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

Status:	Draft Final Report for Panel Review
Release Date:	August 20, 2021
Panel Meeting Date:	September 13 - 14, 2021

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: August 20, 2021

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

Enclosed is the Draft Final Report of the Safety Assessment of Red Algae-Derived Ingredients as Used in Cosmetics (*redalg092021rep*). At the March 2021 meeting, the Panel issued a Tentative Report for public comment, with the conclusion that 11 of the 60 ingredients are safe as used in cosmetics, in the present practices of use. Data were insufficient to make a determination of safety of the remaining 49 ingredients. Insufficiencies include systemic toxicity data (via use in food, GRAS status, or oral toxicity) and/or sensitization data.

Since the March 2021 meeting, unpublished data on the sensitization potential of a moisturizer formulation containing 0.000545% Porphyridium Cruentum Extract were received (*redalg092021data1*). The HRIPT was performed on 107 subjects, and the test substance was considered to be non-irritating and non-sensitizing. Although sensitization data are now available, GRAS status/food use/systemic toxicity data are still needed for this ingredient to determine safety. In addition, it has been reported that *Corallina officinalis* can be used in foods as an emulsifying agent. With the addition of this new information, along with existing sensitization data on Corallina Officinalis Extract, the Panel should evaluate whether these data are sufficient to determine safety for Corallina Officinalis Extract, Corallina Officinalis Powder, Corallina Officinalis Thallus Extract, Hydrolyzed Corallina Officinalis, and Hydrolyzed Corallina Officinalis Extract.

Comments on the Tentative Report were received and addressed (*redalg092021pcpc*). Also included in this package for your review are the report history (*redalg092021hist*), flow chart (*redalg092021flow*), minutes (*redalg092021min*), literature search strategy (*redalg092021strat*), and updated data profile (*redalg092021prof*). In addition, a data supplement has been provided presenting which ingredients have sufficient data, and those ingredients that are lacking GRAS status/food use/systemic toxicity and/or sensitization data. This data supplement can be found in the packet as *redalg092021data2*.

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

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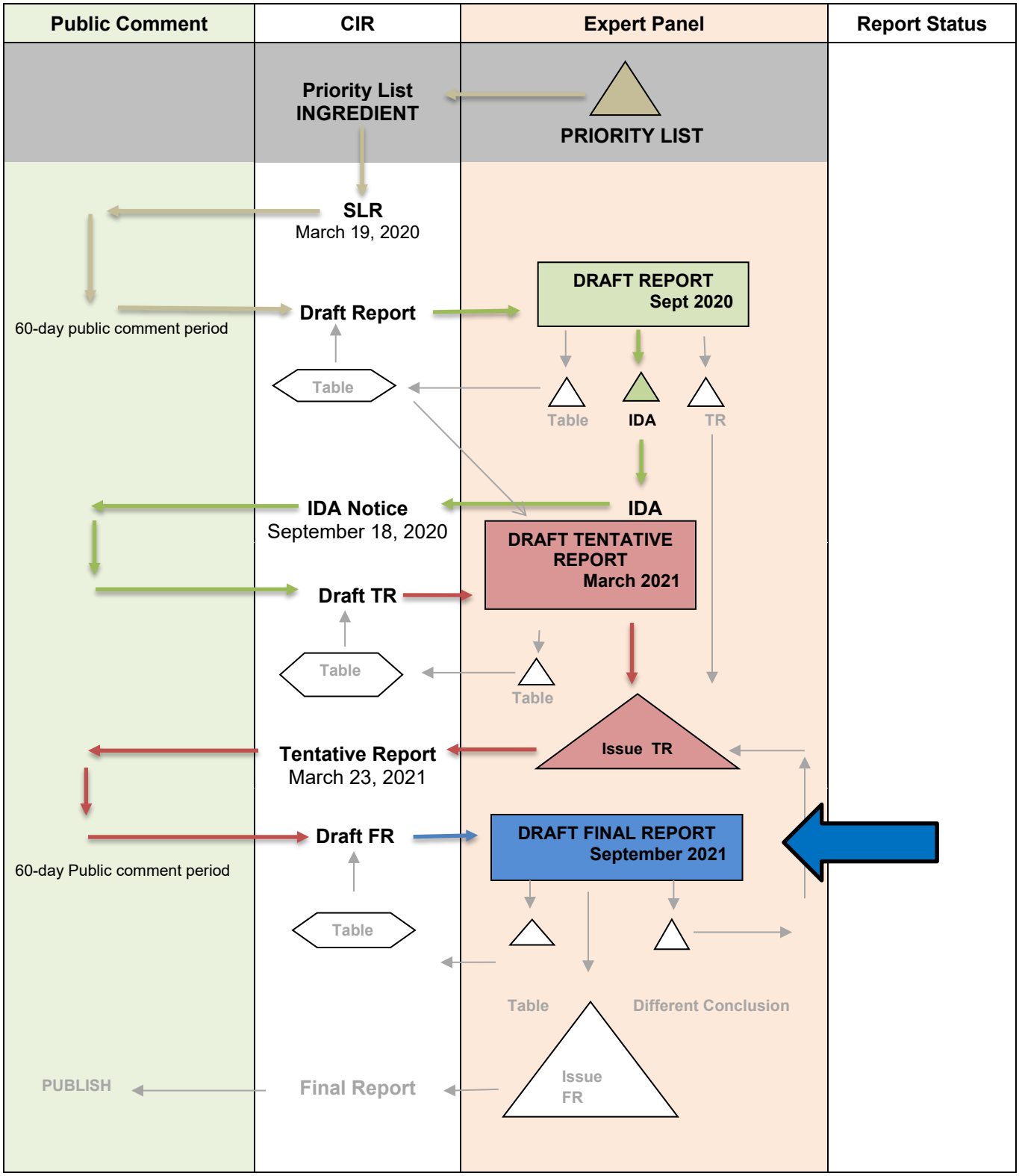
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Red-Algae Derived Ingredients

MEETING September 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 and issues a Tentative Report for public comment; safe as used conclusion for 11 ingredients, insufficient data for remaining 49 ingredients

-Comments on Draft Tentative Report received from Council

April 2021

-Comments on Tentative Report received from Council

-unpublished data received: HRIPT on a moisturizer formulation containing Porphyridium Cruentum Extract

September 2021

-Panel reviews Draft Final 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																			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.

MARCH 2021 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – March 11, 2021

DR. BELSITO: Bart, you're killing our team giving us red algae as the last ingredient of the day.

DR. HELDRETH: Should I put silicates at the end?

DR. SNYDER: No. That's what I was going to say.

DR. BELSITO: No. Okay. So this is Priya's as well. Let me make sure I save this. I guess I did. Okay. So I went by Priya's table, and it's very confusing because there are things that have GRAS designation. And then there are things in there that we're told are used as foods in Asia and then foods in France that weren't specifically said to be GRAS.

Anyway, at the September meeting, we asked for composition/impurities data for ingredients without a GRAS designation. So I don't know if there are reported food uses. Even if it's not been reported as generally accepted as safe by the U.S. government, we can eliminate those needs. And then we asked for a 28-day dermal tox on *Corallina officinalis* extract at the current concentration of use, 2 percent. And we didn't get that -- and then dermal sensitization data on all ingredients.

DR. SNYDER: Which we got quite a bit of sensitization data.

DR. BELSITO: Yeah. We got a lot of data there. So I was of the mindset to the GRAS ones -- and I had questioned to you. Can we also add those where we have limited data on composition and impurities? And can we use those that are reported as foods in France and in Asia that we didn't list as being GRAS and say those products, if they have sensitization and irritation, are okay. If we know the composition and impurities or they're GRAS or they're fruits in other countries and they have sensitization and irritation, are they all okay or not?

DR. LIEBLER: So Don, I just went from Priya's Table 1, and my understanding was the rule that we had was that if it has sensitization data and either GRAS, food, or tox data, we're good with it.

DR. BELSITO: Okay.

DR. LIEBLER: And so that's 11 in (audio skip).

DR. BELSITO: Okay. So let me just go down the list here. So I'll just look at what I found as food ingredients. So the first one is *Chondrus crispus* extract is a food, and we have a dermal sensitization on it.

DR. LIEBLER: Excuse me, Don. First one is *Chondrus crispus*.

DR. BELSITO: Yeah. That's what I said.

DR. LIEBLER: Oh, you said extract.

DR. BELSITO: Well, it's the extract we have the sensitization on. But I think we --

DR. LIEBLER: We have both. We have sensitization --

DR. BELSITO: No.

DR. LIEBLER: -- on both of them, don't we?

DR. BELSITO: No. Just go back --

DR. LIEBLER: I'm looking at Table 1, PDF 73.

MS. CHERIAN: It's marked as both because, just like for brown algae, if I had data for a genus and species, then I --

DR. BELSITO: Okay. What I used was the table from pages 9 and 10.

DR. SNYDER: Yeah. 73 is easier, Don.

DR. BELSITO: Okay. I was going to clear all the *Chondruses* -- all the *Chondrus crispus* just based on the extract sensitization.

DR. LIEBLER: I think what Priya's already done is essentially sort of a read-across on sensitization for us.

DR. BELSITO: Okay.

DR. LIEBLER: If (audio skip) ingredient within a genus has got sensitization data, then all of them qualify.

DR. BELSITO: Okay.

DR. LIEBLER: Do I have that right, Priya?

MS. CHERIAN: That's correct.

DR. BELSITO: Okay. Then let me put out my list and then see if there's anything to add. So *Chondrus crispus*, *Chondrus crispus* extract, *Chondrus crispus* powder --

DR. LIEBLER: Hydrolyzed.

DR. BELSITO: Yeah. And hydrolyzed *Chondrus crispus* extract are fine. Then the *Gelidiella acerosa* extract would be the next one? Does someone have one before that?

DR. LIEBLER: No.

DR. BELSITO: Okay. Then the next one I have is -- let's see. We have dermal irritation but no sensitization on the *Gigartina stellata* extract. So no. And then we have -- the next one would be the *Hypnea musciformis* extract?

DR. LIEBLER: Yep.

DR. BELSITO: And then the *Kappaphycus alvarezii* extract.

DR. LIEBLER: No.

DR. BELSITO: No?

DR. LIEBLER: That one doesn't have GRAS, food, or tox.

DR. BELSITO: Oh, that's right, yeah. Okay. Sorry. And then the *Palmaria palmata* right?

DR. LIEBLER: Yeah. So two of those.

DR. BELSITO: Right. The extract and the powder. And then the *Porphyra umbilicalis* extract powder and the hydrolyzed -- well, we don't have sensitization on the *Porphyra yezoensis* do we?

DR. LIEBLER: No.

DR. BELSITO: Okay. And then that's it, right?

DR. LIEBLER: *Rhodymenia*.

DR. BELSITO: Oh, yeah. Sorry.

DR. LIEBLER: At the end.

DR. BELSITO: *Rhodymenia palmata* extract. Would it be safe as used in all of the others? All of the other food ones would need sensitization, and the nonfood ones would need composition and impurities and sensitization and irritation at concentration for use. And then we still need the 28-day dermal on *Corallina*, right?

DR. LIEBLER: Correct.

DR. EISENMANN: For *Corallina,* I'd like you to look a little bit at the composition information. It's my understanding it's primarily minerals. This is an algae that has calcium deposits in the cell wall, and they use it to get calcium for dietary supplements. We have sensitization data on it. So I'm hoping, based on composition and the sensitization data, you might go okay for that one.

DR. LIEBLER: So you're saying that it's sort of atypical?

DR. EISENMANN: Right. Well, there's another one that's primarily minerals, but we don't have sensitization, the *Lithothamnion calcareum*. And *Corallina*, so it's coral like is the name.

DR. LIEBLER: Yeah. Trying to remember why we asked for the data on that one specifically.

DR. SNYDER: Because that's the one with the maximum concentration of use.

DR. LIEBLER: Oh.

DR. EISENMANN: Right.

DR. SNYDER: Most used and the highest concentration, 2 percent.

DR. LIEBLER: So it's the highest use, but it's kind of different from the others. So we wanted it as it's highest use and also implicitly because it would be representative, to some extent, of the others?

DR. EISENMANN: I suppose. I don't know.

DR. LIEBLER: Yeah.

DR. EISENMANN: I don't know the maximum concentration. We have sensitization data on it. I'd have to look that up.

MS. CHERIAN: I think we (audio skip) *Palmeria palmata* at 25 percent.

DR. BELSITO: So then it's also -- I mean, if you just follow this out, it's sort of illogical for us to be asking for a 28-day dermal on *Corallina officinalis* because you're saying it's an oddball and it's primarily just sort of fossilized seaweed. Is that right, Carol? Is that a good summary?

DR. EISENMANN: Yes. It's primarily minerals, calcium, magnesium, things. And I did check the -- you got a HRIPT in a product containing -- a powder product containing 2 percent. It was tested moistened.

DR. BELSITO: Right.

DR. LIEBLER: Well, do you think we'd do any better with *Chondrus crispus*? That's 1.4 is the max concentration versus 2 for the *Corallina officinalis*, pretty close. Any sense that we'd get better data for that one if we were requesting that?

DR. EISENMANN: I think you have some on *Chondrus crispus*. Oh, you mean a 28-day?

DR. LIEBLER: Yeah. Or other relevant tox.

DR. EISENMANN: You're not going to get it. Because that's food, I don't think anybody would do a tox study on it.

DR. LIEBLER: Okay. Well, it's food. Oh, I see. So that's the next highest use. And then the next one after that looks like it's probably -- oh, *Chondrus crispus* extract. And then we're at *Asparagopsis armata* extract is 0.33.

DR. BELSITO: Okay. That's not a food. We have sensitization on it, but we don't have -- and we have oral tox -- acute oral tox. We have in vitro genotox, in vitro irritation, no sensitization, in vitro oc tox, and no clinical reported studies. I mean, we could ask for a 28-day dermal on that one.

DR. EISENMANN: I'm not sure which one you're --

DR. BELSITO: *Asparagopsis armata* extract --

DR. EISENMANN: Oh, that's right.

DR. BELSITO: -- is not a food, and it's the first nonfood that has the highest level of use after *Corallina officinalis*. So you want to do that, Dan, Curt, Paul?

DR. LIEBLER: Potentially. Let's just retrace our reasoning. We wanted the *Corallina officinalis* 28-day dermal because --

DR. BELSITO: We didn't have a lot of tox endpoints.

DR. LIEBLER: Yeah.

DR. BELSITO: In fact, we virtually have very little.

DR. SNYDER: We have no absorption data for anything.

DR. BELSITO: Right.

DR. LIEBLER: But we have a lot of food uses.

DR. SNYDER: Yeah.

DR. LIEBLER: So I'm wondering if we could flip this on its head and say the food uses may drive the safety of the overall group because the use concentrations that are the highest are the ones that have food uses.

DR. SNYDER: That's what I was thinking. I think we can clear a lot of these because now we've gone from 2 percent down to 0.33 percent.

DR. LIEBLER: Yeah.

DR. BELSITO: And these aren't -- it's really even lower because they're not supplied as pure.

DR. LIEBLER: Right.

DR. BELSITO: That's under -- where did I read that? Yeah. So look at *Chondrus crispus*. This is on PDF page 30, I think. Let me get out of search mode and close comments so I can actually see this. So if you look at PDF page 30, *Chondrus crispus* is -- no, not 30, sorry. Where was it?

DR. SNYDER: Yeah. *Chondrus crispus* is top of 30. Composition?

DR. BELSITO: Yeah. But there's one where it said the composition -- yeah, 27, dah, dah, dah. And so the two trade name mixtures containing *Chondrus crispus* extract, 20 percent and 3.5 percent. So what's commercially available for blending are not pure *Chondrus crispus* extracts, right? So the concentration -- and I presume it's going to be the same for all of these. The concentration of the actual material will be even less?

DR. EISENMANN: Not necessarily. When I send the survey, I tell them I want the concentration of the extract, not the other stuff -- not of the -- the plant part of it, not the rest of it. But whether or not they all do that, I can't guarantee it.

DR. BELSITO: Okay. Well, we have the safe as used ones already checked off. And what are we doing with the others? We're staying with composition and impurities, sensitization, and a 28-day dermal tox on *Asparagopsis armata* extract, which is the highest nonfood that's used other than *Corallina* which is basically going to be calcium?

DR. LIEBLER: We could do that. That sort of implies that one of these for a 28-day dermal would clear the others, and -- because they're at lower concentration, even though their composition may be distinctly different.

DR. BELSITO: Right.

DR. LIEBLER: It's something that we really haven't done before, used one as kind of the example for a diverse class of sort of botanicals. I don't think we've ever done that.

DR. BELSITO: Right.

DR. LIEBLER: Maybe the more conservative approach that's justified by the way we've handled algae in the past is to use our combination of sensitization plus either GRAS, food, or tox data. And that gives us 11 that we can definitely stand behind. It's the same standard we applied to the previous algae reports and leave it at that, if the others are insufficient for the 28-day dermal and sensitization and irritation at concentration of use.

DR. BELSITO: Well, not all of the others because there are ones where we have food uses and we don't have sensitization.

DR. LIEBLER: Oh, yeah. Right.

DR. BELSITO: So I can read those. We have food use for the first one, *Ahnfeltiopsis concinna*. We have a food use for *Gelidium amansii*. We have a food use for *Gigartina stellata*. We have a food use for *Gracilaria verrucosa*. We have a food use for *Lithothamnium calcareum*. And then we have a food use for *Porphyra yezoensis*. So those would just need sensitization, right?

DR. LIEBLER: Yep.

DR. BELSITO: And then the others would require the 28-day dermal on the *Asparagopsis armata* extract and, if absorbed, other tox endpoints and sensitization. Some of them may have sensitization. Like *Kappaphycus alvarezii* has sensitization, but we don't have tox data. But we have a lot of composition data on that one. Does that help us out?

DR. LIEBLER: We can't really infer from composition to tox safety with these I'm afraid.

DR. BELSITO: Okay. So then we can go down. The next step would be to 28-day dermal, and then, if negative, other tox endpoints would be needed for the nonfood materials. And then we would need sensitization for the nonfood materials that we don't have sensitization for. We can get that out of Priya's table. I used the introductory table, but I imagine that -- so it's Table 13, right?

DR. LIEBLER: I think Priya can easily put that together from what we've described. Is that okay, Priya?

MS. CHERIAN: That's okay for me. But are we specifying that we need a 28 dermal on *Asparagopsis armata* still?

DR. BELSITO: Yeah.

MS. CHERIAN: Or are we saying --

DR. BELSITO: Are we? I don't know. I thought we said we wanted it.

DR. LIEBLER: Yeah. We don't have -- yes.

MS. CHERIAN: Okay. So are we saying if we get 28-day dermal on *Asparagopsis armata*, that's kind of in lieu of those ingredients that have sensitization but don't have food?

DR. LIEBLER: No. I think we decided we're not going to be able to just clear one seaweed with other seaweeds.

MS. CHERIAN: Okay.

DR. BELSITO: For absorption?

DR. LIEBLER: No. For dermal tox.

DR. BELSITO: Right. But if they're not absorbed, we're not looking for other systemic endpoints other than dermal tox?

DR. LIEBLER: Yeah. Yeah. Okay. I mean, yes, in principle and then question is what assay do you do to show there's no absorption?

DR. BELSITO: Well, lack of effect from a 28-day dermal on the *Asparagopsis*, no?

DR. LIEBLER: Okay. Yeah. So you would infer no absorption if a 28-day dermal is negative?

DR. BELSITO: Right.

DR. LIEBLER: But it could possibly be that it's well absorbed and it's just not at all toxic.

DR. BELSITO: Right.

DR. LIEBLER: So you don't really know about absorption. You're inferring absorption from that.

DR. BELSITO: Right. Well, absorption of materials that would be of concern.

DR. LIEBLER: Right. Fair enough. But we're not using any one seaweed to clear other seaweeds on a dermal tox endpoint?

DR. BELSITO: No.

DR. SNYDER: Not today we're not. But we may be --

DR. LIEBLER: I know. Last time we said we would do that with *Corallina officinalis*, whatever, but things have changed.

DR. BELSITO: Well, we could do it. I don't have a problem. I mean, these are used in very low concentrations.

DR. LIEBLER: Yeah. But I think it's important that we -- I think it's important that we stick with the approach we established with the other seaweeds.

DR. BELSITO: Right. Okay. That's fine. We'll see what the Cohen team says. And the discussion, yeah, the botanical boilerplate definitely needs to be in with those concentrations of arsenic and other metals. Okay. I think the discussion looks fine. And then just what we want, a list of the food ones that don't have sensitization and then the nonfood ones that have sensitization pending the 28-day dermal, and the others pending a 28-day dermal and sensitization at concentration of use, which we probably won't get. I don't know. And then we can look and see whether we want to change our mind. Anything else?

DR. LIEBLER: That's it?

DR. BELSITO: A lot.

DR. SNYDER: Bart, why are your decanters empty behind you? Has it been a bad winter?

DR. HELDRETH: Or a really good one.

DR. SNYDER: Or a really good one, yeah.

DR. BELSITO: Anything else on this? Priya, you pretty much have a sense of where we are?

MS. CHERIAN: Yes. I think I've got it. Thank you.

DR. BELSITO: Great. So that's it. Wow, 3:30. I thought we were going to be going to 5:00.

DR. LIEBLER: Oh, no.

DR. BELSITO: Good. Okay.

Cohen Team – March 11, 2021

DR. COHEN: Okay. Okay. Let's move on to -- wait, we have a -- wait a second. We should have red algae here, right?

DR. BERGFELD: Good luck.

DR. COHEN: Yeah. Yeah. All right. We have red algae. I'm just pulling that one up.

DR. BERGFELD: Oh, God.

DR. COHEN: Okay. This is Priya's. This is a draft tentative report. In September, the group issued insufficient data for composition impurities data, without a GRAS designation -- for those without a GRAS designation, 28-day dermal tox at the max use concentration of 2 percent.

And then, if that was positive, we'd need further information on dermal sensitization data on all ingredients. Since then, we've gotten a note that kappaphycus alvarezii extract has been added to the ingredient group, which is also derived from red algae. Any comments or questions because I think we're at 60 or more ingredients here so far?

DR. PETERSON: Well, I divided them into use with sufficient data, use with no data or insufficient data, and then no data/no use. And I thought that perhaps for the no data/no use they should be insufficient. That the ones where they were not used but had some data -- I don't -- yeah, I wasn't quite sure how to handle those. Anyway, I'll let somebody else talk.

DR. COHEN: We saw some impurities in the new one, arsenic, heavy metals, and I suppose we'll use our heavy metals and pesticides --

DR. SHANK: Boilerplate.

DR. COHEN: -- boilerplate for that?

DR. PETERSON: Yeah. That's what I thought.

DR. COHEN: We had irritation and sensitization up to 4 percent on the Corallina and that was -- that one has the highest max use. We have oral tox on Corallina. We have sensitization on eight of them, including kappaphycus. We have in vitro phototox data.

And I already mentioned the human data on Corallina for dermal. But I wanted some feedback on this microcirculation assay and what the team thought of that. Ron, you have any comments?

DR. SHANK: No. I'm trying to sort out the Corallina. Your question was about an assay? I'm sorry.

DR. COHEN: Yeah. In the dermal tox, there's a microcirculation assay on 30 subjects with Corallina --

DR. SHANK: Okay. Can you give me the page number?

MS. FIUME: PDF page 34.

DR. SHANK: 34.

MS. FIUME: Under short term tox studies.

DR. SHANK: Yeah. No. I don't know what that test is.

DR. SLAGA: I don't either.

DR. COHEN: Yeah. Well, I didn't know what to make of it. I was hoping you guys might be able to shed some light on it. So I think we need to start articulating what we're going to ask for.

And I know this has been a very hard group to sort of corral together because there's so many items, and many are used in very low concentrations, I would say, except for Corallina and Chondrus Crispus and 1.4 percent. So --

DR. SHANK: Well, I guess I can start. I had 11 of the ingredients as safe as used. We have enough data. A list of ingredients where we need skin sensitization. For the Corallina Officinalis Extract at 2 percent, I have a 28-day dermal tox. And then composition and impurities for the 12 ingredients that are not foods.

DR. COHEN: Composition impurities on the non-food ones?

DR. SHANK: On the -- there are 12 of them that are not foods. And we need to composition and impurities on that.

DR. COHEN: And for the Corallina -- Ron, what did you say about the Corallina? You wanted --

DR. SHANK: Corallina Officinalis Extract at 2 percent, a 28-day dermal because we have no data on that at all, except sensitization.

DR. ANSELL: The extraction -- this material according to our notes is essentially calcium. That's all --

DR. SHANK: Pardon me?

DR. ANSELL: It's calcified, so the extraction for that material is basically calcium. So we agree with all the other things you said, but I think that that one should be included in the safe category.

DR. SHANK: You say it's calcified? I don't understand.

DR. ANSELL: The note we have is that it's -- let me -- I'm going through my notes. We conclude similarly the food and sensitization that the Corallina officialis and the lithothamnium calcareum are both calcified species for which the ingredients are mainly minerals.

DR. SHANK: Okay. So there is composition data? That's not in the report. Is that what you're saying?

DR. ANSELL: Yes.

DR. SHANK: Okay. Well, we need to see that. So then I'll hold off on that request for 28 dermal tox until we see that. Because if it's just a mineral applied to the skin, probably be little penetration.

DR. BERGFELD: How many of those are there, Jay?

DR. ANSELL: It's just the two.

DR. BERGFELD: So you have the food group that you can put on the safe side, the two minerals, maybe?

DR. ANSELL: That's right. So we did the same cut that the food with sensitization is 11 materials. There is a group which has sensitization but no food use and then a group that have no data on either, and we agree that they should continue with insufficient, although we point out that most of them have no uses either. So it was just those two which have sensitization but no food use that we think should be elevated to the safe list. So we would bring it up to 13.

DR. BERGFELD: 13.

DR. SHANK: Okay.

MS. FIUME: So can I ask -- you were talking about the Corallina officinalis extract, is that correct? The composition, Jay?

DR. SHANK: Yes.

DR. ANSELL: Yes.

MS. FIUME: So the information is on PDF page 30. Is that the composition information you're referring to?

DR. ANSELL: I will have to look.

DR. COHEN: It's in yellow. It was recently added, right?

MS. FIUME: Yes. Because this is the ingredient that had that microcirculation assay, and that information was very summary. It was 28-day dermal. It's on PDF page 167, but it was very summary information. It didn't really explain the assay.

DR. COHEN: So then we're back to Ron's request for the 28-day tox because I didn't know what that microcirculation assay was.

MS. FIUME: We struggled with it as well in house from CIR because that's not something we had ever come across before either.

DR. BERGFELD: So who could answer that?

DR. SLAGA: Yeah.

MS. FIUME: Jay, do you have any information? Did they --

DR. ANSELL: No. Not here. I mean, we could ask, and we'll see what we can find. But basically, our takeaway was where Ron was going is that the food use materials and -- with sensitization data were okay. And that these two materials there would be no relevance in doing additional assessments because, you know, it's just minerals. But that's pretty much all I have.

DR. COHEN: So --

DR. BERGFELD: I'm sorry, on your tabulation, how many were in the no use/insufficient category?

DR. ANSELL: Okay.

DR. SHANK: How many?

DR. ANSELL: 24 have no food uses or sensitization.

MS. FIUME: And I believe Priya did a really good job of trying to provide the panel with that information. And that list of the 24 ingredients -- I believe they should be the same -- is on PDF page 73. It's the Data 2 Supplement.

DR. COHEN: Data 2 Supplement. Okay.

MS. FIUME: With the original mailing. I'm sorry. It was the original mailing, but the name of it is Data 2. And for those of you looking at the PDF, it's PDF page 73.

DR. COHEN: Okay.

DR. BERGFELD: Wait.

DR. COHEN: So just so I have this clear because I think I have this one -- I think I have most of the extracts tomorrow. I just --

MS. FIUME: It's your lucky day, David.

DR. COHEN: Yeah. Remember, this is only my second meeting, guys. It's a trial by fire. So for the 24 food use for sensitization data, we're going to have an IDA for that, right?

DR. SHANK: Yes.

DR. COHEN: And we're requesting, irritation, sensitization. What else? What else do we want on those 24?

MS. FIUME: So just to give a little history on the algae ingredients because I know several panel members weren't here. And Priya, please correct me if I don't get it all right -- or any of the other panel members. When the brown algae was reviewed -- and I think that group was even bigger than this one -- I was so impressed with the panel and the way you all looked at the information.

And I think what it came down to was the GRAS systemic tox was the one part, and the sensitization issues were the other. And if you had both components and that information was available for any of the ingredients that had the same genus and species, then those ingredients would be safe. If either of those components were missing, it was insufficient for the missing component.

DR. COHEN: Got it.

MS. FIUME: If both components were missing, it was insufficient for both components.

DR. SHANK: Very well stated.

MS. FIUME: Did I get that right?

MS. CHERIAN: Right.

MS. FIUME: Does that sound right?

DR. SHANK: Yes.

MS. CHERIAN: Yeah. So for this list on page 73 of the PDF, if there is a checkmark under GRAS or food and sensitization, it would be considered safe or if it had a check mark under tox and sensitization.

DR. COHEN: All right. I'll have to find that because I'm using -- this is not in the data supplement? This is in the original report?

DR. BERGFELD: Right.

MS. FIUME: Right. And then Priya, to take it that one step further, if that combination was available for any of the ingredients of the same genus/species --

MS. CHERIAN: Right.

MS. FIUME: -- then it covered all of those ingredients.

MS. CHERIAN: Those checkmarks are placed for the genus and species. So if I have data for one, I put a checkmark for --

MS. FIUME: Oh, okay. Okay.

DR. COHEN: Oh, I see it. Okay. Okay. So --

DR. BERGFELD: Fantastic, actually.

DR. COHEN: Yeah. That's really helpful. All right. So I'll refer to that. It's Table 1, right -- listed as Table 1?

MS. CHERIAN: Yeah.

DR. COHEN: All right. I have my homework set out for me tonight. Okay.

DR. SHANK: That's a great table you --

DR. COHEN: That is the table of the day.

DR. SHANK: Very helpful.

MS. FIUME: Priya did a great job.

DR. SHANK: Yes.

DR. COHEN: Oh, my gosh.

MS. CHERIAN: I've had practice.

MS. FIUME: Awesome.

DR. COHEN: Okay. So I will, Monice, articulate what you mentioned and just sort of boil it down in the discussion so it's not very protracted tomorrow. Is that -- that's what we're looking for. When we have checkmarks for both, we're clear.

MS. FIUME: Yes.

DR. COHEN: And if we have checkmarks for GRAS or food, either/or, we want the other for the tox, and if we have nothing, it's nothing -- it's an IDA for both.

MS. CHERIAN: Right.

MS. FIUME: Well, it's -- so I believe this --

DR. COHEN: Awesome.

MS. FIUME: -- should be going as a tentative report. Is that correct?

MS. CHERIAN: Yes.

DR. COHEN: This is a tentative report. And IDA would be the proper terminology?

MS. FIUME: Insufficient data.

DR. COHEN: Insufficient data.

MS. FIUME: Yeah. IDA is the stage a draft report will go if there's not enough information, and then we go into the formal tentative report and final report.

Full Panel – March 12, 2021

DR. COHEN: Yes, this is my fourth botanical today.

DR. BERGFELD: Lucky boy.

DR. BELSITO: We wanted to get you up to speed quickly, David.

DR. COHEN: Yeah, it's like a hazing. So this is a draft tentative report. In September of 2020 we issued an insufficient data announcement asking for compositions and impurities for ingredients without a GRAS designation, 28-day dermal tox for Corallina at the max concentration of two percent, and if necessary systemic tox, DART, genotox and dermal sensitization on all of the ingredients.

Since the meeting, we had late breaking information about adding Kappaphycus Alvarezii Extract to the ingredient list as it's a Red Algae derivative and it's Red Algae species. The concentration for use of this ingredient has been received and incorporated in the report.

And, I think for the sake of brevity, because this is a very large group, we're looking at 61 different ingredients. We went to the table on PDF Page 73 and removing as safe as used for 11 ingredients that had both sensitization data and a food or GRAS designation. I believe we're also including Corallina, which is largely calcified algae, and the Kappaphycus. The others are insufficient for either sensitization, and GRAS or food. That's a motion.

DR. BERGFELD: Is there a second, or discussion?

DR. BELSITO: Yeah, so, let's just go through this. So, the Chondrus species are safe as used. The Gelidiella, safe as used. Gelidium, safe as used. The Hypnea Musciformis, safe as used?

DR. COHEN: Yeah, Hypnea, safe as used.

DR. BELSITO: Palmaria?

DR. COHEN: Yes.

DR. BELSITO: Porphyra Tenera and Porphyra Umbilicalis?

DR. COHEN: No, did we have sensitization data on Tenera, Don? I didn't see that.

DR. BELSITO: Yes we had it on Tenera -- oh, wait a minute. No.

DR. COHEN: I know we have it on Umbilicalis.

DR. BELSITO: Yeah, so, I'm sorry, David, you're right. Porphyra Umbilicalis and Rhodymenia Palmata.

DR. COHEN: Correct.

DR. BELSITO: But, you're also including Corallina even though we don't have -- it's not a food use.

DR. COHEN: I think I'm representing the discussion -- well, it was a very long one -- in that Corallina is effectively calcium, calcified algae. Ron, what was your recollection on how we adjudicated that one?

DR. SHANK: Our understanding was that this is basically a mineral. If that's not the case, then I think we need 28-day dermal on it. If it's just a mineral, then it's probably not absorbed.

DR. LIEBLER: It's an algae. It was described to us in our discussion yesterday as being highly calcified. And, that was interesting, but I felt that we should stick to the framework for (audio skip) that we developed with the previous algae reports we did. Which essentially is, if it's got sensitization data and either GRAS or food use, or tox data, we can accept it.

And so we came up with 11 from that checklist on Page 93 that did not include the Corallina. Because, honestly, we weren't sure how to interpret the highly calcified part. Yeah, I mean, I agree with you, Ron, that's going to really prevent most absorption, but we don't really know. And there's certainly some algae, or it wouldn't be an algae. So, that's why we didn't have Corallina in our good list.

DR. SHANK: Okay. So, what do you want on the Corallina Extract, 28-day?

DR. LIEBLER: Yeah.

DR. BELSITO: Or, if we got information on the composition. I mean, this is just a verbal that we got. There's nothing in the documents stating that.

DR. SHANK: Right.

DR. BELSITO: So, if we could get, you know, what's actually in this, the composition, then perhaps we could go on that. But we don't have that data.

DR. SHANK: Okay.

DR. BELSITO: So, I think in the absence of that data we do a 28-day.

DR. SHANK: Okay, I agree.

DR. LIEBLER: Yeah, me too. I'm fine with that. Let's just get some information on paper.

DR. COHEN: And Don and Dan would you say the same thing about Kappaphycus?

DR. BELSITO: Kappaphycus --

DR. LIEBLER: Yeah, we got sensitization and we do not have food, GRAS or tox.

DR. COHEN: Yeah.

DR. LIEBLER: So, if we had either GRAS, food or tox, we're good with that too.

DR. COHEN: So Wilma, can I amend my motion?

DR. BERGFELD: Yes, you may.

DR. COHEN: So, the motion would be safe as used in present practice for the 11 ingredients that have both sensitization data and GRAS, or food, or tox. And, Don, I'll read through them. The Chondrus species, the Gelidiella, the Hypnea Musciformis, the Palmaria, the Porphyra Umbilicalis, and the Rhodymenia.

DR. BELSITO: Good.

DR. COHEN: And those are 11 safe as used. The others are insufficient for the information requested.

DR. BELSITO: So, but the information requested depends upon, if we have sensitization then we need either a 28-day dermal or composition. And, there are some that have food uses that we don't have sensitization on and so you would need sensitization on those.

DR. COHEN: Right. There're a lot of or's in the ask.

DR. BELSITO: Right.

MS. CHERIAN: So basically, we're just extending our requirement for that systemic tox, we can go with composition too.

DR. BELSITO: Well, you know --

MS. CHERIAN: (Audio distorted).

DR. BELSITO: Right.

MS. CHERIAN: Or, food or GRAS use.

DR. BELSITO: Right. So, composition or a 28-day dermal. You know, assuming the composition is similar to what we know about other algae that we (audio skip) safe either through a 28-day dermal, or through the fact that they're food.

DR. BERGFELD: It might be best to reorganize this table, which is Table 1, into the categories that have been stated. So one could see that and know exactly what you do in each category.

DR. COHEN: And one other comment.

DR. BERGFELD: (Audio skip) -- yes, please.

DR. COHEN: At least as far as the progress of the report, if we could just highlight across the rows the species that made it, so to speak. So we can look at the other more easily.

DR. BERGFELD: Okay. Is there agreement then on 11 safe, and the remainder (audio skip)?

DR. BELSITO: Yeah, so on the next iteration the ones that we approved they can put green. They got the green light.

DR. BERGFELD: Okay. Do we need any other discussion? We've had a motion that's been amended, are you seconding that, Don?

DR. BELSITO: Yes.

DR. BERGFELD: Okay. And we all have the understanding that there'll be reorganization according to the categories that were discussed, so that we'd know which would be needing what. Okay. All right, I think that I'll call for the vote then. All those in favor of the motion 11 safe and the remainder insufficient with the appropriate needs for each category. All those opposed?

DR. BELSITO: All those in favor?

DR. BERGFELD: Nope, sorry, I'm going to do it the other way. Opposed? Abstaining? So it's approved. Do we need to add any other discussion or comments at this time? Hearing none we're going to move on to the next ingredient, which is Diacetone Alcohol, Dr. Belsito.

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

Status: Draft Final Report for Panel Review
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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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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of red algae-derived ingredients. Sixty 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 in cosmetics 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 11 red algae-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the data are insufficient to make a determination of safety that the remaining 49 ingredients are safe under the intended conditions of use in cosmetic formulations.

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 in cosmetics 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. It should be noted that some of these reported functions (e.g., skin bleaching and anti-microbial agents) are not considered a cosmetic function in the United States (US), and therefore, use as such does not fall under the purview of the Expert Panel for Cosmetic Ingredient Safety (Panel).

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* phylum; red algae should not be confused with members of the *Pyrrhophyta* family, which encompass the unicellular algae and protozoa responsible for harmful algal 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-dehydrocholesterol, 7-dehydrocholesterol, 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.

Digenea Simplex Extract

A *Digenea simplex* sample was reported to contain sodium, calcium, phosphorus, magnesium, potassium, and lead, in amounts of 1198, 432, 368, 398, 7744, and 0.01 mg/100 g dry weight, respectively.[19] The most prevalent fatty acids found in this sample were palmitic (14.02 mg/g), arachidic (30.78 mg/g), palmitoleic (6.50 mg/g), and linoleic (6.52 mg/g) fatty acids. Non-essential and essential amino acids were present in amounts of 28.52 and 40.78 g/100 g, respectively. Amino acids present in the largest quantities included aspartic acid (5.01 g/100 g), glutamic acid (7.50 g/100 g), tyrosine (4.40 g/100 g), leucine (5.70 g/100 g), lysine (6.50 g/100 g), methionine (4.87 g/100 g), phenylalanine (10.74 g/100 g), and threonine (7.52 g/100 g).

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.[20] 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).[21] 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.[22]

Gelidium Sesquipedale Extract

A heavy metal and mineral analysis was performed on a trade name mixture containing 4% Gelidium Sesquipedale Extract; Table 6.[23] Iodine was detected in an amount of 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).[24] 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.[25] 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.[26] 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.[27] 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.[28] 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.[29] 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.[29] 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.[30]

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.[31] 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.[32] 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.[29]

Levels of iodine in *Palmaria palmata* can exhibit a wide range of value (10 - 100 µg/g) depending on location and time of harvest.[31] 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.[33] 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.[29] 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.[34] 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.[35]

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.[36] 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.[36] 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.[37] 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).[38] 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, Corallina Officinalis Extract, and Kappaphycus Alvarezii 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.[39] 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-derived ingredients are reported to be in use. 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).[40] 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.[41]

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 used 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.[42,43] 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.[44,45] 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.[46-48]

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.[49]

Non-Cosmetic

Several species of red algae (e.g., *Palmaria palmata*) have become established as part of popular international cuisine.[50] 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).[51] Due to its high mineral content, *Corallina officinalis* can be used as an emulsifier in the food industry in several products such as soft drinks, cakes, and candies.[52] 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.[51] *Gloiopeltis tenax* has also been reported to be used in China to treat diarrhea and colitis.[24] In Japan and the Mediterranean area, *Gelidium cartilagineum* and *Chondrus Crispus* were used in diarrhea and urinary tract irritation treatment.[51] 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.[53] 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.[54] 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.[26] *Grateloupia livida* is also an edible and medicinal seaweed used to treat sore throat, stomachache, ascariasis, and dysentery.[55] 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.[28,51] *Corallina officinalis* extract is a popular ingredient in traditional Asian medicine used for the treatment of various ailments.[56] 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.[21,57]

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.[58] 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).[27] 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.[54] 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.[54] 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. Gross necropsy and histopathologic evaluation of 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.[59] 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 days 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.[15,58,60-62] A chemiluminescent 3D genotoxicity assay performed on a test substance containing 48% Porphyra Umbilicalis Extract also yielded negative results.[63]

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).[64] 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.[65] 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).[66] 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).[67] 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.

Gracilaria Verrucosa 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.[25] 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*.[68] 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.[69] 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.

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%).[15,58,60,70,71] 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.[72]

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)), Porphyra Umbilicalis Extract (0.0004%)), and Porphyridium Cruentum Extract (0.000545%))[73] were negative.[15,18,20,29,74-83]

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.[63] 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.[70] 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).[71,84,85] 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).[60] 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.[58,63,85-88] 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.[20] 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 days 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.[67] 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 was 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%), 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)), Porphyra Umbilicalis Extract (0.0004%), and Porphyridium Cruentum Extract (0.000545%)) 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 Sanguinea 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.

DISCUSSION

The Panel reviewed the red algae-derived ingredients in this report, and concluded that although 11 of the 60 ingredients are safe as used in cosmetics in the present practices of use, data were insufficient to determine the safety of the remaining 49 ingredients. Ingredient data profiles were considered sufficient when composition data or systemic toxicity data (via use in food, GRAS status, or oral toxicity) and sensitization data were available. (The need for systemic toxicity data was mitigated for those ingredients that are used in foods or are considered GRAS, because exposure via ingestion would be far greater than exposure via cosmetics.) Ingredients lacking some or all of these data components were considered to have insufficient safety data, and depending on which data were lacking, systemic toxicity data, sensitization data, or both are required. As for those ingredients that are formulated differently, but are derived from the same genus and species and would be similar in composition (e.g., Chondrus Crispus Extract and Chondrus Crispus Powder), the Panel confirmed that if there are sufficient data to support the safety of one of these ingredients, all related ingredients of the same genus and species would be considered safe as well.

The Panel noted that elevated levels of heavy metals, arsenic, and pesticide residues may be present in these red algae-derived ingredients. The Panel stressed that the cosmetics industry should continue to use cGMPs to limit these impurities. The Panel also noted the presence of kainic acid (a potential neurotoxin) 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 concern for the presence of these constituents is mitigated as the final concentration of these substances would be minimal in cosmetic formulations.

The Panel discussed the issue of incidental inhalation exposure that could result with the use of some of 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

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 11 of the 60 red algae-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Chondrus Crispus
Chondrus Crispus Extract
Chondrus Crispus Powder
Gelidiella Acerosa Extract
Hydrolyzed Chondrus Crispus Extract
Hypnea Musciformis Extract
Palmaria Palmata Extract
Palmaria Palmata Powder*
Porphyra Umbilicalis Extract
Porphyra Umbilicalis Powder*
Rhodymenia Palmata Extract

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

The Panel also concluded that the available data are insufficient to make a determination that the remaining 49 ingredients are safe under the intended conditions of use in cosmetic formulations.

Ahnfeltiopsis Concinna Extract
Asparagopsis Armata Extract
Betaphycus Gelatinum Extract**
Botryocladia Occidentalis Extract**
Calliblepharis Ciliata Extract**
Ceramium Kondoi Extract**
Ceramium Rubrum Extract**
Chondracanthus Teedei 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
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 Corallina Officinalis**
Hydrolyzed Corallina Officinalis Extract
Hydrolyzed Porphyra Yezoensis**
Kappaphycus Alvarezii Extract
Lithothamnion Calcareum Extract
Lithothamnion Calcareum Powder
Lithothamnion Corallioides Powder**
Mesophyllum Lichenoides Extract**
Phymatolithon Calcareum Extract
Pikea Robusta Extract**
Polysiphonia Lanosa Extract**
Porphyra Linearis Powder**
Porphyra Tenera Extract**
Porphyra Tenera Sporophyte Extract**
Porphyra Yezoensis Extract
Porphyra Yezoensis Powder**
Porphyridium Cruentum Culture Conditioned Media**
Porphyridium Cruentum Extract
Porphyridium Purpureum Extract
Sarcodiotheca Gaudichaudii Extract**

*** There are currently no uses reported for these ingredients,*

Ingredients in blue type were considered sufficient in systemic toxicity data, however, sensitization data or composition data are required by the Panel to determine safety.
Ingredients in green type were considered sufficient in sensitization data, however, systemic toxicity data are required by the Panel to determine safety.
Ingredients in red type were considered insufficient in both systemic toxicity and sensitization data.

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 ciliata.*	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
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

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

Ingredient	Definition	Function
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	*See Phymatolithon Calcareum Extract*	
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 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	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
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
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
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[89]

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	89,90
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	-widely distributed in South and West -larger lower intertidal pools and subtidal on stones, maerl, and shells -occasionally abundant on bedrock	89
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	91
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	56
Cyanidium caldarium	-unicellular -prefers low pH and high temperature for growth -contains phycocyanin	-mostly found in acidic hot springs and soils -reported to be found in the US, Italy, New Zealand, Japan, Iceland, and Central America -fresh water	92
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	89
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	89
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	89
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	89
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	93

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

Species	Description	Distribution/Habitat/Ecology	References
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	94
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	95
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	89
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	89
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	89
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	89
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	96
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	89

Table 4. Methods of manufacture for red 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	97
Asparagopsis Armata Extract	algae → grinding → extraction with water → stabilization with vegetable glycerin →filtration	98
Asparagopsis Armata Extract	fresh seaweed → grinding → cold cellular extraction → filtration → concentration → freeze-drying under neutral atmosphere	99
Asparagopsis Armata Extract	harvesting/identification → washing → grinding → extraction with solvents (propanediol and water) → filtration → quality control → packaging → quality control	100
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	101
Chondrus Crispus Powder	harvesting → naturally dried via sun exposure → grinding/sieving → packaging → sterilized via gamma ray treatment	102
Chondrus Crispus Powder	harvesting/identification → drying → cutting → ionization → quality control → packaging → quality control	103
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	104
Corallina Officinalis Extract	dried grounded algae → extraction with water → testing → sifting → centrifugation → ultrafiltration → testing → homogenization → testing → sterile filtration → testing → packing	105
Digenea simplex extract	Dried algal powder (200 mg) extracted with 6 ml 80% methanol → ultrasonic bath → vortex → centrifuge → filtration → drying	106

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

Ingredient (characterization)	Method of Manufacture	Reference
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	62
Gelidium amansii extract	algae collection → washing → dried at room temperature → grinding → powder extracted with 80% ethanol for 24 h → freeze-drying	22
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	26
Hydrolyzed Corallina Officinalis Extract	harvesting/identification → extraction with water → addition of sodium methylparaben or 2-phenoxyethanol → filtration →quality control → packaging →quality control	5,107
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	29
Lithothamnion Calcareum Powder	harvesting → drying → grinding → micronisation → ionization → mixture → addition of mannitol, zinc sulfate, and diatomaceous earth → packaging → quality control	108
Palmaria Palmata Extract	solubilization of powder of *Palmaria palmata* in water → separation of soluble and insoluble phases → concentration of soluble phase → membrane sterilization	29
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	34
Porphyra Umbilicalis Extract	dried grounded algae → extraction with water → testing → centrifugation → ultrafiltration → testing → sterile filtration → testing → packaging	109

Table 5. Mineral and metal analysis of a trade name mixture consisting of 50% glycerin; 30% water; 18.5 % undaria pinnatifida extract; and 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[23]

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*[24]

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
methyl 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)[38]

	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%), and Corallina Officinalis Extract (3.97%)[39]

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[40,41,110]

	# 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

	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

Table 10. Frequency (2021) and concentration of use (2020) of red algae-derived ingredients[40,41,110]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	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

	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

Table 10. Frequency (2021) and concentration of use (2020) of red algae-derived ingredients[40,41,110]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	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

	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, according to the VCRP and Council survey

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

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	[111]
Chondrus crispus	Used as thickener/gelling agent; used in drinks; also known as Irish moss; eaten whole	[112]
Corallina officinalis	Emulsifying agent in food products	[52]
Gelidiella sp.	Used in jellies	[51]
Gelidium amansii	Used in jellies	[22]
Gigartina stellata	Used interchangeably with Chondrus crispus; thickener/gelling agent	[51,89]
Gracilaria sp.	Used in jellies	[51]
Gracilaria verrucosa	Eaten whole, with salads	[112]
Hypnea musciformis	Eaten whole, dried	[113]
Lithothamnion calcareum	Used as vegetables and condiments in France	[9]
Palmaria palmata	Eaten fresh or dry; used in breads and cakes	[29,50]
Porphyra tenera	Typically, dried and used to make sushi; nori, spices, seasoning, flavoring (GRAS)	21CFR184.1121, [36]
Porphyra umbilicalis	Typically, dried and used to make sushi	[96,112]
Porphyra yezoensis	Typically, dried and used to make sushi, nori	[36,114]
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	[60]
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	[58]
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	[61]
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	[62]
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	[63]

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	[70]
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	[60]
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	[58]
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	[71]
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	100%; dose not reported	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	[60]
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	[115]
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	[116]
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	[117]
Chondrus Crispus Powder	Chondrus Crispus Powder (100%)	100%; 0.02 ml	12	24-h patch test; occlusive conditions	Non-irritating	[118]
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	[119]
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	[120]
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	[20]
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	[121]
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	[122]
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	[123]
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	[124]
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	[72]
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	[29]
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	[125]
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	[29]
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	[126]
Rhodymenia Palmata Extract	Eye cream containing 0.0375% Rhodymenia Palmata Extract	100%; 0.2 g	38	7-d exposure; semi-occlusive conditions	Non-irritating	[127]
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	[128]
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	[74]
Betaphycus Gelatinum Extract	Mixture containing 7% Betaphycus Gelatinum Extract	100%; dose not reported	56	HRIPT under semi-occlusive conditions	Non-irritating; Non-sensitizing	[81]
Chondrus Crispus Extract	Product containing 0.49% Chondrus Crispus Extract	100%; dose not reported	113	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	[75]
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 moistened with distilled water	dilution not reported; 0.1 – 0.15 g	102	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	[80]
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	[20]
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	[20]
Gelidiella Acerosa Extract	Product containing 0.0028% Gelidiella Acerosa Extract	100%; dose not reported	105	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	[76]
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	[77]
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	[78]
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	[29]
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	[83]
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	[29]
Porphyra Umbilicalis Extract	Product containing 0.0004% Porphyra Umbilicalis Extract	100%; dose not reported	103	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	[79]
Porphyridium Cruentum Extract	Moisturizer containing 0.000545% Porphyridium Cruentum Extract	dilution not reported; 0.1 – 0.15 g	107	HRIPT under occlusive conditions	Non-irritating; Non-sensitizing	[73]

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	[70]
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	[60]
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	[58]
After-shave balm containing 0.8% Chondrus Crispus (other components not specified)	100%; 100 µl	3	MatTek EpiOcular™ MTT assay	Non-irritating	[84]
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	[71]
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	[87]
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	[20]
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	[86]
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	[88]
Trade name mixture consisting of 52% water, 48% Porphyra Umbilicalis Extract	100%; dose not reported	6	HET-CAM assay	Weakly irritating	[63]
Eye cream containing 0.0375% Rhodymenia Palmata Extract	100%; 100 µl	8	MatTek EpiOcular™ MTT assay	Non-irritating	[85]
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-diphenyltetrazoliumBromide; NR = not reported

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 29, 2021

SUBJECT: Porphyridium Cruentum Extract

Anonymous. 2019. Clinical safety evaluation: Repeated insult patch test (moisturizer containing 0.000545% Porphyridium Cruentum Extract).

[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

moisturizer contains 0.000545% Porphyridium Cruentum Extract

Sponsor

[redacted]

Sponsor Representative

[redacted]

Clinical Testing Facility

[redacted]

[redacted]

Date of Final Report

2-5-19

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted], MD
Board-Certified Dermatologist
Medical Investigator

2/11/19
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

4 Feb 2019
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: [redacted], BA
Principal Investigator: [redacted] PhD, DABT, BCFE
Medical Investigator: [redacted], MD, Board-Certified Dermatologist

5.0 STUDY DATES

Study initiation: December 5, 2018 ([redacted])
December 12, 2018 ([redacted])

Final evaluation: January 11, 2019 ([redacted])
January 18, 2019 ([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 November 19, 2018 and identified as follows:

[redacted]	Test Article ID	Description
[redacted]	[redacted]	Pink Lotion

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. The site was scored 24 and 72 hours after application. 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 110 subjects (17 males and 93 females ranging in age from 19 to 79 years) were empanelled for the test procedure. One hundred seven (107/110) subjects satisfactorily completed the test procedure on Test Article: LM Multitasking Moisturizer. Three (3/110) 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 107 subjects, Test Article: LM Multitasking Moisturizer was "Dermatologist-Tested" and was not associated with skin irritation or allergic contact dermatitis in human subjects.

TABLE 1

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj.	Induction Evaluation Number									Challenge Virgin Site	
No.	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	Discontinued									
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	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]

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	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	0	0	0	0	0	0	0	0	0
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	0	0	0	0	0	0	0	0	0	0
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	Discontinued	
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)

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj.	Induction Evaluation Number									Challenge Virgin Site	
No.	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	Discontinued										
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	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]

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	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	0	0	0	0	0	0	0	0	0
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	0	0	0	0	0	0	0	0	0	0
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)
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4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

Table 1. Red algae ingredients with sufficient data*

Ingredient	GRAS	Food	Tox	Sensitization data
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**		✓		✓
Gelidiella Acerosa Extract		✓		✓
Hypnea Musciformis Extract		✓		✓
Palmaria Palmata Extract (synonymous with Rhodymenia Palmata Extract)	✓	✓		✓
Palmaria Palmata Powder	✓	✓		✓
Porphyra Umbilicalis Extract		✓		✓
Porphyra Umbilicalis Powder		✓		✓
Rhodymenia Palmata Extract (synonymous with Palmaria Palmata Extract)	✓	✓		✓

*For tables 1-3, 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.

***Corallina officinalis* can be used as an emulsifier in foods. The Panel should evaluate whether this information is sufficient to satisfy the GRAS status/food use/systemic toxicity requirement for safety. If the data are sufficient, these 5 ingredients will be moved from insufficient to safe in the conclusion of the report. (And if so, 16 ingredients will be considered safe as used, and 44 ingredients will be considered insufficient).

Table 2. Red algae ingredients with GRAS status/food use/systemic toxicity data only*

Ingredient	GRAS	Food	Tox	Sensitization data
Ahnfeltiopsis Concinna Extract		✓		
Gelidium Amansii Extract		✓		
Gelidium Amansii Oligosaccharides		✓		
Gigartina Stellata Extract		✓		
Gracilaria Verrucosa Extract		✓		
Lithothamnion Calcareum Extract (synonymous with Phymatolithon Calcareum Extract)		✓	✓	
Lithothamnion Calcareum Powder		✓	✓	
Phymatolithon Calcareum Extract (synonymous with Lithothamnion Calcareum Extract)		✓	✓	
Porphyra Tenera Extract	✓	✓		
Porphyra Tenera Sporophyte Extract	✓	✓		
Hydrolyzed Porphyra Yezoensis		✓		
Porphyra Yezoensis Extract		✓		
Porphyra Yezoensis Powder		✓		

Table 3. Red algae ingredients with sensitization data only*

Ingredient	GRAS	Food	Tox	Sensitization data
Asparagopsis Armata Extract				✓
Hydrolyzed Asparagopsis Armata Extract				✓
Betaphycus Gelatinum Extract				✓
Delesseria Sanguinea Extract				✓
Furcellaria Lumbricalis Extract				✓
Gelidium Cartilagineum Extract				✓
Kappaphycus Alvarezii Extract				✓
Porphyridium Cruentum Culture Conditioned Media				✓
Porphyridium Cruentum Extract (synonymous with Porphyridium Purpureum Extract)				✓
Porphyridium Purpureum Extract (synonymous with Porphyridium Cruentum Extract)				✓

Ingredients with no GRAS/food data, systemic toxicity data, or sensitization data (21 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
Sardiotheca Gaudichaudii Extract

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: April 13, 2021

SUBJECT: Tentative Report: Safety Assessment of Red Algae-Derived Ingredients as Used in Cosmetics (release date: March 23, 2021)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Red Algae-Derived Ingredients as Used in Cosmetics.

Key Issues

Although *Corallina officinalis* is not eaten as are some other red algae species, it is used to make food additives. See: Magill CL, Magges CA, Johnson MP et al. 2019. Sustainable harvesting of the ecosystem engineer *Corallina officinalis* for biomaterials. *Frontiers in Marine Science*. https://doi.org/10.3389/fmars.2019.00285

Also see the Codif technical information sheet on *Corallina officinalis* that states: "Thanks to its content in enzymes, proteins, high-iron, calcium and magnesium, potassium, phosphorus, sodium and other minerals, Corallina Officinalis can be used as an emulsifier in food industry, for a large number of soft drinks, cakes, candy, frozen fresh-keeping etc." (at http://www.codif-recherche-et-nature.com/wp-content/uploads/2016/02/CONCENTRE-CORALLINE-FICHE-BOTANIQUE-GB.pdf). The use of Corallina officinalis preparations in food should be sufficient to preclude the need for systemic toxicity data for this species.

Additional Considerations

Composition and Impurities, Delesseria Sanguinea Extract – Please correct: "22-dehydrochelesterol"

Composition and Impurities, Palmaria Palmata Extract – In this section, it would be helpful to state the significance of kainic acid. Since a *Digenia simplex* preparation is included in this report, perhaps it should be added to this heading.

Table 1 – In the Definition column, please correct "*ciliate*" to "*ciliata*"

Table 3 – Please indicate whether the species described are salt or freshwater species. Where is *Calliblepharis ciliata* common? It currently says: "in South and West". It would be helpful to add a species to this table that is not a macroalgae, such as *Cyanidium caldarium*.