalis Extract

Anonymous. 2014. Clinical safety evaluation repeated insult patch test (blush powder containing 2.0% Corallina Officinalis Extract).

[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

Sponsor

[redacted]

Sponsor Representative

[redacted]

Clinical Testing Facility

[redacted]

[redacted]

Date of Final Report

2-21-14

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted]
Laboratory Manager
Study Director

2/14/2014
Date

[redacted]
Scientific Director
Principal Investigator

2 11 14
Date

[redacted]
Board-Certified Dermatologist
Medical Investigator

2/14/2014
Date

[redacted]

QUALITY ASSURANCE STATEMENT

This study [redacted] was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in 21 CFR Part 50 (Protection of Human Subjects – Informed Consent) and the Standard Operating Procedures of [redacted]

For purposes of this clinical study:

_X_	Informed Consent was obtained.
____	Informed Consent was not obtained.
_X_	An IRB review was not required.
____	An IRB review was conducted and approval to conduct the proposed clinical research was granted.

To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the applicable study records and report. This report is considered a true and accurate reflection of the testing methods and source data.

[redacted]
Manager, Quality Assurance

21 Feb 2014
Date

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the irritation and/or sensitization potential of the test article after repeated application under occlusive patch test conditions to the skin of human subjects (non-exclusive panel).

2.0 SPONSOR

[redacted]

2.1 Sponsor Representative

[redacted]

3.0 CLINICAL TESTING FACILITY

The study was conducted by:

[redacted]

4.0 CLINICAL INVESTIGATORS

Study Director:
Principal Investigator:
Medical Investigator:
[redacted]

5.0 STUDY DATES

Study initiation: December 11, 2013
December 18, 2013 [redacted]

Final evaluation: January 31, 2014 [redacted]

[redacted]

6.0 ETHICS

6.1 Ethical Conduct of the Study

This study was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in Title 21 of the U.S. Code of Federal Regulations (CFR), the Declaration of Helsinki and/or [redacted] Standard Operating Procedures.

6.2 Subject Information and Consent

This study was conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed Consent was obtained from each subject in the study and documented in writing before participation in the study. A copy of the Informed Consent was provided to each subject.

7.0 TEST MATERIAL

The test article used in this study was provided by:

[redacted]

It was received on December 2, 2013 and identified as follows:

		Description
[redacted]	[redacted]	Mauve Powder*

*The test article was prepared with distilled water to form a paste prior to patch application.

8.0 TEST SUBJECTS

At least 100 male and female subjects ranging in age from 18 to 79 years were to be empanelled for this test.

The subjects chosen were to be dependable and able to read and understand instructions. The subjects were not to exhibit any physical or dermatologic condition that would have precluded application of the test article or determination of potential effects of the test article.

[redacted]

9.0 TEST PROCEDURE

The 9 Repeated Insult (occlusive) Patch Test (9-RIPT)[1] was conducted as follows:

9.1 Induction Phase

A sufficient amount of the test article (approximately 0.1 g – 0.15 g) was placed onto a Parke-Davis Readi-Bandage® occlusive patch (approximately 25 - 38 mg/cm^2 of test material) and applied to the back of each subject between the scapulae and waist, adjacent to the spinal mid-line. This procedure was performed by a trained technician/examiner and repeated every Monday, Wednesday and Friday until 9 applications of the test article had been made.

The subjects were instructed to remove the patch 24 hours after application. Twenty-four hour rest periods followed the Tuesday and Thursday removals and 48-hour rest periods followed each Saturday removal. Subjects returned to the Testing Facility and the site was scored by a trained examiner just prior to the next patch application.

If a subject developed a positive reaction of a level 2 erythema or greater during the Induction phase or if, at the discretion of the Study Director, 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.

9.2 Challenge Phase

After a rest period of approximately 2 weeks (no applications of the test article), the Challenge patch was applied to a previously unpatched (virgin) test site. Due to inclement weather (snow), the original Challenge date for Panel No. 13496 of January 14, 2014 was postponed a week till January 21, 2014. Because of a second snowstorm, the facility was closed on the day of the 24-hour evaluation (January 22, 2014 [redacted]. Subjects were evaluated at 48 hours (January 23, 2014) and 72 hours (January 24, 2014) for that panel. One subject on [redacted] did not complete the Challenge procedure until January 31, 2014. The site was scored 24 and 72 hours after application for the other panel. All subjects were instructed to report any delayed skin reactivity that occurred after the final Challenge patch reading. When warranted, selected test subjects were called back to the Clinic for additional examinations and scoring to determine possible increases or decreases in Challenge patch reactivity.

Dermal responses for both the Induction and Challenge phases of the study were scored according to the following 6-point scale:

0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

All other observed dermal sequelae (eg, edema, dryness, hypo- or hyperpigmentation) were appropriately recorded on the data sheet and described as mild, moderate or severe.

[1] Marzulli FN, Maibach HI. (1976) Contact allergy: predictive testing in man. *Contact Dermatitis*. 2, 1-17.

[redacted]

[redacted]

9.0 TEST PROCEDURE (CONT'D)

9.3 Data Interpretation

Edema, vesicles, papules and/or erythema that persist or increase in intensity either during the Induction and/or Challenge phase may be indicative of allergic contact dermatitis. Allergic responses normally do not resolve or improve markedly at 72-96 hours.

Exceptions to typical skin reactions may occur. These may include, but not be limited to, symptoms of allergic contact sensitivity early in the Induction period to one or more test products. When this occurs in one subject, such a reaction usually suggests either an idiosyncratic response or that the subject had a pre-exposure/sensitization to the test material or component(s) of the test material or a cross-reactivity with a similar product/component. Data for such reactions will be included in the study report but will not be included in the final study analysis/conclusion of sensitization.

10.0 RESULTS AND DISCUSSION

(See Table 1 for Individual Scores)

A total of 113 subjects (27 males and 86 females ranging in age from 18 to 79 years) were empanelled for the test procedure. One hundred two (102/113) subjects satisfactorily completed the test procedure on Test Article: [redacted] Eleven (11/113) subjects discontinued for personal reasons unrelated to the conduct of the study. Discontinued subject data are shown up to the point of discontinuation, but are not used in the Conclusions section of this final report.

Induction Phase Summary

Test Article	Induction Scores (Number of Responses)						Evidence of Irritation
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

Challenge Phase Summary

Test Article	Challenge Scores (Number of Responses)						Evidence of Sensitization
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

There was no skin reactivity observed at any time during the course of the study.

11.0 CONCLUSIONS

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in 102 subjects, Test Article: [redacted] was "Dermatologist-Tested" and was not associated with skin irritation or allergic contact dermatitis in human subjects.

[redacted]

TABLE 1

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

[redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	48hr	72hr
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0
25	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	Discontinued								
28	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

[redacted]

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

[redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	48hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	Discontinued				
34	0	0	0	0	0	0	0	0	0	0	0
35	0	Discontinued									
36	0	0	0	0	0	0	0	0	0	0	0
37	0	Discontinued									
38	0	0	0	0	Discontinued						
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	Discontinued									
45	0	0	0	0	0	0	0	0	0	0	0
46	Discontinued										
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	Discontinued										
50	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0

Scale: 0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

[redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	24hr	72hr
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	Discontinued							
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0
25	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
28	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

[redacted]

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

[redacted]

Subj.	Induction Evaluation Number									Challenge Virgin Site	
No.	1	2	3	4	5	6	7	8	9	24hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0
34	0	0	Discontinued								
35	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0
37	0	Discontinued									
38	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0

Scale: 0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 13, 2020

SUBJECT: Asparagopsis Armata Extract

Anonymous. 2020. Summary information Asparagopsis Armata Extract (aqueous extracts).

May 2020

Summary Information Asparagopsis Armata Extract (aqueous extracts)

Endpoint	Method Reference	Test System	GLP	Year of Test	Tested Product and Concentration	Results
Acute oral toxicity	3T3NRU	Balbc 3T3 cells	No	2017	100% Mixture containing Asparagopsis Armata Extract (1)	Estimated LD50 >2000 mg/kg EU Classification "No Category"
Gene mutation	OECD 471	MPF penta 2 Xenomtrix kit	No	2017	100% Mixture containing Asparagopsis Armata Extract (1)	No mutagenic activity under the conditions of the test
Skin irritation	OECD 439 reconstructed human epidermis test method	RHE Skin ethic	Yes	2017	100% Mixture containing Asparagopsis Armata Extract (1)	Non-irritant
Eye irritation	French government publication dataed 29/11/1996 Annex IV	HET CAM	Yes	2006	100% Mixture containing Asparagopsis Armata Extract (2)	Non-irritant
Acute toxicity	OECD 423 acute toxicity by oral route	Rat	Yes	2007	Asparagopsis Armata Extract (3) 2000 mg/kg	The oral LD50 of the test substance is greater than 2000 mg/kg

(1) 80% Asparagopsis Armata Extract (4% dry extract); 20% Methylpropanediol

(2) 98.6% Asparagopsis Armata Extract (4% dry extract); Butylene Glycol 1%; Chlorphenesin 0.2%; Parabens/Phenoxyethanol 0.2%

(3) Dry extract Asparagopsis Armata Extract 100%

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 18, 2020

SUBJECT: Betaphycus Gelatinum Extract

Anonymous. 2020. Betaphycus Gelatinum Extract Specifications.

Anonymous. 2013. Repeated Insult Patch Test (7% w/w% -diluted Betaphycus Gelatinum Extract [extract described in the above specifications]).

SPECIFICATION SHEET

Product name	

1. General Information

is obtained by extracting from the algae of Betaphycus with water.

2. Specifications

Subjects	Standard
Description	s a light yellow to yellow liquid. It has a faint characteristic odor.
Identification	
（1）Amino acid	Positive
（2）Polysaccharide	Positive
pH	6.0 - 8.5
Purity	
（1）Heavy metals	Not more than 20 ppm.
（2）Arsenic	Not more than 2 ppm.
Residue on evaporation	1.0 - 2.0%
Residue on ignition	Not more than 1.0%
Total aerobic microbial count	Not more than 300 CFU/g
Total combined yeasts/moulds count	Not more than 100 CFU/g

3. Storage and Shelf Life Instructions

Store in a dark place at 15-25℃. The quality of the unopened product is guaranteed for 18 months from the Manufacturing date.

Final Report

Repeated Insult Patch Test

CLIENT:

ATTENTION:

TEST MATERIAL: **7 w/w%-diluted Betaphycus Gelatinum Extract**

STUDY NUMBER:

REPORT DATE: **August 22, 2013**

Good Clinical Practice
Quality Assurance Audit Statement

Start Date: July 8, 2013

Completion Date: August 16, 2013

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

Aug 22, 2013
Date

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

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

INVESTIGATIVE SITE

TEST MATERIAL

The following test material was provided by and was received by on June 19, 2013:

Test Material Label	Test Condition	Patch Type
7 w/w%-diluted Betaphycus Gelatinum Extract	Neat *	Semi-occlusive**

*Sample was put in a freezer at and defrosted in the refrigerator the night before patching.

The test material was coded with the following identification number:

STUDY DATES

This study was initiated on July 8, 2013 and was completed on August 16, 2013.

** Semi-occlusive Strip (Strukmyer LLC, Mesquite,TX or equivalent)

PANEL SELECTION

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

Inclusion Criteria

a. Male and female subjects between the ages of 18 and 70 years;

b. Subjects who do not exhibit any skin diseases which might be confused with a skin reaction from the test material;

c. Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;

d. Subjects who agree to refrain from getting patches wet during the course of the study;

e. Subjects willing to sign an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

f. Subjects who have completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

g. Subjects in generally good health who have a current Subject Profile/Medical History on file;

h. Subjects who are dependable and able to follow directions as outlined in the protocol.

Exclusion Criteria

a. Female subjects who are pregnant or nursing;

b. Subjects who report allergies to cosmetics, toiletries or personal care products;

c. Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

d. Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

TEST METHOD

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

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

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

The sites were graded according to the following scoring system:

Dermal Scoring Scale

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

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

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

RESULTS

This study was initiated with 57 subjects. One subjects discontinued study participation for reasons unrelated to the test material. A total of 56 subjects completed the study.

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

CONCLUSION

Based on the test population of 56 subjects and under the conditions of this study, the test material identified as 7 w/w%-diluted Betaphycus Gelatinum Extract did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

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

TABLE I

Summary of Dermal Scores

Test Material:	7 w/w%-diluted Betaphycus Gelatinum Extract

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
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	Discontinued											
13R	0	0	0	0	0	0	0	0	0	0	0	X*
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

R = Replacement Subject
X=Subject Absent
* No reaction was observed at the 96 hour evaluation

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	7 w/w%-diluted Betaphycus Gelatinum Extract

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	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

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	7 w/w%-diluted Betaphycus Gelatinum Extract

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
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

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1	DP	14491	37	F
2	JB	14759	62	F
3	MR	31757	54	F
4	SK	31766	64	F
5	RC	31731	48	F
6	AF	29064	47	F
7	WG	18828	66	F
8	JK	12839	65	M
9	SD	22621	42	F
10	FP	24056	58	F
11	BH	30605	51	F
12	DU	31440	18	F
13	LD	25831	41	F
13R	AA	31755	33	F
14	VM	25890	66	F
15	KL	25144	56	F
16	KT	31548	62	F
17	JA	31556	44	M
18	EB	27827	54	F
19	PW	30026	43	F
20	EH	27444	26	F
21	JD	01639	59	F
22	MS	28605	70	F
23	HT	23880	60	M
24	MW	11203	41	F
25	EJ	17508	64	F
26	ZA	15076	48	F
27	SL	18114	36	F
28	PL	25562	57	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
29	BS	24378	19	F
30	MS	18864	38	F
31	SB	29429	41	F
32	RB	30093	67	F
33	JD	24855	53	F
34	JK	21172	29	F
35	JH	31428	58	M
36	WK	31767	64	M
37	PZ	24915	60	F
38	CH	18972	62	F
39	MI	14669	69	F
40	CL	14668	69	F
41	TG	08029	50	F
42	SH	29051	46	F
43	MV	28318	43	F
44	AG	30249	68	F
45	JA	25430	27	F
46	VM	28951	65	F
47	KE	31704	53	F
48	KP	20259	68	F
49	AK	06659	56	F
50	SD	24185	55	F
51	LC	30993	66	F
52	ML	27186	39	F
53	SJ	29407	40	F
54	MV	25235	66	F
55	SH	30208	57	F
56	LF	23986	50	F

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 18, 2020

SUBJECT: Ceramium Kondoi Extract

Anonymous. 2020. Specifications of a mixture containing Cermaium Kondoi Extract.

SPECIFICATION SHEET

Product name	

1. General Information

) is obtained by extracting from the algae of *Saccharina angustata(Laminaria angustata)* and *Ceramium kondoi* with water.

2. Specifications

Subjects	Standard
Description	is a colorless to yellow liquid. It has a faint characteristic odor.
Identification	
（1）Alginate	Positive
（2）Carrageenan	Positive
pH	5.0 - 7.0
Purity	
（1）Heavy metals	Not more than 20ppm.
（2）Arsenic	Not more than 5ppm.
Residue on evaporation	Not mare than 1.5%
Residue on ignition	Not more than 0.5%
Total aerobic microbial count	Not more than 300 CFU/g
Total combined yeasts/moulds count	Not more than 100 CFU/g

3. Storage and Shelf Life Instructions

Store in a dark place at 15-25℃.
The quality of the unopened product is guaranteed for 18 months from the Manufacturing date.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 19, 2020

SUBJECT: Kappaphycus Alvarezii Extract

Anonymous. 2020. Composition breakdown trade name mixture containing Kappaphycus Alvarezii Extract.

Thomas J. Stephens & Associates, Inc. 2011. Human repeat insult patch test of a trade name mixture containing Kappaphycus Alvarezii Extract.

[redacted]

November 10, 2020

Composition Breakdown

INCI Name	CAS No.	Concentration
KAPPAPHYCUS ALVAREZII EXTRACT	1220882-73-4	0.8%
WATER, AQUA	7732-18-5	79.2%
1,3-BUTYLENE GLYCOL	107-88-0	20.0%

[redacted]

SUMMARY

This modified human repeat insult patch test was conducted for to assess the potential of the Sponsor's test materials to cause irritant and/or allergic contact dermatitis. Fifty- three Japanese subjects completed the study. The Sponsor submitted the following test material to be tested:

- Mixture containing 0.8% Kappaphycus Alvarezii Extract (KA Extract Mix)

For the induction period, subjects were occlusively patched with 50 microliters (µl) of the test material nine times at approximately 48 to 72-hour intervals. An undosed occlusive patch served as the negative control. Subjects removed the patches approximately 48 hours after application, or two hours prior to a study visit, and sites were graded approximately 48 to 72 hours after each application. Twelve days after application of the last induction patches, challenge patches were applied to original and alternate (naive) sites (test materials only; the control was not challenged). Subjects removed the patches approximately 48 hours after application (approximately two hours prior to grading), and sites were graded approximately 48 and 96 hours post-application.

Primary Irritation (Human Patch Test)
The primary irritation scores classified the Sponsor's test material, , KA Extract Mix , and the negative control (blank patch) as "mild material."

Based on raw irritation scores, the level of irritation for , KA Extract Mix is not significantly different (p:c:;0.05) from the level of irritation for the negative control.

Cumulative Irritation Portion
Under the exposure conditions of this test, standardized cumulative irritation scores (raw scores are standardized for 50 subjects and nine visits) classified the Sponsor's test material KA Extract Mix; and control as 'Mild material - no experimental irritation·.

Predictive Allergy Portion
Under the conditions of this test, the test material did not induce contact sensitization (allergic contact dermatitis) in any subject completing the study.

STORAGE, HANDLING, AND DOCUMENTATION OF TEST MATERIALS

The receipt of study material by Thomas J. Stephens & Associates, Inc. was documented in a study material log, which serves as a permanent record of the receipt, storage, return, and disposition of all study materials. All study materials are kept in a locked product-storage room accessible to clinical staff members only. At the Sponsor's request the study materials will be destroyed according to Stephens' Standard Operating Procedures (SOP).

TEST MATERIALS DESCRIPTIONS

Test Material Identification Number (TMIN):	
Sponsor Test Material Identification:	KA Extract Mix
Physical Description:	Light Yellow, transparent liquid
Concentration Tested:	Neat
Patch Type:	Occlusive

INFORMED CONSENT

Written informed consent conforming to 21 Code of Federal Regulations 50.25 was obtained from each subject prior to enrollment in the study. The original signed Informed Consent Agreement for each subject participating in the study will be retained in the study file. Each subject received a signed copy of the agreement. A sample of the Informed Consent Form is included in Appendix III.

ATTRITION

Fifty-four subjects enrolled to participate in this study. Fifty-three subjects completed the study. One subject discontinued participation for the following reason:

Discontinued Subject Summary

- Subject requested withdrawal Subjects 017

A copy of the Attrition Form is included in Appendix IV.

ADVERSE EVENTS

No adverse events were reported by the subjects or observed during the course of the study.

SUBJECT DEMOGRAPHICS

Table 1 contains a summary of the age demographic information for the fifty-three Japanese female subjects completing the study. Demographic information was obtained from each subject's Eligibility and Health Questionnaire.

TABLE 1: SUMMARY OF DEMOGRAPHIC INFORMATION

Demographic Summary (n=53)		
Age (Years)	Mean Age ± Standard Deviation	37.51±6.13
	Minimum Aqe	25.74
	Maximum Age	54.49

A copy of the Demographics Form is included in Appendix V.

PROCEDURES AND METHODS

For the induction period, subjects were occlusively patched with 50 microliters (µl) of the test material nine times at approximately 48 to 72-hour intervals. An undosed occlusive patch served as the negative control.

At Visit 1, prospective subjects completed an Eligibility and Health Questionnaire and read and signed an Informed Consent Agreement, a HIPAA Agreement, and a Confidentiality/Photography Release Agreement. Qualified subjects were prepared for patch application by having the test sites wiped with alcohol and air-dried. During the induction phase of the study, subjects were patched with the test material and control nine times at approximately 48 to 72-hour intervals. Subjects were instructed to remove and discard the induction patches 48 hours after application, or two hours prior to a study visit. Reactions at the application sites were graded approximately 48 to 72 hours after each application by a trained clinician.

The following scales and symbols were used to grade the test sites during the induction phase:

Induction Grading Scale

Erythema and Elevated Responses

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Effects on Superficial Layers of the Skin

A	0	Slight glazed appearance
B	1	Marked glazing
C	2	Glazing with peeling and cracking
D	3	Glazing with fissures
E	3	Film of dried serous exudate covering all or portion of the patch site
F	3	Small petechial erosions and/or scabs

Other Responses/Recording Designations

W	Weeping - evidence of release of fluid from a vesicular or bullous reaction
T	Marked reaction to adhesive (patch relocated)
X	Succeeding patch not applied and succeeding grade is for residual reaction
R	Subject did not remove the patch at the assigned time
L-1	Subject report of lost patch (came off) during first 12 hours of exposure
L-2	Subject report of lost patch (came off) between 12 and 48 hours of exposure
(-)	Subject absent

PROCEDURES AND METHODS (continued)

Letter grade numerical equivalents (i.e., A = O; B = 1; C = 2; and D, E, and F = 3) were added to the numerical scores (e.g., 2C = 2 + 2 = 4). Any single or combined score of 3 or higher was considered to be a 3 for the remainder of the test, and applications for that test site were relocated to an alternate site.

Twelve days after application of the last induction patches, challenge patches (test material only, the control was not challenged) were applied to original and to alternate (narve) sites. Subjects were instructed to remove and discard the challenge patches 48 hours after application, or two hours prior to the 48-hour challenge visit. Reactions at the original and alternate (naive) sites were graded approximately 48 and 96 hours post-application by a trained clinician.

The following scoring scale and symbols were used to grade the test sites during the challenge phase:

Challenge Grading Scale

Erythema Scale: This scale was used only for grading degree of erythema (redness).

0	No visible erythema
1	Mild erythema (faint pink to definite pink)
2	Moderate erythema (definite redness)
3	Severe erythema (very intense redness)

Designation for Elevated Responses: Edema, papules, vesicles, and bullae, if present, were graded as independent responses.

E	Edema - definite swelling
P	Papules - small, red, solid elevations; surface of reaction has granular feeling
V	Vesicles - small, circumscribed elevations having translucent surfaces so that fluid is visible (blister-like); vesicles are no larger than 0.5 cm in diameter
B	Bullae - vesicles with a diameter >0.5 cm; vesicles may coalesce to form one or a few large blisters that fill the patch site

Other Response Characteristics

S	Spreading - evidence of the reaction beyond the chamber area (does not include obvious signs of leakage of test material away from chamber)
W	Weeping - evidence of release of fluid from a vesicular or bullous reaction

Other Recording Designations

T	Marked reaction to adhesive
R	Subject did not remove the patch at the assigned time
L-1	Subject report of lost patch (came off) during first 12 hours of exposure
L-2	Subject report of lost patch (came off) between 12 and 48 hours of exposure
(-)	Subject absent
X	Patch not applied due to residual reaction from Induction

BIOSTATISTICS AND DATA MANAGEMENT

Patch test sites are assigned a numerical score according to the scale on page 6. As needed, the numerical scores are also combined with a letter score as previously described. Frequency tables of the converted numerical + letter scores were generated for each site. Challenge scores are also included in the frequency tables.

To obtain classifications of the test materials, subjects' induction scores are totaled for each test site. For sites for which the patch has been moved, only the score of 3 for the original site is included in the calculation. The standardized interpretation system established by Berger and Bowman[1] has been adjusted proportionally for nine induction visits and for base n=50. Scores appearing in the table below reflect these adjustments.

BIOSTATISTICS AND DATA MANAGEMENT (continued)

The following classification system is used for interpretation of primary irritation results (Categories are based on ranges of the maximum possible score of 3 for two visits and for 50 subjects.)

Primary Irritation Classification System	
Score	Indications from Test
0 to 23.57	Mild material
>23.57 to 95.0	Probably mild
>95.0 to 213.57	Possibly mild
>213.57 to 276.43	Cumulative irritant
>276.43 to 300	Primary irritant

The following classification system is used for interpretation of cumulative irritation results (Categories are based on ranges of the maximum possible score of 3 for nine visits and for 50 subjects.)

Cumulative Irritation Classification System		
Score	Indications from Test	Description of Observed Responses
0 to 106.07	Mild material- no experimental irritation	Essentially no evidence of cumulative irritation under conditions of test (i.e., continuous at concentration specified)
>106.07 to 427.5	Probably mild in normal use	Evidence of slight potential for very mild cumulative irritation under conditions of test
>427.5 to 961.07	Possibly mild in normal use	Evidence of moderate potential for mild cumulative irritation under conditions of test
>961.07 to 1243.93	Experimental cumulative irritant	Evidence of strong potential for mild-to-moderate cumulative irritation under conditions of test
>1243.93 to 1350	Experimental primary irritant	Evidence of potential for primary irritation under conditions of test

Mean cumulative irritation scores were compared among the sites using analysis of variance (ANOVA) with pairwise comparisons (Fisher's LSD). All differences are considered significant at the p :c;; 0.05 level.

Data Interpretation

Persisting reactions with edema, vesicles, papules, or spreading that develop in the induction phase and/or at both challenge sites may be indicative of allergic contact dermatitis. Allergic responses normally do not improve markedly at 72 to 96 hours. Edema or infiltration which persists or increases in intensity is indicative of allergic contact dermatitis. Other indicators are "flares" at former application sites or responses which develop between induction and challenge.

Exceptions to the typical patterns are known to occur. For example, a subject having a pre-test sensitivity will begin responding relatively early in the induction series. Such a response indicates exposure to a component in the test material and development of at least some degree of patch reactivity prior to test exposure. Data for such subjects is not included in the final statistical analysis.

MAINTENANCE OF RECORDS

All original records (including the study protocol, clinical grading records, medical histories, informed consent agreements, attrition form, and any other records or forms used in this study) and a copy of the final report will be retained on file in the Thomas J. Stephens & Associates, Inc. archives for two years from the date of study completion. When the archive time has expired, the study files will either be sent to the Sponsor at the Sponsor's expense or destroyed.

RESULTS

The following tables present the primary and cumulative score frequencies for the test material and control at each grading time point during the induction and challenge phases. (Please note: G=Grading, O=Original site, A=Alternate site, 48=48-hour observation, and 96=96-hour observation.)

TABLE 5: SCORE FREQUENCIES FOR SITE 4: KA Extract Mix

	Induction Phase									Challenge Phase			
	G1	G2	G3	G4	G5	G6	G7	G8	G9	480	960	96A	
0	53	50	50	47	45	52	49	49	51	49	51	47	50
1	0	2	2	2	2	1	3	3	1	3	0	4	2
1E	0	0	0	0	0	0	0	0	0	0	0	2	0
1EP	0	0	0	0	0	0	0	0	0	1	0	0	0
1P	0	0	0	0	0	0	0	0	0	0	1	0	1
2	0	1	1	4	6	0	0	0	0	0	0	0	0
2§5-	0	0	0	0	0	0	0	0	0	0	1	0	0
3	0	0	0	0	0	0	1	1	1	0	0	0	0
Total	53	53	53	53	53	53	53	53	53	53	53	53	53

RESULTS (continued)

TABLE 6: SCORE FREQUENCIES FOR SITE 16: NEGATIVE CONTROL (UNDOSED PATCH)

	Induction Phase								
	G1	G2	G3	G4	G5	G6	G7	GS	G9
0	53	53	53	53	53	53	53	53	53
Total	53	53	53	53	53	53	53	53	53

Table 7 presents the primary irritation (Human Patch Test) potential of the test material and negative control during the induction phase from least to greatest level of irritation, according to standardized cumulative Berger and Bowman scores, categories, and classifications. Raw scores are standardized for 50 subjects and two visits.

TABLE 7: STANDARDIZED PRIMARY IRRITATION SCORES, CATEGORIES, AND CLASSIFICATIONS

Test Material	Standardized Cumulative Score Based on n=50 and Two Visits	Category	Classification
Site 16: Negative control (Undosed Patch)	0.0	I	Mild material
Site 4: KA Extract Mix	3.8	I	Mild material

Based on raw primary irritation scores, the level of irritation for KA Extract Mix · is not significantly different (p:<;0.05) from the level of irritation for the negative control..

Table 8 ranks the cumulative irritation potential of the test material and negative control during the induction phase, from least to greatest level of irritation, according to standardized cumulative Berger and Bowman scores and classifications. Raw scores are standardized for 50 subjects and nine induction visits.

TABLE 8: STANDARDIZED CUMULATIVE IRRITATION, CATEGORIES, AND CLASSIFICATIONS

Test Material	Standardized Cumulative Score Based on n=50	Category	Classification
Site 16: Negative control (Undosed Patch)	0.0	I	Mild material - no experimental irritation
Site 4: KA Extract Mix	46.2	I	Mild material - no experimental irritation

RESULTS (continued)

Table 9 lists the induction and challenge scores observed for subject 049 suggestive of delayed contact sensitization (allergic contact dermatitis). (Note: G=Grading, O=Original site, A=Alternative site, 48=48 hour observation and 96=96 hour observation).

TABLE 9: INDUCTION AND CHALLENGE SCORES FOR SUBJECT 049

	Induction Phase								Challenge Phase			
	G1	G2	G3	G4	G5	G6	G7	GS	G9	8 0	96 0	48 A | 96 A
KA Extract Mix	0	1	0A	0A	OB	0A	1	1	1	1	1P	1E | 1P

Per the Sponsor's request, subject 049 participated in a rechallenge of test.materials: ,
j< KA Extract Mix. Table 10 presents the results of the rechallenge observations. (Note: G=l:irading, O=Original site, A=Alternative site, 48=48 hour observation and 96=96 hour observation). Copies of the rechallenge documents are included in Appendix VIII

TABLE 10: RECHALLENGE SCORES FOR SUBJECT 049

Subject	Test Material	Rechallenge Test			
		48 0	96 0	48A	96A
049	KA Extract Mix	1P	1	1	0

DISCUSSION AND CONCLUSIONS

Primary Irritation (Human Patch Test)

The primary irritation scores classified the Sponsor's test material KA Extract Mix and the negative control (blank patch) as "mild material."

Cumulative Irritation Portion

The cumulative irritation scores classified the Sponsor's test materials KA Extract Mix and the negative control (blank patch) as "mild material-no experimental 1rntat1on."

Predictive Allergy Portion

The reactions obtained from the rechallenge test did not confirm allergy. Under the conditions of this test, the test materials did not induce contact sensitization (allergic contact dermatitis) in any subject completing the study.

REFERENCES

[1] R.S. Berger and J. P. Bowman, A reappraisal of the 21-day cumulative irritation test in man, *J. Toxicol.- Cut. & Ocular Toxico!.* 1(2): 109-115, 1982.

STATEMENT OF QUALITY ASSURANCE

All data and supporting documentation for this study have been audited by the Thomas J. Stephens & Associates, Inc. Quality Assurance Department and found to be accurate, complete, and in compliance with the requirements of the protocol and Stephens & Associates' Standard Operating Procedures. This report has been reviewed and accurately reflects all aspects of the conduct of the study.

All clinical research studies that are performed by Thomas J. Stephens & Associates, Inc. are in accordance with federal regulations and Good Clinical Practice guidelines.

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Monae Miller, MHA, CCRC
Quality Assurance Manager

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Date

REPORT APPROVAL

Report approved by:

THOMAS J. STEPHENS & ASSOCIATES, INC.

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Ronald L. Rizer, Ph.D. Date
Study Investigator

Shoichiro Yano I - 21 --t J

Shoichiro Yano, M.D. Date
Study Physician/Sub-Investigator

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 20, 2020

SUBJECT: Corallina Officinalis Extract, Delesseria Sanguinea Extract and Furcellaria Lumbricalis Extract

Anonymous. 2020. Summary Information Corallina Officinalis Extract.

Anonymous. 2020. Summary Information Delesseria Sanguinea Extract.

Anonymous. 2020. Summary Information Furcellaria Lumbricalis Extract.

November 2020

Summary Information Corallina Officinalis Extract

Ingredient: Water and Corallina Officinalis Extract

Method of manufacture: Extraction with water

Concentration of Algae in the Mixture: 0.2-4%

Composition information:	Vitamins such as vitamin C (140 µg/100 mL), vitamin B1 (35 µg/100 mL), vitamin B2 (75 µg/100 mL), vitamin B3 (386 µg/100 mL), vitamin B6 (26 µg/100 mL) and vitamin PP (2,61 µg/100 mL) are found in this product. Minerals such as chlorides (2500 mg/l), total nitrogen (kjeldahl, 431 mg/l), calcium (50-250 mg/l), magnesium (50-250mg/l), phosphorus (17mg/l), zinc (6.2 mg/l), iron (2.1mg/l) and potassium (1.1mg/l).
Iodine:	<9 mg/kg (alkaline mineralisation and potentiometric method)
Oral toxicity data:	Evaluation of acute toxicity by oral route in rat, Results obtained under experimental conditions enabled to conclude that the product ingested directly by oral route, is upper to 5g/kg. Conditions of test : 10 rats, product applied at 100%
Ocular Irritation data:	Evaluation of the primary ocular tolerance on the rabbit, Under experimental conditions retained the product was found to be slightly irritant. Conditions of test : 3 rabbits, method describe on French J.O. dated 9th july 1992, product applied at 100%.
Dermal toxicity data:	Evaluation of the micro circulation effect, Because of the results obtained under these experimental conditions, the product applied 27 consecutive days over 30 volunteers was found to be very well tolerated, product applied at 5%.
Dermal irritation data:	Evaluation of the primary cutaneous tolerance on the rabbit, Under experimental conditions retained the product was found to be non irritant. Conditions of test: 3 rabbits, method describe on French J.O. dated 21th february 1982, product applied at 100%.
Other relevant studies:	MTT Cytotoxicity evaluation on normal human dermal fibroblasts (NHDF), in vitro study, Concentration tested: 10 % maximum. In conclusion, under the experimental conditions selected, the product does not show cytotoxic effect for concentrations lower that 10%.

Ingredient:	Water and Corallina Officinalis Extract
Method of manufacture:	Extraction with water
Concentration of algae in the mixture:	0.2-4%
Composition information:	Minerals such as calcium (50-120 mg/L)
Genotoxicity data:	Evaluation of the mutagenicity with bacterial reverse mutation method, The results obtained in the reserved experimental conditions allowed to conclude that the product is non mutagenic, non pro-mutagenic. Conditions of test: Ames test according to the OECD 471, on 4 strains of *Salmonella typhimurium* and one strain of *Escherichia coli,* in the presence and in the absence of an exogenous metabolic activation system.
Phototoxicity data:	Evaluation of the phototoxicity of the product with 3T3NRU method, The results obtained in the reserved experimental conditions allowed to conclude that the product is non phototoxic. Conditions of test : according to the OECD 432, in vitro test
Other relevant studies:	MTT Cytotoxicity evaluation on normal human dermal fibroblasts (NHDF), in vitro study, Concentration test: 10 % maximum. In conclusion, under the experimental conditions selected, the product does not show cytotoxic effect for concentrations lower that 10%.

Ingredient:	Sea Water (and) Corallina officinalis extract (and) Propylene glycol (and) calcium chloride
Method of manufacture:	Extraction with sea water

Concentration of algae in the mixture: 0.2-4%

Iodine: <1 mg/kg (colorimetry method)

Ocular irritation data:	Acute ocular tolerance study. The results obtained under the experimental conditions used allow the conclusion that the product is slightly irritant. Test conditions: predisafe assay
Dermal toxicity:	Study of acute skin tolerance in vitro. The results obtained under the experimental conditions used allow the conclusion that the product is non-irritant or very slightly irritant. Test conditions: reconstructed skinethic epidermis models. Concentration test: 100 %.

Ingredient: Sea Water (and) Corallina officinalis extract (and) calcium carbonate (and) calcium chloride

Method of manufacture: Extraction with sea water

Concentration of Algae in the Mixture: 0.2-4%

Composition information: Magnesium analysis: 10-25 g/L

Dermal sensitization: Evaluation of the sensitizing potential with Marzulli-Maibach method. This study was realized on 103 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non irritant, non sensitizing. Concentration test : 100 %. Kinetics : induction : 3 weeks/ Rest : 2 weeks/ Challenge : 1 week

Genotoxicity: Evaluation of the mutagenicity with bacterial reverse mutation method. The results obtained in the reserved experimental conditions allowed to conclude that the product is non mutagenic, non pro-mutagenic. Conditions of test : Ames test according to the OECD 471, on 5 strains of *Salmonella typhimurium*, in the presence and in the absence of an exogenous metabolic activation system.

Phototoxicity data: Evaluation of the phototoxicity of the product with 3T3NRU method, The results obtained in the reserved experimental conditions allowed to conclude that the product is non phototoxic. Conditions of test: according to the OECD 432, in vitro test.

November 2020

Summary Information Delesseria Sanguinea Extract

Ingredient: Water (and) Dipropylene glycol (and) Delesseria Sanguinea Extract

Method of manufacture: Extraction with water

Concentration of Algae in the Mixture: 0.2-4%

Composition information: The chemical composition of the algae is characterized by: 2 non-halogenated phenolic compounds of original structure: cyclohexadienone and delesserin (no known equivalent in other marine organisms). the combination of sodium mannoglycerate + trehalose, the absence of floriside, choline sulfate a fraction of free amino acids with, in particular, taurine and proline (78.2%) non-gelling sulfated galactoxylan-type matrix polysaccharides

The sterolic composition of the algae is characterized by: sterols in C27 (cholesterol, 22-dehydrocholésterol, 7-dehydrocholésterol) and in less quantity of sterols in C28 and C29. There is the presence of a C26 sterol (nor-24-cholestadiene-5,22-ol-3B).

Iodine: <9 mg/kg (alkaline mineralisation and potentiometric method)

Impurities: arsenic (0.064 ppm); chromium (0.168 ppm); no antimony, nickel, cobalt, silver, cadmium, antimony, lead, mercury detected / method : ICP MS

Oral toxicity: Evaluation of acute toxicity by oral route in rat, Results obtained under experimental conditions enabled to conclude that the product had an innocuity by oral administration upper than 2 ml/kg.. Conditions of test: 10 rats, product applied at 100%, guideline EEC 84/449 L251 25/04/84

Ocular irritation: Evaluation of the primary ocular tolerance on the rabbit, Under experimental conditions retained the product was found to be slightly irritant. Conditions of test: 3 rabbits.

Dermal irritation: Evaluation of the primary cutaneous tolerance on the rabbit, the product was found to be non irritant. Conditions of test: 3 rabbits, method described on French J.O. dated 21th

Ingredient: Water (and) Dipropylene glycol (and) Delesseria Sanguinea Extract

Method of manufacture: Extraction with water and dipropylene glycol

Concentration of Algae in the Mixture: 0.2-4%

Ocular irritation: Evaluation of ocular tolerance, the results obtained under the experimental conditions used allow the conclusion that the product have negligible cytotoxicity. Test conditions: method registered in the JORF of 27/12/1999). NNR (Neutral Red Release) method Concentration test : 100 %

Dermal toxicity: 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 12 volunteers, was found to be non irritating. Concentration test : 100 %.

Dermal sensitization: Assessment of the sensitizing potential after repeated epicutaneous applications on 104 volunteers. The results obtained in the experimental conditions retained permitted to conclude that the product was found to be non irritating and non sensitizing. Concentration test : 100 % with Marzulli-Maibach method.

November 2020

Summary Information Furcellaria Lumbricalis Extract

Ingredient: Water (and) Furcellaria Lumbricalis Extract

Method of manufacture: Extraction with water

Concentration of Algae in the Mixture: 0.2-4%

Dermal toxicity: Study of acute skin tolerance on human subject: 48 hours single patch-test: Results obtained under experimental conditions showed that the product, when applied pure under an occlusive dressing for 48 hours, on the skin of 10 volunteers, was found to be non irritant.

Dermal sensitization: Evaluation of allergic potential by the repeated patch methods on 50 adults 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 contact allergy. Concentration test : 100 % with Marzulli-Maibach method.

Ingredient: Water (and) Furcellaria Lumbricalis Extract (and) Sea Salt

Method of manufacture: Extraction with water and partial depolymerization with supercritical CO_2

Concentration of Algae in the Mixture: 0.2-4%

Composition information: Composition: 80% of sugar Tracer: total galactose (1.6 – 2.4 g/l)

Iodine: <1 mg/kg (method: ICP MS) standard NF EN 15111

Impurities: Arsenic (As), Cadmium (Cd), Mercury (Hg) and Lead (Pb) contents are below the limit of quantification of 0.025 mg/kg; Nickel (Ni), Chromium (Cr), Cobalt (Co), Silver (Ag) and Antimony (Sb) contents are below the limit of quantification of 0.125 mg/kg. method: ICP MS

Ocular irritation: Evaluation of the ocular irritation by cytotoxicity investigating after spreading on agarose gel. The results obtained in the reserved experimental conditions allowed to conclude that the cytotoxicity is low. Reference documents for method : Official Journal of the French Republic No. 302 of December 30, 1999: Decree of 27 December 1999 on methods of analysis necessary for checking composition of cosmetic products – Appendix V pages 19817-19818: Official Method of assessing the potential irritancy by determination of the cytotoxicity after diffusion in agarose gel. Concentration test: 100 %

Dermal toxicity: Evaluation of the cutaneous compatibility with occlusiv 48 hours patch test method - applied pure. This study was realized on 11 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non irritating.

Dermal sensitization: Evaluation of the sensitizing potential with Marzulli-Maibach method - applied pure. This study was realized on 105 volunteers. The results obtained in the reserved experimental conditions allowed to conclude that the product is non irritant and non sensitizing. Concentration test: 100 %.