Safety Assessment of Polysaccharide Gums as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	August 28, 2015
Panel Date:	September 21-22, 2015

The 2015 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: August 28, 2015
Subject: Draft Final Report on Polysaccharide Gums

At the June15-16, 2015 CIR Expert Panel meeting, the Panel issued a tentative report for public comment with the conclusion that the polysaccharide gums reviewed in this safety assessment are safe in the present practices of use and concentration, with the exception that the available data are insufficient for determining the safety of hydrolyzed carrageenan in cosmetic products. The insufficient data conclusion is based on the absence of information on the manufacturing methods and impurities of the ingredient hydrolyzed carrageenan. To date, these data have not been received. The current safety assessment (draft final report) is identified as *plpogu092015rep* in the pdf document. Comments received from the Council (*plpogu092015pcpc1)* have been addressed.

Included in this package for your review is the Draft Final Report on Polysaccharide Gums (*plpogu092015rep*), the CIR report history (*plpogu092015hist*), Literature search strategy (*plpogu092015strat*), Ingredient Data profile (*plpogu092015prof*), 2015 FDA VCRP data (*plpogu092015FDAdata*), and the June 2015 Panel meeting minutes (*plpogu092015min*).

After considering the data included in this safety assessment, the Panel will need to determine whether a final report with the conclusion stated at the beginning of this memorandum should be issued.

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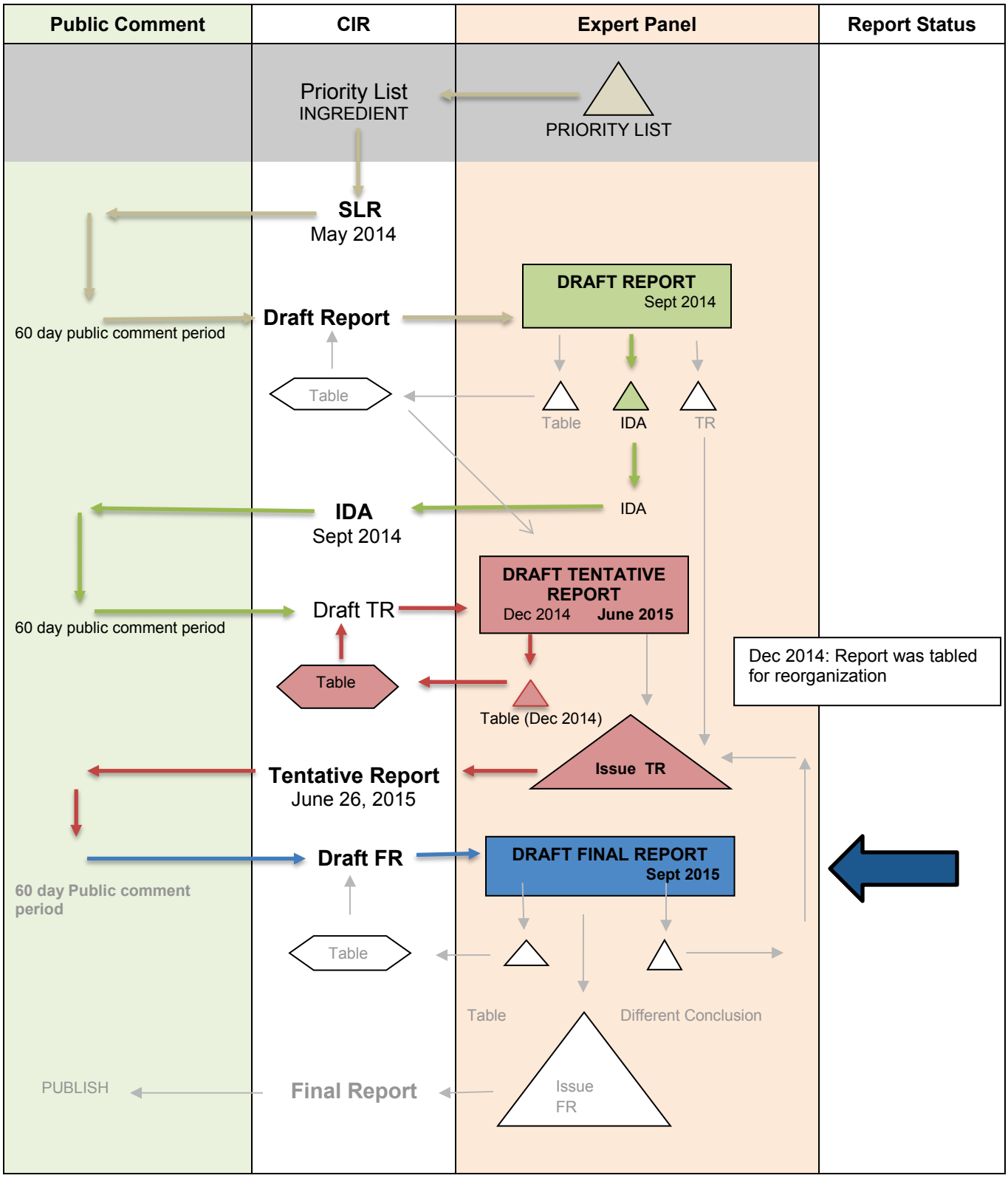
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Polysaccharide Gums

MEETING Sept 2015



CIR History of:

Plant Polysaccharide Gums

A Scientific Literature Review (SLR) was announced on May 29, 2014. Comments and safety test data from the Personal Care Products Council (Council) were received during the 60-day comment period. Use concentration data were received from the Council prior to issuance of the SLR.

Draft Report, Belsito and Marks Teams/Panel: September 8-9, 2014

Comments and safety test data (ocular irritation and HRIPT data on an eye gel containing maltodextrin) received from the Council have been addressed/incorporated.

At the September 8-9, 2014 CIR Expert Panel meeting, the Panel agreed that the ingredients in this safety assessment on polysaccharide gums should be organized to reflect the following 4 major categories that are based on chemical structure: linear, branched, cyclic, and unknown. With this in mind, the Panel issued an insufficient data announcement, requesting method of manufacture and impurities data on each of the ingredients subcategorized within these 4 major categories including, in particular, the hydrolyzed polysaccharide gums and other modified polysaccharide gums reviewed in this safety assessment. Thus, data were requested on polysaccharide gums classified as: linear-modified, branched-modified, cyclic-modified, and unknown structural configuration-modified.

The hydrolyzed polysaccharide gums and other modified polysaccharide gums are of concern in light of available data indicating that dietary degraded carrageenan (poligeenan), unavailable commercially but manufactured via the acid hydrolysis of a certain type of seaweed, induced colorectal tumors in rats. The Panel anticipated that method of manufacture and impurities data on the hydrolyzed/modified polysaccharide gums would provide clarity as to whether these gums are chemically dissimilar to poligeenan.

The Panel determined that glucomannan should be added to the safety assessment based on industry comments to the effect that this cosmetic ingredient induces respiratory tract sensitization, supported by published data. Other issues relating to ingredient safety that were discussed will be included in the Discussion that will be developed.

Draft Tentative Report, Belsito and Marks Teams/Panel: December 8-9, 2014

The following unpublished data received from the Council/industry have been added to the draft report

- Method of manufacture and safety information on hydrolyzed furcellaran
- Composition of products tested in study summaries on hydrolyzed furcellaran clarified
- Method of manufacture, specifications, and MSDS's on modified dextrin and inulin ingredients: dextrin palmitate, dextrin myristate, dextrin isostearate, dextrin palmitate/ethylhexanoate, and stearoyl inulin
- Toxicology data summaries on a material that is structurally similar to corn starch modified
- Toxicology data summaries on a material that is structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate
- Heavy metals analysis on a sodium hydrolyzed potato starch dodecenylsuccinate trade name material
- Eye irritation data on a material that is structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate
- 21-day human cumulative irritation study on a material that is structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate
- Buehler animal skin sensitization study on a material that is structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate
- HRIPT on a cleanser containing sodium hydrolyzed potato starch dodecenylsuccinate
- 3T3 *in vivo* phototoxicity assay on sodium hydrolyzed potato starch dodecenylsuccinate
- Ames test on sodium hydrolyzed potato starch dodecenylsuccinate

The draft tentative report was also revised to include the Panel's recommendations and additional published data.

The Panel tabled the draft tentative safety assessment on polysaccharide gums pending reorganization of the report and to allow sufficient time for industry to provide additional data.

The Panel noted that dividing these ingredients into 5 proposed categories based on their chemical structures helped to clarify the structural similarities among the ingredients, but the presentation of the safety data in the report was not conducive to evaluating these ingredients based on their structural similarities. Thus, the ingredients and the safety data will be reorganized under two major headings, namely Modified and Unmodified polysaccharide gums. The ingredients in the Modified subgroup will be further subdivided into Linear, Branched, Cyclic, and Unknown Structural Configuration. The ingredients in the Unmodified sugroup will be subdivided into Linear Polysaccharides and Salts Thereof, Branched - Natural/Unmodified, Cyclic, and Unknown Structural Configuration.

The Panel also requested information on the method of manufacture and impurities of hydrolyzed carrageenan and glucomannan. Further information is sought to better understand the difference between the cosmetic ingredient hydrolyzed carrageenan and degraded carrageenan (poligeenan), because the data provided suggest the induction of colon tumors in a study in which rats received degraded carrageenan (poligeenan) in the diet or in drinking water. However, the Panel noted that the available studies indicate that carrageenan did not cause dose-related gross or microscopic changes in monkeys in a 7.5-year feeding study, suggesting that carrageenan did not degrade to yield a toxic substance in the gut.

The Panel requested additional data to clarify a report that inhalation of konjac flour induced respiratory sensitization in test animals. Glucomannan is the principle component of konjac flour, but it is not clear to what extent the pulmonary hypersensitivity observed in these animals can be attributed to glucomannan, rather than to some other component of the flour.

The Panel invites additional information on the alkylating and other agents, such as epoxides, anhydrides, and chlorinated compounds that are used to modify polysaccharide gums.

Draft Tentative Report, Belsito and Marks Teams/Panel: June 15-16, 2015

The Panel issued a tentative report for public comment with the conclusion that the polysaccharide gums reviewed in this safety assessment are safe in the present practices of use and concentration, with the exception that the available data are insufficient for determining the safety of hydrolyzed carrageenan in cosmetic products.

The Panel was concerned about the absence of adequate information to distinguish between the cosmetic ingredient hydrolyzed carrageenan and degraded carrageenan (poligeenan). A study suggested the induction of colon tumors in rats that received degraded carrageenan (poligeenan) in the diet. Although composition data on hydrolyzed carrageenan and degraded carrageenan (poligeenan) were not available, the Panel noted that, given the no-observed-effect level (NOEL) for colon carcinogencity in the oral studies and the maximum use concentration of polysaccharide gums in lipstick products, the burden to the colon that would result from the incidental ingestion of lipstick would be well below the NOEL.

Additional information was received on a previous report that indicated the inhalation of konjac flour induced respiratory sensitization in test animals. Additional research suggested that the purified antigen AG40D-2 (acidic protein) was responsible for the respiratory sensitization observed, and that this effect was not attributed to glucomannan. Thus, the Panel's concerns relating to the respiratory sensitization potential of glucomannan were addressed.

The Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities. They agreed that the same concern and suggestion are applicable to alkylating and other agents (e.g., haloethylaminopropionic acid; 3-(dodecenyl)-2,5-furandione; and 2,3-epoxypropyltrimethylammonium chloride) that are used to modify polysaccharide gums.

Draft Final Report, Belsito and Marks Teams/Panel: September 15-16, 2015

Comments received from the Council have been addressed.

Polysaccharide Gums Check List for September, 2015. Analyst – Wilbur Johnson

			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Maltodextrin												**X**		**X**		**X**				
Agar																			**X**	
Agarose																				
Algae Exopolysaccharides														**X**		**X**				
Algin								**X**											**X**	
Alginic Acid																				
Ammonium Alginate																	X			
Amylodextrin																				
Amylopectin																				
Amylose																				
Aphanothece Sacrum Polysaccharide																				
Arabinoxylan																		**X**		
Astragalus Gummifer Gum																				
Avena Sativa (Oat) Starch																				
Calcium Alginate																				
Calcium Starch Isododecenylsuccinate																				
Calcium Starch Octenylsuccinate																				
Cassia Angustifolia Seed Polysaccharide																				
Cichorium Intybus (Chicory) Root Oligosaccharides																				
Corn Starch Modified				**X**		**X**						**X**	**X**	**X**	**X**	**X**		**X**		
Cyclodextrin	X		**X**					**X**									**X**		**X**	
Cyclodextrin Hydroxypropyltrimoni-um Chloride																				
Cyclodextrin Laurate																				
Cyclotetraglucose																				
Dextrin														**X**		**X**				
Dextrin Behenate																				
Dextrin Isostearate																		**X**		
Dextrin Laurate																				
Dextrin Myristate				**X**		**X**						**X**	**X**	**X**	**X**	**X**		**X**		
Dextrin Palmitate				**X**		**X**						**X**	**X**		**X**			**X**		
Dextrin Palmitate/Ethylhexano-ate																				
Dextrin Stearate																				
Echinacin																				
Galactoarabinan																				
Glyceryl Alginate																				
Glyceryl Dimaltodextrin																				
Glyceryl Starch																				
Hydrogenated Potato Starch																				
Hydrogenated Starch Hydrolysate																				

Polysaccharide Gums Check List for September, 2015. Analyst – Wilbur Johnson																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Hydrolyzed Corn Starch Hydroxyethyl Ether																				
Hydrolyzed Corn Starch Octenylsuccinate																				
Hydrolyzed Furcellaran																		X		
Hydrolyzed Pectin																				
Hydrolyzed Soy Starch																				
Hydrolyzed Starch																				
Hydrolyzed Triticum Spelta Starch																				
Hydrolyzed Wheat Starch																				
Hydroxyethyl Cyclodextrin																				
Hydroxypropyl Cyclodextrin																				
Hydroxypropyltrimoni-um Hydrolyzed Corn Starch												X	X	X		X				
Hydroxypropyltrimoni-um Hydrolyzed Wheat Starch																				
Hydroxypropyl Oxidized Starch																				
Hydroxypropyl Starch																				
Hydroxypropyltrimoni-um Maltodextrin Crosspolymer																				
Inulin			X					X										X	X	
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch																				
Magnesium Alginate																				
Mannan																				
Methyl Cyclodextrin													X							
Palmitoyl Inulin																				
Pectin								X									X	X	X	
Phaseolus Angularis Seed Starch																				
Phaseolus Radiatus Seed Starch																				
Pisum Sativum (Pea) Starch																				
Polianthes Tuberosa Polysaccharide																				
Potassium Alginate																				
Potassium Dextrin Octenylsuccinate																				
Potassium Undecylenoyl Alginate																				
Potato Starch Modified				X		X				X		X	X		X			X		
Propylene Glycol Alginate								X									carra geen an			
Pueraria Lobata Starch																				

Polysaccharide Gums Check List for September, 2015. Analyst – Wilbur Johnson

			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Sodium Algin Sulfate																				
Sodium Carboxymethyl Inulin								X		X			X		X			X		
Sodium Carboxymethyl Starch																				
Sodium Dextrin Octenylsuccinate																				
Sodium Hydroxypropyl Oxidized Starch Succinate																				
Sodium Oxidized Starch Acetate/Succinate																				
Sodium Starch Octenylsuccinate																				
Sodium/TEA-Undecylenoyl Alginate																				
Solanum Tuberosum (Potato) Starch								X												
Starch Acetate			X					X											X	
Starch Acetate/Adipate																				
Starch Diethylaminoethyl Ether																				
Starch Hydroxypropyltrimoni-um Chloride																				
Starch Laurate																				
Starch Tallowate																				
Stearoyl Inulin													X		X			X		
Tamarindus Indica Seed Gum																				
Tapioca Starch			X																	
Tapioca Starch Crosspolymer																				
TEA-Alginate																				
TEA-Dextrin Octenylsuccinate																				
Triticum Vulgare (Wheat) Starch																				
Undecylenoyl Inulin																				
Xyloglucan																				
Calcium Carrageenan																	X			
Carrageenan			X		X												X	X	X	
Ghatti Gum								X										X		
Hydrolyzed Carrageenan																				
Potassium Carrageenan																				
Potassium Undecylenoyl Carrageenan																				

Polysaccharide Gums Check List for September, 2015. Analyst – Wilbur Johnson																					
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization						
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Prunus Persica (Peach) Gum																					
Sodium Carrageenan																	X				
Sterculia Urens Gum			X	X				X									X	X			
Glucomannan				X		X	X	X							X		X	X	X		
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate				X								X	X	X	X	X		X			

Polysaccharide Gums

SciFinder Search - 7/1/2013;PubMed Search 11/26/2013

Maltodextrin
Acacia Catechu Gum,
Acacia Farnesiana Gum,
Acacia Senegal Gum,
Acacia Seyal Gum
Agar
Agarose
Algae Exopolysaccharides
Algin
Alginic Acid
Ammonium Alginate
Amylodextrin
Amylopectin
Amylose
Aphanothece Sacrum Polysaccharide
Arabinoxylan
Astragalus Gummifer Gum
Avena Sativa (Oat) Starch
Boswellia Serrata Gum (45)
Boswellia Serrata Gum Extract
Calcium Starch Isododecenylsuccinate
Calcium Starch Octenylsuccinate
Calcium Alginate (65 – Review)
Calcium Carrageenan
Carrageenan
Cassia Angustifolia Seed Polysaccharide
Cichorium Intybus (Chicory) Root Oligosaccharides
Corn Starch Modified
Croscarmellose
Cyclodextrin
Cyclodextrin Hydroxypropyltrimonium Chloride
Cyclodextrin Laurate
Cyclotetraglucose
Dextrin
Dextrin Behenate
Dextrin Isostearate
Dextrin Laurate
Dextrin Myristate
Dextrin Palmitate
Dextrin Palmitate/Ethylhexanoate
Dextrin Stearate
Echinacin
Galactoarabinan
Ghatti Gum
Glyceryl Alginate
Glyceryl Dimaltodextrin
Glyceryl Starch
Hydrogenated Potato Starch
Hydrogenated Starch Hydrolysate
Hydrolyzed Carrageenan
Hydrolyzed Corn Starch Hydroxyethyl Ether
Hydrolyzed Corn Starch Octenylsuccinate
Hydrolyzed Furcellaran
Hydrolyzed Pectin
Hydrolyzed Soy Starch
Hydrolyzed Starch
Hydrolyzed Triticum Spelta Starch
Hydrolyzed Wheat Starch
Hydroxyethyl Cyclodextrin
Hydroxypropyl Cyclodextrin
Hydroxypropyltrimonium Hydrolyzed Corn Starch
Hydroxypropyltrimonium Hydrolyzed Wheat Starch
Hydroxypropyl Oxidized Starch
Hydroxypropyl Starch
Hydroxypropyltrimonium Maltodextrin Crosspolymer
Inulin
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch
Magnesium Alginate
Mannan (570 – Review)
Methyl Cyclodextrin (112)
Natto Gum
Olibanum
Palmitoyl Inulin
Pectin
Phaseolus Angularis Seed Starch
Phaseolus Radiatus Seed Starch
Pistacia Lentiscus (Mastic) Gum
Pisum Sativum (Pea) Starch
Polianthes Tuberosa Polysaccharide
Potassium Alginate
Potassium Carrageenan
Potassium Dextrin Octenylsuccinate
Potassium Undecylenoyl Alginate
Potassium Undecylenoyl Carrageenan
Potato Starch Modified
Propylene Glycol Alginate
Prunus Persica (Peach) Gum
Pueraria Lobata Starch
Sodium Algin Sulfate
Sodium Carboxymethyl Inulin
Sodium Carboxymethyl Starch
Sodium Carrageenan
Sodium Dextrin Octenylsuccinate
Sodium Hydroxypropyl Oxidized Starch Succinate
Sodium Oxidized Starch Acetate/Succinate
Sodium Starch Octenylsuccinate
Sodium/TEA-Undecylenoyl Alginate
Sodium/TEA-Undecylenoyl Carrageenan
Solanum Tuberosum (Potato) Starch
Starch Acetate
Starch Acetate/Adipate
Starch Diethylaminoethyl Ether

Starch Hydroxypropyltrimonium Chloride
Starch Laurate
Starch Tallowate
Stearoyl Inulin
Sterculia Urens Gum
Styrax Benzoin Gum
Tamarindus Indica Seed Gum
Tapioca Starch
Tapioca Starch Crosspolymer
TEA-Alginate
TEA-Dextrin Octenylsuccinate**)**
Triticum Vulgare (Wheat) Starch
Undecylenoyl Inulin
Xyloglucan
Glucomannan **(Search performed on 9/19/2014)**

Search Updated

Hydrolyzed Carrageenan (years 2014 and 2015) – 2/2/2015

Day 1 of the June 15-16, 2015 CIR Expert Panel Meeting – Dr. Belsito's Team

Polysaccharide Gums

DR. BELSITO: Anything else? So let me save this, and we move on to polysaccharide gum. So, we tabled this in December because we wanted some additional time to digest a lot of data that was dumped on us by industry and had also suggested that -- was this the one? Yeah that we wanted it broken down into cyclic, polycyclic, undefined, et cetera et cetera, and quite honestly that break-down still didn't help me to wrap my brain around this huge group of chemicals and at the end of the day I still was sort of confused whether there were any issues within that we really needed to be concerned about, and reading through the minutes it was clear that the other group wanted to go safe as used.

And then there was that whole issue with the degraded carrageenan and colonic tumors that we're concerned about that I don't think we still necessarily have an answer to, except that it doesn't really appear that these get absorbed, at least from what I could see, so I wasn't -- another question that I had back to us is, are these absorbed? And if they're not absorbed, why we were so concerned about all this carcinogenic effect in animals? And then there were just huge amounts of verbiage that I thought could be just gotten rid of and summarized in tables. I mean those carcinogenicity and co-carcinogenicity and carcinogenicity preventing pages went on and on and on. So I guess my first question now to my colleagues is, you know from a skin scent point, I'm really not concerned about these, so are they absorbed and are you concerned about all of the other data that we have here?

DR. LIEBLER: So I'd like to start out by thanking Wilbur for reorganizing the report as we asked him to because you know, we had a lot of discussion on how best to organize this -- this is basically a somewhat disorganized group of very heterogeneous chemicals. And, I take my hat off to you Wilbur, you did exactly what we asked you to, and it's still a little confusing, but that's because of the collection of ingredients we have here, so it is what it is. As far as the degraded carrageenan or hydrolyzed carrageenan, the problem I have is that we cite this study on, there are actually several studies on colon carcinogenicity by this degraded carrageenan. And then we never really discussed about whether it's absorbed. If it's not absorbed, these studies are really pretty irrelevant. However, an industry representative or somebody told us at the first meeting we talked about this, that the degraded carrageenan, and hydrolyzed carrageenan were different. But no one ever showed us any data to prove that. We don't have any literature citation; we just have the statement that's different.

DR. BELSITO: We do have, I don't know if this is part of the literature but on page 64 of the PDF under carrageenan it says that the product called degraded carrageenan has been produced from extracts of Eucheuma spinosum seaweed by treatment with dilute hydrochloric acid. And then it goes on to say the most common forms are designated capiota and landum.

DR. LIEBLER: But that doesn't explain how the hydrolyzed carrageenan is produced.

DR. BELSITO: No, I understand.

DR. LIEBLER: And the descriptions in the papers about the carcinogenesis, the colon carcinogenesis, don't give a precise description either about how that's produced except that it's hydrolyzed in acid.

DR. BELSITO: Right, so I mean we don't basically know that they are different.

DR. LIEBLER: We don't know that they are different.

DR. BELSITO: But if it's not absorbed, do we really care?

DR. LIEBLER: Right it's not going to cause colon carcinogenesis, because in those studies it was administered bicophage. So you're right, I mean I think the issue goes away in the discussion. We never did get the information we asked for, but the lack of absorption makes it pretty much a moot point. So we have to note the carcinogenesis studies and then simply say in the discussion that these aren't absorbed.

DR. KLAASEN: From the skin.

DR. LIEBLER: From the skin. Right.

DR. KLAASEN: And our problem in responding to that is the degraded is apparently a lab sample material and there is no supplier of hydrolyzed. So --

DR. LIEBLER: But it's in the dictionary, which is why it's in our report, basically. So we're just stuck with this stuff.

(laughter)

DR. ANSELL: Right, it has no uses, no supplier.

DR. LIEBLER: Right. So how'd it get in the dictionary?

DR. ANSELL: The dictionary does not relate to safety. It is simply a unified nomenclature system.

DR. LIEBLER: I see, okay.

DR. SNYDER: So I think we'll be okay with that hydrolyzed versus degraded. It just has to be captured in the discussion, and then, what I didn't see in this newest version was we had that information on the sensitization in the Kojak flower where they actually have now found that it's actually a specifically protein and it's not glucomannan, whatever it is. And so I think we need to capture that -- you haven't incorporated that yet, have you?

DR. LIEBLER: No it has not, but I might mention that in the dictionary, conjacmannan is listed as a technical name for glucomannan and in the World Health Organization report on Konjak flower; conjacmannan is listed as a common term for that. So at this point I don't whether or not Konjak flower is a trade name material that you know basically is glucomannan in a cosmetic product or not.

DR. SNYDER: But I guess the point I was making was that it's not the glucomannan component of Kojak flower that causes the sensitization.

DR. ANSELL: It's the protein.

DR. SNYDER: It's the protein yes, so we need to make that clear in the discussion and bring that data and that material into the body of the document.

MS. WEINTRAUB: So are you more focused on the respiratory sensitization or on the inhalation, or do they go together, since the respiratory sensitization is occurring because of the inhalation?

DR. SNYDER: Yes.

MS. WEINTRAUB: Okay.

DR. SNYDER: Yes.

MS. WEINTRAUB: And you feel like the data addressed this?

DR. SNYDER: Well, it's not due to the glucomannan, it's due to a separate protein, this AG40D-2, and it's not just that being present but it's in, at least, from what I read in that report, it's sort of ratio of the acidic version to the basic version, and so I think that we've gotten the issues to be discussed.

DR. BELSITO: Okay, in terms of lack of absorption, I just want to point out that we have absorption on -- only dermal absorption only on hydroxypropolcylodextrine. So I think, and we're looking at, I don't know, how many ingredients altogether in this report now? I mean, it's huge, right? And they're very disparate from what I can tell, so are we comfortable with, I mean, 102 ingredients. Are we comfortable that all the other 101 are not absorbed? Are we concerned only about carrageenan being absorbed?

DR. LIEBLER: I think we're comfortable based on the size of these molecules that they're not going to be absorbed.

DR. BELSITO: Okay.

DR. LIEBLER: They're very large. The cyclodextrine got put into the report simply because it has chemical similarity in terms of its composition and structure, but it's a much smaller molecule and it is actually -- its primary use is to facilitate absorption of other molecules, so it's the exception that proves the rule, and essentially here, so --

DR. BELSITO: Fine. And then hydrolyzed carrageenan has no reported uses. Carrageenan is a 1.1 percent in a lip product that could be incidentally ingested and you're okay with that? Just want to make sure we have all the bases covered here.

DR. LIEBLER: Yeah, hydrolyzed carrageenan would not be absorbed.

DR. BELSITO: No, what I'm saying is that carrageenan --

DR. LIEBLER: Yeah.

DR. BELSITO: Is used in a lip product up to 1.1 percent. Hydrolyzed

carrageenan is not used in cosmetics or there are no reported uses, am I correct?

DR. LIEBLER: So carrageenan in a lip product at a higher concentration is of no concern.

DR. BELSITO: Okay. And it's of no concern because it's --

DR. SNYDER: Not degraded naturally.

DR. BELSITO: Okay.

DR. LIEBLER: Yeah, it's a mercuric, isn't it, that dietary -- it's a food additive anyway, so, yeah, that's okay.

DR. ANSELL: Carrageenan is extracted from seaweed and is a major thickener in the food products.

DR. BELSITO: Okay.

DR. LIEBLER: So the carrageenan was fine until this hydrolyzed carrageenan thing got introduced and then --

DR. ANSELL: To the extent there continues to be concern, we could just delete the two or go insufficient with those two, or sideline them outside this group.

DR. LIEBLER: Those two meaning --

DR. ANSELL: The hydrolyzed and --

DR. LIEBLER: Degraded --

DR. ANSELL: Degraded.

DR. LIEBLER: Yeah, the only one listed in the dictionary is hydrolyzed carrageenan. Degraded is a term that emerged from the literature.

DR. ANSELL: Right but I -- isn't the concern that hydrolyzed may in fact be degraded?

DR. BELSITO: Yeah. We don't know.

DR. LIEBLER: It's hydrolyzed, and degraded. I mean --

DR. ANSELL: Yeah.

DR. LIEBLER: It's a pejorative way of looking at hydrolysis. Right Jay?

DR. ANSELL: I agree. But to the extent you know that we have a hundred materials that we're comfortable with that are understandable and there's one material which is not used, not an article of commerce, there's no suppliers and if that's what's tying us up, then --

DR. BELSITO: I don't know that it's tying us up. I'm just asking the question.

DR. LIEBLER: We need to figure out a way to deal with it. It's in the report. I didn't realize it was an option to ditch it. But --

DR. ANSELL: Okay.

DR. LIEBLER: So, it's right there.

DR. BELSITO: So we --

DR. LIEBLER: We clearly state it. It's not degraded or absorbed.

DR. BELSITO: Right. Okay. So we're comfortable with including hydrolyzed carrageenan in the report? Or we want to get rid of it?

DR. LIEBLER: Well it would be a lot easier if we could get rid of it. Because we just remove all reference to it from the report. Then we don't have to explain why we're not worried about it.

DR. BELSITO: But then we have a potential cosmetic ingredient out there without a view point on it.

DR. GILL: You have to say why it wasn't included in that.

DR. BELSITO: Right.

DR. ANSELL: And it looks --

DR. BELSITO: Because remember, even though it's not used, if it's in the dictionary, which is a huge issue, it could potentially be used.

DR. ANSELL: Well any material could be potentially used.

DR. BELSITO: I understand, but even more potential and it's a target for anyone who's looking to say okay, you guys looked at it. You now think there's actually an issue with this ingredient and you didn't act on it, so we either think there's an issue and we say it's insufficient for whatever --

DR. SNYDER: I don't think it's insurmountable -- I don't think it's an insurmountable task. Let's deal with it.

DR. BELSITO: Okay, well that's what I'm asking you to deal with it, because on the skin, I'm fine with it. So you tell me how to deal with it.

MS. WEINTRAUB: So are you saying, Dr. Liebler, is that you think it should be insufficient? I mean, if just taking it out isn't really an option?

DR. LIEBLER: So we have options. We could say it's insufficient and wait for data that won't appear, and then it will go to the non-supported. Or we can say, not take -- say that it's insufficient and we can simply say that this material is unlikely to be absorbed. We treat that under discussion and we roll it into the safe as used, but it's not used.

DR. BELSITO: But then -- okay, the safe as used, then we have to look across the board at what level, so we don't think it's absorbed from skin products, and we need to look across the board at the highest mucous membrane use of any of these polysaccharides and carrageenan was like at one point something, but I didn't look at all the others, so where are we with incidental ingestion for the others? What's the highest? Is that summarized in the use section? Or do we have to go through the table? And I just think we need to know what we're dealing with before we act.

DR. LIEBLER: So, Wilbur, is the hydrolyzed carrageenan the hydrolyzed ingredient in this report? I'm scrolling through, but do you know off the top of your head?

DR. BELSITO: Whether it's hydrolyzed cornstarch, hydrolyzed soy starch, hydrolyzed starch, hydrolyzed --

DR. LIEBLER: Or hydrolyzed pectin, sure, yeah, okay. Okay, so maybe what we need to do is simply say that we're insufficient for method of manufacture, chemical composition for hydrolyzed carrageenan because that would be the only way we could differentiate it from the lab material that produced the carcinogenesis results in the rodent studies. And sure we could argue it's not absorbed, but actually if we don't know what the properties are of that material, we can't really say with much confidence that it's not absorbed even though I'd be willing to bet that it's not absorbed. And so we say safe as used for everything except insufficient for the hydrolyzed carrageenan, and we know we won't be getting those data so it will eventually just go to unsupported.

DR. BELSITO: So safe as used except hydrolyzed carrageenan for which we need what, method of manufacture and impurities?

DR. LIEBLER: Yes, chemical composition.

DR. BELSITO: We need chemical composition.

DR. ANSELL: Because it's not going to answer your question. Your question is how is hydrolyzed related to degraded? So if I give you an exact composition of hydrolyzed, it's not going to answer your question.

DR. LIEBLER: Well, certainly -- yeah, you won't know what it is, how it relates to the material in the studies.

DR. ANSELL: Right, so we'd have to do a complete analysis of the degraded, which --

DR. LIEBLER: Is unavailable probably. Okay, method of manufacture and impurities, fair enough.

DR. BELSITO: But we need to know that vis-à-vis the degraded material that was used in that study.

DR. LIEBLER: Right.

DR. BELSITO: We're not going to know that.

DR. ANSELL: No.

DR. BELSITO: Because the material in the study is not further detailed, just the acid hydrolysis. Because that's what you really want to know, Dan, right? How does cosmetic grade hydrolyzed carrageenan differ from this degraded carrageenan that caused cancer of the colon?

DR. LIEBLER: Right.

DR. BELSITO: So the question would be -- we would need dermal absorption for cosmetic grade hydrolyzed carrageenan or a study or something showing us why cosmetic grade hydrolyzed carrageenan would be sufficiently different from this degraded carrageenan used in this study, that it wouldn't produce colon cancers if absorbed.

DR. LIEBLER: Right. So that's not going to happen.

DR. ANSELL: So if we go back to the absorption question, though, that is something we felt comfortable with.

DR. BELSITO: That still raises the issue of use in a lip product.

DR. LIEBLER: Carrageenan used as a lip product is fine.

DR. BELSITO: No, hydrolyzed.

DR. LIEBLER: Yes, hydrolyzed is not used in any product.

DR. BELSITO: I understand, but we're saying assuming --

DR. LIEBLER: If it -- yes -- if it were, right.

DR. BELSITO: Then how high can these products go in a lip product? Some of them are quite high.

DR. LIEBLER: Right.

DR. BELSITO: What's the highest incidental ingestion? That's what I was trying to look for. Is it summarized in the cosmetic use section?

DR. ANSELL: Well, we have a --

DR. BELSITO: So it's up to 50 percent in face masks, 45 percent in hair grooming, so I'm assuming it's not graded at 50 percent in a lip product, but we don't know. We're only given ranges there. I saw one that was 15 percent I think, 1.1 for algal and then the wet products.

DR. ANSELL: Well, we do have a NOEL in the degraded carrageenan feeding studies.

DR. BELSITO: What was that?

DR. ANSELL: 1 percent of the diet.

DR. BELSITO: 1 percent was negative.

MS. FIUME: There is a 15 percent reduction in meristem.

DR. BELSITO: Yeah, that was the highest that I've seen so far.

MS. FIUME: 16.8 for dextrin palmitate.

DR. BELSITO: Yeah. Did you get through them all, Monice, because I'm still scrolling here?

MS. FIUME: Yeah, 16.8 was the highest I saw.

DR. BELSITO: Okay, so if we were to go with the safe as used, at some point that's what we would potentially be allowing in a lip product up to 17 percent. And we just heard that the NOEL was 1 percent in the diet for the degraded carrageenan.

DR. LIEBLER: So I don't think we have a problem.

DR. BELSITO: So if we had data that showed that it wasn't absorbed from the skin, or even if it is absorbed, so is it not a problem? Is it now everything's safe as used or are we still taking the hydrolyzed carrageenan out?

DR. LIEBLER: Well, I think where we're going for the hydrolyzed is insufficient.

DR. BELSITO: But we just heard that the NOEL in the feeding study for the degraded was 1 percent in the diet.

DR. LIEBLER: And you're saying incidental exposure would reach that level?

DR. BELSITO: I'm not saying anything. It's out of my bailiwick. I'm asking you with that information, does that clear it or are we still going insufficient? I'm happy any way. I just want to have some sound reasoning behind why we're doing this.

DR. KLAASSEN: I personally think it's sufficient. I mean the exposure is theoretically two ways. One is from lipstick and we basically concluded from the study that was done by oral administration that there was no problem at these kinds of doses, and number two were out of exposure to the skin and these things are not going to go across the skin to any reasonable amount. Sugar won't go across the skin and polysugar definitely won't go across the skin.

DR. BELSITO: Okay, so we are back to safe as used with a discussion of hydrolyzed carrageenan that the maximum amount that would be in a lip product is 16.8 percent, that the NOEL even for the degraded carrageenan, which we've been told is not a cosmetic product, was at 1 percent in the diet long term, and that these products are not absorbed across the skin. Is that where we're at?

DR. LIEBLER: Yep, I'm fine with that.

DR. BELSITO: Okay, so we're back to safe as used for the whole group with a discussion regarding hydrolyzed carrageenan. Any other comments here before we move on?

DR. LIEBLER: There was one thing, Wilbur, in the discussion, the first paragraph, the last sentence of the first paragraph. You had talked about the similarities of the composition and then you say "therein read-across may be appropriate from one ingredient to the next." So read- across I think makes -- I think it's the wrong word and I would change it to "inference" because I just don't want to invoke the term "read-across" when we don't have sort of a systematic variation of chemical structures that allow us to more systematically select and evaluate analogs and their data. We don't have that here. It's much looser. And so I think we need to be careful when we trot out the term "read- across," so let's just say "inference" instead.

DR. BELSITO: Okay, anything else?

Day 1 of the June 15-16, 2015 CIR Expert Panel Meeting – Dr. Marks' Team

Polysaccharide Gums

DR. MARKS: Okay. I think we have learned a lot about centella asiatica. Next one, polysaccharide gums. Wilbur, you are up again. Our team in December moved all ingredients were safe but the Belsito team wanted it tabled to divide a large group into modified/unmodified, linear, cyclic, et cetera, groups. Has our conclusion changed? You did that, Wilbur, you did it mainly in a table type thing, putting which subdivisions they were in.

DR. SLAGA: In a lot of cases, it wasn't many to subdivide.

DR. MARKS: Right.

DR. SHANK: That did not help me at all.

DR. SLAGA: Me either.

DR. HILL: What is interesting about that is for me, I did not consider hydrolysis would be modified. When I was looking at modified, I was thinking only the things where something is tagged onto the sugar, where we are actually derivatizing the sugar using alkylating agents, those are the ones I would have considered to be modified and not the ones that are just chopped up. In humans, we chop up a lot of these, and the ones that we don't are just going to stay in one big piece.

DR. MARKS: Team, tomorrow do you want me to move a tentative report with a safe conclusion?

DR. SHANK: Yes.

DR. MARKS: Ron Hill?

DR. HILL: I had some issues that I identified. As you recall, I was one of the prime movers in trying to make sure we knew what was being used to modify these things and how, and there was a good bit of data forthcoming, which was heartening, but it raised a couple of issues that weren't there before when we didn't have that information. Even though my first take on all of this when I got to the bottom of it was everything is fine.

DR. MARKS: Okay. In Wilbur's memo, he brought up a couple of issues again. Tom, Ron, do you want to comment about the carrageenan and colon tumors? Is that going to be in the discussion? How do you want that handled?

DR. SLAGA: I think it obviously would have to be in the discussion, but the colon cancer, our understanding from the discussion last time is it is not used in any products that way. If it is un-hydrolyzed, it has really none of that activity. It's only in the laboratory they specifically hydrolyze it.

DR. SHANK: That's right.

DR. JOHNSON: We have an ingredient called hydrolyzed carrageenan. We have a cosmetic ingredient that is hydrolyzed carrageenan.

DR. SHANK: That is not the same as the material used in the cancer study. Is that not correct?

DR. EISENMANN: That's what we believe, although there is no supplier any more for hydrolyzed. If you want to say insufficient data, we're fine with that.

DR. SHANK: Yes, we would need a definition of what is hydrolyzed carrageenan and how does that compare to the laboratory hydrolyzed carrageenan.

DR. MARKS: I'm looking. Where is the hydrolyzed? I see carrageenan. A lot of ingredients here. You would put insufficient for hydrolyzed carrageenan or just mention that in the discussion that we expect it's not the same hydrolyzed carrageenan used in the laboratory? Is that how you would handle it? Is it an ingredient?

DR. EISENMANN: Yes, there is an ingredient called hydrolyzed carrageenan.

DR. MARKS: Somehow I'm missing it. I'm looking under the table right in the beginning of the polysaccharide gums checklist.

DR. EISENMANN: It's on the second from the last page, near the bottom.

MR. MARKS: Maybe I didn't print that out. How do you want to handle the hydrolyzed carrageenan, say it's insufficient?

DR. SHANK: I would say that's insufficient.

DR. EISENMANN: One of them needs to come out of the report. Acanasian is

actually a compound with a glucose, we had it defined incorrectly in the dictionary originally. I provided an updated monograph. There is a structure now we can associate with it. It's not a polysaccharide at all. That can just come out.

DR. MARKS: Then what we would need is for the hydrolyzed carrageenan, insufficient to confirm what, the cosmetic?

DR. SLAGA: Yes, but if it's the same as used in the laboratory relating to colon cancer. What's the difference between the two. There has to be some difference.

DR. HILL: There is information about low molecular weight carrageenans. I think it does address the difference some, but I don't know if low molecular weight carrageenan is similar to hydrolyzed carrageenan.

DR. MARKS: Okay. The second question I had was this respiratory allergy, which Wilbur also mentioned. How are we going to handle that in the discussion?

DR. EISENMANN: There is a review that I provided Wilbur, there has been some work, it's actually a protein that is causing the problem. The question is how it is used in cosmetics, if you want to go with insufficient, and ask that question, that would be fine. There is one company that is using it and they told me they were getting out of it. I'm not going to get any more information.

DR. HILL: Given the composition and method of manufacture table, it's giving 2 to 8 percent protein.

DR. EISENMANN: Most of them have not been purified and I presume it has -- really, it is more purified, but I haven't been able to get that information from the suppliers. That may be a question you want to ask.

DR. HILL: This line puzzled me because it is reporting 3 to 5 percent, which I assumed if you burned the stuff, what is the residual ash and not there is actually ash in the glucomannan.

DR. JOHNSON: I might just add that in the dictionary, it is listed as a technical name for glucomannan, and according to the report on Konjac, konjacmannan is another name for Konjac flower. What I don't really know is whether or not you would consider Konjac flower as a trade name material for glucomannan and that is what is being used in cosmetics.

DR. EISENMANN: I don't know the answer for sure either. That is what I would say is the insufficiency, what is the difference. I don't know how much, are they purifying the Konjac flower, are they getting this protein --

DR. MARKS: So, we will have an insufficient. That takes care of the second ingredient. Does that sound good, team? We will have an insufficient also on the glucomannan. That will be the need is how much protein is in the cosmetic or composition? How do you want to word that?

DR. EISENMANN: A comparative of the composition between it and Konjac flower.

DR. MARKS: It is really the protein we are concerned with, obviously, from respiratory allergy, protein composition. Okay. I think those were the two big -- do you like the report? I know you said it didn't make any difference.

DR. EISENMANN: I have one question, when you say "linear," is that referring to the final compound or is it referring to the polysaccharide? If you take a linear and hook something on it, would you put that in branched? I would put that in linear modified.

DR. HILL: That's what I was saying, from my way of thinking, but I don't know what Dr. Liebler intended. I'd have to go back and read the transcript, was I the one that wanted modified versus unmodified, or did they also want that. I don't remember.

The specific concerns I had, and there are just a few specific derivatizing agents, and I still have remaining concerns that is not addressed in our current discussion, for example, as to how much do we have to worry about, and how does industry assure those levels are kept to a level below toxicological concern.

Because these things are used in high concentration, if we have five percent residual, for example, that might be an issue, but now I don't know because I didn't thoroughly research the toxicology of that one, but my superficial searching didn't turn up anything that satisfied my curiosity, and there were a couple of other agents.

DR. MARKS: Wilbur, we had this NICNAS report. Ron, Tom, do you have

any comments? My comment is what does it mean.

DR. SHANK: NICNAS?

DR. MARKS: Yes. Was it helpful, and if it was --

DR. HILL: Isn't this the one where it was determining -- or a different one, because they are running together in my head, where we thought maybe we already had it from an unpublished data submission earlier.

DR. EISENMANN: Correct. What I got out of it is they use like read across, the other compound is in the report also. In other words, their read across compound is one of the compounds in the report. The data that you have on the potato is already in the report, but the data on the read across is not. I don't think that is in the report and that is a compound in the report -- our report.

DR. MARKS: What is that now?

DR. EISENMANN: They use a read across. I would have to find the NICNAS report.

DR. JOHNSON: It's on sodium hydrolyzed potato starch --

DR. EISENMANN: Yes, but they used an analog, and the analog that they used is also in our report.

DR. MARKS: Is it worth including it as a reference?

DR. EISENMANN: Yes, I think it probably is. We don't have another source of that data.

DR. MARKS: Okay. Any other comments? Tomorrow, I will be moving that we issue a tentative report for these polysaccharide gums with a safe conclusion for all the ingredients except for an insufficient data conclusion on the hydrolyzed carrageenan. We need what is different between the lab and cosmetic grade hydrolyzed carrageenan specifically with reference to colon tumors, and then with the glucomannan, need the composition and cosmetic grade versus Konjac flower, which contains a protein causing respiratory sensitization.

Does that sound good, team?

DR. SHANK: Yes.

DR. MARKS: Any other comments? We will see whether the Belsito team still get hung up on structures. We will let them figure that out. We were happy without them, I hope we don't get in a long discussion as to which ingredient should go on which structure.

DR. SLAGA: Or which category.

DR. MARKS: Or which category; yes. Let me close that.

DR. HILL: Wilbur, after your list, there is a derivatizing agent, I'm trying to find the exact name and I haven't found it. If you look at what is used to make the hydroxypropyltrimonium, you will know what that is and we don't have to waste time while I find it.

DR. JOHNSON: You're concerned about that particular --

DR. HILL: Yes, at really residual levels because these are large molecules across the board, so penetration even in the mucous membranes, my concern was residuals of these modifying agents. I have every reason to believe that across the industry they are working to minimize these if not completely eliminate them below limits of detection, but again, issues were raised that weren't there the last time because there are missing pieces of information.

Day 2 of the June 15-16, 2015 CIR Expert Panel Meeting – Full Panel

Polysaccharide Gums

DR. BERGFELD: Okay. Thank you. Then, we go to the next section, which are reports advancing, and the first one in that group, Dr. Marks, the polysaccharide gums.

DR. MARKS: So, at our December meeting, the CIR expert panel tabled a draft tentative report pending reorganization of the report to allow industry to provide additional data. Our team in December actually felt all of these ingredients were safe and moved to that, but because of the concern about the large group dividing them into modified, unmodified and linear cyclic structures, we decided to, obviously, table it.

Today, our team felt we could move forward with a tentative report with a safe conclusion for all, except insufficient for hydrolyzed carrageenan. And our team wanted to know what was the difference between the laboratory carrageenan which caused colon tumors and cosmetic grade carrageenan.

And then the second ingredient insufficient was the glucomannan. And again, what our team felt was we needed its composition of the cosmetic grade versus the konjac flour that caused respiratory allergy, and is the cosmetic grade free of presumably, the protein that causes this allergy that would be present in the food. So again, move tentative report safe conclusion for all, except insufficient for carrageenan and glucomannan.

DR. BERGFELD: Donald?

DR. BELSITO: Well, we went safe with all of them. In terms of the hydrolyzed carrageenan integrated, it's quite clear that we're not going to get that information. And even if we got the information as to what hydrolyzed was, it doesn't help us, because we would need to know exactly what was the degraded that was used in that study.

However, the study did have the NOEL for the colon carcinoma effects were 1 percent. And we noticed that the highest amount use was 16.8 percent of lip product, and it's not absorbed across the skin. So, that would mean you would have to put on a tremendous amount of lipstick or eat a tremendous amount of lipstick to get to that 1 percent dose. So, we felt that even if the hydrolyzed carrageenan was similar to the degraded, it was not an issue as used in cosmetics. And we did not have issues with the konjac flour, and I'll let Paul and Dan address that.

DR. BERGFELD: Paul?

DR. SNYDER: Well, we received data in, I believe, wave two regarding that the actual protein has been identified that causes that hypersensitivity, and it's not glucomannan. It's that AG40D-2, an acidic protein. And so, I thought that it was -- you know, we could provide documentation that it wasn't glucomannan that was the culprit in that. It was another protein that had been isolated in the konjac flour. So, we didn't feel that that was an issue any longer.

DR. BERGFELD: Dan, do you wish to comment, as well?

DR. LIEBLER: I don't have anything else to add.

DR. BERGFELD: Ron Hill?

DR. HILL: Yeah. Could we make sure that somewhere in the discussion, that's noted?

DR. BERGFELD: Mm-hmm.

DR. HILL: If we go that way? And I don't know that the rest of our team wants to, anyway, but --

DR. MARKS: My feeling is that that's fine, as long as it's captured in the discussion, which obviously, it would be.

DR. BERGFELD: Do you want to rescind your motion and restate it?

DR. MARKS: Yes. I move that tentative report -- well, first let me check with my team. Okay? I move that -- I'll rescind the previous motion and move that a tentative report be issued with a safe conclusion for all of the ingredients.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion?

DR. SHANK: How is the hydrolyzed carrageenan going to be handled in the discussion?

DR. BELSITO: That would be --

DR. SHANK: You can't ignore it.

DR. BELSITO: No, you cannot ignore it. I pointed that out, that there is a NOEL of 1 percent. The highest use is on a lip. That's 16.8 percent. And these are not expected to be absorbed again, across the skin. So, the total internal body burden to the colon will be well below that NOEL.

DR. SHANK: But we usually don't speak of NOELs for carcinogens, so I don't like that terminology.

DR. BELSITO: Okay.

DR. SHANK: Sorry.

DR. BELSITO: Because it's probably not a genotoxic effect in this case. Right?

DR. SHANK: You don't know that, though.

SPEAKER: We don't.

DR. BERGFELD: Would you make a recommendation, Ron, for what you'd like said in the discussion?

DR. SHANK: Well, this was the problem. We would have to say something that the cosmetic grade hydrolyzed carrageenan --

SPEAKER: It's different.

DR. SHANK: -- is different from the special laboratory preparation.

DR. BELSITO: Well, we were told that --

DR. SHANK: Or we're assume that.

DR. BELSITO: -- at the last meeting, but we never got written confirmation of it.

DR. SHANK: Right.

DR. BERGFELD: Jay?

DR. LIEBLER: We really have no data on that, essentially. That was something we were promised initially. No publication, no, you know, certificate of analysis or anything like that.

DR. BERGFELD: Jay, do you want to respond?

DR. ANSELL: Because it's not a material commerce. I mean, you know, that's the problem we faced yesterday, is that the issue is not what is hydrolyzed. The issue is what is the degraded material, since the hydrolyzed doesn't actually exist. It becomes almost a philosophical discussion. So, I think the wave -- you know, we support the approach that the Belsito team took yesterday, and we just need to address it within the discussion. But I have no better verbiage than you.

DR. SHANK: So you're relying on a "NOEL" as far as this carcinogen, and the concentration used in lipstick? Is that what you're saying?

DR. ANSELL: We're relying on the report of a laboratory material is not relevant to the safety assessment of this class of materials.

DR. SHANK: How do we know that?

(No response heard)

DR. SHANK: How do we know that it's not relevant to the hydrolyzed carrageenan used in cosmetics?

DR. SLAGA: You have to address it in a discussion, but I don't see a way out of it right now, because --

(Simultaneous discussion)

DR. SHANK: You go insufficient for the hydrolyzed.

DR. SLAGA: Yes.

SPEAKER: That's what we said.

DR. SLAGA: Yeah, that's --

DR. HILL: So if the logic of a NOEL, whether you call it a NOEL or not, but if that line of thinking is not acceptable, then I'm personally back to the problem of not knowing what it is relative to the stuff that produced the tumors.

DR. SHANK: Right.

DR. HILL: I think the exposure difference is substantial between the rodent study and the maximum amount that would be encountered in the use of a product. But you know,

we're kind of on this endless circle. The stuff is not used; it's not supplied, but it's listed in the dictionary, I guess. It's in our report, and we are not going to be able to resolve the composition issues.

So, we can say insufficient for composition, and it's just a way of dead-ending this argument, because even if we got the composition data, we wouldn't have the composition data on the stuff in the study.

DR. SHANK: Right.

DR. HILL: So, we'll never be able to resolve the issue. So, it will go insufficient and then unsupported.

DR. BERGFELD: Kurt, do you have a comment?

DR. KLAASEN: Even if we had the composition of both of them, it still wouldn't help you, because you wouldn't know which one of those peaks was causing the problem. You know? There might be -- you know, it's not a simple thing.

DR. BERGFELD: Well, we've rescinded one motion, and it looks like we're going to rescind it again. So, do we want to restate the motion (Laughter)? I think that if we have general consensus -- do we not, Don, from your side, to go insufficient?

DR. BELSITO: It's not used -- we'll go insufficient with a hydrolyzed and the data needs would be to further understand the calling carcinogenicity of the degraded carrageenan.

SPEAKER: Yeah.

DR. BERGFELD: Okay.

DR. BELSITO: By whatever means is possible, which is --

(Simultaneous discussion)

DR. SLAGA: And we have to sufficiently discuss that, because it really hangs out there.

DR. LIEBLER: So, the insufficient, then, would be the composition and carcinogenicity.

DR. SLAGA: Right.

DR. BELSITO: Gotcha.

DR. BERGFELD: Dr. Marks, again. (Laughter)

DR. MARKS: I will rescind my previous motion. It must feel like the Belsito's team ought to now make the motion. But I'll rescind my previous motion and move now, that we issue a tentative report with a safe conclusion for all, except the hydrolyzed carrageenan and the concern has been really well discussed here, concerning the production of colon tumors in the laboratory.

DR. BERGFELD: Is there second?

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion? Ron Hill?

DR. HILL: Yeah. Unrelated to that, the industry was wonderfully forthcoming in providing what I, and maybe not only I, asked for last time, which was calculating agents that were used to make some of these modified agents. I just want to make sure we get language -- this is a tentative report, so we'll see it one more time, presumably. Right?

I want to make sure that we get language in there similar to what we've used in polymers, where we have these agents that relate to industry's efforts to minimize any residual levels of these. And I think I gave you three specific ones that were there yesterday, that we needed to make sure might be listed as examples.

DR. BERGFELD: Thank you. I'm going to call the question. All those in favor of the motion, please indicate by raising your hands. Thank you. Unanimous. Good discussions. Moving on to the second ingredient, Dr. Belsito.

Safety Assessment of Polysaccharide Gums as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (the Panel) reviewed the safety of 106 ingredients, which function as viscosity increasing agents in cosmetic products. The Panel reviewed relevant animal and human data on these ingredients. The Panel concluded that most of the polysaccharide gums are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment, but that the available data are insufficient to make a determination that hydrolyzed carrageenan is safe under the intended conditions of use in cosmetics. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. The Panel was concerned about the presence of alkylating and other agents that are used to modify polysaccharide gums in cosmetics. Industry should use good manufacturing practices to limit impurities.

INTRODUCTION

The safety of 106 polysaccharide gums (see Tables 1 and 2) as used in cosmetics is reviewed in this safety assessment. The polysaccharide gums are each naturally derived materials that comprise polysaccharides obtained from plants or algae. Based on the different chemical structures that are associated with polysaccharide gums, these ingredients can be subdivided into categories such as modified, unmodified, linear, branched, and cyclic. Regardless of how they are structured, all of the "moieties" that comprise the molecular structures of these ingredients are polymers composed of monosaccharides.

Although these ingredients could be categorized in multiple ways, all of these ingredients fall into two predominate categories, modified and unmodified. The ingredients in the Modified subgroup have been further subdivided into Linear, Branched, Cyclic, and Unknown Structural Configuration. The ingredients in the Unmodified subgroup have been subdivided into Linear Polysaccharides and Their Salts, Branched - Natural/Unmodified, Cyclic, and Unknown Structural Configuration.

Based on chemical similarities, relevant data on the following are included for use in evaluating the safety of ingredients in this review: wheat bran extract (contains ~ 80% arabinoxylan oligopeptides) - for use in the safety assessment of arabinoxylan (branched - natural/unmodified subgroup); pectin-derived acidic oligosaccharides (mixture of linear oligomers and small polymers of galacturonic acid) - for safety assessment of pectin (branched - natural/unmodified subgroup), which consists chiefly of partially methoxylated polygalacturonic acids; and carboxymethyl inulin - for safety assessment of sodium carboxymethyl inulin (branched - modified subgroup). Many of the polysaccharide gums reviewed in this safety assessment function as viscosity increasing agents in cosmetic products.[1] Other functions are listed in Table 2.

As a group, polysaccharide gums comprise polymers of simple saccharide monomers. Their substantial molecular sizes suggest that skin penetration of these ingredients would be unlikely. Thus, these ingredients are unlikely to have significant systemic accessibility and any major decomposition products are likely to be simple saccharides.

In addition, the Panel has issued "safe as used" conclusions for the following cosmetic ingredients which are structurally similar to some of the ingredients reviewed in this safety assessment: galactomannans,[2] microbial polysaccharide gums,[3] astragalus gummifer gum,[4,5] aloe barbadensis leaf polysaccharides,[6] oryza sativa (rice) starch,[7] zea mays (corn) starch,[8] acacia senegal gum,[9] glyceryl alginate,[10] hyaluronic acid,[11] and triticum vulgare (wheat) starch.[12,13]

CHEMISTRY

Definition and Structure

Polysaccharide nomenclature follows the general principles of established organic and carbohydrate nomenclature. Polysaccharide (glycan) is the name given to a macromolecule consisting of a large number of monosaccharide (glycose) residues joined to each other by glycosidic linkages (Figure 1). The term poly(glycose) is not a synonym for polysaccharide (glycan), because it refers to macromolecules composed of glycose residues joined to each other by non-glycosidic linkages. Polysaccharides may be linear, branched, or cyclic. Definitions, structures, and functions of the polysaccharide gums reviewed in this safety assessment, as used in cosmetics and defined in the *International Cosmetic Ingredients Dictionary and Handbook*, are presented in Tables 1 and 2.[1]

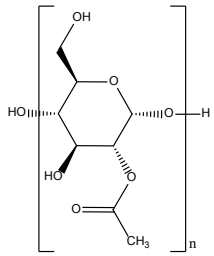


Figure 1. Starch Acetate – an example of a polysaccharide gum

The polysaccharide gums are each naturally derived materials that comprise polysaccharides obtained from plants or algae. Their substantial molecular sizes suggest that skin penetration of these ingredients would be unlikely. While, for the sake of clarity and organization, these ingredients can be subdivided into categories such as linear, branched, cylic, modified, and unmodified, these moieties represent a family of structurally similar polymeric materials, composed of simple saccharide monomers. So, in intended cosmetic application, these ingredients are unlikely to have significant systemic accessibility and any major decomposition products are likely to be simple saccharides, albeit chemically modified ones in some instances (*vide supra*).

Physical and Chemical Properties

Physical and chemical properties of polysaccharide gums are presented in Table 3. These gums have high molecular weights, and many are insoluble in water.

Method of Manufacture

Methods of manufacture of polysaccharide gums are presented in Table 3. The manufacturing processes for hydrolyzed furcellaran and starch hydroxypropyltrimonium chloride are presented in the following sections.

Linear – Modified

Hydrolyzed Furcellaran

The manufacturing process for hydrolyzed furcellaran is presented in Figure 2 below.

Fresh Seaweed
(Furcellaria lumbricalis)
↓
Drying
Extraction (water 90˚C)
Filtration
Sedimentation
Drying
↓
Furcellarane Powder
(Sulfated Polysaccharide)
↓
Depolymerization by sub-critical CO_2
(105˚C, 250 bar) with water (2%)
↓
Hydrolyzed Furcellaran
(Depolymerized Sulfated
Polysaccharide; MW: 200 kDa
on average)

→

Solubilization of Phenoxyethanol in Water
↓
Heating until 70˚C under shaking
↓
Cooling at room temperature
↓
Water
Phenoxyethanol
Hydrolyzed Furcellaran
Sea salt

←

Spray Dried Sea Water
Concentrate

Figure 2. Manufacturing Process for Hydrolyzed Furcellaran.[14]

Branched – Modified

Starch Hydroxypropyltrimonium Chloride

The manufacturing process for starch hydroxypropyltrimonium chloride is presented in Figure 3 below.

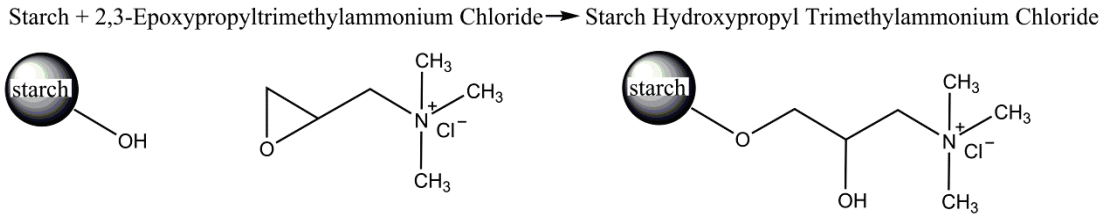


Figure 3. Reaction to form cationic starch ether.[15]

Composition/Impurities

Composition and impurities data on polysaccharide gums are presented in Table 4. Composition/properties data on two hydrolyzed starch products are presented in Table 5.

USE

Cosmetic

Many of the ingredients reviewed in this safety assessment function as viscosity increasing agents in cosmetic products, and the complete list of polysaccharide gum functions in cosmetic products is presented in Table 2.[1] According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), and the results from a survey of ingredient use concentrations conducted by the Personal Care Products Council (Council) in 2013, 59 of these polysaccharide gums are being used in cosmetic products and maltodextrin has the highest reported use frequency.[16,17,18,19]

The Council survey data also indicate that polysaccharide gums are being used in rinse-off cosmetic products at maximum ingredient use concentrations up to 50% (i.e., for algin in paste masks and mud packs), and in leave-on cosmetic products at maximum ingredient use concentrations up to 45.7% (i.e., for corn starch modified in tonics, dressings, and other hair grooming aids).[16,18] Frequency of use/use concentration data for polysaccharide gums are summarized in Table 6.

Cosmetic products containing polysaccharide gums may be applied to the skin and hair or, incidentally, may come in contact with the eyes (maximum ingredient use concentration in these products = 30%) and mucous membranes (maximum ingredient use concentration in these products = 32%). Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Polysaccharide gums are used at concentrations up to 9.5% (avena sativa (oat) starch) in cosmetic products that are sprayed, which also includes use in a pump hair spray at a maximum concentration of 0.45% (corn starch modified), and at concentrations up to 45.7% (corn starch modified) in cosmetic products that possibly are sprayed. Ingredient use in underarm aerosol deodorant sprays is being reported at maximum use concentrations ranging from 0.001% (algin) to 2.5% (cyclodextrin). Hydroxypropyl cyclodextrin is being used in underarm pump deodorant sprays at a maximum use concentration of 0.34%. Additionally, polysaccharide gums are used in cosmetic products (powders) at concentrations up to 33% (tapioca starch). Because polysaccharide gums are used in products that are sprayed, they could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm, compared with pump sprays.[20,21,22,23] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[20,21] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aero-

dynamic equivalent diameters in the range considered to be respirable.[21] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Non-cosmetic

According to the FDA, the following polysaccharide gums are approved direct food additives affirmed as generally recognized as safe (GRAS):[24,25] agar, alginic acid, ammonium alginate, amylose (i.e., high-amylose corn starch is GRAS), calcium alginate, pectin, potassium alginate, dextrin, maltodextrin, solanum tuberosum (potato) starch, solanum tuberosum (potato) starch, starch acetate, tapioca starch, hydroxypropyl starch, propylene glycol alginate, carrageenan, ghatti gum, and sterculia urens gum.

Linear Polysaccharides and Their Salts

Algin

The viscosity of blood substitutes is among the important determinants in restoring microcirculation.[26] Sodium alginate (algin) is frequently mentioned as a viscosity modifier in the development of blood substitutes.

Alginates

Alginate dressings are among the types of absorbent dressings that are used to treat exuding wounds.[27]

Carrageenan

κ-Carrageenan (thickening agent) stabilizes milk proteins and is widely used in dairy products.[28]

At the June 2014 meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Committee concluded that the use of carrageenan in infant formula or formula for special medical purposes at concentrations up to 1000 mg/L is not of concern.[29] Furthermore, the Committee recognized that there is variability in medical conditions among infants requiring formulas for special medical purposes that contain the higher levels of carrageenan, and noted that these infants would normally be under medical supervision. A summary of the discussion on which the Committee's conclusion is based is summarized in the Repeated Dose Toxicity-Oral section of this report.

Inulin

Inulin is a prebiotic, meaning a non-digestible food ingredient that selectively stimulates the growth and/or activity of one or several bacterial species in the colon.[30]

Branched Natural/Unmodified

Ghatti Gum

Ghatti gum (thickening agent) is used to stabilize table syrup emulsions, as a glaze in candy products, and as a component of chewing gum, cough drops, and candy lozenges.[28]

Sterculia Urens Gum

Sterculia urens gum has the following uses in food: formulation aid, stabilizer and thickener, and emulsifier and emulsifier salt.[31] World Health Organization (WHO) reports affirming the safety of karaya gum as a food additive are available.[32,33]

Cyclic

Cyclodextrin

Cyclodextrins have been used to solubilize drugs in aqueous vehicles as guest-host complexes.[34]

TOXICOKINETICS

Non-Human

Linear Polysaccharides and Their Salts

Carrageenan

Carrageenan is not degraded or absorbed in the gastrointestinal tracts of rodents, dogs, and non-human primates.[35]

Branched Natural/Unmodified

Sterculia Urens Gum

A toxicokinetic study on sterculia urens gum was performed using 2 groups of 4 male Sprague-Dawley rats of the CD strain. One group was fed a pelleted diet containing 5% sterculia urens gum for 24 h, and the control group was fed a similar laboratory pelleted diet without the gum. Urine and feces were collected and weighed after 24 h, 48 h, and 72 h. The polysaccharide of sterculia urens gum is composed essentially of rhamnose, galactose and galacturonic acid. Fecal polysaccharide was calculated as sterculia urens gum polysaccharide after correction for background levels of rhamnose, galactose, and galacturonic acid in the control feces. The quantity and monosaccharide composition of the fecal polysaccharide were compared with the dose and original composition of the gum polysaccharide. Aggregated polysaccharide estimated over the 72-h collection period ranged from 81% to 108%, with a mean value of 95% of that consumed. Thus, 95% of the gum ingested was excreted in the feces.[36]

Cyclic

Cyclodextrin

The absorption of orally administered ^{14}C-β-cyclodextrin, in methylcellulose solution, was studied using 4 Wistar R x Long Evans F_1 male rats.[37] Two rats received an oral dose of 36.7 mg/kg, and the other 2 rats received 36.9 mg/kg. The average dose volume was 1.5 ml. The maximum radioactivity of the blood derived from ^{14}C-β-cyclodextrin occurred between the 4th and 11th hour after exposure, and the maximum radioactivity in different experiments ranged from 5% to 17% of the total administered radioactivity. Radioactivity excreted in the urine ranged from 4.2% to 4.8% of the total radioactivity administered. No specific accumulation of ^{14}C-β-cyclodextrin in organs was found after dosing. The large intestine contained 10% to 15% of the ^{14}C-β-cyclodextrin radioactivity at 24 h post-dosing.

In another experiment, a female CFY rat received an oral dose of 313 mg/kg ^{14}C-β-cyclodextrin (homogenized in dextran solution, volume = 2.5 ml). In the 8th hour after dosing, no more than 3 to 50 ppm β-cyclodextrin was detectable in the blood. In a third experiment, a female CFY rat was dosed orally with 36.1 mg/kg ^{14}C-β-cyclodextrin (homogenized in 1 ml dextran solution), and another rat was dosed orally with 313.5 mg/kg ^{14}C-β-cyclodextrin (homogenized in 2.5 ml dextran solution). Three female CFY rats also received an oral dose of 1.88 mg/kg chromatographically purified ^{14}C-β-cyclodextrin (homogenized in 1.5 ml dextran solution). The radioactivity peak was detected in the exhaled air between the 4th to 6th or the 6th to 8th hour, depending on the dose. The total radioactivity exhaled by ^{14}C-β-cyclodextrin-treated rats in 24 h represented 55% to 64% of the administered ^{14}C-β-cyclodextrin. The authors suggested, based on the results of this study, that the rate-determining step in β-cyclodextrin absorption is the enzymatic hydrolysis of β-cyclodextrin to yield linear dextrins, which are rapidly hydrolyzed to maltose and glucose.[37]

Human

Branched Natural/Unmodified

Starch Acetate

The pharmacokinetics of starch acetate (acetyl starch) and hydroxyethyl starch was studied using 2 groups of 16 surgical patients (18 to 70 years old).[38] Patients in one group were initially infused intravenously (i.v.) with 15 mL/kg of a 6% acetyl starch solution, and then up to a maximal dosing volume of 1,000 mL/kg, over a 30-minute period. The other group was infused with a 6% hydroxyethyl starch solution (same dosing volume) according to the same procedure. When compared to hydroxyethyl starch, rapid and nearly complete enzymatic degradation to acetic acid and glucose (and to products that can be excreted renally) was reported for acetyl starch.

Sterculia Urens Gum

Five male volunteers were involved in a study in which 24-h urine samples were collected prior to, and following, the ingestion of 10 g karaya gum for 15 days.[39] Total gum intake was 10-fold greater than the approved average daily intake (ADI) of 0-12.5 mg/kg body weight. The detection limit for rhamnose in the urine was 0.2 µg; however, rhamnose was not detected in any of the urine specimens. The authors noted that if 1% of the rhamnose in 10 g karaya gum appeared in the 24-h urine specimens, it would have been detected. Furthermore, the results of this study confirmed that dietary gum karaya is neither digested nor degraded by enteric bacteria, and is not absorbed to any significant extent in the digestive tract.

Tapioca Starch

Ten men (29 to 41 years old) participated in an oral exposure study.[40] Blood was collected after a 12-h fast. Tapioca starch (30 g) containing 0.1 g aspartame was dissolved in 150 L of water, and the solution or dispersion remained for 3 minutes in boiling water. Subjects then drank the solution 1 to 2 min later. Three tolerance tests were performed, using a crossover design, over three days. Tapioca starch produced a large, rapid increase in plasma glucose concentration, which peaked in 30 minutes and then decreased toward the basal value.

Percutaneous Absorption

Cyclic - Modified

Hydroxypropyl Cyclodextrin

The percutaneous absorption of 2% ^{14}C-2-hydroxypropyl-β-cyclodextrin *in vivo* was studied using 3 to 5 female hairless mice.[41] The test material (100 µL on occlusive patch) was applied to dorsal skin (2 cm^2) for 24 h. Radioactivity in the patches, in the stratum corneum (collected by tape stripping), and in the epidermis and cutis of the skin (obtained by peeling off the treated portion) was measured using a scintillation counter. The percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin through intact skin was extremely low, i.e., ~ 0.02% of the amount applied to the skin. The absorption rate of ^{14}C-2-hydroxypropyl-β-cyclodextrin through skin from which the stratum corneum had been removed by tape stripping was approximately 24% of the amount applied to the skin. The latter finding suggests that the stratum corneum may act as a barrier to the percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin. Thus, the results of this study clearly demonstrate that 2-hydroxypropyl-β-cyclodextrin has low permeability through hairless mouse skin.

TOXICOLOGICAL STUDIES

A toxicity profile of β-cyclodextrin (a cyclic polysaccharide gum) is available from the WHO.[42] The toxicity profile of cyclodextrins can differ depending on the route of administration. For example, β-cyclodextrin administered orally induces limited toxicity.[43,44] In both rats and dogs, β-cyclodextrin is considered to be non-toxic at a daily dose less than 600 mg/kg body weight or at 3% or less in the diet.[45] However, if β-cyclodextrin is administered at higher doses in animals via a subcutaneous (s.c.) route, it will cause a decrease in body weight gain, a decrease in liver weight, and nephrotoxicity, with an increase in kidney weight, proximal tubular nephrosis and cellular vacuolation.[45,46] In another study (rats), s.c. administration of β-cyclodextrin (≥ 450 mg/kg) induced similar changes in kidney proximal tubules.[47] Acute and repeated dose toxicity studies on polysaccharide gums (according to type of exposure) are summarized in Tables 7 and Table 8, respectively. The following acute toxicity studies (according to type of exposure) on polysaccharide gums are summarized in Table 7: inhalation, oral, dermal,

intravenous, intrapleural, and transbronchial. Oral and dermal repeated dose toxicity studies on polysaccharide gums are summarized in Table 8.

Cytotoxicity

Linear Polysaccharides and Their Salts

Calcium Alginate

In a cytotoxicity assay, calcium alginate fibers were introduced into human embryonic kidney cells and human fibroblasts.[48] A total of nine experimental groups were prepared according to the following weights of calcium alginate fibers: 0.005, 0.01, 0.02, 0.03, 0.04, 0.05, 0.08, 0.10, and 0.15 g. Next, 1-cm lengths of fibers were cut and sterilized with UV irradiation prior to their addition to the cells. The cells were in their exponential growth phase, and were incubated for 48 h. Calcium alginate fibers were not cytotoxic.

Allergenicity/Immune System Effects

Non-Human

Linear Polysaccharides and Their Salts

Polianthes Tuberosa Polysaccharide

The potential for a modulatory effect on the murine self-defense system by an acidic polysaccharide (ANK-102) produced by *Polianthes tuberosa* cells in liquid culture was examined.[49] The pretreatment (intraperitoneal [i.p.] injection) of C3H/HeN mice with ANK-102 (2 mg in 0.2 ml solution) deteriorated murine survival against lethal infection with *Listeria monocytogenes*, an intracellular gram positive bacterium eliminated mainly by macrophages through the T-cell mediated immune response. Pretreatment with ANK-102 resulted in the accumulation of Mac 1 and Mac 2 positive cells in the peritoneal cavity of the infected animals and the reduction of Thy 1.2 expression on the surface of the thymocytes. ANK-102 was classified as an immunosuppressive polysaccharide.

Potassium Carrageenan

Male Sprague-Dawley rats (8 animals, 7 weeks old) were injected i.p. with potassium carrageenan (50 mg in 5 ml PBS).[50] The control group received a single injection of PBS (0.5 ml). At 3 weeks post-injection, serum levels of IgM, IgG and slow α_1- and slow α_2-globulins were measured using quantitative radial immunodiffusion (IgG) or immunoelectrophoresis (IgM and slow α-globulins). There was a significant elevation in levels of IgM and slow α_1 globulin that was maximal on day 4; levels returned to normal by day 14. Slow α_2-globulin was detectable within 24 h, reached a peak at day 2, and, in most animals, was no longer measurable by day 14. Levels of IgG were not affected by potassium carrageenan injection.

Branched Natural/Unmodified

Sterculia Urens Gum (a.k.a. Karaya Gum)

The allergenicity of karaya gum was studied in adult male and female guinea pigs (number not stated).[51] Karaya gum (1 g/kg) was dissolved in normal saline to make a 3% solution, which was injected i.p. The gum was also administered orally (1 g/animal daily) for 3 months, or mixed with food (single feeding of 5 g/animal). Egg albumen served as the control in each experiment. Animals that received single i.p. injections or single oral doses were killed at intervals within a range of 4 to 12 weeks after the attempted sensitization. Animals dosed orally daily for 3 months were killed either on the day after the last dose or after an interval of 6 weeks after the last dose. Isolated pieces of small intestine from treated males and females, seminal vesicles from males, and the uterus of females were suspended in an organ bath and exposed to karaya gum or egg albumen for 10 minutes. The organs of

animals exposed *in vivo* to karaya gum where challenged first with egg albumen and, later, with karaya gum, and *vice versa*. Study results indicated that allergic sensitivity did not develop in guinea pigs dosed orally (single or repeated doses) or i.p. Injection of albumen resulted in marked allergic sensitization.

An animal model was used to investigate the immunogenicity of karaya gum (*Sterculia* spp.).[52] Groups of [(C57BL/6J x DBA/2)F_1] (BDF_1) mice were intradermally immunized with the gum in Freund's complete adjuvant. Serum antibody levels were measured using an enzyme-linked immunosorbent assay (ELISA), and delayed hypersensitivity responses assayed by a footpad swelling test. Karaya gum elicited systemic immune responses after immunization. Further processing reduced immunogenicity, although there was no evidence that systemic immunity to complex polysaccharide antigen responses could be completely abolished by processing or purification. Karaya gum caused considerable footpad swelling when injected intradermally.

Human

Branched - Modified

Propylene Glycol Alginate

Following a 7-day control period, 5 male volunteers consumed propylene glycol alginate at a dose of 175 mg/kg body weight for 7 days.[53] This regimen was followed by dosing with 200 mg/kg body weight for an additional 16 days. No allergic responses were reported by, nor observed in, any of the volunteers.

In Vitro

Linear Polysaccharides and Their Salts

Potassium Alginate

The acute tissue reactions to potassium alginate, locally applied to a microvascular bed, were studied using the vital microscopic hamster cheek-pouch model and correlative histology.[54] This experimental model permitted the study of microvascular permeability, blood flow, vessel diameters and leucocyte adhesion to vessel walls intravitally, and leucocyte migration and mast cell degranulation histologically. Deionized water alone and potassium alginate with flavor and color mixed in saline was found to cause severe microvascular alterations, while potassium alginate, without flavor and color, mixed in saline and applied to the microvasculature resulted in a minor inflammatory reaction

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity data on polysaccharide gums are summarized in Table 9. Except for a dose-dependent increase (40-600 mg/kg) in the incidence of missing skeletal sternebrae in rabbits dosed orally with *kappa/lambda*- carrageenan, the results for polysaccharide gums in reproductive and developmental toxicity studies were essentially negative.

GENOTOXICITY

Genotoxicity data (bacterial and mammalian) on polysaccharide gums are summarized in Table 10. In bacterial assays, the following were not genotoxic either with or without metabolic activation: arabinoxylan, carboxymethyl inulin, carrageenan, ghatti gum, glucomannan, and pectin-derived acidic oligosaccharides. In mammalian assays with and without metabolic activation, wheat bran extract, carboxymethyl inulin, carrageenan, ghatti gum, and glucomannan were not genotoxic. However, results for pectin-derived acidic oligosaccharides in mammalian assays were either equivocal or it was classified as clastogenic, only at highly cytotoxic concentrations. Sterculia urens gum was not genotoxic in cytogenetic assays (*in vitro* and *in vivo*) or in the *in vivo* dominant lethal gene test.

CARCINOGENICITY

Studies relating to the carcinogenicity of polysaccharide gums are summarized in Table 11. Agar (50,000 ppm in diet) was not carcinogenic in rats, and up to 25% sodium alginate in the didet was not carcinogenic in mice. Results relating to the carcinogenic potential of carrageenan were mixed. Carrageenan (25% in the diet) was not carcinogenic in mice, but 15% carrageenan in the diet enhanced the colon tumor incidence in azoxymethane (AOM)- and N-nitrosomethylurea (NMU)-treated rats. In the aberrant crypt focus (ACF) assay, 10% carrageenan in the diet did not initiate colon tumors, 0.25% carrageenan reduced the number of ACF, and 2.5% carrageenan promoted the growth of ACF in rats. In another study, carrageenan (up to 5% in the diet) did not possess promoting activity for colorectal carcinogenesis in rats. It should also be noted that 5% carrageenan in the diet increased colonic cell proliferation in rats, but that it was concluded that this response was probably adaptive, and would not contribute to the increased risk of colon neoplasia in rats. There was no evidence of carcinogenicity in mice fed 55% starch acetate or in rats fed 5% cyclodextrin in the diet. Pectin (2.5% in diet) caused mucosal hyperplasia of the small intestine of rats. Degraded carrageenan, which may or may not be similar to the cosmetic ingredient hydrolyzed carrageenan, caused colon cancer in rats at dietary concentrations of 5% and 10%, but not 1%, in rats. Degraded carrageenan (also known as poligeenan) results from a manufacturing process of seaweed that involves intentional extensive acid hydrolysis, resulting in sulfated galactose polymers with an average molecular weight of approximately 15,000 Da.[35]

Inulin (15 g in basal diet) inhibited the growth of 2 tumor cell lines that were implanted in mice, and the dietary intake of 4.8% arabinoxylan reduced the occurrence of preneiplastic lesions in rats. Glucomannan (10% in the diet) inhibited the development of spontaneous liver tumors in mice.

IRRITATION AND SENSITIZATION

Dermal Irritation and Sensitization

Skin irritation and sensitization studies on polysaccharide gums are summarized in Table12. The results of animal and human tests indicate that these gums can be mild skin irritants, but are non-sensitizers.

Phototoxicity

Branched - Modified

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

The phototoxicity of a sodium hydrolyzed potato starch dodecenylsuccinate was evaluated using the *in vitro* neutral red uptake phototoxicity assay.[55] The trade name material (in Hanks' balanced salt solution) was evaluated at concentrations ranging from 68.1 to 1,000 µg/ml in BALB/3T3 clone A31 mouse embryo fibroblast cultures. Chlorpromazine served as the positive control. Following incubation, cultures were irradiated for 50 minutes with 1.7 mW/cm^2 UVA to achieve an irradiated dose of 5 J/m^2. A positive result was defined as a photo-irritant factor (PIF) > 5. The PIF was defined as the EC_{50} without solar simulated light (SSL)/ EC_{50} with SSL. The test material was not considered to have phototoxicity potential (PIF = 0.8). A PIF of 27.9 was reported for the chlorpromazine positive control.

Clinical Trial

Linear Polysaccharides and Their Salts

Calcium Alginate

Fourteen patients (7 males) with spina bifida were treated for pressure sores. Each patient had calcium alginate dressings applied for 4 to 6 weeks.[56] The mean number of dressings removed per week was 3.5 ± 2.1. Good tolerance to treatment was reported for each patient. It was also noted that no severe side effects were recorded during the trial.

Case Reports

Linear Polysaccharides and Their Salts

Calcium Alginate

A 50-year-old woman was referred for treatment after the discovery of adenoid cystic carcinoma in an excised left submandibular gland.[57] Treatment involved clearing the left submandibular fossa, and selective neck dissections. After removal of the clot (submandibular hematoma), a calcium alginate fiber pack was left in place to control the bleeding. After an extended period, the pack was reported to have stimulated a foreign body reaction which, on a computed tomogram, mimicked a recurrence of the tumor.

Alginate

A 52-year-old general practitioner injected 0.1 ml of an alginate solution into the deep dermis of her left arm.[58] Ten days later, she observed a small pink nodule at the injection site; a bluish papule was observed at 3 months post-injection. A biopsy was performed 2 months after injection. At histopathological examination, a granulomatous reaction involving the deep dermis and the subcutaneous fat was observed. The papule regressed, having resolved completely at 5 months post-injection.

Four of 10 patients injected with an aesthetic injectable resorbable filler consisting of purified alginate (extracted from crusted brown algae), into tear troughs and⁄or dorsa of the hands, developed severe granulomatous reactions within months after injections.[59] The 40% incidence of this disfiguring effect was considered high.

Sodium Carrageenan

Within minutes of receiving a barium enema solution that contained sodium carrageenan, a 26-year-old female had an anaphylactic reaction associated with the following signs/symptoms:[60] abdominal cramps, mild generalized pruritus, generalized urticaria, hypotension, transient loss of consciousness, chest tightness, wheezing, and cyanosis. A skin prick test for a component of the barium enema solution, 0.4% weight/volume sodium alginate, were positive (i.e., an 8 mm wheal diameter with surrounding flare). This is the only component of the barium enema solution that yielded a positive reaction.

Ocular Irritation

Non-Human

Linear Polysaccharides and Their Salts

Algin

The ocular irritation potential of algin (2%) was studied in 3 experiments using rabbits (number not stated).[61] Instillation of the test substance was followed by scoring after 1 h, 24 h, 2 days, 3 days, 4 days, and 7 days. Corneal opacity and ulceration or granulation were evaluated. Ocular irritation was graded on a scale of 0 to 110, and an ocular irritation index (OII) was calculated. It was noted that a compound does not provoke any significant injury to the mucous membrane of the eye when no opacity of the cornea occurs and when the ocular irritation index is less than 15. OII values of 3.00, 9.17, and 5.50 were reported in the 3 experiments, respectively. Pathological lesions of the ocular mucosa were not observed.

Carrageenan

Food grade *iota*-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units) was not irritating to unrinsed eyes of rabbits and was minimally irritating to rinsed eyes.[62]

Branched – Modified

Calcium Starch Isododecenylsuccinate and Corn Starch Modified

A material described as structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn starch modified was evaluated for ocular irritation potential in a study involving 6 New Zealand White rabbits.[63,64,65] The OECD 405 test protocol was used. The powder (0.1 ml) was placed in one eye of each animal. Iritis was observed in 2 rabbits, and reactions had cleared by day 1. Conjunctival irritation was observed in 6 rabbits, and reactions had cleared by day 3. There was no evidence of corneal opacity or abnormal systemic signs during the observation period. The test material was classified as a minimal ocular irritant.

Corn Starch Modified

Corn starch modified, dry powder form, was placed in one eye of each of 6 New Zealand White rabbits (5 males, 1 female).[66] Iritis was observed in 1 of 6 rabbits, and the reaction had cleared by 24 h post-administration. Mild conjunctival irritation was observed in all 6 rabbits, and reactions had cleared by 48 h post-administration. There was no evidence of corneal opacity or abnormal physical signs in any of the animals tested. The test substance was classified as minimally irritating to the eye.

Dextrin Myristate

The ocular irritation potential of dextrin myristate was studied using 6 New Zealand white rabbits. The test concentration and protocol were not stated. Ocular irritation was not observed.[67]

Dextrin Palmitate

In an ocular irritation study involving 3 New Zealand white rabbits per test substance, dextrin palmitate (concentration and test protocol not stated) did not cause reactions in the cornea or iris. Slight conjunctival redness was observed in one rabbit at 1 h post-instillation, but had resolved after 24 h.[68,69]

Potato Starch Modified

A 16.8% aqueous suspension of potato starch modified was evaluated in an ocular irritation study involving 3 rabbits (strain not stated), according to the OECD 405 test guideline. Conjunctival irritation/edema was observed in the 3 rabbits, and all reactions had cleared in 2 rabbits by 24 h post-instillation. In the remaining rabbit, slight swelling of the conjunctivae remained at 24 h, and the reaction had cleared by 48 h post-instillation. It was concluded that the potato starch modified suspension was slightly irritating to the eyes of rabbits.

The ocular irritation potential of potato starch modified (28-1808) was evaluated according to the OECD 405 protocol using 3 New Zealand White rabbits.[70] An 18.5% solids solution of the test substance (0.1 ml) was instilled into one eye of each animal, and reactions were scored for up to 72 h post-instillation. Abnormal physical signs were not observed during the observation period. Conjunctival irritation was observed in all animals, having cleared by 48 h. Neither corneal opacity nor iritis was observed during the study. Potato starch modified (28-1808) was classified as a minimal ocular irritant.

Stearoyl Inulin

The ocular irritation potential of steraroyl inulin (test concentrations and protocol not stated) was evaluated in two tests, each using 6 Japanese white rabbits. The test substance was classified as practically non-irritating.[71,72]

In Vitro

Linear - Modified

Hydrolyzed Furcellaran

The ocular irritation potential of a trade name mixture containing 1.35% furcellaran powder and 1% phenoxyethanol was evaluated in a cytotoxicity assay involving cultured fibroblasts (source not stated). The method of diffusion on agarose gel was used. The product (pure) was applied to cultures during a 24-h period, and was classified as slightly toxic. This finding was interpreted as almost non-irritating to slightly irritating to the eyes.[73] The ocular irritation potential of another trade name mixture containing 1.35% furcellaran powder, 0.1% potassium sorbate, and 0.05% citric acid was evaluated according to the same procedure, and the same results were reported.[73]

Maltodextrin

The ocular irritation potential of maltodextrin was evaluated using the *in vitro* bovine corneal opacity and permeability assay.[74] In this assay, plastic cassettes mimicking eye structure are used as holders for excised corneas. The posterior chamber was filled with cell support media, and the anterior chamber was filled with an eye gel containing 2.45% maltodextrin. After a 10-minute period, opacity was measured by passing visible light from an opacitometer through the cornea and on to the surface of a light sensor. It was noted that a clear cornea unchanged by the test substance would allow light to pass through and be detected by the sensor. Opaque corneas would produce light scattering (Tyndall effect) and reduced detection that is proportional to the degree of ocular damage. Also, following exposure, fluorescein was added to the anterior chamber of the cassette. The amount of dye passing through the cornea and into the posterior chamber is a measure of corneal permeability, and an increase in corneal permeability is indicative of corneal damage. Based on the results of this study, the eye gel was classified as a non-irritant. The positive control, 5% benzalkonium chloride, was classified as a severe irritant.

In addition, the EPI-Ocular® skin model assay was used to evaluate the ocular irritation potential of an eye gel containing 2.45% maltodextrin.[75] In this assay, the degree of ocular irritation is based on the amount of cytotoxicity observed in tissues exposed to the test substance. Cytotoxicity is measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye. The end point established in this assay is the time required for the test substance to reduce tissue viability by 50% (ET_{50}). An $ET_{50} > 4$ h (non-irritant) was reported for the eye gel. The positive control, Triton X-100, was classified as a mild irritant ($ET_{50} = 28.8$ minutes).

Branched – Modified

Hydroxypropyltrimonium Hydrolyzed Corn Starch

The ocular irritation potential of hydroxypropyltrimonium hydrolyzed corn starch was evaluated using the hen's egg test – utilizing the chorioallantoic membrane (HET-CAM).[76] Fertile White leghorn eggs were used. The chorioallantoic membrane (CAM) of the chick embryo responds to injury with a complete inflammatory reaction that is comparable to that induced in the rabbit ocular irritation test. The test substance (0.3 ml) was administered to the CAM at concentrations of 5%, 10%, and 15%. Results indicated that hydroxypropyltrimonium hydrolyzed corn starch would have practically no irritation potential *in vivo*. It was noted that the CAM results at 5%, 10%, and 15% are equivalent to Draize test results for the test substance at concentrations of 10%, 20%, and 30%.

Mucous Membrane Irritation and Sensitization

Non-Human

Branched Natural/Unmodified

Glucomannan

Konjac flour was evaluated in the following study, but the composition of konjac flour is not stated. However, according to one source, every 100 g of konjac flour contains the following:[77] glucomannan (79.37 mg), protein (1.64 g), fat (0.004 g), phosphorus (57 mg), iron (4.06 mg), zinc (123 mg), manganese (0.2 mg), chromium (0.25 mg), and copper (0.08 mg). Prior to initiation of the study, a sensory irritation study on konjac flour (primary polysaccharide component is glucomannan) was performed using ND4 Swiss Webster mice (number not stated).[78] Sensory irritation was evaluated by monitoring the decrease in respiratory rate during 30 minutes of exposure to

konjac flour. The concentration of konjac flour that caused a 50% decrease in the respiratory rate (RD_{50}) was 110 mg/m^3.

A study was performed to investigate whether exposure to food grade konjac flour could produce respiratory hypersensitivity.[78] The composition of the sample tested was in agreement with *Food Chemical Codex* specifications of <8% protein, >75% carbohydrate, and <5% ash. Groups of male Hartley guinea pigs were randomly assigned to the following 4 groups (whole-body exposure in chambers): negative control (4 animals, air-exposed), positive control (4 animals, trimellitic anhydride [TMA] exposure), and konjac flour exposure group (8 animals). Test animals were exposed to konjac flour on days 1-5 of the study (42 minutes/induction exposure), and challenged (35 minutes/challenge exposure) on days 19, 26, and 40. The mean (± S.D.) konjac flour concentration during induction exposure was 111 ± 8.3 mg/m^3, and the mean exposure concentration during the challenge phase ranged from 50 to 68 mg/m^3. The days of exposure (induction and challenge) for positive control animals exposed to TMA aerosol were identical to those for the test group. The target exposure concentrationof TMA was 94 mg/m^3 for induction and challenge. Negative control animals were exposed to room air on days 1-5, but were challenged with konjac flour (target concentration = 114 mg/m^3) only on day 40 to avoid the possibility of repeated challenges resulting in sensitization.

The criteria used to define respiratory tract sensitization (increase in respiratory rate of 36% and change in respiratory waveform) were achieved in 25% of the animals during each challenge in the konjac flour exposure group. Additionally, a few animals responded with slightly lower increases in respiratory frequency and a change in waveform that were suggestive of a slight pulmonary hypersensitivity response.[78] According to a more recent publication, the purified antigen from konjac flour is named Ag40D-2 (acidic protein; ~ 24,000 daltons), suggesting that the respiratory sensitizer in konjac flour is actually a protein, rather than glucomannan.[79]

Cyclic - Modified

Methyl Cyclodextrin

The acute histological effects of methylated β-cyclodextrin on the epithelium of the nasal cavity has been investigated in rats using light microscopy.[80] After a single nasal administration of 2% randomly methylated β-cyclodextrin, only minor changes were observed in the appearance of the cilia and the apical cell membranes, and small amounts of mucus were excreted into the nasal cavity. These effects were similar to those noted for control animals dosed with physiological saline (0.9% NaCl). Using confocal laser scanning microscopy, no changes in nasal epithelial cell morphology were observed after a single intranasal administration of 2% randomly methylated β-cyclodextrin, whereas 1 % sodium taurodihydrofusidate resulted in swelling of the cells and substantial mucus extrusion.

Human

Branched Natural/Unmodified

Glucomannan

The inhalation of konjac dust in factories producing konnyaku, a popular food in Japan made from konjac tubers, has been reported to produce allergic bronchial asthma (known as konnyaku asthma) in sensitized individuals.[81] Furtherhmore, bronchial asthma that was likely triggered by the inhalation of Maiko powder has been associated with residents near a konjac milling plant in Japan.[79] Konjac root is dried and ground into powder in the process of manufacturing the food known as konjac. Maiko is a fine konjac root powder that is blown by air pressure to obtain konjac powder for commercial use.

EPIDEMIOLOGY

Linear Polysaccharides and Their Salts

Carrageenan, Agar, and Alginate

An epidemiology study was performed to examine the hypothesis that the increasing incidence of mammary carcinoma in the United States in the twentieth century may be related to the consumption of carrageenan and possibly other water-soluble polymers.[82] A time-trend analysis using age-adjusted incidence data and consumption data from established sources was used to test this hypothesis. Statistical analysis, using Pearson and Spearman correlation coefficients, was performed to identify associations between water-soluble polymer consumption and cancer incidence. Lag periods of 10, 15, 20, 25, 30, and 35 years were introduced to consider a latent effect between intake and the occurrence of breast cancer.

At least 4 values for consumption and corresponding incidence were required for inclusion in the correlation analysis. Consumption data on the polysaccharide gums studied were reported as pounds/person/year. These water-soluble polymer utilization data, obtained from several libraries throughout the United States, were predominantly from published data compiled as research for the food industry. For carrageenan, 80% of total consumption was identified as food consumption, and the remainder was attributed to products such as toothpaste, deodorants, room deodorizers, etc. Food consumption data on other gums were as follows: sterculia urens gum (< 10%), agar (50%), alginates (60%), and pectin (80 to 95%). Incidence data for breast cancer were obtained from published sources and were presented as the age-adjusted incidence data per 100,000 population using the 1970 census data.

The following positive correlations between gum consumption and the incidence of mammary carcinoma were found. For carrageenan, positive correlations (statistically significant) were found at 25 years ($r = 0.88$; $P = 0.048$) and 30 years ($r = 0.96$; $P = 0.042$). The Spearman correlation coefficient for carrageenan at 30 years was also statistically significant ($r = 1.0$; $P < 0.0001$). Statistically significant positive correlations were also reported for alginate (at 30-year lag period) and agar (at 10- and 25-year lag periods). The Spearman correlation coefficient was significant for pectin at at 30 years. Sterculia urens gum did not demonstrate any statistically significant correlations. This analysis demonstated that polysaccharide gum consumption correlated positively with increased incidence of breast carcinoma.

Branched Natural/Unmodified

Pectin and Sterculia Urens Gum

Epidemiology data on pectin and sterculia urens gum are included in the preceding study on carrageenan, agar and alginate.[82]

MISCELLANEOUS STUDIES

Endocrine Function and Vitamin D Absorption

Branched Natural/Unmodified

Glucomannan

A double-blind trial on the efficacy of glucomannan in the treatment of pediatric obesity was performed.[83] The study involved 60 children under the age of 15 (mean age: 11.2 years; mean overweight: 46%). Thirty children received 1 g of glucomannan twice daily for two months, and the other 30 children received a placebo according to the same schedule. Clinical side effects were evaluated in both groups by measuring indicators of intestinal absorption, lipid metabolism, and thyroid and adrenocortical function. When the 2 groups were compared, there were no significant differences in intestinal absorption, thyroid or adrenocortical function, or clinical symptoms. However differences in lipid metabolism were significant. The treated group had decreased α-lipoprotein and increased pre-β-lipoprotein and triglyceride. The authors suggested that the metabolic alteration observed may have been due to a primary decrease in α-lipoprotein, most likely because of inadequate water intake. It was noted that these study results question the efficacy of glucomannan in the treatment of childhood obesity.

Antifungal Activity

Linear Polysaccharides and Their Salts

Calcium Alginate

The antifungal properties of calcium alginate fiber were studied using *Candida albicans*.[48] Fungal inhibitory rates were measured using the plate-count method, following the shake-flask test. Additionally, an inhibition-zone test and observation by scanning electron microscopy were performed. The inhibitory rate of calcium alginate fibers was 49.1%, and was classified as weak when compared to zinc alginate (92.2% inhibitory rate). The inhibitory rate was calculated using the following equation: Inhibitory rate = [(A – B)/A] x 100%. A was defined as the number of fungal colony on blank control plates. B was defined as the number of fungal colony on test plates.

Muscle Inflammation

Linear Polysaccharides and Their Salts

Carrageenan

Local muscle inflammation was induced by injecting carrageenan (10 mg/kg) into the right tibialis anterior muscle in 22 healthy ARC mice (6 weeks old).[84] The contralateral muscle was injected with sterile isotonic saline, and the muscles were removed after 24 h for measurement of contractile function and cytokine concentration. Carrageenan significantly reduced maximum specific force, decreased the maximum rate of force development, altered the force-frequency relationship, and increased intramuscular levels of pro-inflammatory cytokines and chemokines. These results indicate that injected carrageenan directly affects contractile function and causes skeletal muscle weakness.

Anti-inflammatory/Antioxidant Activity

Linear Polysaccharides and Their Salts

Alginic Acid

Alginic acid, isolated from brown algae (*Sargassum wightii*), was evaluated in a study involving groups of 6 arthritic adult male Sprague-Dawley rats.[85] The oral dosing of alginic acid (100 mg/kg) in arthritic rats reduced paw edema and the activities of enzymes such as cyclooxygenase, lipoxygenase and myeloperoxidase. Reduction in the level of C-reactive protein, ceruloplasmin, and rheumatoid factor were also observed in arthritic rats treated with alginic acid. Additionally, reduced lipid peroxidation and enhanced activities of antioxidant enzymes were reported, which suggest the antioxidant potential of the compound. Histopathological analysis indicated that alginic acid treatment reduced paw edema and inflammatory infiltration in arthritic rats. Overall, study results suggest that alginic acid isolated from *Sargassum wightii* exhibits potent anti-inflammatory and antioxidant activity.

SUMMARY

The polysaccharide gums are naturally derived materials that comprise polysaccharides obtained from plants or algae. As a group, they comprise polymers of simple saccharide monomers. Based on the different chemical structures that are associated with polysaccharide gums, these ingredients can be subdivided into categories such as modified, unmodified, linear, branched, and cyclic. Many of the polysaccharide gums reviewed in this safety assessment function as viscosity increasing agents in cosmetic products. According to information supplied to the FDA by industry as part of the VCRP and results from a Council survey of ingredient use concentrations, 59 polysaccharide gums are being used in cosmetic products.

The Council survey data also indicate that polysaccharide gums are being used in cosmetics at maximum ingredient use concentrations up to 50% (i.e., for algin in paste masks and mud packs). Polysaccharide gums are used at concentrations up to 9.5% (avena sativa (oat) starch) in cosmetic products that are sprayed, which also includes use in a pump hair spray at a maximum concentration of 0.45% (corn starch modified), and at concentrations up to 45.7% (corn starch modified) in cosmetic products that possibly are sprayed. Additionally, polysaccharide gums are used in cosmetic products (powders) at concentrations up to 33% (tapioca starch). Because polysaccharide gums are used in products that are sprayed, they could possibly be inhaled.

Maltodextrin, the most frequently used cosmetic ingredient reviewed in this safety assessment, is prepared as a white powder or concentrated solution by partial hydrolysis of corn starch, potato starch, or rice starch. It is an approved direct food additive affirmed as GRAS by the FDA. The following other polysaccharide gums reviewed in this safety assessment have also been classified as GRAS direct food additives: agar, alginic acid, ammonium alginate, amylose (i.e., high amylose corn starch is GRAS), calcium alginate, pectin, potassium alginate, dextrin, solanum tuberosum (potato) starch, starch acetate, tapioca starch, hydroxypropyl starch, propylene glycol alginate, ghatti gum, and sterculia urens gum.

In 2014, the JECFA concluded that the use of carrageenan in infant formula or formula for special medical purposes at concentrations up to 1,000 mg/L is not of concern.

Data on native carrageenans extracted from different types of algae indicate that different types of carrageenan have reasonable stability to heating at 75°C down to pH 4, and that the rate of depolymerization increases dramatically as the pH decreases from 4 to 3. These data indicate the susceptibility of carrageenan to acid hydrolysis under certain conditions.

The results of a percutaneous absorption study involving hairless mouse skin indicate that 2-hydroxypropyl-β-cyclodextrin had extremely low permeability, i.e., approximately 0.02% of the amount applied to the skin.

In studies involving rats, there was no specific accumulation of orally administered cyclodextrin in organs, and it was rapidly hydrolyzed to maltose and glucose. In another study, 95% of ingested sterculia urens gum was excreted in the feces of rats. Carrageenan was not degraded or absorbed from the gastrointestinal tract of rodents, dogs, and non-human primates, and rapid and nearly complete enzymatic degradation of starch acetate was reported. Dietary sterculia urens gum was neither digested nor degraded by enteric bacteria in humans, which is similar to what was observed in rats. In a human oral feeding study on tapioca starch, a rapid increase in plasma glucose was observed after dosing.

An LC_{50} > 0.0015 mg/l was reported for glucomannan in an acute inhalation toxicity study involving rats. The transbronchial injection of 0.75% carrageenan (in physiological saline) induced pneumonmia in rabbits.

Acute oral dosing of rats with sterculia urens gum at a dose of 10 g/kg body weight did not cause death, and the same was true for rats dosed with 5,000 mg/kg potato starch modified, 5,000 mg/kg calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified), 2,000 mg/kg corn starch modified, 2,000 mg/kg dextrin palmitate, 2,000 mg/kg dextrin myristate, or 2,000 mg/kg stearoyl inulin. Acute oral LD_{50} values of > 2,800 mg/kg body weight (mice) and > 5,000 mg/kg body weight (rats) have been reported for glucomannan.

In acute dermal toxicity studies on corn starch modified, potato starch modified, dextrin myristate, and dextrin palmitate, an LD_{50} of > 2,000 mg/kg (rats) was reported. The same results were reported for glucomannan in an acute dermal toxicity study involving rabbits.

Repeated dose oral toxicity studies on the following were performed: algin (25% in diet, mice) starch acetate (55% in diet, mice), arabinoxylan (~ 80% arabinoxylan oligopeptides in wheat bran extract [extract test concentrations up to 7.5% in diet], rats), inulin (7.5% in diet, rats), carboxymethyl inulin (31.1% aqueous at doses up to 1,000 mg/kg/day, rats), carrageenan (up to 5% in diet [rats]; up to 25% in diet [mice]; up to 500 mg/kg/day [monkeys]), cyclodextrin (up to 50,000 ppm in diet [rats]; up to 20% in diet [dogs]), ghatti gum (up to 5% in diet, rats), glucomannan (up to 8% in diet, rats), pectin (up to 10% pectin-derived acid oligosaccharides in diet, rats),

solanum tuberosum (potato) starch (up to 10% in diet, rats), and sterculia urens gum (5 g/kg/day, rats; 7% in diet, rats). Sodium alginate was nephrotoxic in mice, but results for starch acetate were of little, if any, toxicological significance. The NOAEL for wheat bran extract in rats was 4.4 g/kg/day, the highest dose administered; there were no remarkable findings in control rats dosed with inulin. There were no toxicologically significant findings in rats dosed with carboxymethyl inulin, and the same was true for ghatti gum. The liver and kidney were identified as target organs for toxicity in rats dosed with β-cyclodextrin, but there was no evidence of systemic toxicity in dogs. There were no treatment-related effects in dogs dosed with γ-cyclodextrin. Treatment-related histopathological changes in the urinary bladder were observed in rats fed pectin-derived acidic oligosaccharides in the diet. No adverse effects were observed in rats dosed repeatedly with sterculia urens gum. Transient fatty degeneration, with focal necrosis of the liver was observed in rats fed glucomannan in the diet.

Repeated oral feeding of humans with propylene glycol alginate (up to 200 mg/kg/day) or sterculia urens gum (10.5 g in diet/day) did not cause toxicity.

Systemic toxicity was not observed in guinea pigs that received repeated dermal applications of 31.1% aqueous carboxymethyl inulin, or in rats dosed dermally (2 g/kg body weight/day) with potato starch modified.

There were no changes in cell morphology of the nasal epithelium of rats after intranasal administration of methyl cyclodextrin.

Pathological lesions of the ocular mucosa were not observed after 2% algin was instilled into the eyes of rabbits. Carrageenan was non-irritating to the unrinsed eyes of rabbits, but was minimally irritating to rinsed eyes. Ocular irritation was not observed in rabbits tested with dextrin myristate, dextrin palmitate, or stearoyl inulin. An eye gel containing 2.45% maltodextrin was classified as a non-irritant in the *in vitro* bovine corneal opacity and permeability assay, and in the *in vitro* EPI-Ocular® assay. Corn starch modified and calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified) were minimally irritating to the eyes of rabbits. Potato starch modified and a 16.8% aqueous suspension of potato starch modified were slightly irritating to the eyes of rabbits. Hydroxypropyltrimonium hydrolyzed corn starch had practically no irritation potential at concentrations of 5%, 10%, and 15% in the *in vitro* HET-CAM ocular irritation assay. Mixtures containing 1.35% hydrolyzed furcellaran were classified as slightly toxic in a cytotoxicity assay involving cultured fibroblasts, and this finding was classified as almost non-irritating to slightly irritating to the eyes.

In a primary skin irritation study, results were negative for 2% algin in rabbits. In a cumulative skin irritation study involving rabbits, the results observed at macroscopic or microscopic examination indicated that 2% algin did not induce a severe reaction. Potato starch modified (10% solids aqueous solution) caused minimal to slight acanthosis in rabbits, and a 50% slurry of calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified) was mildly irritating to the skin of rabbits. At a dose of 2,000 mg/kg in an acute dermal toxicity study, corn starch modified (30% solids in distilled water) was classified as a mild skin irritant in rabbits.

Skin irritation was not observed in albino guinea pigs patch tested with 100% carboxymethyl inulin. Erythema and edema were observed in an acute dermal toxicity study involving rats dosed with 2 g/kg potato starch modified; all reactions cleared by 72 h. Neither erythema nor edema was observed in rats that received repeated dermal applications of the same dose of potato starch modified. Dextrin palmitate or dextrin myristate did not cause skin irritation in rabbits or skin sensitization in guinea pigs evaluated in the maximization test. A trade name mixture containing 1.35% hydrolyzed furcellaran was classified as non-irritating to the skin of human subjects. A trade name mixture containing 0.6% hydrolyzed furcellaran was classified as non-irritating and non-sensitizing when applied to the skin of human subjects.

In the guinea pig maximization test, corn starch modified (20% solution) and 31.1% aqueous carboxymethyl inulin did not induce sensitization. In the Buehler test for skin sensitization, potato starch modified (18.5% aqueous suspension) caused faint erythema during induction, but there was no evidence of sensitization in animals tested. Also, in the Buehler test, a paste of 50% calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified) was not a

sensitizer in guinea pigs. ι-Carrageenan and konjac flour (glucomannan is primary polysaccharide component; the antigen is an acidic protein [AG40D-2]) were also non-sensitizing to the skin of guinea pigs.

Corn starch modified (7.5%) did not induce cumulative skin irritation in 26 subjects or skin sensitization in 113 subjects tested. A 50% w/v slurry or 50% solids slurry of calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified) was classified as a probable mild irritant in a 21 day cumulative skin irritation study involving 23 human subjects.

Algae exopolysaccharides (1%) did not cause skin irritation or sensitization in an HRIPT involving 50 subjects. An eye gel containing 2.45% maltodextrin did not induce allergic contact dermatitis in an HRIPT involving 103 subjects. Results were negative for skin irritation and allergic contact dermatitis in 12 male subjects patch-tested with 20% aqueous sodium alginate. Negative results for skin sensitization were also reported for 227 subjects in a human RIPT on a cleanser containing 10 wt% sodium hydrolyzed potato starch dodecenylsuccinate. Neither skin irritation nor sensitization was observed in the following HRIPT's: 54 subjects tested with a rinse-off facial product containing 42.69% dextrin, 51 subjects tested with a leave-on facial product containing 0.3% dextrin myristate, and 47 subjects tested with hydroxypropyltrimonium hydrolyzed corn starch (15%).

Allergenicity was not associated with the oral dosing of human subjects with propylene glycol alginate, and dermal application of a calcium alginate dressing to patients did not cause any side effects that were classified as severe.

Sodium hydrolyzed potato starch dodecenylsuccinate was evaluated for phototoxicity at concentrations ranging from 68.1 to 1,000 µg/ml in the *in vitro* neutral red uptake phototoxicity assay (BALB/3T3 clone A31 mouse embryo fibroblast cultures). The test material was not considered to have phototoxicity potential.

The concentration of konjac flour that caused a 50% decrease in respiratory rate (RD_{50}) in mice in a sensory irritation evaluation was 110 mg/m^3. In a subsequent study, the criteria used to define respiratory tract sensitization (increase in respiratory rate of 36% and change in respiratory waveform) were achieved in 25% of the 8 guinea pigs challenged with konjac flour (mean exposure concentration range = 50 to 68 mg/m^3). The inhalation of konjac dust in factories producing konnyaku, a popular food in Japan made from konjac tubers, has been reported to produce allergic bronchial asthma in sensitized individuals.

In studies evaluating effects on the immune system, an acidic polysaccharide produced by *Polianthes tuberosa* cells was classified as an immunosuppressive polysaccharide. The injection (i.p.) of potassium carrageenan into rats resulted in significant elevation of serum IgM, but not IgG.

In pregnant mice that received doses of kappa/lambda-carrageenan (from *C. crispus*, sodium or calcium salt) at oral doses up to 900 mg/kg/day during gestation, there was a dose-dependent decrease in the number of live pups and in pup weight. Skeletal maturation was also retarded. In another study in which pregnant mice received oral doses of the same test substance (sodium or calcium salt) at doses up to 600 mg/kg/day during gestation, there was a dose-dependent increase in the incidence of missing skeletal sternebrae. However, feeding with the test substance (calcium salt) at dietary concentrations up to 5% prior to mating in a three-generation feeding study, no specific external, skeletal, or soft-tissue anomaly could be correlated with dosage. In a study in which calcium carrageenan was fed at dietary concentrations up to 1.8% prior to mating, during breeding, and throughout gestation, lactation, and post-weaning, there were no differences between test and negative control groups regarding length of gestation, litter size, or sex distribution.

The oral dosing of pregnant hamsters with doses of kappa/lambda-carrageenan (from *C. crispus*, sodium or calcium salt) up to 600 mg/kg/day during gestation resulted in some evidence of a dose-dependent delay in skeletal maturation. In a similar study in which hamsters received oral doses of the test substance (sodium or calcium salt) up to 200 mg/kg/day during gestation, there were no dose-related teratogenic or fetotoxic effects. When pregnant rabbits were dosed orally with the test substance (sodium or calcium salt) at doses up to 600 mg/kg/day during gestation, the numbers of skeletal or soft tissue abmormalities did not differ from those of controls.

Neither reproductive nor developmental toxicity was observed in rat dietary feeding studies on cyclodextrin (up to 20%), and pectin-derived acidic oligosaccharides (10%). Sterculia urens gum was not teratogenic when

administered in a corn oil suspension to rats (doses up to 900 mg/kg/day) rabbits (doses up to 635 mg/kg/day) or mice (doses up to 170 mg/kg/day) during gestation. Cyclodextrin also did not cause reproductive or developmental toxicity in rabbits when administered at dietary concentrations up to 20%, and the same was true when pregnant cats were fed 2% glucomannan in the diet during gestation.

In bacterial assays, the following were not genotoxic either with or without metabolic activation: arabinoxylan, carboxymethyl inulin, carrageenan, corn starch modified, ghatti gum, glucomannan, a trade name mixture containing 0.6% hydrolyzed furcellaran, pectin-derived acidic oligosaccharides, calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified), and a sodium hydrolyzed potato starch dodecenylsuccinate tradename material. In mammalian assays with and without metabolic activation, wheat bran extract, carboxymethyl inulin, carrageenan, ghatti gum, and glucomannan were not genotoxic. However, results for pectin-derived acidic oligosaccharides in mammalian assays were either equivocal or it was classified as clastogenic. Sterculia urens gum was not genotoxic in cytogenetic assays (*in vitro* and *in vivo*) or in the *in vivo* dominant lethal gene test.

Agar, isolated from Pterocladia, was not carcinogenic in F344 rats or $B6C3F_1$ mice that received concentrations of 25,000 ppm or 50,000 ppm in the diet. Neither algin (25% in diet) nor starch acetate (55% in diet) was found to be carcinogenic in an oral feeding study involving mice. When fed in the diet to rats, carrageenan (up to 25% in diet), and cyclodextrin (up to 675 mg/kg/day), also were not carcinogenic. Carrageenan (up to 5% in diet) was not carcinogenic when fed to hamsters. In a co-carcinogenicity study, carrageenan (15% in the diet) enhanced the incidence of colon tumors in female Fischer 344 rats injected with azoxymethane or *N*-nitrosomethylurea.

Colorectal tumors were found in Sprague-Dawley rats fed 5% or 10% degraded carrageenan, but not 1% degraded carrageenan, in the diet for up to 24 months. Colorectal tumors were also observed in Sprague-Dawley rats that received 5% degraded carrageenan in drinking water for 15 months, and in Sprague-Daweley rats dosed with 1 g/kg or 5 g/kg degraded carrageenan by gastric intubation for 15 months. Fischer 344 rats that received 10% degraded carrageenan in the diet for up to 9 months also had colorectal tumors.

The feeding of rats with an inulin-enriched diet (10% in diet) resulted in the promotion of adenoma growth. Mucosal hyperplasia in the small intestine was observed in rats fed 2.5% pectin in the diet. In another feeding study, 5% methoxylated pectin in the diet increased the multiplicity of colon tumors in rats injected with DMH. In another co-carcinogenicity study, carrageenan (15% in the diet) enhanced the incidence of colon tumors in female Fischer 344 rats injected with azoxymethane or *N*-nitrosomethylurea.

Anticarcinogenic effects have been associated with arabinoxylan and inulin in studies involving rats, with glucomannan in mice, and with konjac flour in rats. The antitumor/anticarcinogenic activity of wheat bran arabinoxylan in mice and arabinoxylan-oligosaccharides in rats has also been reported.

In an epidemiology study, a positive correlation between polysaccharide gum consumption and the incidence of mammary carcinoma was found for carrageenan, alginate, agar, and pectin, but not for sterculia urens gum.

DISCUSSION

The polysaccharide gums comprise polysaccharides obtained from plants or algae. Based on the different chemical structures of polysaccharide gums, these ingredients can be subdivided into categories such as modified, unmodified, linear, branched, and cylic. Regardless of how they are categorized, the molecular structures of these ingredients are polymers composed of monosaccharides. Based on chemical similarities, relevant data have been included on analogous polysaccharide ingredients. Therein, inference may be appropriate from one ingredient to the next, and from one ingredient to one subgroup of polysaccahrides, of which that ingredient or analogue is a member.

The substantial molecular sizes of many of these polysaccharides suggest that skin penetration would be unlikely. Specifically, the percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin through intact hairless mouse skin was extremely low, i.e., approximately 0.02% of the amount applied to the skin. Thus, during cosmetic

use, these ingredients are unlikely to have significant systemic bioavailability and decomposition products are likely to be simple saccharides.

The use concentration data provided indicate that algin is being used in cosmetics at concentrations up to 50% (in mud packs). The Expert Panel acknowledged the absence of skin irritation and sensitization data on algin at this concentration, but noted that results were negative when carboxymethyl inulin was tested at concentrations up to 100% in a skin irritation study involving guinea pigs, and the absence of clinically relevant reactions to polysaccharide gums in dermatologic practice. The Panel is aware of severe granulomatous reactions in patients injected intradermally with an aesthetic injectable filler consisting of purified alginate; however, it was determined that these findings are not relevant to the use of alginates as cosmetic ingredients. Furthermore, systemic toxicity is not a concern in relation to repeated exposure to polysaccharide gums during cosmetic use, considering the absence of gross or microscopic changes in monkeys dosed orally/fed carrageenan in the diet for 7.5 years.

Genotoxicity data for pectin-derived acidic oligosaccharides in mammalian assays were equivocal, but some were classified as clastogenic. However, the Panel noted that clastogenicity was observed only at highly cytotoxic concentrations. The Panel reviewed data indicating that degraded carrageenan (also known as poligeenan) in the diet induced colorectal tumors in rats. Degraded carrageenan used in those studies was produced by acid hydrolysis of a certain type of seaweed. In light of this information and the colon carcinogenicity data, the Panel expressed concern about the use of hydrolyzed carrageenan as a cosmetic ingredient, in the absence of data demonstrating that hydrolyzed carrageenan is chemically dissimilar to poligeenan and does not share its carcinogenic properties. Thus, the Panel determined that method of manufacture and impurities data on the hydrolyzed carrageenan are needed for completion of this safety assessment.

Polysaccharide gums are used at concentrations up to 9.5% (avena sativa (oat) starch) in cosmetic products that are sprayed, which also includes use in a pump hair spray at a maximum concentration of 0.45% (corn starch modified), and in cosmetic products (powders) at concentrations up to 33% (tapioca starch). The available data indicate that food grade konjac flour (primary polysaccharide component is glucomannan) induced sensory irritation of the respiratory tract in mice and respiratory tract sensitization in guinea pigs. Furthermore, the inhalation of konjac dust in factories in Japan has produced allergic bronchial asthma in sensitized individuals. Additional research suggested that the purified antigen AG40D-2 (acidic protein) was responsible for the respiratory sensitization observed, and that this effect was not attributed to glucomannan. Transbronchial injection of 0.75% carrageenan (in physiological saline) induced pneumonia, followed by emphysema, in rabbits. In consideration of these data, the Panel discussed the potential for incidental inhalation exposures to polysaccharide gums in products that are sprayed or in powder form and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone and ingredient use, incidental inhalation would not lead to local respiratory effects or systemic effects.

Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. The Panel also expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities. They agreed that the same suggestion is applicable to alkylating and other agents (e.g., haloethylaminopropionic acid; 3-(dodecenyl)-2,5-furandione; and 2,3-epoxypropyltrimethylammonium chloride) that are used to modify polysaccharide gums.

CONCLUSION

The CIR Expert Panel concluded that the following 105 ingredients are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment, and that the available data are insufficient for determining the safety of hydrolyzed carrageenan in cosmetic products.

Linear Polysaccharides and Their Salts

Agar
Agarose
Algin
Alginic Acid
Ammonium Alginate*
Amylose*
Astragalus Gummifer Gum
Calcium Alginate
Calcium Carrageenan*
Carrageenan
Magnesium Alginate*
Mannan
Polianthes Tuberosa Polysaccharide
Potassium Alginate
Potassium Carrageenan*
Sodium Carrageenan
TEA-Alginate*

Linear – Modified

Amylodextrin
Hydrolyzed Furcellaran*
Maltodextrin
Potassium Undecylenoyl Carrageenan*
Sodium Algin Sulfate*
Sodium/TEA-Undecylenoyl Carrageenan*

Branched Natural/Unmodified

Amylopectin*
Aphanothece Sacrum Polysaccharide*
Arabinoxylan*
Avena Sativa (Oat) Starch
Cassia Angustifolia Seed Polysaccharide
Cichorium Intybus (Chicory) Root Oligosaccharides
Triticum Vulgare(Wheat) Starch
Galactoarabinan
Ghatti Gum*
Glucomannan
Inulin
Pectin
Phaseolus Angularis Seed Starch*
Phaseolus Radiatus Seed Starch*
Pisum Sativum (Pea) Starch*
Pueraria Lobata Starch
Solanum Tuberosum (Potato) Starch
Starch Acetate
Sterculia Urens Gum
Tamarindus Indica Seed Gum
Tapioca Starch
Xyloglucan*

Branched – Modified

Calcium Starch Isododecenylsuccinate*
Calcium Starch Octenylsuccinate*
Corn Starch Modified
Dextrin
Dextrin Behenate*
Dextrin Isostearate*
Dextrin Laurate*
Dextrin Myristate
Dextrin Palmitate
Dextrin Palmitate/Ethylhexanoate
Dextrin Stearate
Glyceryl Alginate
Glyceryl Dimaltodextrin*
Glyceryl Starch
Hydrolyzed Pectin
Hydroxypropyltrimonium Hydrolyzed Corn Starch
Hydroxypropyltrimonium Hydrolyzed Wheat Starch
Hydroxypropyl Oxidized Starch*
Hydroxypropyl Starch
Hydroxypropyltrimonium Maltodextrin Crosspolymer
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch
Palmitoyl Inulin*
Potassium Dextrin Octenylsuccinate*
Potassium Undecylenoyl Alginate*
Potato Starch Modified
Propylene Glycol Alginate
Sodium Carboxymethyl Inulin*
Sodium Carboxymethyl Starch
Undecylenoyl Inulin*
Sodium Dextrin Octenylsuccinate*
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate
Sodium Hydroxypropyl Oxidized Starch Succinate*
Sodium Oxidized Starch Acetate/Succinate
Sodium Starch Octenylsuccinate
Sodium/TEA-Undecylenoyl Alginate*
Starch Acetate/Adipate*
Starch Diethylaminoethyl Ether
Starch Hydroxypropyltrimonium Chloride
Starch Laurate*
Starch Tallowate*
Stearoyl Inulin
Tapioca Starch Crosspolymer*
TEA-Dextrin Octenylsuccinate*

Cyclic

Cyclodextrin
Cyclotetraglucose*

Cyclic – Modified

Hydroxyethyl Cyclodextrin
Hydroxypropyl Cyclodextrin
Cyclodextrin Hydroxypropyltrimonium Chloride*
Cyclodextrin Laurate
Methyl Cyclodextrin

Unknown Structural Configuration

Algae Exopolysaccharides*
Cassia Angustifolia Seed Polysaccharide*
Prunus Persica (Peach) Gum*

Unknown Structural Configuration – Modified

Hydrogenated Potato Starch*
Hydrogenated Starch Hydrolysate
Hydrolyzed Corn Starch Hydroxyethyl Ether*
Hydrolyzed Corn Starch Octenylsuccinate
Hydrolyzed Soy Starch*
Hydrolyzed Starch
Hydrolyzed Triticum Spelta Starch*
Hydrolyzed Wheat Starch

*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.

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

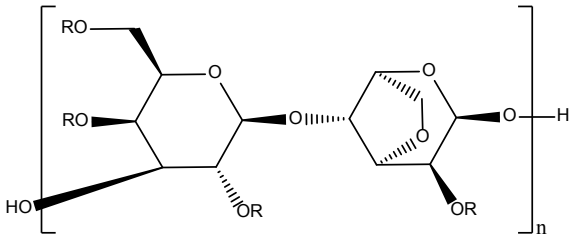
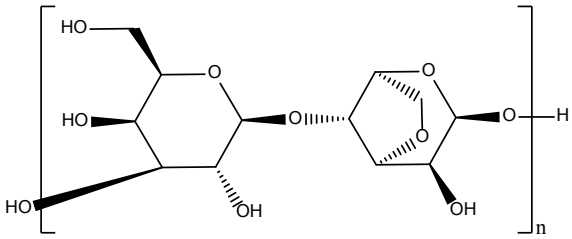
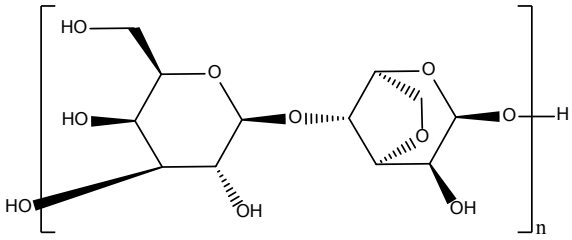
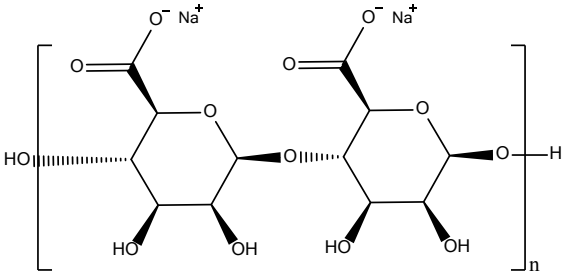
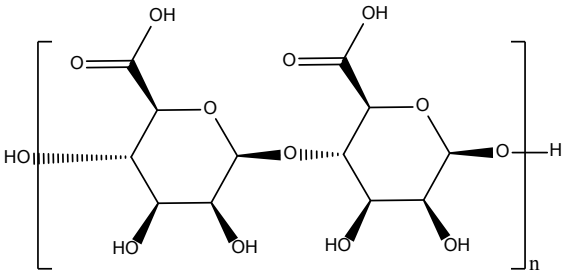
Ingredient CAS No.	Definition	Formula/structure
Linear polysaccahrides and their salts		
Agar 9002-18-0	Agar is the dried, hydrophilic, colloidal polygalactoside derived from various Gelidium species or closely related red alga. *Agar is typically a mixture of agarose and agaropectin.*[86]	 and  wherein R is hydrogen, sulfate, or pyruvate
Agarose 9012-36-6	Agarose is the polysaccharide extracted from the red seaweed Gracilaria.	
Algin 9005-38-3	Algin is the sodium salt of Alginic Acid. *Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.* Other source: Algin is a linear polymer of anhydro-β-D-mannuronic acid. The main structural feature of this molecule is a chain of 1,4-linked-β-D-mannuronic acid residues.[87]	
Alginic Acid 9005-32-7	Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae. *Alginic acid is a polysaccharide comprised of 1,4-linked-β -D-mannuronic and α-L-guluronic acids.*[88]	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

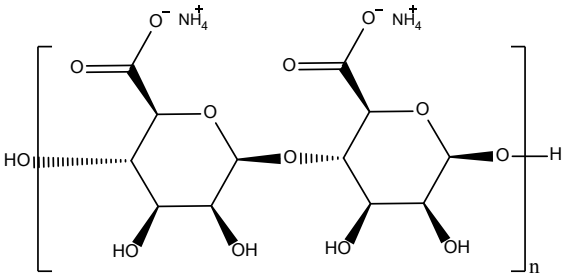
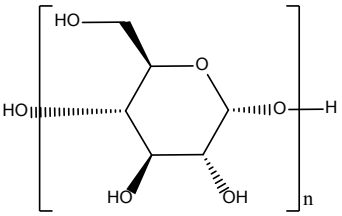
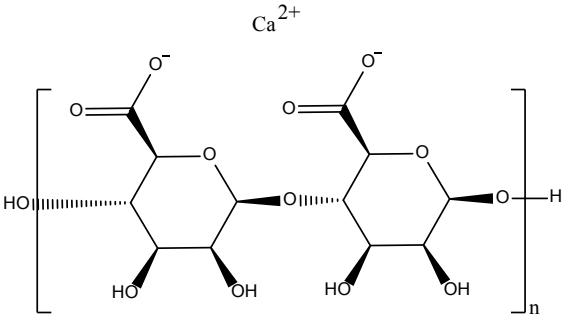
Ingredient CAS No.	Definition	Formula/structure
Ammonium Alginate 9005-34-9	Ammonium Alginate is the ammonium salt of Alginic Acid. *Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.* Other sources: Alginate, a term that refers to salts and derivatives of alginic acid, is a gelling polysaccharide and a structural component extracted from marine brown algae (*Phaeophyceae*), in which it is present in the cell wall as water-insoluble salts.[89] Alginates are polymers composed of β-1,4-D-mannuronic acid (M) and α-1,4-L-guluronic acid (G). Alginates have been determined to be true block copolymers, organized in homopolymeric blocks consisting of either mannuronate or guluronate, or mixed in heteropolymeric MG-block structures. Alginate, the monovalent salt form of alginic acid, is a non-repeating copolymer that contains two uronic acid monomers, 1,4- linked-β-D-mannuronic and α-L-guluronic acid.[90] These residues exist in linear polysaccharide chains that can dimerize to form hydrogels at room temperature in the presence of divalent ions such as calcium.	
Amylose 9005-82-7	Amylose is the carbohydrate stored by plants that consists of a linear (1→4)-(structure)-D-glucan polymer. Other source: Starch is composed of two polysaccharides, amylose and amylopectin.[91] Amylose is a complex α-glucan. It is an essentially linear polymer made up of α(1-4)-linked glucopyranose units.	
Astragalus Gummifer Gum	Astragalus Gummifer Gum is a dried resinous exudate obtained from Astragalus gummifer. It *is a complex polysaccharide composed of D-galacturonic acid, D-galactose, D-xylose, and L-arabinose, with associated calcium, and potassium cations.*	
Calcium Alginate 9005-35-0	Calcium Alginate is the calcium salt of Alginic Acid. *Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.*	
Calcium Carrageenan 9049-05-2	Calcium Carrageenan is the calcium salt of Carrageenan.	
Carrageenan 9000-07-1	Carrageenan is the plant material obtained from various members of the *Gigartinaceae* or *Solieriaceae* families of the red seaweed, *Rhodophyceae*. Other sources: Carrageenan is a high-molecular-weight sulfated polygalactan derived from several species of red seaweeds of the class *Rhodophyceae*.[35] Native carrageenan is defined as a hydrocolloid isolated from red algae (seaweed) and consisting mainly of varying amounts (depending on the processing methods) of the ammonium, calcium, magnesium, potassium or sodium salts of sulfate esters of galactose and 3,6-anhydrogalactose copolymers (the two hexose units are alternately linked α-1,3 and β-1,4 in the polymer).[92] A product called 'degraded carrageenan' has been produced from extracts of *Eucheuma spinosum* seaweed by treatment with dilute hydrochloric acid. The most common forms of carrageenan are designated as kappa-, iota-, and lambda carrageenans.[93] Kappa carrageenan is mostly the alternating polymer of D-galactose-4-sulfate and 3,6-anhydro-D-galactose. Iota carrageenan is similar, but with the 3,6-anhydro-D-galactose sulfated at the 2-hydroxyl. Between kappa and iota carrageenan, there is a continuum of intermediate compositions that differ only in the degree of sulfation at the 2-OH. Lambda carrageenan has alternating monomeric units composed mostly of D-galactose-2-sulfate (1,3- linked) and D-galactose-2,6-disulfate (1,4-linked).	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
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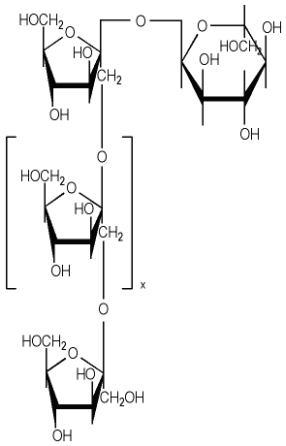
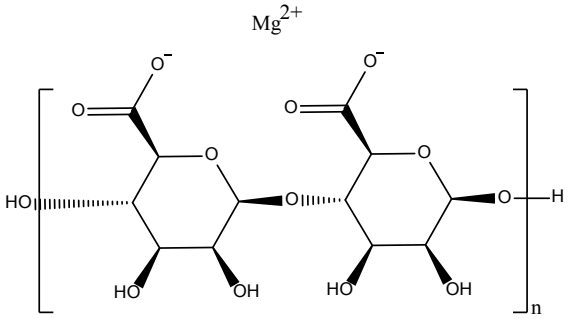
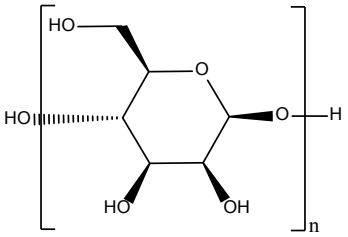
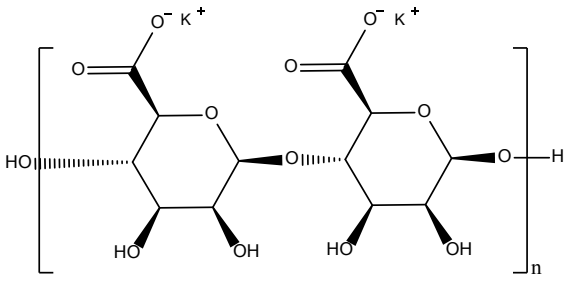
Ingredient CAS No.	Definition	Formula/structure
Inulin 9005-80-5	Inulin is the polysaccharide that conforms to the formula below. Other sources: Inulin has been identified as a fructan, a general term that is used to refer to naturally occurring plant oligo- and polysaccharides.[94] The term refers to any carbohydrate (linear or branched) in which one or more fructosyl-fructose links constitute the majority of the glycosidic bonds. Within the inulin-type fructans are two general groups of materials, inulin and its subsets, including oligofructose and fructooligosaccharides (FOS). FOS always terminate with a glucose molecule. Oligofructose most often contains only fructose molecules, but may end with a glucose molecule. Inulin is a polydisperse carbohydrate consisting mainly of β(2→1) fructosyl-fructose links and contains both GF_n and F_m compounds. The *n* or *m* represents the number of fructose units (F) linked to each other, which can vary from 2 to 70 with one terminal glucose (G). The terms oligofructose and FOS refer to inulin-type fructans with a maximum average degree of polymerization (DP) less than 10. Additionally, total hydrolysis of inulin yields fructose and glucose.[94]	
Magnesium Alginate 37251-44-8	Magnesium Alginate is the magnesium salt of Alginic Acid.	
Mannan 9036-88-8 51395-96-1	Mannan is a natural polysaccharide consisting of a polymer of Mannose.	
Polianthes Tuberosa Polysaccharide	Polianthes Tuberosa Polysaccharide is the polysaccharide fraction produced by the cultured cells of *Polianthes tuberosa.*	
Potassium Alginate 9005-36-1	Potassium Alginate is the potassium salt of Alginic Acid.	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

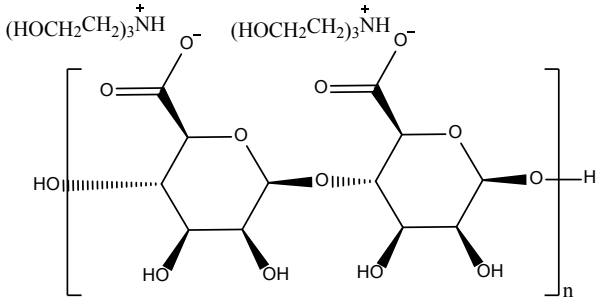
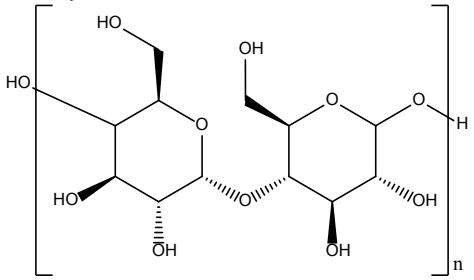
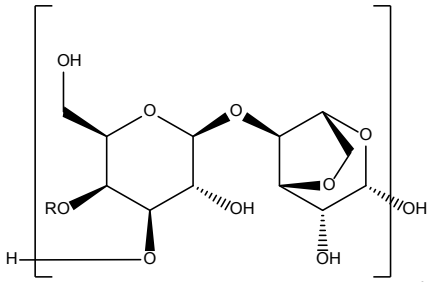
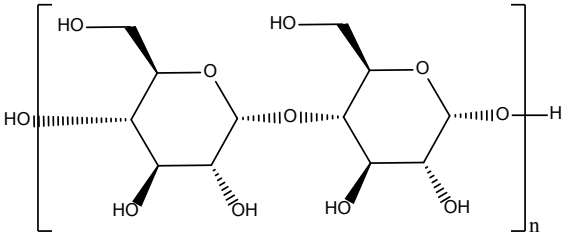
Ingredient CAS No.	Definition	Formula/structure
Potassium Carrageenan 64366-24-1	Potassium Carrageenan is the potassium salt of Carrageenan.	
Sodium Carrageenan 60616-95-7 9061-82-9	Sodium Carrageenan is the sodium salt of Carrageenan.	
TEA-Alginate	TEA-Alginate is the triethanolamine salt of Alginic Acid.	
Linear - modified		
Amylodextrin 9005-84-9	Amylodextrin is the product obtained by treating potato or corn starch with dilute hydrochloric acid.	
Hydrolyzed Carrageenan 53973-98-1	Hydrolyzed Carrageenan is the hydrolysate of Carrageenan derived by acid, enzyme or other method of hydrolysis.	
Hydrolyzed Furcellaran 73297-69-5	Hydrolyzed Furcellaran is the hydrolysate of furcellaran derived by acid, enzyme or other method of hydrolysis. *Furcellaran is composed of D-galactose, 3,6-anhydro-D-galactose and D-galactose- 4-sulfate.* Other source: Information relating to the algal source of hydrolyzed furcellaran indicates that this ingredient is a carrageenan (Kappa type) that is obtained from red algae, *Furcellaria lumbricallis*.[73]	 where R is hydrogen or SO_3^{2-}
Maltodextrin 9050-36-6	Maltodextrin is the saccharide material obtained by hydrolysis of starch. *Maltodextrin is a linear-chain oligosaccharide of glucose, usually obtained from starch by partial, enzymatic treatment.*[95] *The term "maltodextrin" can be applied to any starch hydrolysis product that contains fewer than 20 dextrose (glucose) units linked together.*	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

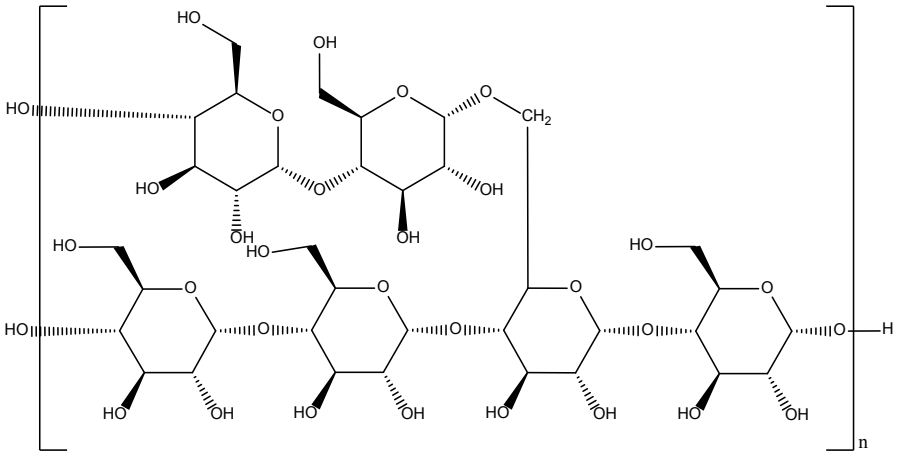
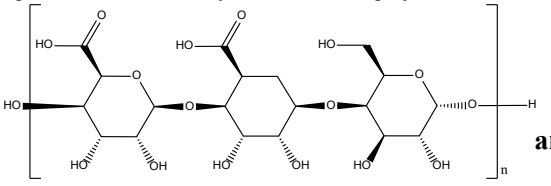
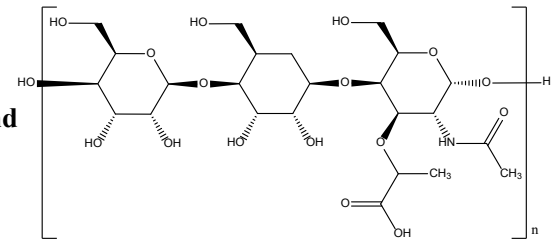
Ingredient CAS No.	Definition	Formula/structure
Potassium Undecylenoyl Carrageenan	Potassium Undecylenoyl Carrageenan is the potassium salt of the condensation product of undecylenic acid chloride and Carrageenan.	
Sodium Algin Sulfate 9010-06-4	Sodium Algin Sulfate is the sulfate ester of Algin.	
Sodium/TEA-Undecylenoyl Carrageenan	Sodium/TEA-Undecylenoyl Carrageenan is the mixed sodium and triethanolamine salt of the condensation product of undecylenic acid chloride and Carrageenan.	
Branched – natural/unmodified		
Amylopectin 9037-22-3	Amylopectin is the branched chain polysaccharide portion of starch. Other sources: Amylopectin is a complex α-glucan.[91] It is a highly branched polysaccharide composed of segments of linear α(1→4)-linked glucopyranose units joined at branching points via α(1→6) glycosidic linkages to give a structure that resembles a dendrimer. Amylopectin consists of numerous short chains of α(1→4)-linked D-glucopyranosyl residues with a chain length of approximately 6 to 35 units.[96] The chains are α(1→6)-linked into clusters defined as groups of chains, in which the internal chain length between the branches is less than 9 residues.	
Aphanothece Sacrum Polysaccharide	Aphanothece Sacrum Polysaccharide is the polysaccharide fraction isolated from the alga, Aphanothece sacrum.	 **and** 

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

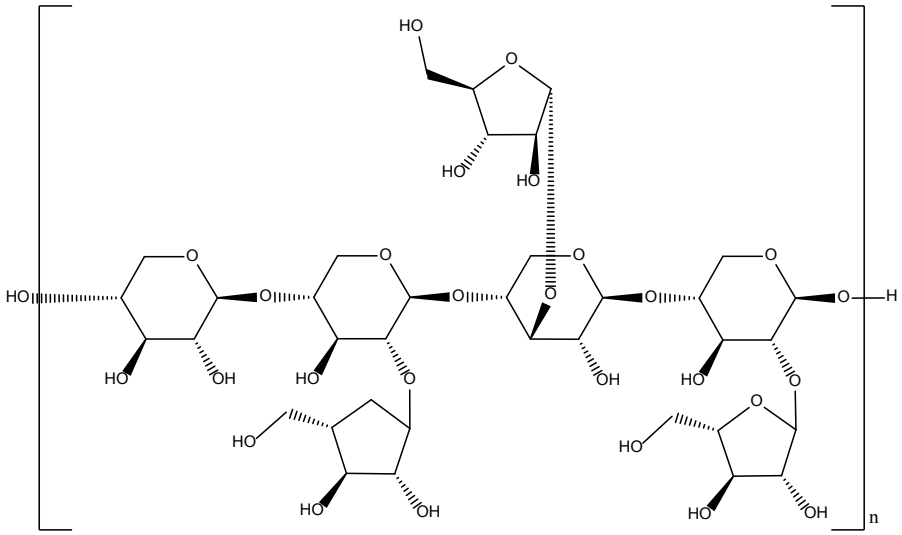
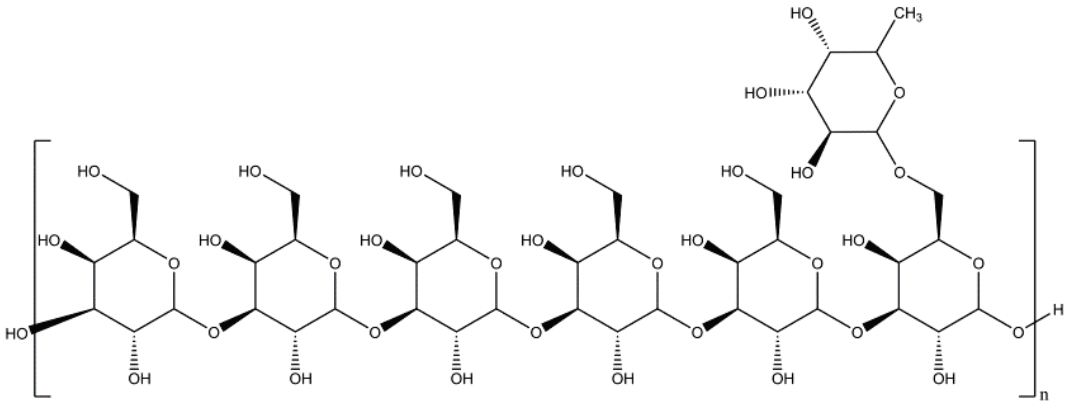
Ingredient CAS No.	Definition	Formula/structure
Arabinoxylan 9040-27-1	Arabinoxylan is a polysaccharide composed of a xylose backbone with arabinose side chains. Other sources: Arabinoxylan is a non-starch polysaccharide, and is also described as a pentosan.[97] It can also be sub-categorized as water-extractable arabinoxylan and water-unextractable arabinoxylan. Arabinoxylans consist of D-xylopyranosyl residues, connected together by β-(1/4) glycosidic bonds.[98,99] Moreover, acetic acid, hydroxycinnamic acids, ferulic acid, and p-coumaric acid are linked with xylose residues in arabinoxylan.[100,101] The attached moieties are partly or wholly lost when arabinoxylan is extracted from cereal or cereal subfractions using alkaline extraction.[97,102,103]	
Avena Sativa (Oat) Starch 9005-25-8 (generic)	Avena Sativa (Oat) Starch is a starch obtained from oats, Avena sativa.	
Cichorium Intybus (Chicory) Root Oligosaccharides	Cichorium Intybus (Chicory) Root Oligosaccharides is the carbohydrate fraction isolated from the roots of Chicorium intybus.	
Galactoarabinan 9036-66-2	Galactoarabinan is the polysaccharide obtained from the extraction of one or more species of the larch tree, *Larix.* The structure of galactoarabinan is:[104]	
Ghatti Gum 9000-28-6	Ghatti Gum is the dried, gummy exudate obtained from the stems and bark of *Anogeissus latifolia.* Other sources: Ghatti gum has been defined as the dried exudate of *Anogeissus latifolia*.[28] Degradation studies have shown that ghatti gum is a polysaccharide that consists of a backbone of galactose units to which other sugars are attached.[105] The side chains can consist of arabinose residues and aldobiuronic acids.	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

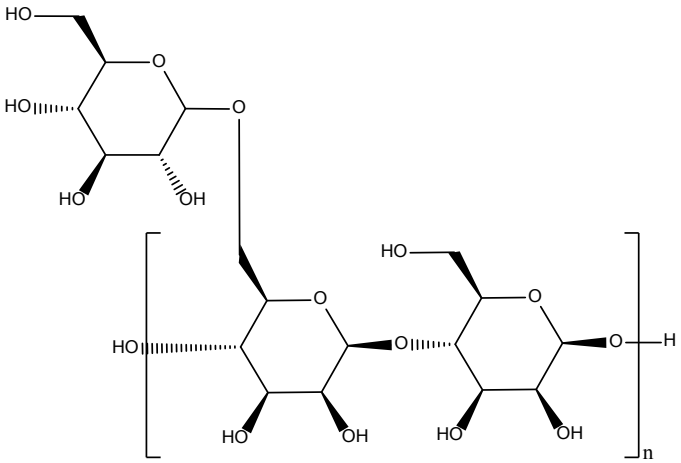
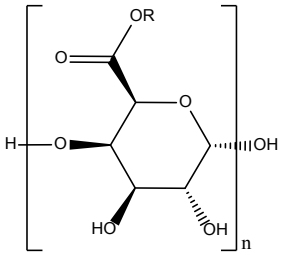
Ingredient CAS No.	Definition	Formula/structure
Glucomannan 37220-17-0 11078-31-2 76081-94-2	Glucomannan is the polymer of mannose containing side chains of glucose. Other sources: Glucomannan (a.k.a. konjac flour or konjac mannan) is a β-D-(1→4)-linked linear copolymer of glucose and mannose substituted with *O*-acetate every 9-19 sugar units.[106] It is derived from the tubers of *Amorphophallus* konjac. Due to the ß-glycosidic linkages between the glucose and mannose building blocks (β-1→4 linkages in the main chain and β-1→3 linkages at the branch points), glucomannan is commonly regarded as a non-digestible polysaccharide. Additionally, glucomannan contains acetyl groups, approximately one acetyl group per 19 sugar residues.[107]	
Pectin 9000-69-5	Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.	 where R is hydrogen or methyl
Phaseolus Angularis Seed Starch	Phaseolus Angularis Seed Starch is a starch obtained from the bean, *Phaseolus angularis.*	
Phaseolus Radiatus Seed Starch	Phaseolus Radiatus Seed Starch is the starch obtained from the seeds of the bean, *Phaseolus radiatus.*	
Pisum Sativum (Pea) Starch	Pisum Sativum (Pea) Starch is a starch obtained from *Pisum sativum.*	
Pueraria Lobata Starch 9005-25-8 (generic)	Pueraria Lobata Starch is the starch obtained from the roots of *Pueraria lobota.*	
Solanum Tuberosum (Potato) Starch 9005-25-8 (generic)	Solanum Tuberosum (Potato) Starch is a polysaccharide obtained from the potato, *Solanum tuberosum.*	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

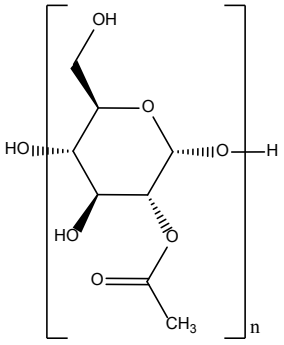
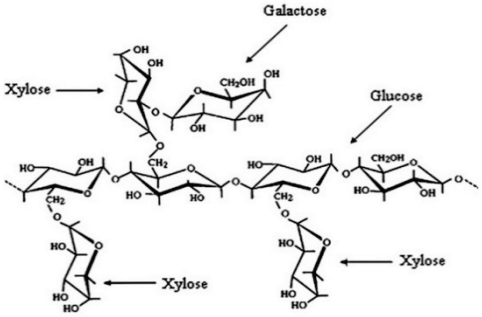
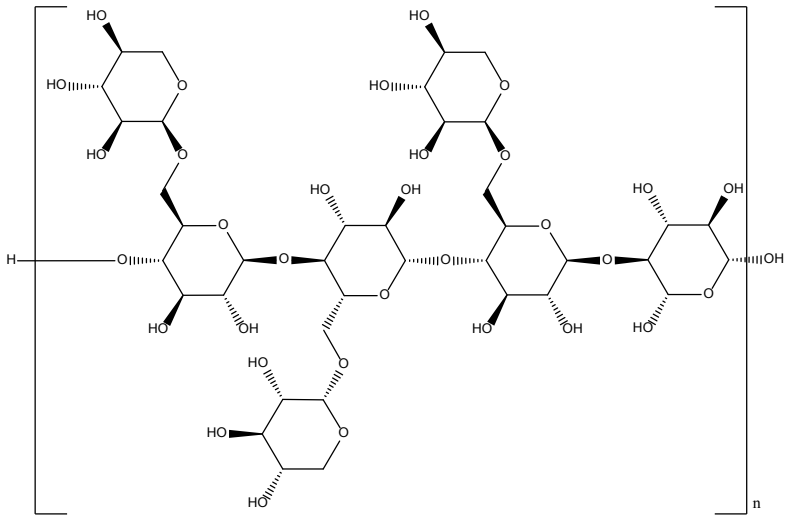
Ingredient CAS No.	Definition	Formula/structure
Starch Acetate 9045-28-7	Starch Acetate is the product obtained by the reaction of acetic acid with starch.	
Sterculia Urens Gum 9000-36-6 [VCRP name: Karaya Gum]	Sterculia Urens Gum is a dried exudate from the tree, *Sterculia urens.* Other source: Sterculia urens gum (a.k.a. karaya gum), the dried exudate of *Sterculia wens* Roxb. and other *Sterculia* spp. (fam. *Sterculiaceae),* is a complex, partially acetylated polysaccharide with a very high molecular weight.[39] Karaya gum is composed of the sugars galactose, rhamnose, and galacturonic acid.	
Tamarindus Indica Seed Gum 39386-78-2	Tamarindus Indica Seed Gum is the gum obtained from the seeds of *Tamarindus indica.*	
Tapioca Starch 9005-25-8	Tapioca Starch is the starch obtained from the roots of *Manihot esculenta.* It consists primarily of amylose and amylopectin.	
Triticum Vulgare (Wheat) Starch 9005-25-8 (generic)	Triticum Vulgare (Wheat) Starch is a starch obtained from wheat, *Triticum vulgare.*	
Xyloglucan 37294-28-3	Xyloglucan is an oligosaccharide containing a 1,4-β-glucan backbone with 1,6-α-xylosyl residues attached to the 6-position of β-glucosyl residues. Other source: The xyloglucan derived from tamarind seeds is composed of a (1-4)-β-glucan backbone chain, which has (1-6)-α-D-xylose branches that are partially substituted with (1-2)-β-D-galactoxylose.[108]	
Branched – modified **(i.e., added sidechains are larger than acetate)**		
Calcium Starch Isododecenylsuccinate 194810-88-3	Calcium Starch Isododecenylsuccinate is the calcium salt of the product formed by the reaction of starch with isododecenylsuccinic anhydride.	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

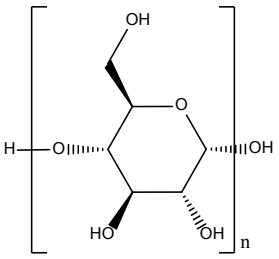
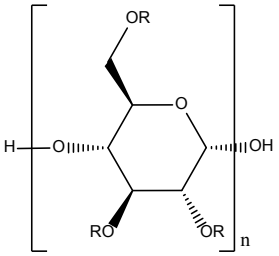
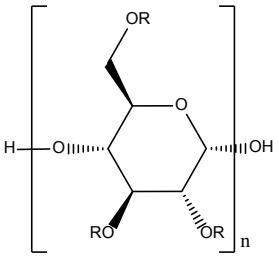
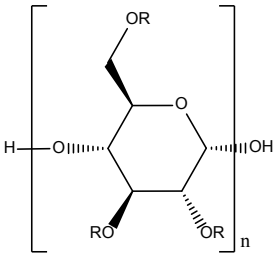
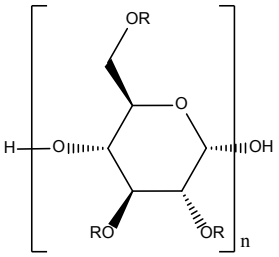
Ingredient CAS No.	Definition	Formula/structure
Calcium Starch Octenylsuccinate	Calcium Starch Octenylsuccinate is the calcium salt of the reaction product of octenylsuccinic anhydride with Zea Mays (Corn) Starch.	
Corn Starch Modified	Corn Starch Modified is the calcium salt of the ester formed from the reaction of 3-(dodecenyl)dihydro-2,5-furandione and corn starch in which the degree of substitution per glucose unit is less than 0.1.	
Dextrin 9004-53-9	Dextrin is a gum produced by the incomplete hydrolysis of starch.	
Dextrin Behenate 112444-74-3	Dextrin Behenate is the ester of Dextrin and Behenic Acid.	 wherein R is the residue of behenic acid
Dextrin Isostearate	Dextrin Isostearate is the ester of Dextrin and Isostearic Acid.	 wherein R is the residue of isostearic acid
Dextrin Laurate 79748-56-4	Dextrin Laurate is the ester of Dextrin and Lauric Acid.	 wherein R is the residue of lauric acid
Dextrin Myristate 93792-77-9	Dextrin Myristate is the ester of Dextrin and Myristic Acid.	 wherein R is the residue of myristic acid

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

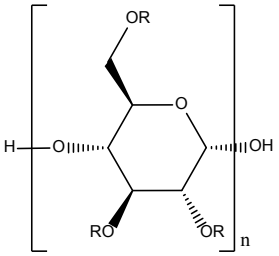
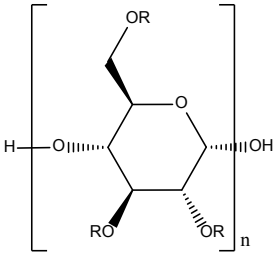
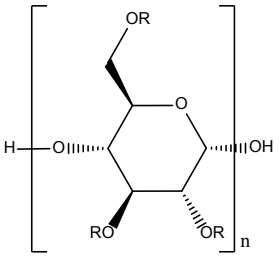
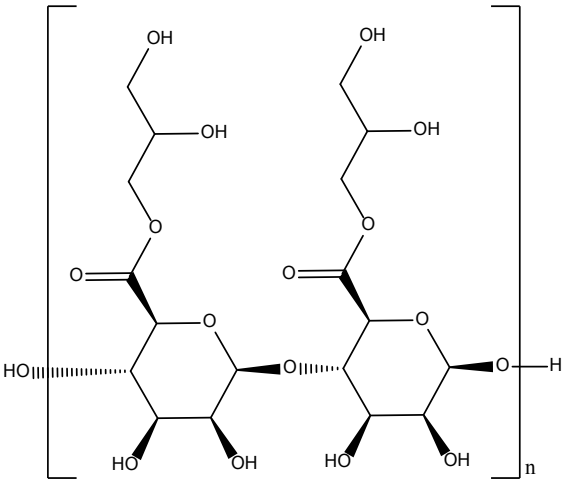
Ingredient CAS No.	Definition	Formula/structure
Dextrin Palmitate 83271-10-7	Dextrin Palmitate is the palmitic acid ester of Dextrin.	 wherein R is the residue of palmitic acid
Dextrin Palmitate/Ethylhexanoate 183387-52-2	Dextrin Palmitate/Ethylhexanoate is the mixed ester of Dextrin with palmitic and ethylhexanoic acids.	 wherein R is the residue of palmitic or ethylhexanoic acid
Dextrin Stearate 37307-33-8	Dextrin Stearate is the ester of Dextrin and Stearic Acid.	 wherein R is the residue of stearic acid
Glyceryl Alginate	Glyceryl Alginate is the ester of glycerin and Alginic Acid.	
Glyceryl Dimaltodextrin	Glyceryl Dimaltodextrin is the reaction product of Glycerin and Maltodextrin.	
Glyceryl Starch	Glyceryl Starch is a partially crosslinked corn starch.	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

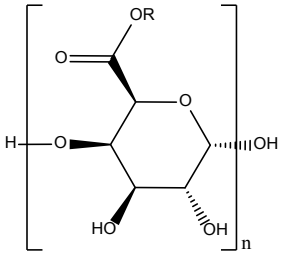
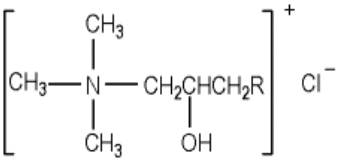
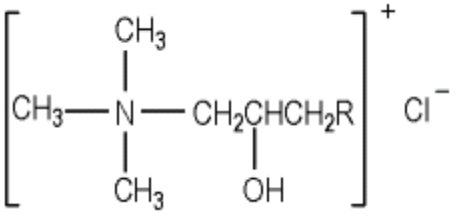
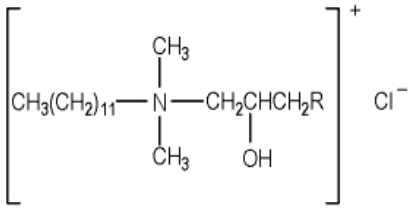
Ingredient CAS No.	Definition	Formula/structure
Hydrolyzed Pectin	Hydrolyzed Pectin is the hydrolysate of Pectin derived by acid, enzyme or other method of hydrolysis. *Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.*	 where R is hydrogen or methyl
Hydroxypropyltrimonium Hydrolyzed Corn Starch	Hydroxypropyltrimonium Hydrolyzed Corn Starch is the quaternary ammonium salt that conforms generally to the formula:	 where R represents the hydrolyzed corn starch moiety.
Hydroxypropyltrimonium Hydrolyzed Wheat Starch	Hydroxypropyltrimonium Hydrolyzed Wheat Starch is the quaternary ammonium salt that conforms generally to the formula:	 where R represents the hydrolyzed wheat starch moiety.
Hydroxypropyl Oxidized Starch	Hydroxypropyl Oxidized Starch is the reaction product of oxygen and Hydroxypropyl Starch.	
Hydroxypropyl Starch 68584-86-1 9049-76-7	Hydroxypropyl Starch is a propylene glycol ether of starch.	
Hydroxypropyltrimonium Maltodextrin Crosspolymer	Hydroxypropyltrimonium Maltodextrin Crosspolymer is a crosslinked polymeric quaternary ammonium salt prepared by the reaction of maltodextrin and glycidyltrimethylammonium chloride with epichlorohydrin.	
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch	Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch is the quaternary ammonium chloride that conforms generally to the formula:	 where R represents the hydrolyzed wheat starch moiety.

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

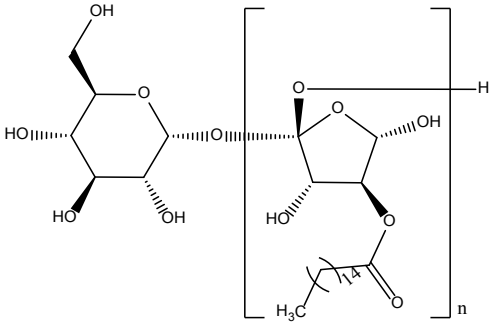
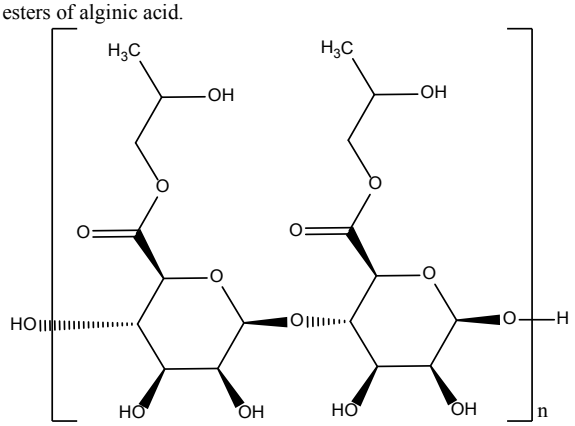
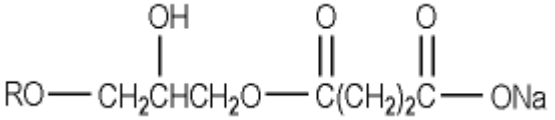
Ingredient CAS No.	Definition	Formula/structure
Palmitoyl Inulin	Palmitoyl Inulin is the condensation product of palmitic acid chloride and the carbohydrate, Inulin.	
Potassium Dextrin Octenylsuccinate	Potassium Dextrin Octenylsuccinate is the potassium salt of the reaction product of octenylsuccinic anhydride with Dextrin.	
Potassium Undecylenoyl Alginate	Potassium Undecylenoyl Alginate is the potassium salt of the condensation product of undecylenic acid chloride and Alginic Acid.	
Potato Starch Modified	Potato Starch Modified is the ether formed from the reaction of haloethylaminodipropionic acid and potato starch in which the degree of substitution per glucose unit is less than 0.1.	
Propylene Glycol Alginate 9005-37-2	Propylene Glycol Alginate is a mixture of the propylene glycol esters of alginic acid.	
Sodium Carboxymethyl Inulin 430439-54-6	Sodium Carboxymethyl Inulin is the sodium salt of the product obtained by the reaction of chloroacetic acid with Inulin.	
Sodium Carboxymethyl Starch 9063-38-1	Sodium Carboxymethyl Starch is the sodium salt of a carboxymethyl derivative of starch.	
Sodium Dextrin Octenylsuccinate	Sodium Dextrin Octenylsuccinate is the sodium salt of the reaction product of octenylsuccinic anhydride with Dextrin.	
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate	Sodium Hydrolyzed Potato Starch Dodecenylsuccinate is the sodium salt of the product obtained by the reaction of dextrin with dodecenylsuccinic anhydride.	
Sodium Hydroxypropyl Oxidized Starch Succinate	Sodium Hydroxypropyl Oxidized Starch Succinate is the organic compound that conforms to the formula:	 where R represents the oxidized starch moiety.
Sodium Oxidized Starch Acetate/Succinate	Sodium Oxidized Starch Acetate/Succinate is the sodium salt of product of the esterification of oxidized starch with acetic acid and succinic acid anhydrides.	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

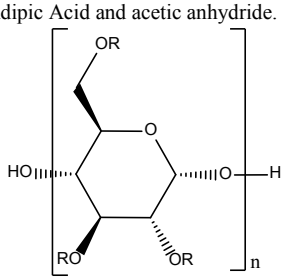
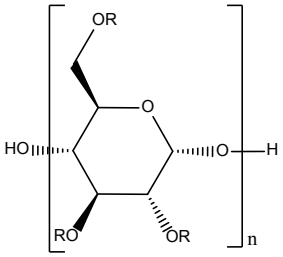
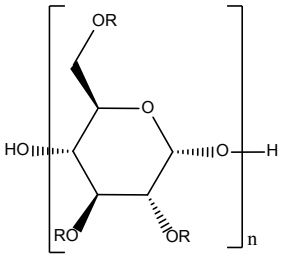
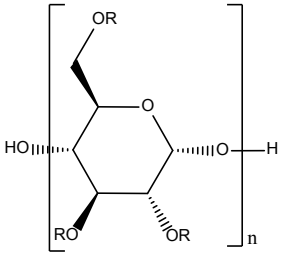
Ingredient CAS No.	Definition	Formula/structure
Sodium Starch Octenylsuccinate 52906-93-1 66829-29-6 70714-61-3	Sodium Starch Octenylsuccinate is the sodium salt of the reaction product of octenylsuccinic anhydride with Zea Mays (Corn) Starch.	
Sodium/TEA-Undecylenoyl Alginate	Sodium/TEA-Undecylenoyl Alginate is the mixed sodium and triethanolamine salt of the condensation product of undecylenic acid chloride and Alginic Acid.	
Starch Acetate/Adipate 63798-35-6	Starch Acetate/Adipate is the product obtained by the reaction of Zea Mays (Corn) Starch with Adipic Acid and acetic anhydride.	 where R is adipate or acetate
Starch Diethylaminoethyl Ether 9041-94-5	Starch Diethylaminoethyl Ether is the product obtained by conversion of some hydroxyl groups in starch to diethylaminoethyl ether groups.	 where R is hydrogen or constitutes, with the attached oxygen, diethylaminoethyl ether
Starch Hydroxypropyltrimonium Chloride 56780-58-6	Starch Hydroxypropyltrimonium Chloride is the quaternary ammonium compound formed by the reaction of starch with 2,3-epoxypropyltrimethylammonium chloride. Other source: One of the starch hydroxypropyltrimonium chloride trade name materials is defiuned as an aqueous solution of a naturally derived cationic polysaccharide produced from food grade potato starch.[109]	 where R is hydrogen or constitutes, with the attached oxygen, hydroxypropyltrimonium
Starch Laurate	Starch Laurate is the product obtained by the reaction of lauric acid with starch.	 where R is hydrogen or laurate

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

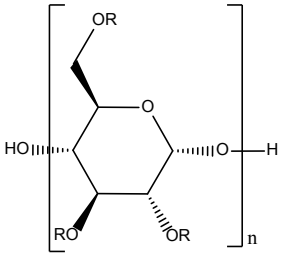
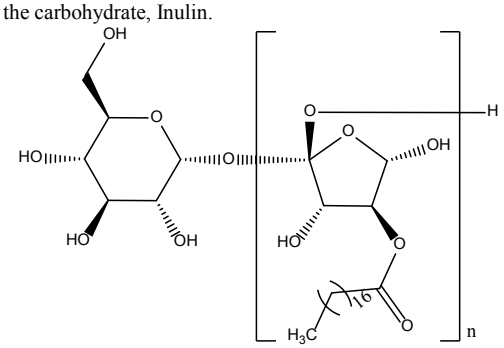
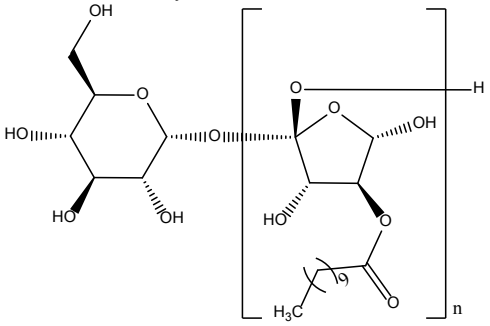
Ingredient CAS No.	Definition	Formula/structure
Starch Tallowate	Starch Tallowate is the ester of starch with the fatty acids derived from Tallow.	 where R is hydrogen or the residue of a fatty acid from tallow
Stearoyl Inulin	Stearoyl Inulin is the condensation product of stearic acid chloride with the carbohydrate, Inulin.	
Tapioca Starch Crosspolymer	Tapioca Starch Crosspolymer is Tapioca Starch crosslinked with epichlorohydrin.	
TEA-Dextrin Octenylsuccinate	TEA-Dextrin Octenylsuccinate is the triethanolamine salt of the reaction product of octenylsuccinic anhydride with Dextrin.	
Undecylenoyl Inulin	Undecylenoyl Inulin is the condensation product of undecylenic acid chloride with the carbohydrate, Inulin.	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

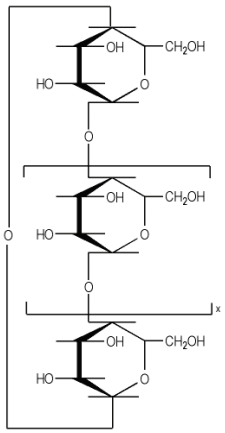
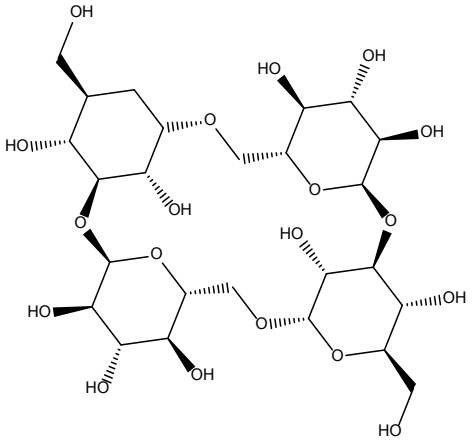
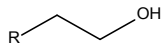
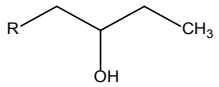
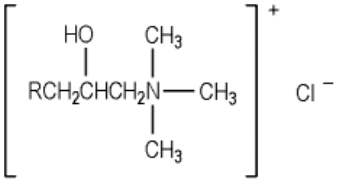
Ingredient CAS No.	Definition	Formula/structure
Cyclic		
Cyclodextrin 12619-70-4 7585-39-9	Cyclodextrin is a cyclic polysaccharide comprised of six to eight glucopyranose units. It conforms to the formula below: Other sources: Cyclodextrins are cyclic amylose-derived oligomers composed of a varying number of α-1-4-linked glucose units.[110] Cyclodextrins contain 6, 7, or 8 glucose units. β-Cyclodextrin is a carbohydrate consisting of seven glucose units.[111]	 where x may have values from 4 to 6.
Cyclotetraglucose 159640-28-5	Cyclotetraglucose is a cyclic polysaccharide comprised of four Glucose units.	
Cyclic - modified		
Hydroxyethyl Cyclodextrin	Hydroxyethyl Cyclodextrin is the hydroxyethyl ether of Cyclodextrin.	 where R represents the Cyclodextrin polymer.
Hydroxypropyl Cyclodextrin 128446-33-3 128446-35-5	Hydroxypropyl Cyclodextrin is a propylene glycol ether of Cyclodextrin.	 where R represents the Cyclodextrin polymer.
Cyclodextrin Hydroxypropyltrimonium Chloride	Cyclodextrin Hydroxypropyltrimonium Chloride is the organic compound that conforms to the formula:	 where R represents the Cyclodextrin polymer.

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

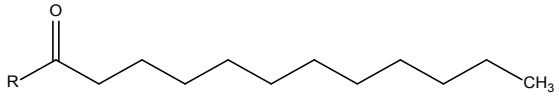
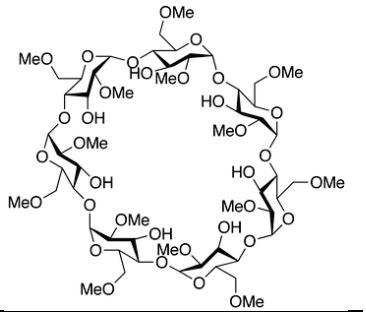
Ingredient CAS No.	Definition	Formula/structure
Cyclodextrin Laurate	Cyclodextrin Laurate is the product obtained by the reaction of Cyclodextrin and lauric acid chloride.	 where R represents the Cyclodextrin polymer.
Methyl Cyclodextrin 128446-36-6	Methyl Cyclodextrin is the product obtained by the methylation of Cyclodextrin.	
Unknown structural configuration		
Algae Exopolysaccharides	Algae Exopolysaccharides (Retired) are exopolysaccharides released by the fermentation of various species of microalgae of the divisions, Rhodophyta and Chlorophyta. The INCI Name, Algae Exopolysaccharides, originally published in 2010, was designated with a retired status in 2015. For an interim period of time, trade name assignments formerly published with the INCI Name Algae Exopolysaccharides will be retained in the retired monograph, and also published with the new name assignment based on the current genus and species name for the specific alga. For further information, consult the Introduction, Retired INCI Names.	
Cassia Angustifolia Seed Polysaccharide	Cassia Angustifolia Seed Polysaccharide is the polysaccharide fraction derived from the seed of Cassia angustifolia. Other source: Cassia angustofolia seed polysaccharide has been defined as a water-soluble galactomannan, consisting of D-galactose and D-mannose in the molar ratio of 3:2, isolated from the seeds of *Cassia angustifolia*.[112]	
Prunus Persica (Peach) Gum	Prunus Persica (Peach) Gum is the dried, gummy exudate obtained from *Prunus persica*.	
Unknown structural configuration - modified		
Hydrogenated Potato Starch 68412-29-3 (generic)	Hydrogenated Potato Starch is the end product of the controlled hydrogenation of Solanum Tuberosum (Potato) Starch.	
Hydrogenated Starch Hydrolysate 68425-17-2	Hydrogenated Starch Hydrolysate is the end-product of the controlled hydrogenation of hydrolyzed starch.	
Hydrolyzed Corn Starch Hydroxyethyl Ether	Hydrolyzed Corn Starch Hydroxyethyl Ether is the hydroxyethyl ether of Hydrolyzed Corn Starch.	
Hydrolyzed Corn Starch Octenylsuccinate 125109-81-1	Hydrolyzed Corn Starch Octenylsuccinate is the reaction product of octenylsuccinic anhydride with Hydrolyzed Corn Starch.	
Hydrolyzed Soy Starch 68412-29-3 (generic)	Hydrolyzed Soy Starch is the hydrolysate of soy starch derived by acid, enzyme or other method of hydrolysis.	
Hydrolyzed Starch 34612-38-9 68412-29-3 (generic)	Hydrolyzed Starch is the hydrolysate of starch obtained from *Ipomoea batatas, Manihot esculenta, Solanum tuberosum* or *Zea mays* by acid enzyme or other method of hydrolysis.	
Hydrolyzed Triticum Spelta Starch	Hydrolyzed Triticum Spelta Starch is the hydrolysate of the starch obtained from the grain, *Triticum spelta* derived by acid, enzyme or other method of hydrolysis.	
Hydrolyzed Wheat Starch 68412-29-3 (generic)	Hydrolyzed Wheat Starch is the hydrolysate of wheat starch derived by acid, enzyme or other method of hydrolysis.	

Table 2. Ingredient Functions in Cosmetic Products.[1]

Linear polysaccahrides and their salts	
Agar	Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Agarose	Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Algin	Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Alginic Acid	Binders; Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Aqueous
Ammonium Alginate	Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Amylose	Skin-Conditioning Agents - Humectant
Astragalus Gummifer Gum	Adhesives; Binders; Emulsion Stabilizers; Film Formers; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Calcium Alginate	Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Calcium Carageenan	Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Carrageenan	Binders; Fragrance Ingredients; Hair Conditioning Agents; Viscosity Increasing Agents - Aqueous
Magnesium Alginate	Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Mannan	Film Formers; Viscosity Increasing Agents - Aqueous
Polianthes Tuberosa Polysaccharide	Skin-Conditioning Agents - Miscellaneous
Potassium Alginate	Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Potassium Carrageenan	Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Sodium Carrageenan	Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
TEA-Alginate	Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Linear - modified	
Amylodextrin	Absorbents; Bulking Agents
Hydrolyzed Carrageenan	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Furcellaran	Skin Protectants
Maltodextrin	Absorbents; Binders; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Film Formers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Potassium Undecylenoyl Carrageenan	Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Sodium Algin Sulfate	Skin-Conditioning Agents - Humectant
Sodium/TEA-Undecylenoyl Carrageenan	Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Branched – natural/unmodified	
Amylopectin	Binders; Viscosity Increasing Agents - Aqueous
Aphanothece Sacrum Polysaccharide	Absorbents; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Arabinoxylan	Film Formers
Avena Sativa (Oat) Starch	Absorbents
Cassia Angustifolia Seed Polysaccharide	Skin-Conditioning Agents - Emollient
Cichorium Intybus (Chicory) Root Oligosaccharides	Skin-Conditioning Agents - Miscellaneous
Galactoarabinan	Film Formers; Fragrance Ingredients
Ghatti Gum	Binders; Emulsion Stabilizers; Surfactants - Emulsifying Agents; Viscosity Increasing Agents - Aqueous
Glucomannan	Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Inulin	Skin-Conditioning Agents - Humectant
Pectin	Binders; Emulsion Stabilizers; Oral Health Care Drugs; Viscosity Increasing Agents - Aqueous
Phaseolus Angularis Seed Starch	Absorbents
Phaseolus Radiatus Seed Starch	Abrasives; Bulking Agents
Pisum Sativum (Pea) Starch	Absorbents; Opacifying Agents; Slip Modifiers

Table 2. Ingredient Functions in Cosmetic Products.[1]

Pueraria Lobata Starch	Absorbents; Opacifying Agents; Slip Modifiers
Solanum Tuberosum (Potato) Starch	Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous
Starch Acetate	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient
Sterculia Urens Gum	Adhesives; Binders; Emulsion Stabilizers; Fragrance Ingredients; Hair Fixatives; Viscosity Increasing Agents - Aqueous
Tamarindus Indica Seed Gum	Adhesives; Emulsion Stabilizers; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Tapioca Starch	Viscosity Increasing Agents - Aqueous
Triticum Vulgare (Wheat) Starch	Abrasives; Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous
Xyloglucan	Humectants
Branched – modified **(i.e., added sidechains are larger than acetate)**	
Calcium Starch Isododecenylsuccinate	Absorbents; Skin-Conditioning Agents - Emollient
Calcium Starch Octenylsuccinate	Absorbents; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Corn Starch Modified	Absorbents; Film Formers; Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Nonaqueous
Dextrin	Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous
Dextrin Behenate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Isostearate	Skin-Conditioning Agents - Miscellaneous
Dextrin Laurate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Myristate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Palmitate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Palmitate/Ethylhexanoate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Stearate	Anticaking Agents; Surfactants - Emulsifying Agents
Glyceryl Alginate	Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Aqueous
Glyceryl Dimaltodextrin	Humectants; Skin-Conditioning Agents - Humectant
Glyceryl Starch	Absorbents; Binders
Hydrolyzed Pectin	Skin-Conditioning Agents - Miscellaneous
Hydroxypropyltrimonium Hydrolyzed Corn Starch	Antistatic Agents; Film Formers; Hair Conditioning Agents; Hair Fixatives; Hair-Waving/Straightening Agents
Hydroxypropyltrimonium Hydrolyzed Wheat Starch	Antistatic Agents; Hair Conditioning Agents
Hydroxypropyl Oxidized Starch	Film Formers
Hydroxypropyl Starch	Dispersing Agents - Nonsurfactant; Viscosity Increasing Agents - Aqueous
Hydroxypropyltrimonium Maltodextrin Crosspolymer	Dispersing Agents - Nonsurfactant
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch	Antistatic Agents; Hair Conditioning Agents
Palmitoyl Inulin	Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Potassium Dextrin Octenylsuccinate	Emulsion Stabilizers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Potassium Undecylenoyl Alginate	Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Potato Starch Modified	Viscosity Increasing Agents - Aqueous
Propylene Glycol Alginate	Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Sodium Carboxymethyl Inulin	Chelating Agents; Viscosity Increasing Agents - Aqueous
Sodium Carboxymethyl Starch	Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Sodium Dextrin Octenylsuccinate	Emulsion Stabilizers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents

Table 2. Ingredient Functions in Cosmetic Products.[1]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate	Surfactants – Foam Boosters
Sodium Hydroxypropyl Oxidized Starch Succinate	Film Formers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Miscellaneous
Sodium Oxidized Starch Acetate/Succinate	Film Formers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Miscellaneous
Sodium Starch Octenylsuccinate	Absorbents; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Sodium/TEA-Undecylenoyl Alginate	Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Starch Acetate/Adipate	Viscosity Increasing Agents - Aqueous
Starch Diethylaminoethyl Ether	Film Formers; Skin-Conditioning Agents - Miscellaneous
Starch Hydroxypropyltrimonium Chloride	Antistatic Agents; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Hair Conditioning Agents; Viscosity Increasing Agents - Aqueous
Starch Laurate	Abrasives
Starch Tallowate	Skin-Conditioning Agents - Emollient
Stearoyl Inulin	Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Tapioca Starch Crosspolymer	Absorbents; Binders
TEA-Dextrin Octenylsuccinate	Emulsion Stabilizers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Undecylenoyl Inulin	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
Cyclic	
Cyclodextrin	Absorbents; Chelating Agents
Cyclotetraglucose	Binders; Bulking Agents; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Cyclic - modified	
Hydroxyethyl Cyclodextrin	Skin-Conditioning Agents - Miscellaneous
Hydroxypropyl Cyclodextrin	Chelating Agents; Emulsion Stabilizers
Cyclodextrin Hydroxypropyltrimonium Chloride	Film Formers; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Cyclodextrin Laurate	Film Formers; Skin Protectants; Skin-Conditioning Agents - Humectant
Methyl Cyclodextrin	Chelating Agents
Unknown structural configuration	
Algae Exopolysaccharides	Film Formers; Skin Protectants; Skin-Conditioning Agents - Humectant; Slip Modifiers
Prunus Persica (Peach) Gum	Viscosity Increasing Agents - Aqueous
Unknown structural configuration - modified	
Hydrogenated Potato Starch	Viscosity Increasing Agents - Aqueous
Hydrogenated Starch Hydrolysate	Film Formers; Humectants; Oral Care Agents; Skin-Conditioning Agents - Humectant
Hydrolyzed Corn Starch Hydroxyethyl Ether	Emulsion Stabilizers; Humectants; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Hydrolyzed Corn Starch Octenylsuccinate	Absorbents; Binders; Film Formers
Hydrolyzed Soy Starch	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Starch	Humectants; Skin Protectants; Skin-Conditioning Agents - Humectant
Hydrolyzed Triticum Spelta Starch	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Wheat Starch	Skin-Conditioning Agents - Humectant

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Linear Polysaccharides and Their Salts

Carrageenan

Average Molecular Weight: > 100,000 Da.[35] **Molecular Weight Range:** 196,000–257,000 Da.[113]

Stability: Data on carrageenans (in their sodium ion form without co-gelling cations) included κ-carrageenan from *Euchema cottoni*i, ι-carrageenan from *Eucheuma spinosoum*, a κ/λ mixture extracted from Chondrus crispus, and a κ/λ hybrid carrageenan from *Gigartina radula*. Reasonable stability to heating at 75˚C down to pH 4, and the rate of depolymerization increases dramatically as the pH decreases from 4 to 3. ι-Carrageenan is the most stable form, while κ-carrageenan has the greatest susceptibility to acid hydrolysis. The carrageenans from *Gigartina radula* and *Chondrus crispus* have intermediate stability.[114]

Carrageenan in the presence of co-gelling cations is much more stable than carrageenan in sodium ion form at 37˚C. However, at higher temperatures, the carrageenan is in the random coil state and is more susceptible to acid degradation. Studies of the stability of κ-carrageenan in the presence of potassium ions have shown that acid-catalyzed hydrolysis occurs at temperatures between 55˚C and 95˚C. Degradation was described as a first-order random hydrolysis process. A 25% reduction in molecular weight was produced at pH 3 after 1.4 h at 50˚C, and after only 28 seconds at 90˚C. At pH 4, a similar reduction in molecular weight was recorded after 8 h at 50˚C and after 15 minutes at 90˚C.[114]

Inulin

Method of Manufacture: Extraction from the roots of *Cichorium intybus*.[115]

Linear - Modified

Amylodextrin

Method of Manufacture: Prepared from waxy maize by enzymatic hydrolysis with pullulanase.[116]

Hydrolyzed Furcellaran

Method of Manufacture: The polymer furcellaran (a carrageenan [Kappa type]) obtained from *Furcellaria lumbricallis* is depolymerized by sub-critical CO_2 with a low percentage of water, and the product is an opalescent liquid **(See Figure 2)**.[73]

Maltodextrin

Method of Manufacture: Prepared as a white powder or concentrated solution by partial hydrolysis of corn starch, potato starch, or rice starch with suitable acids and enzymes.[117]

Branched Natural/Unmodified

Arabinoxylan

Molecular Weight: 65 to 66 kDa (obtained by sedimentation),[118] 800 - 5000 kDa (obtained by gel filtration),[119] and 70 - 1,000 kDa (obtained by gel filtration).[120]

Cichorium Intybus (Chicory) Root Oligosaccharides

Method of Manufacture: Extraction from the roots of Cichorium intybus.[115]

Ghatti Gum

Molecular Weight: ≈ 8.94 x 10^7 Da.[121]

Glucomannan

Average Molecular Weight: 1,000,000 Da; between 200,000 and 2,000,000 Da (commercial samples).[122]

Form: biphasic liquid crystal phase in water at 7 weight% concentration; becomes completely anisotropic at >10 weight%.[107]

Decomposition: Begins to decompose at approximately 250˚C; decomposition is complete at 350˚C.[122]

Method of Manufacture: Obtained by a dry milling process of thin tuber (*Amorphophallus konjac*) slices.[106] Can also be obtained from monocot storage organs other than tubers, such as leaves, bulbs, roots, or seeds.[122] Glucomannan is found in specific large-sized idioblast cells located in the protoplast, and raphide crystal bundles of oxalic acid are enveloped in the polysaccharide. During processing, focus is placed on eliminating the protein membrane of these cells and removing the needle-shaped oxalic acid crystals by sieving, to give residual levels of approximately 0.2% for crude powder and lower for refined grades.[122]

Branched - Modified

Carboxymethyl Inulin

Method of Manufacture: Synthesized by reacting inulin with the sodium salt of monochloroacetic acid in the presence of sodium hydroxide.[123]

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Corn Starch Modified

Method of Manufacture: aqueous corn starch slurry reaction with 3-(dodecenyl) dihydro-2,5-furandione.[66,124]

Dextrin

Method of Manufacture: Dilute acid (e.g. HNO3) is added to native starch, and the starch is pre-dried. Next, pre-dried-starch is roasted at a temperature between 110°C and 150°C until the color of the starch changes to what is described as appropriate whiteness.[125] Another production method begins with the suspension of starch in water and adjustment of the pH to between 6 and 8. An enzyme (e.g., liquefying-type amylase) is added to the slurry, which is liquefied at 80°C and 90°C. Starch syrup is degraded to an appropriate viscosity, and the enzyme is made inactive. The syrup is purified by diatomite, active-carbon, ion-exchange resin and then dried.[125]

Dextrin Myristate

Form: Powder or particles.[67]

Color: White to pale yellow.[67]

Odor: Odorless or characteristic.[67]

Melting Point/Freezing Point: 50 ~ 150˚C.[67]

Flash Point: 210˚C.[67]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[67]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[126]

Dextrin Isostearate

Form: Soft solid.[127]

Color: Colorless to pale yellow.[127]

Odor: Odorless or characteristic.[127]

Melting Point/Freezing Point: 60 ~ 70°C.[127]

Flash Point: > 200°C.[127]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[127]

Method of Manufacture: The method of manufacture for dextrin isostearate begins with an esterification reaction involving 3-methylpyridine (beta-picoline) and n-heptane, followed by percolation, washing (methanol), drying, and filtration.[128]

Dextrin Palmitate

Form: Powder or particles.[68,69]

Color: White to pale yellow.[68,69]

Odor: Odorless or characteristic.[68,69]

Melting Point/Freezing Point: 50 ~ 130˚C; 100 ~ 130˚C.[68,69]

Flash Point: 200 ~ 250˚C.[68,69]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[68,69]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[126]

Dextrin Palmitate/Ethylhexanoate

Form: Powder or particles.[129]

Color: White to pale yellow.[129]

Odor: Odorless or characteristic.[129]

Melting Onset Temperature: 120°C.[129]

Flash Point: 216°C.[129]

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Dextrin Palmitate/Ethylhexanoate

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[129]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[126]

Glyceryl Dimaltodextrin

Method of Manufacture: Production of maltodextrins involves the obtention of products consisting of D-glucose units that are linked primarily by α(1→4) bonds and having dextrose equivalents less than 20.[130]

Hydroxypropyl Starch

Method of Manufacture: Sodium sulfate (Na2SO4) and sodium hydroxide (NaOH) are dissolved in water, and starch and propylene oxide are added, and heated to 38°C to 42°C. After the reaction is finished, the slurry is neutralized by acid (H2SO4). The starch is then dewatered, washed, and dried. The slurry of hydroxyl-propyl starch may also be degraded by an enzyme (e.g., liquefying-type amylase), purified by diatomite and active-carbon, and then dried.[125]

Potato Starch Modified

Method of Manufacture: An aqueous potato starch slurry is reacted with haloethylaminopropionic acid. This reaction is followed by washing, filtration, and drying.[70]

Sodium Dextrin Octenylsuccinate

Method of Manufacture: Method 1: The slurry of sodium starch octenylsuccinate is degraded by an enzyme (e.g., liquefying-type amylase), purified by diatomite and active-carbon, and dried. The dried starch film is crushed into a fine powder. **Method 2:** Dextrin solution and octenylsuccinic anhydride are esterified, whereby the pH value is adjusted between 7 and 8 with alkaline (triethanolamine; sodium hydroxide solution, potassium hydroxide solution). The sodium dextrin octenylsuccinate manufactured according to this method is sold as a liquid. **Method 3:** Dextrin solution and octenylsuccinic anhydride are esterified, whereby the pH value is adjusted between 7 and 8 with sodium hydroxide solution. The solution is then dried.[125]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

Solubility: Soluble in water (149.5 - 158.2 g/l).[131]

Method of Manufacture: Reaction of a hydrolyzed starch with dodecenylsuccinic anhydride.[132]

Sodium Hydroxypropyl Oxidized Starch Succinate

Method of Manufacture: Native starch (CAS No. 9005-25-8) and oxidized starch (CAS No. 065996-62-5) can be modified by reacting starch with etherifying and/or esterifying reagents in the presence of an alkaline catalyst.[15,133]

Reaction to form 2-hydroxypropyl, oxidized starch succinate

Starch 2-Hydroxypropyl Ether, Oxidized + Succinic Anhydride → Starch, 2-Hydroxypropyl, Oxidized, Succinic Acid Ester

$$\text{ST-O-CH}_2\text{-CH-CH}_3\text{OH} \qquad \text{C}_4\text{H}_4\text{O}_3\text{CH}_2 \qquad \text{ST-O-(C-CH}_3)_x\text{-(C}_4\text{H}_4\text{O)}_y$$

$$\text{O} \qquad\qquad\qquad\qquad\qquad\qquad \text{O}$$

Sodium Starch Octenylsuccinate

Method of Manufacture: Starch is suspended in water, and octenylsuccinic anhydride is added. The slurry is heated to approximately 40°C, and the pH value is adjusted between 6 and 9 with dilute sodium hydroxide solution. The pH value of the solution is stable between 7 and 8, and the slurry is neutralized by acid (H2SO4). The starch is then dewatered, washed, and dried. Sodium starch octenylsuccinate may also be suspended in water and dried. The dried starch film is crushed into a find powder.[125]

Starch Hydroxypropyltrimonium Chloride

Molecular Weight: 2,000,000 Da.[109]

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Starch Hydroxypropyltrimonium Chloride

Form: Clear to slightly hazy liquid (clear in 1:5 water solution).[109]

Dry Substance (%) 31-33.[109]

Color, Gardner: ≤ 2.5.[109]

Odor: Very mild; slightly sweet.[109]

pH @ 20°C: 3.5-4.5.[109]

Method of Manufacture: The starting materials for the production of starch hydroxypropyltrimonium chloride are: oxidized starch and the cationic reagent 3-chloro-2-hydroxypropyltrimethylammonium chloride (CAS No. 3327-22-8).[133] The reaction to form cationic starch ether appears below:[133]

Starch + 2,3-Epoxypropyltrimethylammonium Chloride → Starch Hydroxypropyl Trimethylammonium Chloride

ST-OH CH_2-CH-CH_2-$N^+(CH_3)_3$ Cl ST-O-CH_2-CH-$CH_2N^+(CH_3)_3$-Cl

According to another source, starch hydroxypropyltrimonium chloride is produced by an aqueous starch slurry reaction with 2,3-epoxypropyltrimethylammonium chloride in the presence of isopropanol. This reaction is followed by washing with isopropanol/water, and the material is then filtered and dried.[134]

Stearoyl Inulin

Form: Powder or particles.[71,72]

Color: White to pale yellow.[71,72]

Odor: Odorless or characteristic.[71,72]

Melting Onset Temperature: 64˚C; 68.2˚C.[71,72]

Flash Point: 210˚C; 214˚C.[71,72]

Solubility: Insoluble in water, methanol, and ethanol.[71,72]

Cyclic

Cyclodextrin

Solubility: Low aqueous solubility (1.85 g/100mL, β-Cyclodextrin).[135]

Unknown Structural Configuration

Algae Exopolysaccharides

Method of Manufacture: Microalgae is grown in fermenters under conditions that promote the production of the exopolysaccharide, which is secreted by the microalgae. The exopolysaccharides are removed from the cells via filtration or centrifugation, followed by precipitation with alcohol. The exopolysaccharide is then dried and ground to a fine powder. The supplier of this information stated that the CAS number for the ingredient produced (algae exopolysaccharides) is 1122611-69-1, and that the empirical formula for this ingredient is (C27H44O27S)n. Additionally, it was noted that this is the CAS number for D-galactopyranose.[136]

Cassia Angustifolia Seed Polysaccharide

Average Molecular Weight: 9.66 x 10^4 Da.[137]

Unknown Structural Configuration - Modified

Hydrolyzed Starch

Method of Manufacture: Raw Material (Starch) →Starch slurry→Liquefaction by thermostable α-amylase→Saccharification by isoamylase (to debranch starch amylose) and exomaltotetraohydrolase (to produce maltotetraose)→Heat treatment (inactivation of enzymes)→Filtration→Concentration→Decoloration→Filtration→Storage →Filling and weighing→Hydrolyzed starch.[138,139]

Table 4. Composition/Impurities Data on Polysaccharide Gums

Linear Polysaccharides and Their Salts

Algin

After exhaustive methylation of alginic acid, reduction to the corresponding mannoside derivative, and hydrolysis, chromatographic separation indicated that the hydrolyzate contained 88% 2,3-dimethylmannose, 4.5% monomethylmannose, 1% 2,3,4-trimethylmannose, and 6% dimethylglucose.[87]

Carrageenan

The low-molecular-weight forms of carrageenan are <5% of the total composition of the commercial product.[35]

Twenty-nine samples of food-grade refined carrageenan were analyzed using high-performance liquid gel permeation chromatography. Each sample had no obvious peak of poligeenan (which is defined as degraded carrageenan, detection limit ≈ 5%).[140] Poligeenan is produced by a different manufacturing process of seaweed that involves intentional extensive acid hydrolysis, resulting in sulfated galactose polymers with a weight average molecular weight of ~ 15,000 Da.[35] Furthermore**,** according to another source, the molecular weight of poligeenan is in the range of 10,000 to 20,000 Da.[141]

Inulin

According to the *Food Chemicals Codex*, inulin should contain no more than the following: 1 mg/kg lead, 0.2% ash, and 15% (combined) of monosaccharides (as fructose and glucose) and disaccharides (as sucrose), calculated on the dried basis.[115]

Linear - Modified

Hydrolyzed Furcellaran (Mixtures).[73,142]

Mixture 1: Components: hydrolyzed furcellaran (0.6%), concentrate of sea water (0.05%), phenoxyethanol (1%), and water (98.35%). **Impurities:** contains heavy metals at a concentration < the limit of quantification, except for Cr (4.74 mg/kg), Ni (1.93 mg/kg), Pb (0.23 mg/kg), Co (0.17 mg/kg), and As (0.11 mg/kg); contains iodine at a concentration < the limit of quantification (i.e., 1 ppm; contains polychlorobiphenyl (PCB) at a concentration < the limit of quantification (i.e., 2 µg/kg) and research pesticides at a concentration < the limit of quantification (i.e., 10 ng/g).

Mixture 2: Components: hydrolyzed furcellaran (1.35%), phenoxyethanol (1%), and water (97.65%)

Mixture 3: Components: hydrolyzed furcellaran (1.90%), citric acid (0.05%), potassium sorbate (0.10%), and water 97.95%). **Impurities:** contains heavy metals at a concentration < the limit of quantification, except for Cr (0.162 mg/kg) and Pb (0.08 mg/kg); contains iodine at a concentration < the limit of quantification (i.e., 9 ppm); contains PCB at a concentration < the limit of quantification (i.e.,10 µg/kg) and research pesticides at a concentration < the limit of quantification (i.e., 10 ng/g).

Maltodextrin

According to the *Food Chemicals Codex*, maltodextrin should contain no more than the following: 0.5 mg/kg lead, 0.0025% sulfur dioxide, 1% maltodextrins produced from high-amylose starches, and 0.5% all other types of maltodextrins.[115]

Branched - Natural/Unmodified

Arabinoxylan

Arabinoxylans are complex, as the side branches of the main chain arabinose and xylose units contain small amounts of xylopyranose, galactopyranose, and α-D-glucuronic acid or 4-*O*-methyl-α-D-glucuronic acid.[143]

Glucomannan

Konjac flour consists of the following: carbohydrates (as water-soluble fiber, ~75% of glucomannan composition), protein (2-8%), fat (<1%), ash (3-5%), and moisture (<15%).[106]

Sterculia Urens Gum

Commercial sterculia urens gum contains 19%-21% of rhamnose and similar proportions of galactose and galacturonic acid.[36] Nitrogen content (probably non-protein in nature) of 0.07% has also been reported.[51]

Branched - Modified

Dextrin Myristate

Dextrin myristate contains: dextrin myristate (> 95%); moisture, based on loss of drying (< 1%); myristic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detection limit).[144]

Dextrin Palmitate

Dextrin palmitate contains: dextrin palmitate (> 95%); moisture, based on loss on drying (< 1%); palmitic acid (< 5%); 3-methylpyridine (beta-picoline) (< 300 ppm; < 1,000 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detection limit).[145,146]

Dextrin Palmitate/Ethylhexanoate

Dextrin Palmitate/Ethylhexanoate contains: dextrin palmitate/ethylhexanoate (> 95%); moisture, based on loss on drying (< 3%); palmitic acid and 2-ethylhexanoic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm).[147]

Table 4. Composition/Impurities Data on Polysaccharide Gums

Dextrin Isostearate

Dextrin isostearate contains: dextrin isostearate (> 95%); isostearic acid (< 5%); 3-methylpyridine (beta-picoline) (< 300 ppm); heptane (< 200 ppm); and methanol (< 5 ppm, detection limit).[148]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

Impurities: antimony (7.53 mg/kg), arsenic (< 2 mg/kg), barium (0.271 mg/kg), cadmium (< 0.2 mg/kg), chromium (< 0.25 mg/kg), cobalt (< 1.5 mg/kg), copper (<0.25 mg/kg), lead (< 1.5 mg/kg), nickel (< 1 mg/kg), selenium (< 4.86 mg/kg), zinc (1.49 mg/kg), and mercury (< 0.1 mg/kg).[149]

Starch Hydroxypropyltrimonium Chloride

Starch hydroxypropyltrimonium chloride consists of approximately 30% solids, and is preserved with food grade sodium benzoate.[109]

Impurities/residuals data: diol levels (< 2%), enol levels (< 1.5%), and quaternizing agent (< 0.1%).[134]

Stearoyl Inulin

Stearoyl inulin contains: stearoyl inulin (> 95%); moisture, based on loss on drying (< 1%); stearic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detection limit).[150]

Unknown Structural Configuration

Cassia Angustifolia Seed Polysaccharide
The purified seed galactomannan contains mannose:galactose in a ratio of 2.90:1.[137]

Unknown Structural Configuration – Modified

Hydrolyzed Starch

Composition/Properties data on two hydrolyzed starch products are available **(See Table 5)**.[138,139]

Table 5. Composition/Properties Data on Two Hydrolyzed Starch (unknown structural configuration – modified) Products.[138,139]

Product 1	Product 2
G1 (glucose): 2% (not more than 5% for the specification)	G1 (glucose): 2.5% (not more than 5% for the specification)
G2 (maltose): 7%	G2 (maltose): 6%
G3 (maltotriose)*: 10%	G3 (maltotriose)*: 9.5%
G4 (maltotetraose)**: 53% (not less than 50% for the specification)	G4 (maltotetraose)**: 74% (not less than 70% for the specification)
G5 (maltopentaose)***: 2%	G5 (maltopentaose)***: 0.5%
≥ G6****: 26%	≥ G6****: 8%
Loss on drying (water content): ≈ 25% (solids specification: not less than 74%)	Loss on drying (water content): ≈ 28% (solids specification: not less than 72%)
Residue on ignition: ≤ 0.05%	Residue on ignition: ≤ 0.05%
Heavy metals (as lead): ≤ 5 ppm	Heavy metals (as lead): ≤ 5 ppm
Arsenic (as As_2O_3): ≤ 2 ppm	Arsenic (as As_2O_3): ≤ 2 ppm

*_O_-α-glucopyranosyl-(1→4)-_O_-α-D-glucopyranosyl-(1→4)-D-glucose (maltotriose)

**_O_-α-glucopyranosyl-[(1→4)-_O_-α-D-glucopyranosyl]$_2$-(1→4)-D-glucose (maltotetraose)

***_O_-α-glucopyranosyl-[(1→4)-_O_-α-D-glucopyranosyl]$_3$-(1→4)-D-glucose (maltopentaose)

****_O_-α-glucopyranosyl-[(1→4)-_O_-α-D-glucopyranosyl]$_n$-(1→4)-D-glucose (n ≥ 4)

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18,19]

	Maltodextrin		**Glucomannan**		**Agar**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	542	0.00001-4	NR	0.3-17	67	0.002-1
Duration of Use						
Leave-On	327	0.00001-3	NR	NR	49	0.002-1
Rinse off	188	0.00006-3	NR	0.3-17	17	0.0043-0.015
Diluted for (bath) Use	27	0.22-4	NR	NR	1	NR
Exposure Type						
Eye Area	42	0.001-2.5	NR	17	3	1
Incidental Ingestion	13	0.00075-0.6	NR	NR	NR	NR
Incidental Inhalation- Sprays	189	0.00012-0.38	NR	NR	24	0.0075-1*
Incidental Inhalation- Powders	178	0.005-1	NR	NR	25	0.0075**
Dermal Contact	377	0.00001-4	NR	0.3-17	64	0.002-1
Deodorant (underarm)	NR	0.0045-0.12	NR	NR	NR	NR
Hair - Non-Coloring	80	0.00012-2	NR	NR	3	1
Hair-Coloring	65	0.0001-0.0033	NR	NR	NR	NR
Nail	NR	0.0015-3	NR	NR	NR	NR
Mucous Membrane	80	4	NR	NR	5	NR
Baby Products	2	NR	NR	NR	NR	NR
	Agarose		**Algin**		**Alginic Acid**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	10	0.2-0.7	326	0.001-50	13	NR
Duration of Use						
Leave-On	10	0.2-0.7	194	0.001-18	12	NR
Rinse off	NR	NR	131	0.01-50	1	NR
Diluted for (bath) Use	NR	NR	1	0.1	NR	NR
Exposure Type						
Eye Area	NR	NR	40	0.025-0.75	3	NR
Incidental Ingestion	NR	NR	NR	1.1	NR	NR
Incidental Inhalation- Sprays	1	NR	111	0.001-0.025	6	NR
Incidental Inhalation- Powders	1	NR	119	0.025	6	NR
Dermal Contact	10	0.2-0.7	315	0.001-50	13	NR
Deodorant (underarm)	9	0.7	NR	0.001	NR	NR
Hair - Non-Coloring	NR	NR	3	0.001-0.05	NR	NR
Hair-Coloring	NR	NR	1	1.3	NR	NR
Nail	NR	NR	1	0.002	NR	NR
Mucous Membrane	NR	NR	3	0.01-1.1	NR	NR
Baby Products	NR	NR	4	NR	1	NR
	Amylodextrin		**Astragalus Gummifer Gum**		**Avena Sativa (Oat) Starch**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	2	0.00004	7	NR	5	0.1-9.5
Duration of Use						
Leave-On	2	NR	5	NR	3	0.1-9.5
Rinse off	NR	0.00004	2	NR	2	3.6
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	1	NR	3	NR	2	0.1-9.5
Incidental Inhalation- Powders	1	NR	3	NR	3	0.1
Dermal Contact	2	NR	4	NR	5	0.1-9.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.00004	2	NR	NR	NR
Hair-Coloring	NR	NR	1	NR	NR	3.6
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Calcium Alginate		**Carrageenan**		**Cassia Angustifolia Seed Polysaccharide**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	9	0.01-3	249	0.003-15.7	36	0.002-0.75
Duration of Use						
Leave-On	9	0.01-3	181	0.003-15.7	35	0.002
Rinse off	NR	0.01	63	0.003-3.7	1	0.025-0.75
Diluted for (bath) Use	NR	NR	5	0.1-3	NR	NR
Exposure Type						
Eye Area	NR	NR	18	0.2-3.7	3	NR
Incidental Ingestion	NR	NR	25	1-1.1	3	0.002
Incidental Inhalation- Sprays	2	0.016-1	118	0.03-15.7*	15	0.0025*-0.075*
Incidental Inhalation- Powders	3	0.4-3	11	NR	21	0.0025**-0.025**
Dermal Contact	9	0.01-3	206	0.003-3.7	33	0.0025-0.025
Deodorant (underarm)	NR	0.016-1	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	14	0.003-15.7	NR	0.025-0.75
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	2	NR	NR	NR
Mucous Membrane	NR	NR	35	0.1-3	3	0.002
Baby Products	NR	NR	1	NR	NR	NR

	Cichorium Intybus (Chicory) Root Oligosaccharides		**Corn Starch Modified**		**Cyclodextrin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	2	NR	86	0.0062-45.7	128	0.000025-4
Duration of Use						
Leave-On	2	NR	75	0.12-45.7	101	0.000025-4
Rinse off	NR	NR	10	0.0062-3	26	0.0042-1.6
Diluted for (bath) Use	NR	NR	1	9	1	NR
Exposure Type						
Eye Area	NR	NR	7	0.9-8	19	0.05-0.25
Incidental Ingestion	NR	NR	2	0.4	2	0.1
Incidental Inhalation- Sprays	2	NR	48	0.45-45.7*	69	0.08-2.5
Incidental Inhalation- Powders	2	NR	33	0.44**-15	59	0.2
Dermal Contact	2	NR	59	0.0062-15	118	0.0005-4
Deodorant (underarm)	NR	NR	NR	0.12	NR	2.5-4
Hair - Non-Coloring	NR	NR	17	0.45-45.7	5	0.000025-1.6
Hair-Coloring	NR	NR	4	NR	3	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	6	0.0062-9	4	0.1-0.73
Baby Products	NR	NR	2	NR	NR	NR

	Cyclodextrin Laurate		**Dextrin**		**Dextrin Myristate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	5	0.0035	177	0.000008-43	NR	0.05-19
Duration of Use						
Leave-On	5	0.0035	159	0.000008-30	NR	0.094-19
Rinse off	NR	NR	18	0.001-43	NR	0.05-7
Diluted for (bath) Use	NR	NR	NR	5	NR	NR
Exposure Type						
Eye Area	2	NR	21	0.000008-30	NR	0.094-19
Incidental Ingestion	NR	NR	1	0.008	NR	7-15
Incidental Inhalation- Sprays	3	NR	95	0.00037-2.8	NR	0.099-18
Incidental Inhalation- Powders	3	0.0035**	96	0.0044-2.8	NR	0.3**-16**
Dermal Contact	5	0.0035	168	0.000008-43	NR	0.05-19
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	2	0.00026-0.001	NR	0.099-1
Hair-Coloring	NR	NR	2	NR	NR	NR
Nail	NR	NR	4	0.2	NR	NR
Mucous Membrane	NR	NR	3	0.008-5	NR	7-15
Baby Products	NR	NR	NR	NR	NR	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Dextrin Palmitate		**Dextrin Palmitate/Ethylhexanoate**		**Dextrin Palmitate/Stearate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	77	0.0001-16.8	4	NR	NR	0.1-18
Duration of Use						
Leave-On	71	0.0001-16.8	4	NR	NR	0.1-18
Rinse off	6	0.0002-0.0097	NR	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	13	0.0001-2	NR	NR	NR	0.3-18
Incidental Ingestion	37	0.1-16.8	2	NR	NR	4.5-5
Incidental Inhalation- Sprays	5	NR	1	NR	NR	NR
Incidental Inhalation- Powders	5	0.1-0.5**	1	0.1-3**	NR	0.1-3**
Dermal Contact	33	0.0001-13	2	NR	NR	0.1-10
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	0.025	NR	NR	NR	NR
Mucous Membrane	38	0.1-16.8	2	NR	NR	4.5-5
Baby Products	NR	NR	NR	NR	NR	NR
	Galactoarabinan		**Glyceryl Alginate**		**Glyceryl Starch**	
	# of Uses	# of Uses	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	97	NR	NR	0.5	1	4
Duration of Use						
Leave-On	73	NR	NR	0.5	NR	4
Rinse off	24	NR	NR	NR	1	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	21	NR	NR	NR	NR	NR
Incidental Ingestion	2	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	21	NR	NR	NR	NR	NR
Incidental Inhalation- Powders	21	NR	NR	0.5**	NR	4**
Dermal Contact	76	NR	NR	0.5	1	4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	5	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Hydrogenated Starch Hydrolysate		**Hydrolyzed Corn Starch Octenylsuccinate**		**Hydrolyzed Pectin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	60	0.00007-3.8	13	0.06-0.67	14	NR
Duration of Use						
Leave-On	41	0.00007-0.75	11	0.06	12	NR
Rinse off	19	0.13-3.8	2	0.18-0.67	2	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	0.00007-0.5	NR	NR	1	NR
Incidental Ingestion	1	0.065-3.8	NR	NR	NR	NR
Incidental Inhalation- Sprays	33	3.8*	7	NR	10	NR
Incidental Inhalation- Powders	29	0.0007**-0.54**	7	NR	10	NR
Dermal Contact	49	0.00007-0.75	13	0.06-0.67	14	NR
Deodorant (underarm)	NR	NR	3	NR	NR	NR
Hair - Non-Coloring	10	0.13	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.065-3.8	NR	0.67	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Hydrolyzed Starch		Hydrolyzed Wheat Starch		Hydroxyethyl Cyclodextrin	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	NR	0.000013-0.00046	274	0.000003-0.31	NR	1.2
Duration of Use						
Leave-On	NR	0.00046	114	0.00005-0.31	NR	1.2
Rinse off	NR	0.000013	156	0.000003-0.25	NR	NR
Diluted for (bath) Use	NR	NR	4	0.000003	NR	NR
Exposure Type						
Eye Area	NR	NR	6	0.03-0.038	NR	1.2
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	0.00046*	66	0.00005-0.02	NR	NR
Incidental Inhalation- Powders	NR	NR	6	0.0002**-0.06**	NR	NR
Dermal Contact	NR	NR	58	0.000003-0.06	NR	1.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.00046	186	0.000003-0.31	NR	NR
Hair-Coloring	NR	0.000013	26	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	47	0.000003-0.003	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Hydroxypropyl Cyclodextrin		Hydroxypropyltrimonium Hydrolyzed Corn Starch		Hydroxypropyltrimonium Hydrolyzed Wheat Starch	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%
Totals/Conc. Range	53	0.00001-2	11	0.19-0.65	8	NR
Duration of Use						
Leave-On	52	0.00001-2	3	0.24-0.65	NR	NR
Rinse off	1	0.02-0.1	8	0.19-0.43	8	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	13	0.02-1.3	NR	0.65	NR	NR
Incidental Ingestion	NR	0.75	NR	NR	NR	NR
Incidental Inhalation- Sprays	33	0.34-1	3	0.24*	NR	NR
Incidental Inhalation- Powders	29	0.1-2	NR	NR	NR	NR
Dermal Contact	50	0.00001-2	NR	0.65	8	NR
Deodorant (underarm)	1	0.34-2	NR	NR	NR	NR
Hair - Non-Coloring	2	1	11	0.19-0.43	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.02	NR	NR	NR	NR
Mucous Membrane	NR	0.75	NR	NR	8	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Hydroxypropyl Starch		Hydroxypropyltrimonium Maltodextrin Crosspolymer		Inulin	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	9	0.25-8.2	NR	0.00045	41	0.0005-3
Duration of Use						
Leave-On	8	0.25-8.2	NR	0.00045	14	0.0005-3
Rinse off	1	0.5-6	NR	NR	27	0.25
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	NR	NR	NR	1	0.0005
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	6	0.25-0.88	NR	NR	8	NR
Incidental Inhalation- Powders	NR	8.2**	NR	NR	9	0.0008**-2.5**
Dermal Contact	3	0.5-8.2	NR	0.00045	22	0.0005-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	6	0.25-1.4	NR	NR	18	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.5	NR	NR	4	0.25
Baby Products	NR	NR	NR	NR	1	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch		**Mannan**		**Methyl Cyclodextrin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	6	0.017	19	0.01-0.25	20	4-5
Duration of Use						
Leave-On	NR	NR	16	0.01-0.25	20	4-5
Rinse off	6	0.017	3	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	11	NR	10	5
Incidental Inhalation- Powders	NR	NR	11	0.01**	NR	NR
Dermal Contact	6	0.017	17	0.01-0.25	19	4-5
Deodorant (underarm)	NR	NR	NR	NR	3	NR
Hair - Non-Coloring	NR	NR	2	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	6	0.017	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Pectin		**Polianthes Tuberosa Polysaccharide**		**Potassium Alginate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	87	0.0001-9	2	0.001-0.1	37	1
Duration of Use						
Leave-On	33	0.001-0.05	2	0.001-1	1	1
Rinse off	54	0.0001-9	NR	NR	36	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	4	NR	NR	NR	NR	NR
Incidental Ingestion	NR	0.09-9	NR	NR	NR	NR
Incidental Inhalation- Sprays	25	0.05	2	0.001-0.1*	1	NR
Incidental Inhalation- Powders	17	NR	2	0.001-0.05**	1	NR
Dermal Contact	57	0.05	2	0.001-0.1	37	1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	30	0.0001-0.05	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	0.09-9	NR	NR	NR	NR
Baby Products	1	NR	NR	NR	NR	NR
	Potato Starch Modified		**Propylene Glycol Alginate**		**Pueraria Lobata Starch**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	61	0.3-1.3	16	0.00001-0.15	NR	3.6
Duration of Use						
Leave-On	40	0.3-1.3	16	0.00001-0.15	NR	NR
Rinse off	21	1.3	NR	NR	NR	3.6
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	2	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	9	1.3*	9	0.005-0.03*	NR	NR
Incidental Inhalation- Powders	5	0.3**	9	0.00001**-0.15**	NR	NR
Dermal Contact	11	0.3-1.3	15	0.00001-0.15	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	49	1.3	1	0.005-0.03	NR	NR
Hair-Coloring	1	NR	NR	NR	NR	3.6
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Sodium Carboxymethyl Starch		**Sodium Carrageenan**		**Sodium Hydrolyzed Potato Starch Dodecenylsuccinate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	11	0.05-4.7	3	NR	2	NR
Duration of Use						
Leave-On	3	1.9-4.7	1	NR	NR	NR
Rinse off	8	0.05-2.5	2	NR	2	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	4.7	NR	NR	NR	NR
Incidental Ingestion	NR	NR	2	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	1	NR	NR	NR
Incidental Inhalation- Powders	NR	NR	1	NR	NR	NR
Dermal Contact	2	0.05-4.7	1	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	1.9	NR	NR	2	NR
Hair-Coloring	8	2.5	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Sodium Oxidized Starch Acetate/Succinate		**Sodium Starch Octenylsuccinate**		**Solanum Tuberosum (Potato Starch)**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	7	0.05	35	0.0001-0.26	4	3.4-3.6
Duration of Use						
Leave-On	1	0.05	22	0.0001-0.26	2	NR
Rinse off	5	NR	13	0.0023-0.026	2	3.4-3.6
Diluted for (bath) Use	1	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	1	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.026	NR	NR
Incidental Inhalation- Sprays	1	0.05	16	0.048-0.05	1	NR
Incidental Inhalation- Powders	1	NR	15	NR	1	NR
Dermal Contact	3	NR	21	0.048-0.26	3	NR
Deodorant (underarm)	NR	0.05	4	0.048	NR	NR
Hair - Non-Coloring	4	NR	12	0.0001-0.05	1	3.4
Hair-Coloring	NR	NR	1	NR	NR	3.6
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	1	0.026	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Starch Acetate		**Starch Diethylaminoethyl Ether**		**Starch Hydroxypropyltrimonium Chloride**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	11	2	1	NR	18	0.002-1.2
Duration of Use						
Leave-On	1	NR	NR	NR	1	0.02-1.2
Rinse off	10	2	1	NR	17	0.002-0.39
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	NR	NR	1	0.05-1.2*
Incidental Inhalation- Powders	NR	NR	NR	NR	NR	0.02**
Dermal Contact	NR	NR	1	NR	2	0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	11	2	NR	NR	16	0.002-1.2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	NR	2	NR
Baby Products	NR	NR	NR	NR	2	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Stearoyl Inulin		**Sterculia Urens Gum**		**Tamarindus Indica Seed Gum**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	9	0.44-4.8	NR	0.2-0.7	NR	0.01-0.3
Duration of Use						
Leave-On	9	0.44-4.8	NR	0.2-0.7	NR	0.05-0.3
Rinse off	NR	NR	NR	NR	NR	0.01-0.25
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	7	0.44-4.8	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Powders	NR	NR	NR	NR	NR	0.3**
Dermal Contact	9	0.44-4.8	NR	0.7	NR	0.01-0.3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	0.25
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	0.2	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Tapioca Starch		**Triticum Vulgare (Wheat) Starch**			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Totals/Conc. Range	154	0.45-33	27	0.01-6		
Duration of Use						
Leave-On	123	0.5-33	17	0.01-6		
Rinse off	28	0.45-15	9	0.03-3.6		
Diluted for (bath) Use	2	0.86-32	1	NR		
Exposure Type						
Eye Area	13	NR	5	NR		
Incidental Ingestion	NR	NR	2	0.01		
Incidental Inhalation- Sprays	76	1-15*	1	NR		
Incidental Inhalation- Powders	84	3.7-33	9	NR		
Dermal Contact	115	0.5-33	24	0.03-6		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	18	0.45-15	1	NR		
Hair-Coloring	8	3.6	NR	3.6		
Nail	NR	NR	NR	NR		
Mucous Membrane	4	0.86-32	6	0.01		
Baby Products	1	NR	NR	NR		

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for (Bath)Use Product Uses.

*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

**It is possible that these products may be powders, but it is not specified whether the reported uses are powders.

***Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 7. Acute Toxicity Studies on Polysaccharide Gums

Inhalation

Branched - Natural/Unmodified

Glucomannan (in konjac flour): An acute inhalation toxicity study on glucomannan was performed using male and female rats (number and strain not stated). An LC50 of > 0.0015 mg/l was reported.[151]

Oral

Branched - Natural/Unmodified

Glucomannan: Male and female mice (number and strain not stated). LD_{50} > 2,800 mg/kg body weight. No abnormalities with respect to the following: appearance, behavior, body weight changes, occult blood in the urine and feces, or macroscopic findings.[152]

Glucomannan (in konjac flour): Male and female rats (number and strain not stated. LD_{50} > 5,000 mg/kg body weight.[151]

Sterculia Urens Gum: Vehicle: corn oil. 5 fasted male Sprague-Dawley rats. LD_{50} > 10,000 mg/kg body weight. Transient depression, but no other toxic effects.[153]

Branched - Modified

Calcium Starch Isododecenylsuccinate: Material structurally similar to this gum tested. 5 male and 5 female Wistar albino rats. OECD Guideline 401 test protocol. Dosing followed by 14-day observation period. No abnormal systemic signs. LD_{50} > 5,000 mg/kg body weight.[63,64,154]

Corn Starch Modified: Vehicle: distilled water. 5 male and 5 female Wistar albino rats. Organisation for Economic Co-operation and Development (OECD) 401 protocol. 14-day observation period. Alopecia in one animal. LD_{50} > 2,000 mg/kg body weight.[66]

Dextrin Myristate: Rats (number and strain not stated). LD_{50} > 2,000 mg/kg body weight.[67]

Dextrin Palmitate: Rats (number and strain not stated). LD_{50} > 2,000 mg/kg body weight.[68,69]

Potato Starch Modified: 30% aqueous solution. Albino rats (5 males, 5 females). OECD 401 protocol. 14-day observation period. Soft stool (1 female); and no other signs. Body weight changes at necropsy normal. LD_{50} > 5,000 mg/kg body weight.[70,155]

Stearoyl Inulin: Rats (number and strain not stated). Protocol not stated. LD_{50} > 2,000 mg/kg body weight.[71,72]

Dermal

Branched - Natural/Unmodified

Glucomannan (in konjac flour): Male and female rabbits (number and strain not stated). Protocol not stated. LD_{50} > 2,000 mg/kg body weight.[151]

Branched - Modified

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs (4 weeks old). Maximization test. No mortality occurred and no clinical signs of systemic toxicity. Body weights and weight gains similar in treated and control groups.[156]

Corn Starch Modified: Corn starch modified (Amaze® [28-1890]) in distilled water (30% solids). 5 male and 5 female New Zealand White rabbits. OECD 402 protocol. 14-day observation period. Nine of 10 rabbits survived. LD_{50} > 2,000 mg/kg body weight.[66]

Dextrin Myristate: Rats (number and strain not stated). Occlusive dressing technique (details not included). LD_{50} > 2,000 mg/kg body weight.[67]

Dextrin Palmitate: Rats (number and strain not stated). Occlusive dressing technique (details not included). LD_{50} > 2,000 mg/kg body weight.[68,69]

Potato Starch Modified: 10 rats (strain not specified). OECD 402 test guideline. LD_{50} > 2,000 mg/kg body weight.[155]

Potato Starch Modified: 18.5% solids aqueous solution. 10 New Zealand White rabbits (5 males and 5 females). Semi-occlusive patch application. Dose per cm^2 was not stated. Very slight to slight erythema/edema at application sites (all animals); reactions had cleared by 72 h. Signs of local irritation may have been due to mechanical trauma. LD_{50} > 2,000 mg/kg body weight.[70]

Intravenous

Linear Polysaccharides and Their Salts

Carrageenan and Potassium Carrageenan: ι-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units) or potassium carrageenan (2 mg in phosphate-buffered saline [PBS]). Groups of 5 female MF1 mice. i.v. injection (lateral tail vein). Controls injected with PBS (0.3 ml). Animals killed at 1 h and 24 h post-injection, and tissues prepared for microscopic examination. Carrageenan persisted for at least 6 months in livers and kidneys. Within 24 h of i.v. injection, damage to liver Küpffer cells and changes in the microcirculation characteristic of disseminated intravascular coagulation (DIC) in the liver and kidney observed. No adverse effects in hepatocytes, but chronic renal damage observed. ι-carrageenan less toxic to liver and kidney, compared to the potassium carrageenan (less pure, compared to ι-carrageenan).[157]

Carrageenan and Potassium Carrageenan: ι-carrageenan or potassium carrageenan in saline (0.5 ml or 1 ml i.v. injection). Groups of 9 to 15 female CAF_1 mice (Balb/c x A/He). 7- or 14-day observation period. Treatment with either compound induced anemia, granulocytosis, and early profound thrombocytopenia. Treatment with ι-carrageenan caused an early lymphocytosis, and both compounds induced lymphopenia by 18 h post-treatment. Treatment with either compound was associated with an early moderate reduction in the number of nucleated cells and granulocyte/macrophage colony-forming cells per femur. Each compound induced splenomegaly, and ι-carrageenan-treated mice developed hypoplasia of the thymus by 18 h post-injection. Sustained increase in numbers of colony-forming cells in spleen after treatment with each compound.[158]

Table 7. Acute Toxicity Studies on Polysaccharide Gums

Intrapleural

Linear Polysaccharides and Their Salts

Carrageenan: Groups of 6 adult female Balb/c mice (6 to 7 weeks old). One group received single intrapleural injection of 0.1 ml sterile saline (0.9% NaCl) and λ-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units; 1% in solvent [not stated]), which induced pleurisy. Another group each received single intrapleural injection of 1% λ-carrageenan (0.1 ml) only. Animals were killed, and lung tissue samples obtained for microscopic examination at 4 h and 24 h post-injection. Dense inflammation with lobar lung pneumonia and thickened alveolar septum (with occasionally obliterated alveoli) were observed.[159]

Carrageenan: Injection of 2% λ-carrageenan in saline (200 mg/kg) into pleural cavity. Groups of 10 mice. Dosing caused pleurisy, characterized by marked accumulation of fluid and the migration of leukocytes to the site of inflammation in lung.[160]

Transbronchial

Linear Polysaccharides and Their Salts

Carrageenan: Transbronchial injection of 0.75% carrageenan in physiological saline. 27 male albino rabbits. Surviving animals were killed according to the following schedule: 2 at 24 h; 3 each at 3 days, 1 and 2 weeks, and 1 month; 5 at 2 months; and 8 at 4 months. Pneumonia, followed by emphysema in the insulted lung, observed. Of the 8 animals injected with carrageenan and killed at 4 months, 3 were deemed inappropriate for morphometry because of developing fibrosis, abscesses and/or emphysematous bullae in the lungs. Thus, the lungs (mild to severe erythema observed) of the remaining 5 animals injected with carrageenan and of the 5 control rabbits killed at 4 months were prepared for morphometric analysis. Scattered infiltration of polymorphonuclear leukocytes throughout the affected lobe, subsequently replaced by accumulation of carrageenan-laden macrophages; changes lasted for 1 to 2 months. Enlargement of alveoli and alveolar ducts observed at 2 weeks to 2 months post-injection, and pulmonary emphysema observed at 4 months. The lobes not injected with carrageenan had normal appearance throughout study.[161]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Oral - Non-Human

Linear Polysaccharides and Their Salts

Algin: 25% Sodium alginate (also known as algin) in diet. Mice (75 males and 75 females). Feeding with sodium alginate in the diet for 89 weeks. At week 87, half of the surviving male and female mice in each test group placed on control diet (containing 55% pregelatinized potato starch). During feeding period, dietary levels of test substances gradually increased until diets contained (by weight) 25% sodium alginate. All survivors killed during weeks 89 to 92. Sodium alginate caused increased water consumption, distinct caecal and colonic enlargement, and a slightly increased incidence of intratubular nephrosis. Sodium alginate was nephrotoxic, causing increased kidney weights, distension of the renal calyx and high incidence of dilated distal tubules.[162]

Carrageenan: 25,000 ppm or 50,000 ppm kappa carrageenan. Groups of Fischer 344 rats (20/sex/group). Feeding in diet for 90 days. Clinical signs limited to soft feces in high dose rats, and to a lesser extent, in low dose rats. No treatment-related effects on body weights, urinalysis, hematology or clinical chemistry parameters, or on organ weights or ophthalmic, macroscopic or microscopic findings. Gastrointestinal tract appeared normal in detailed histopathological evaluation. NOAEL = 50,000 ppm (mean calculated test material consumption of 3394 ± 706 mg/kg/day in males and 3867 ± 647 mg/kg/day in females).[113]

Carrageenan: kappa/lambda-carrageenan (from *C. crispus* or *G. mamillosa)* at concentrations of 0, 0.1, 5, 15, or 25%. Five male and five female mice of 2 unidentified strains. Lifetime dietary feeding had no adverse effect. Same test material and dietary concentrations. Five male and 5 female rats of 2 unidentified strains. Lifetime dietary feeding. Evidence of hepatic cirrhosis, only at the 25% concentration, with no effect on mortality.[62]

Carrageenan: Extracts of kappa-carrageenan (from *Hypnea musciformis* or *Irideae crispata)* at concentration of 1% or 5%. Groups of 15 male and female Sprague-Dawley rats. Feeding in diet for 1 year. Weight loss ($p = 0.05$) in all treatment groups, compared to control (alphacel) group. Livers of rats fed 1% concentration normal at gross and microscopic examination. Livers from rats given 5% kappa-carrageenan from *H. musciformis* normal at gross and microscopic examination, except for nodules in 2 of 12 livers. Gross examination of livers from rats fed 5% kappa-carrageenan (from *I. crispata*) showed decreased size, rough surface, and vascularization in 10/13 rats, probably treatment-related. Microscopically, these livers were normal, except for focal necrosis in 1 of 10 livers. No evidence of storage of carrageenan-like material (metachromatic) in liver cells of any of the treated rats, and no fibrillar material observed using electron microscopy. No changes observed in stools of rats receiving 1% of either carrageenan. Loose stools in female rats given 5% kappa-carrageenan from *I. crispata* and in males given either carrageenan at 5% concentrations. Blood found sporadically in stools, but frequency was not significant.[62]

Carrageenan: kappa/lambda-carrageenan. Groups of 19 male and 21 female rhesus monkeys. Feeding (gavage) with 0, 50, 200, or 500 mg/kg body weight (6 days/week for five years, and dietary feeding for an additional 2.5 years. Random distribution of loose stools, chronic intestinal disorders, poor appetite, and emaciation. Stool consistency decreased in dose-related trend over entire 7.5 years of the study; findings of fecal occult blood increased in similar fashion. Mean survival time similar in all groups; no gross or microscopic changes in tissues examined. Sporadic differences in body weight observed randomly. Females had significant body-weight depression (not dose-related) in last 2.5 years of study. No consistent, statistically significant changes in hematological or clinical chemical values, absolute organ weights, or organ-to-body weight ratios after 7.5 years of feeding. Cytochemical and ultrastructural observations revealed no storage of carrageenan-like material in livers, obtained at biopsy or in other organs obtained at necropsy; no dose-related gross or microscopic changes in other tissues.[62]

Inulin: 7.5% inulin. 20 Wistar rats of the Crl:(WI)BR strain (10 males, 10 females). Daily dietary feeding for 13 weeks. No remarkable microscopic or macroscopic findings.[163]

Branched - Natural/Unmodified

Arabinoxylan: Wheat bran extract (~ 80% arabinoxylan oligopeptides) at concentrations of 0.3%, 1.5%, and 7.5%. 3 groups of 20 Wistar rats of the Crl:(WI)BR strain (10 males/group, 10 females/group). Feeding resulted in average daily intakes of 0.2 g/kg (0.3% concentration), 0.9 g/kg (1.5%), and 4.4 g/kg (7.5%) for 13 weeks. No evidence of test substance-related adverse macroscopic or microscopic findings. At histopathological examination, minimal bilateral hypertrophy of renal cortical tubules in males and females, particularly in highest-dose group. Findings were not accompanied by degenerative changes or changes in kidney weight, and were considered non-toxic and suggestive of an adaptive response. No remarkable findings in control rats fed basal diet. NOAEL = 4.4 g/kg/day.[163]

Ghatti Gum: Ghatti gum concentrations of 0, 0.5, 1.5 and 5%. Groups of Sprague-Dawley rats (10 males/group, 10 females/group). Dietary feeding (in basal diet) for at least 90 days. Ghatti gum intake at 5% dietary level ranged from 3044 to 3825 mg/kg body weight/day. Feed consumption among treated and control groups was similar for males and females. 2 of 10 females in 5% ghatti gum group had a single colon ulcer, with associated acute inflammation. Ulcers were considered sporadic occurrences, possibly attributable to basal diet. NOAEL = 5% in diet; NOAELs for males and females estimated at 3044 and 3309 mg/kg/day, respectively.[164]

Ghatti Gum: 5% Ghatti gum. Groups of 20 female Sprague-Dawley rats. Dietary feeding for at least 90 days. Single colon ulcer, with associated acute inflammation, in 1 of 20 control females given basal diet. Colon ulcer considered sporadic, possibly attributable to basal diet. Statistically significant alterations in clinical chemistry were considered sporadic and unrelated to treatment. Feed consumption among treated and control groups similar for each sex. NOAEL = 5% in diet; NOAELs at 3670 and 3825 mg/kg/day for different control diets.[164]

Glucomannan: 10% konjac (plant consisting mostly of glucomannan). Groups of four male Sprague-Dawley rats were fed either 5% cellulose (control), 10% pectin, or 10% konjac for 28 days. After dosing period, rats were fasted for 24 h, fed 5 g/kg body weight brown rice, and killed 5 h later. No indication of toxicity.[165,166]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Branched - Natural/Unmodified

Glucomannan: 2.5%, 5%, or 10% refined konjac meal. Groups of 12 five-week-old Sprague-Dawley rats of each sex . Feeding with either a normal basal diet, a hypercholesterolaemic diet (control diet containing 1% cholesterol), or one of three test diets. Because refined konjac meal contains ~ 80% glucomannan, the highest concentration of glucomannan tested was ~ 8%. Four animals of each sex from each group killed after 4, 8, and 12 weeks of feeding. Histological and gross examination of livers from rats fed 1% cholesterol showed spreading fatty degeneration with focal necrosis and a nonspecific inflammation reaction. Similar changes observed in group receiving refined konjac meal at the end of 4 weeks, but the changes disappeared gradually with longer feeding times, and the morphology of the liver was similar to that in the normal control group at the end of 12 weeks. Changes were also observed at gross examination of the liver.[167]

Glucomannan: Basal diet in which 1% of the cornstarch replaced with refined glucomannan (i.e., 1% konjac meal). Groups of 15 Sprague-Dawley rats of each sex. Dietary feeding for 18 months. At the end of feeding period, the animals were killed and the brain, liver, aorta, kidney, spleen, and heart removed. At microscopic examination, the livers of treated rats contained smaller, more lightly stained nuclei and reduced bile-duct proliferation in the portal area. Endothelial cells in the aorta of treated animals were smaller and there was less thickening of the aortic wall. These changes were related to less senescence in the treated group than in the control group. No evidence of treatment-related pathological changes. NOAEL = 1% konjac meal, equivalent to an intake of 500 mg/kg body weight per day.[165]

Pectin and Solanum Tuberosum (Potato) Starch: Test diets containing 5% or 10% pectin-derived acidic oligosaccharides (pAOS). Two groups of F_1 rats (from outbred strain of Wistar rats (Crl:WI(WU); number not stated). Dietary feeding with test (±7 g/kg body weight/day) and control diets for 13 weeks. To keep the total level of added test substance equal in each diet, the low-dose diet (5% pAOS) was adjusted with 5% potato starch. One control group received the standard rodent diet supplemented with 10% potato starch, and the other control group received 10% short-chain FOS (scFOS) in the diet. No treatment- related clinical signs observed, and none of the rats died . Ophthalmoscopic examination did not reveal any treatment-related ocular changes. Neurobehavioral examination and motor activity assessment did not indicate any neurotoxic potential. No relevant differences in body weight, growth rate and feed intake. Macroscopic examination at necropsy did not reveal any adverse effects. Microscopic examination revealed treatment-related histopathological changes in the urinary bladder of animals of the 10% pAOS group. One male and one female of the 5% pAOS group and one male of the control group showed diffuse hyperplasia (very slight). In addition, two males and two females of the 5% pAOS group showed simple hyperplasia in a part of the urinary bladder lining ('focal hyperplasia'). No treatment-related hyperplasia of the transitional epithelium was observed in the kidney. Administration of pAOS at dietary levels up to 10% (equivalent to 7.1 g/kg body weight/day) did not reveal any relevant effects that could be attributed to the ingestion of acidic oligosaccharides.[168]

Starch Acetate: 55% Starch acetate (a chemically modified potato starch) in diet. Mice (75 males and 75 females per test substance). Feeding with starch acetate in the diet for 89 weeks. At week 87, half of the surviving male and female mice placed on control diet (containing 55% pregelatinized potato starch). During feeding period, dietary level of test substance gradually increased until diet contained (by weight) 55% starch acetate. All survivors killed during weeks 89 to 92. Starch acetate caused increased water consumption, distinct caecal and colonic enlargement, and a slightly increased incidence of intratubular nephrosis. Increased incidence of gastric trichobezoars. Concretions in renal pelvis with slight urinary changes, such as increased amounts of amorphous material in the urine and increased urinary calcium content, in the mice fed starch acetate not toxicologically significant. The incidence of intratubular calcinosis or concretions in the pelvic space was not reduced during the recovery period. Caecal and colonic enlargement and changes in urinalysis results were found to be reversible.[162]

Sterculia Urens Gum: 5 non-fasted male Sprague-Dawley rats. Animals intubated with 5 g/kg/day, daily for 5 days. No adverse effects.[153]

Sterculia Urens Gum: 7% (w/w) sterculia urens gum. Albino Wistar rats (rats housed 3 per cage; number tested not stated) Transmission electron microscopy used to study ultrastructure of jejunum, ileum, and cecum after dietary supplementation for 45 days [15 micrographs analyzed] for 45 days. No abnormalities in any of the organelles.[169]

Branched - Modified

Carboxymethyl Inulin: Carboxymethyl inulin (31.1% aqueous). Groups of five male and five female Wistar Crl rats. Doses of 0, 50, 150 and 1000 mg/kg/day (by gavage) for 4 weeks. In all dose groups, no treatment-related effects with respect to: body weight, feed consumption, mortality, hematology, clinical blood chemistry, organ weights or gross or microscopic pathology.[156]

Cyclic

Cyclodextrin: β-cyclodextrin (12,500, 25,000 and 50,000 ppm). Groups of 40 (20 males, 20 females/group) CrI:CD (SD) BR Sprague-Dawley rats. Feeding in the diet for 52 weeks. Control group fed basal diet. The liver and kidney were identified at histopathological examination as target organs for toxicity at concentrations of 50,000 ppm and 25,000 ppm, with the hepatic changes associated with increased plasma liver enzyme and decreased plasma triglyceride concentrations. The only finding for kidneys was a statistically significant ($p < 0.01$) increased incidence of minimal/trace amounts of pigment in the epithelium of the cortical tubules in female rats that received 25,000 ppm or 50,000 ppm β-cyclodextrin in the diet. The "non-toxic dietary inclusion level" of β-cyclodextrin was 12,500 ppm (equivalent to 654 or 864 mg/kg/day for males or females, respectively).[44]

Cyclodextrin: β-cyclodextrin (6200, 12,500 and 50,000 ppm). Groups of 8 (4males, 4 females/group) pure-bred Beagle dogs. Preceding test protocol in rat study used. No pathological evidence of systemic toxicity, although there were minor changes in urinalysis and biochemical parameters and a slightly higher incidence of liquid feces. These changes were considered to be of no toxicological importance. The "non-toxic dietary inclusion level" of β-cyclodextrin was 50,000 ppm (equivalent to 1,831 or 1,967 mg/kg/day for males or females, respectively).[44]

Cycodextrin: γ-cyclodextrin (5%, 10%, or 20%). Groups of 8 (4 males, 4 females) Beagle dogs. Feeding in the diet for 13 weeks. Control group fed basal diet. No treatment-related changes in behavior or appearance and no mortalities. No treatment-related differences with respect to ophthalmoscopic examinations, hematological parameters, clinochemical analyses of the plasma, and semiquantitative urine analyses. Relative ovary weights ignificantly increased in the 10% and 20% concentration groups, but this observation was probably a result of an unusually low ovarian weight in the controls. An increase in relative liver weights in males of the 10% and 20% concentration groups was also considered to lack toxicological relevance, because this observation was not associated with changes in plasma enzyme levels or with histopathological changes. No treatment-related abnormalitiesobserved at necropsy. At microscopic examination, no treatment-related effects in any of the various organs and tissues. Daily consumption of up to 20% γ-cyclodextrin in the diet (≈ 7.7 g/kg body weight in males and 8.3 g/kg body weight in females) did not cause toxicity.[170]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Oral - Human

Branched Natural/Unmodified

Sterculia Urens Gum: 5 male volunteers (30 to 56 years old). Ingestion of sterculia urens gum (10.5 g in diet) daily for 21 days. No toxicity or significant effects on plasma biochemistry, hematological indices, or urinalysis parameters were noted.[171]

Branched – Modified

Propylene Glycol Alginate: 5 male volunteers. Following a 7-day control period, the men consumed an amount of propylene glycol alginate equal to 175 mg/kg body weight during the first 7 days of the test period. The amount consumed was increased to 200 mg/kg body weight for the remainder (i.e., 16 days) of the 23 days of dietary supplementation. No significant effect (statistical analysis not performed) on the following: hematological indices, plasma biochemistry parameters, urinalysis parameters, blood glucose levels, plasma insulin concentrations, and expired hydrogen concentrations. Ingestion of propylene glycol alginate caused no adverse dietary or physiological effects. The enzymatic indicators of toxicological effects remained unchanged.[53]

Dermal - Non-Human

Branched - Modified

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs. Maximization test. 5 female guinea pigs (vehicle controls). No mortalities or clinical signs of systemic toxicity were observed. Body weights and weight gains were considered similar when treated and control groups were compared.[156]

Potato Starch Modified: Rats (10 males, 10 females). Applied to skin under occlusive dressing for 28 days (2 g/kg body weight/day) according to OECD 410 test guideline. Sporadic gains and losses of body weight. Compared to the vehicle control group, statistically significant (p value not stated) decrease in body weight gain in treated females during weeks 1 and 4. Clinical biochemical test results indicated statistically significant (p value not stated) decrease in serum triglycerides and slight increase in serum calcium, sodium, and phosphorus in treated males, but not in females. However, none of the other test parameters supported these findings. Decreased organ weights and differences in hematologic test parameters, but these findings were within historical control ranges for this strain of rat. Signs of systemic toxicity not observed at gross examination of treated animals. NOAEL $\geq$ 2,000 mg/kg body weight/day.[155]

Potato Starch Modified: 10% solids aqueous solution. New Zealand albino rabbits (10 males and 10 females) tested; 20 rabbits (controls). Applied to skin under a non-occlusive patch (dose = 2 g/kg bodyweight). Area of application and concentration/dose per cm^2 were not stated. Distilled water, under a non-occlusive patch, applied to controls. Daily evaluations for signs of systemic toxicity, mortality, or morbidity occurred daily; necropsy on day 28. The following considered within normal parameters: body weights, food consumption, gross pathology, and histopathology. Minor differences in organ weight and clinical chemistry changes observed, but considered irrelevant. No significant toxic effects in rabbits.[70]

Table 9. Reproductive and Developmental Toxicity Studies on Polysaccharide Gums

Ingredient	Animals	Procedure	Results
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 22 to 27 pregnant CD-1 mice	Oral doses of 10, 45, 470, or 900 mg/kg body weight/day on days 6-15 of gestation	Number of fetal resorptions and/or fetal deaths increased. Dose-dependent decrease in number of live pups and pup weight. Skeletal maturation was retarded. A no-observed-effect level was not reported.[62]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 21 to 27 pregnant rats (strain not stated)	Oral doses of 40, 100, 240, or 600 mg/kg body weight/day on days 6-15 of gestation	Increased fetal resorptions, with no decrease in the number of live pups. Dose-dependent increase in incidence of missing skeletal sternebrae.[62]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 21 to 24 pregnant rats (strain not stated)	Feeding with 1% or 5% in diet on days 6-16 of gestation	Neither salt was teratogenic.[62]
kappa/lambda-Carrageenan (from *C. crispus*) calcium salt	40 male and 40 female Osborne-Mendel rats	Three-generation study. Feeding with 0.5, 1, 2.5, or 5% in diet 12 weeks prior to mating	In F_{2c} and F_{3c} litters, no specific external, skeletal, or soft-tissue anomaly could be correlated with dosage.[62]
Calcium Carrageenan	Sprague-Dawley rats (number not stated)	Feeding with 0.45, 0.9, or 1.8% in diet prior to mating, during breeding, and throughout gestation, lactation, and post-weaning	No differences between test and negative control groups regarding length of gestation, litter size, or sex distribution.[62,172]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 23 to 30 pregnant hamsters (strain not stated)	Oral doses of 40, 100, 240, or 600 mg/kg body weight on days 6-10 of gestation	No significant effect on nidation or on maternal or fetal survival. Some evidence of dose-dependent delay in skeletal maturation.[62]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 21 to 26 pregnant hamsters	Feeding with 1% or 5% in diet on days 6-11of gestation	Neither salt was teratogenic.[62]
Carrageenan (sodium or calcium salt) or degraded Carrageenan	21 pregnant female Syrian hamsters per dose of carrageenan; 8 pregnant females per dose of degraded carrageenan	Oral doses of 10, 40, 100, or 200 mg/kg body weight on days 6-10 of gestation	No dose-related teratogenic or fetotoxic effects.[62]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 12 to 13 pregnant female rabbits (strain not stated)	Oral doses of 40, 100, 240, or 600 mg/kg body weight on days 6-18 of gestation	The numbers of skeletal or soft tissue abnormalities did not differ from those of controls.[62]
γ-Cyclodextrin	Groups of 25 pregnant female Wistar Crl (WI)WU BR rats	Concentrations of 1.5%, 5%, 10%, and 20% in the diet on gestation days 0 to 21.	No fetotoxic embryotoxic, or teratogenic effects. NOAEC ≈ 20% in diet (≈ 11 g/kg body weight per day).[173]
α-Cyclodextrin	Groups of 25 pregnant female Wistar Crl (WI)WU BR rats	Concentrations of 1.5%, 5%, 10%, and 20% in the diet on gestation days 0 to 21.	No fetotoxic embryotoxic, or teratogenic effects. NOAEC = 20% in diet (≈ 13 g/kg body weight per day).[174]
γ-Cyclodextrin	Groups of 16 pregnant female New Zealand White rabbits	Concentrations of 5%, 10%, or 20% in the diet on gestation days 0 to 29.	No effect on reproductive performance, and not fetotoxic, embryotoxic, or teratogenic.[175]

Table 9. Reproductive and Developmental Toxicity Studies on Polysaccharide Gums

Ingredient	Animals	Procedure	Results
α-Cyclodextrin	Groups of 16 pregnant female New Zealand White rabbits	Concentrations of 5%, 10%, or 20% in the diet on gestation days 0 to 29.	No effect on reproductive performance, and not fetotoxic, embryotoxic, or teratogenic.[176]
Glucomannan (from *Amorphophallus oncophyllus*)	6 pregnant British short-hair domestic cats	Concentration of 2% in the diet during gestation. Actual intake during week prior to parturition ranged from 0.98 to 3.08 mg/kg body weight per day	All pregnant females completed lactation and a normal gestation period. No adverse effect on mean birth weight or mean litter size.[106]
Pectin-derived acidic oligosaccharides (pAOS)	Groups of 24 (16 females, 8 males per group) parental (F_0) Wistar rats of the crl:WI(WU) outbred strain	Concentrations of 5% or 10% in the diet prior to mating, and throughout mating, gestation, and lactation periods	No effect on estral cycle length and normality. No relevant changes in sperm motility, sperm count, or morphologic changes. No effects on reproductive indices, including litter size, pup viability, and difference in sex ratio.[168]
Sterculia Urens Gum (suspension in anhydrous corn oil)	Groups of 87 to 90 pregnant female Dutch-belted rabbits	Oral doses up to 635 mg/kg/day for 13 consecutive days (gestation daysa 8-18).	Not teratogenic.[177]
Sterculia Urens Gum (suspension in anhydrous corn oil)	Groups of 87 to 90 pregnant female albino CD-1 mice	Oral doses up to 170 mg/kg body weight on days 6 through 15 of gestation	No clearly discernible effect on nidation or on maternal or fetal survival. No difference in soft or skeletal tissue abnormalities between test animals and sham-treated controls. Not teratogenic.[177]
Sterculia Urens Gum (suspension in anhydrous corn oil)	28 pregnant female albino CD-1 mice	Oral dose of 800 mg/kg body weight on days 6 through 15 of gestation	Significant number of maternal deaths (9 of 28). Surving dams were completely normal and delivered normal fetuses, with no effect on rate of nidation, or live pup survival *in utero*. Not teratogenic.[177]
Sterculia Urens Gum (suspension in anhydrous corn oil)	Groups of 87 to 89 pregnant female Wistar-derived albino rats	Oral doses up to 900 mg/kg body weight on days 6 through 15 of gestation	Dams were completely normal and delivered normal fetuses, with no effect on rate of nidation, or live pup survival *in utero*. Not teratogenic.[177]
Ammonium Alginate	Fertile eggs from Single-comb White Leghorn chickens	Single injection of ammonium alginate (in corn oil, ≤ 100 µl) into groups of 20 or more eggs; doses up to 0.5 mg/egg)	Injection did not result in significant numbers of abnormal birds.[178]
Propylene Glycol Alginate	Fertile eggs from Single-comb White Leghorn chickens	Single injection of propylene glycol alginate (in water, ≤ 100 µl) into groups of 20 or more eggs; doses up to 1 mg/egg)	Injection did not result in significant numbers of abnormal birds.[178]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
		Bacterial Assays		
Arabinoxylan	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *Escherichia coli* (*E. coli*) strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[163]
Carboxymethyl inulin	Same as above	Ames test	Same as above	Not genotoxic.[156]
Carrageenan (natural grade [PNG]) or refined Carrageenan	*Salmonella typhimurium* strain TA100	Ames test	Concentrations up to 100 mg/ml (PNG) and up to 25 mg/ml (refined) without metabolic activation	Not genotoxic.[179]
kappa/lambda-Carrageenan (from *C. crispus*)	*Salmonella typhimurium* strains TA1535, TA1537, and TA1538. *Saccharomyces cerevisiae* strain D4.	Ames test	Test concentrations not stated	Not genotoxic.[62]
PNG or Refined Carrageenan	Mice (strain not stated). *Salmonella typhimurium* strain His G 46	Host-mediated assay	Mice received PNG at oral doses up to 2,500 mg/kg body weight or refined carrageenan at a dose of 700 mg/kg body weight. Bacterial strain tested without metabolic activation	Mutation frequency in injected indicator organism not affected by dosing with carrageenan. Neither PNG nor refined carrageenan was genotoxic.[179]
PNG or Refined Carrageenan	*Bacillus subtilis*	Rec assay for DNA -damaging potential	PNG and refined carrageenan tested at concentrations up to 100 mg/ml and 28 mg/ml, respectively	Neither PNG nor refined carrageenan was genotoxic.[179]
Corn starch modified (Amaze® [28-1890])	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, or TA 1537; *E. coli* strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[66]
Dextrin myristate (Rheopearl MKL2)	*Salmonella typhimurium* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[67]
Dextrin palmitate (Rheopearl KL2 and Rheopearl TL2)	*Salmonella typhimurium* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[68,69]
Dextrin isostearate (Unifilma HVY)	*Salmonella typhimurium* and *E. coli* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[127]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
Ghatti gum	*Salmonella typhimurium* strains TA97a, TA98, TA100, and TA 1535; *E. coli* strain WP2uvrA pKM101	Ames test	6 mg/plate, with and without metabolic activation	Not genotoxic.[180]
Glucomannan (in konjac flour)	*Salmonella typhimurium* (5 strains, not stated)	Ames test	With and without metabolic activation (doses not stated)	Not genotoxic.[151]
Hydrolyzed furcellaran trade name mixture (0.6% hydrolyzed furcellaran, 0.05% concentrate of sea water, 1% phenoxyethanol, and 98.35% water)	*Salmonella typhimurium* strains TA97a, TA98, TA100, and TA 1535; *E. coli* strain WP2uvrA pKM101	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[73]
Pectin-derived acidic oligosaccharides (mixture of linear oligomers and small polymers of galacturonic acid) (for genotoxicity evaluation of Pectin)	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *E. coli* strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[168]
Calcium Starch Isododecenylsuccinate	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *E. coli* strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[63]
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate trade name material (PS-111 hydrophobically modified starch powder)	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *E. coli* strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[181]
Stearoyl inulin (Rheopearl ISK2 and Rheopedarl ISL2)	*Salmonella typhimurium* and *E. coli* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[71,72]
Sterculia urens gum	Mice (strain not stated). *Salmonella typhimurium* strains G46 and TA1530 and *Saccharomyces cerevisiae* strain D3	Host-mediated assay	3 groups of mice intubated with 5,000 mg/kg, 2500 mg/kg, and 30 mg/kg, respectively, followed by injection with tester strains	Not genotoxic in plated tester strains.[153]
	Mammalian Assays			
Wheat bran extract (contains ~ 80% arabinoxylan) (for genotoxicity evaluation of Arabinoxylan)	Chinese hamster lung fibroblasts	Chromosome aberrations assay	up to 5,000 µg/ml, with and without metabolic activation	Not genotoxic or clastogenic.[163]
Carboxymethyl inulin	Chinese hamster ovary (CHO-WBL) cells	Chromosome aberrations assay	up to 5,060 µg/ml, with and without metabolic activation	No significant increases in chromosomal aberrations, polyploidy, and endoreduplication.[156]
PNG or Refined Carrageenan	Bone marrow cells from Swiss mice	Micronucleus test	Mice received PNG at doses up to 2,500 mg/kg body weight or refined carrageenan at a dose of 700 mg/kg body weight	Neither PNG nor refined carrageenan was genotoxic.[179]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
Ghatti gum	Chinese hamster ovary (CHO-WBL) cells	Chromosome aberrations assay	up to 6,000 µg/ml, with and without metabolic activation	Not genotoxic.[180]
Ghatti gum	B6C3F1 mice	Combined micronucleus/Comet assay	Mice dosed orally with up to 2,000 mg/kg/day for 4 days	No effect on micronucleated reticulocyte frequency in peripheral blood. No DNA damage in blood leukocytes or liver.[180]
Glucomannan	L5178Y $tk^{+/-}$ mouse lymphoma cells	Mouse lymphoma assay	Up to 1,000 µg/ml and up to 997 µg/ml with and without metabolic activation, respectively	Not genotoxic.[165]
Glucomannan	CD-1 (ICR) mouse bone marrow cells	Micronucleus test	Mice dosed orally with 5,000 mg/kg body weight	Not genotoxic.[165]
Pectin-derived acidic oligosaccharides (for genotoxicity evaluation of Pectin)	L5178Y mouse lymphoma cells	Mouse lymphoma assay	up to 4370 µg/ml, with and without metabolic activation	Equivocal results.[168]
Pectin-derived acidic oligosaccharides (for genotoxicity evaluation of Pectin)	Chinese hamster ovary cells	Chromosome aberrations assay	up to 4,220 µg/ml, with and without metabolic activation	Clastogenic. Dose-related genotoxicity at ≥ 2,530 µg/ml without metabolic activation. Positive results only at highly cytotoxic concentrations.[168]
Pectin-derived acidic oligosaccharides (for genotoxicity evaluation of Pectin)	F_1 rats (from outbred strain of Wistar rats (Crl:WI(WU))	Micronucleus test	Oral administration of diet containing pectin-derived acidic oligosac-charides (pAOS) (±7 g/kg body weight/day) for 13 weeks.	Compared to control, no increase in mean number of micronuclei in rat erythrocytes.[168]
Potato starch modified	Mice (strain not stated)	Mouse lymphoma assay. OECD 476 test guideline.	Not stated	Not genotoxic.[155]
Sterculia urens gum	Sprague-Dawley rats	Cytogenetic assay	Groups of rats intubated with 5,000 mg/kg, 2500 mg/kg, and 30 mg/kg, respectively. Metapase chromo-somes from rat bone marrow analyzed.	No adverse effect on rat bone marrow chromosomes.[153]
Sterculia urens gum	WI-38 human embryonic lung cells	Cytogenetic assay	up to 1,000 µg/ml	No effect on anaphase chromosomes.[153]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
Sterculia urens gum	Sprague-Dawley rats	Dominant lethal gene test	Groups of rats intubated with 5,000 mg/kg, 2500 mg/kg, and 30 mg/kg, respectively	No consistent responses suggestive of genotoxicity.[153]

Table 11. Carcinogenicity of Polysaccharide Gums

Oral

Linear Polysaccharides and Their Salts

Agar: 25,000 ppm or 50,000 ppm agar. Groups of 50 F344 rats and 50 B6C3F1 mice of each sex. Feeding in diet for 103 weeks. Untreated mice and rats served as controls. No clinical signs of toxicity. Increased incidence (not statistically significant) of adrenal cortical adenomas in female rats fed 50,000 ppm agar. Statistically significant increase ($p = 0.007$) in incidence of hepatocellular adenomas in male mice fed 50,000 ppm agar. Incidence of total liver tumors did not differ statistically among control, 25,000 ppm, and 50,000 ppm groups. Increased incidences of adrenal cortical adenomas and liver tumors not considered test substance-related. Agar was non-carcinogenic.[182]

Algin: Up to 25% sodium alginate. Mice (75 males; 75 females). Feeding in diet for 89 weeks (dietary levels gradually increased to maximum concentration of 25%). At week 87, half of surviving male and female mice placed on control diet containing 55% pregelatinized potato starch. Algin was non-carcinogenic.[162]

Carrageenan: 5% ι-carrageenan. Groups of 16 Fischer 344 rats. Feeding for up to 91 days. Proliferating cell nuclear antigen (PCNA) served as a marker of cell proliferation. Immunohistochemical staining for PCNA-positive cells in distal colon performed. Intact layer of columnar epithelial cells lining the mucosa. PCNA-positive cells not found at the luminal surface.[183]

Carrageenan: 0.5%, 1.5%, and 5% ι-carrageenan. Groups of four F344 rats. Feeding in diet for 28 days. Control diet fed to additional group. Thymidine kinase enzymatic activity and PCNA served as markers of cell proliferation. No increase in PCNA-positive cells. Increased thymidine kinase levels observed only in the 5% ι-carrageenan dietary group, corresponding to a 4-fold increase in colonic cell proliferation.[183]

Carrageenan: ι-carrageenan. F344 rats. Feeding in diet for 64 days, followed by 28-day recovery period. During recovery period, proliferating cells returned to level similar to those in rats fed control diet. Results suggest that the quantitative changes in cell proliferation were probably adaptive, and would not contribute to an increased risk of colon neoplasia.[183]

Carrageenan: 0.1, 5, 15, and 25% carrageenan. Groups of 5 male and 5 female mice of two strains. Feeding in the diet for lifespan. Additional group fed control diet. Non-carcinogenic.[184]

Carrageenan: 1, 5, 15, and 25% carrageenan. Groups of 5 male and 5 female mice of two strains. Feeding in diet for up to 24 months. Additional group fed control diet. Hepatic sclerosis at 25% concentration. Non-carcinogenic.[184]

Carrageenan: 0.5, 2.5, and 5% κ-carrageenan. MRC outbred rats and randomly bred Syrian golden hamsters from the Eppley colony (30 males and 30 females per species). Average daily intake of carrageenan estimated to be 4022 mg/kg/day (rats) and 3719 mg/kg/day (hamsters) for lifetime. 100 females and 100 males per control dietary group. No increased mortality, clinical signs of toxicity, or tumor formation.[185]

Carrageenan: Groups of female Fischer 344 rats. Co-carcinogenicity of carrageenan in presence of azoxymethane (AOM) or N- nitrosomethylurea (NMU) evaluated. Treatment groups: control diet (15 rats); 15% carrageenan in control diet (15 rats); 15% carrageenan in control diet + 10 weekly s.c. injections of 8 mg/kg bw (AOM) (30 rats); 2 mg NMU (intrarectal instillations) twice weekly for 3 weeks (30 rats); AOM s.c. alone (30 rats), and NMU i.r. alone (30 rats). Animals killed 40 weeks after the initial injection of AOM or 30 weeks after the initial injection of NMU. Carrageenan enhanced the incidence of colon tumors in AOM- and NMU-treated rats ($p < 0.01$): AOM + carrageenan (26/26, 100%) versus AOM alone (17/30, 57%); NMU + carrageenan (29/29, 100%) versus NMU alone (20/29, 69%); control diet (0/15); and 15% carrageenan in control diet (1/15, 7%).[186]

Carrageenan: Carrageenan (0.25%, 2.5%, or 10%). Aberrant crypt focus (ACF) assay for assessment of initiation and promotion of cancer. 24 rats randomly allocated to 3 groups in initiation experiment: 9 rats given carrageenan (as a 10% jelly [24.7 g/kg body weight per day] for 8 days) in initiation experiment, 9 rats were given pure water (negative controls), and 6 rats received AOM injection (5 mg/kg i.p., positive controls). Promotion experiment: 30 rats received single azoxymethane injection (20 mg/kg i.p.) to initiate colon cancer. Seven days later, the rats were randomly allocated to the following 3 groups of 10: control group (received distilled water), group 1 (received water supplemented with 0.25% carrageenan [liquid] for 100 days), and group 2 (received water supplemented with 2.5% carrageenan [solid gel] for 100 days). In initiation experiment, no ACF found in negative controls or in rats fed carrageenan. In promotion experiment, administration of liquid 0.25% carrageenan reduced number of ACF/rat, and did not change the ACF multiplicity when compared to controls. In contrast, administration of carrageenan jelly (2.5%) for 100 days promoted growth of aberrant crypt foci ($P = 0.016$). Thus, carrageenan jelly did not initiate colon tumors; however, long-term administration of carrageenan jelly enhanced intestinal tumor growth in rats.[187]

Carrageenan: κ-carrageenan (0.5%, 2.5%, or 10%). 54 conventional female Fischer 344 (F-344) rats (harboring a normal rat flora) and 52 germ-free female F-344 rats maintained in isolators. Intiating effect of κ-carrageenan studied by comparing number of ACF in the colon of rats given pure water or κ-carrageenan (as a 10% gel in tap water) for 8 days. Promoting effect of κ-carrageenan studied by comparing multiplicity of ACF (crypts/ACF) in rats that received pure water, liquid κ-carrageenan (0.25% in water), or κ-carrageenan gel (2.5% in water) during 100 days, beginning 7 days after a single AOM injection. κ-carrageenan (10%) did not initiate ACF. In conventional rats, the 2.5% κ-carrageenan gel promoted the growth of ACF as follows: 2.98 ± 0.29 and 3.44 ± 0.48 crypts/AF in control and treated rats, respectively ($p < 0.02$). 0.25% κ-carrageenan gel did not promote ACF.[188]

Carrageenan: 2.5% κ-carrageenan. 8 HFA ratsgiven κ-carrageenan and an additional 8 given water; 4 rats received AOM injection. No promotion effect: $2.81 \pm 0.1$and 2.78 ± 0.38 crypts/ACF in control and treated rats, respectively ($p = 0.80$).[188]

Carrageenan: Carrageenan (1.25%, 2.5%, or 5.0%). Groups of 18 rats or 6 rats. Groups of 18 initiated with DMH, followed by feeding with 1.25%, 2.5%, or 5% in diet for 32 weeks. Groups of 6 received saline and were then treated with 0% and 5.0% carrageenan. Detailed histopathological examination did not demonstrate any carrageenan-induced enhancement of carcinogenesis. Thus, carrageenan did not possess any promoting activity for colorectal carcinogenesis at any dietary concentration.[189]

Carrageenan: In a monograph published by the International Agency for Research on Cancer (IARC) in 1983, IARC concluded that the available data do not provide evidence that native (undegraded) carrageenan is carcinogenic to experimental animals, and, in the absence of epidemiological data, that no evaluation of the carcinogenicity of native carrageenan in humans could be made.[92]

Inulin: Inulin-enriched diet (10% w/w). Group of 10 to 15 Min/+ mice (has heterozygous mutation in the Apc gene, resulting in the truncated Apc protein and development of numerous intestinal adenomas.[190,191]) fed from the age of 5 weeks to 8 or 15 weeks. Additional group fed control diet. Results indicated that dietary inulin can activate mucosal β-catenin signaling, which, in the presence of Apc mutation, induces adenoma growth.[192]

Table 11. Carcinogenicity of Polysaccharide Gums

Inulin: 3 Groups of 10 Sprague-Dawley rats, consisting of control group, group treated s.c.with DMH, and group given DMH and inulin in the diet. When compared to the DMH only group, inulin in diet decreased the expression of IL-2, TNFα, and IL-10 and also decreased the numbers of COX-2- and NFκB-positive cells in the *tunica mucosae* and *tela submucosae* of the colon. Thus, dietary intake of inulin prevented preneoplastic changes and inflammation that promote colon cancer development.[193]

Inulin: Inulin (15 g) in basal diet (85 g). Groups of 20 to 22 Balb/c mice. Feeding for 7 days prior to tumor (TLT and EMT6 tumor cell lines) transplantation. Growth of both tumor cell lines significantly inhibited by supplementing the diet with inulin.[194]

Branched - Natural/Unmodified

Arabinoxylan: Groups of 15 rats treated (s.c.) with the colon carcinogen DMH and fed either a control diet or a diet containing arabinoxylan-oligosaccharides (4.8% w/w). Two types of preneoplastic lesions (ACF and mucin-depleted foci [MDF]) detected in colon. Thirteen weeks after DMH treatment, MDF counts significantly lower in entire colon of arabinoxylan-oligosaccharides fed rats (MDF/colon were 7.5 ± 0.6 and 5.5 ± 0.6, in control and arabinoxylan-oligosaccharides groups, respectively; means ± SE [p = 0.05]). Arabinoxylan-oligosaccharides fed rats had significantly fewer ACF in the distal part of the colon than control rats (ACF/distal colon were 135.5 ± 15 and 84.4 ± 11, in control and arabinoxylan-oligosaccharides groups, respectively; means ± SE [p = 0.05]). Thus, dietary intake of arabinoxylan-oligosaccharides by rats reduced the occurrence of two types of preneoplastic lesions, suggesting a chemopreventive effect on colon carcinogenesis.[195]

Arabinoxylan: Groups of 10 ICR male mice. mice were injected i.p. with mouse sarcoma S180 cells, human chronic myelogenous K562 cells, or human leukemia HL-60 cells, and dosed orally with arabinoxylan (100, 200, or 400 mg/kg body weight). All three doses conferred significant inhibitory activity against solid tumor formation in S180 tumor-bearing mice, with inhibitory ratios of 14.34%, 31.37%, and 56.73%, respectively. Arabinoxylan did not have any effect on growth of K562 or HL-60 cells in *vitro*.[196]

Glucomannan: 10% Glucomannan. Groups of 30 C3H/He male mice fed either a powdered commercial diet (control group) or the same diet containing 10% glucomannan. At age 1 year, slight decrease in the number of animals with liver tumors in glucomannan group (control: 63% of 24 mice; glucomannan: 48% of 23 mice) and a statistically significant decrease ($p<0.05$) in the mean number of tumor nodules per mouse in the glucomannan group (control: 1.1; konjac mannan: 0.5). Thus, spontaneous liver tumors in C3H/He mice were inhibited by maintaining the mice on a diet containing 10% glucomannan.[197]

Glucomannan: 5% Glucomannan. Fisher 344 rats (20/group) fed either a commercial diet or similar diet containing 5%glucomannan for 13 weeks. Animals also injected i.p. with DMH weekly. Incidence of DMH-induced colon tumors significantly lower in glucomannan-fed group (39%) when compared to control group (75%). Number of colon adenocarcinomas per rat also significantly lower in glucomannan-fed rats (0.22) than in control rats (0.75). No significant effect on the incidence of tumors of the small intestine, all of which were adenocarcinoma (control: 45%; konjac mannan: 33%).[198]

Pectin: 2.5% Pectin. Male Wistar rats (groups of 4). Feeding in diet for 14 days. Statistically significant increase in the villus height and crypt depth, indicating that feeding with pectin caused mucosal hyperplasia in small intestine.[199]

Starch Acetate: 55% Starch Acetate. Mice (75 males ,75 females) fed starch acetate in diet for 89 weeks. Dietary levels of the test substance gradually increased until diet contained (by weight) 55% starch acetate. At week 87, half ofsurviving male and female mice placed on control diet (containing 55% pregelatinized potato starch). No evidence of carcinogenicity.[162]

Cyclic

Cyclodextrin: 2.5% or 5% β-cyclodextrin. 2 groups of Fischer 344 (F344) rats (50 males and 50 females/group) fed 2.5%and 5% β-cyclodextrin, respectively, for 104 weeks. Control diet fed to additional group. All neoplastic lesions observed were histologically similar to those known to occur spontaneously in this strain of rat; no statistically significant increase in the incidence of any tumor found for either sex in treated groups. It was concluded that the high dose, which was approximately 340-400 times higher than the current daily human intake from ingestion as a food additive and from pharmaceutical use, did not have carcinogenic potential in F344 rats.[111]

Cyclodextrin: β-cyclodextrin . 5 groups of 50 Fischer 344 rats and 52 CD-1 outbred mice of each sex. 4 groups per strain received β-cyclodextrin in the diet at doses of 25, 75, 225, and 675 mg/kg per day, respectively for 93 weeks (males) and between weeks 129 and 130 (females). Fifth group received control diet. No treatment-related carcinogenic effects.[200]

Degraded Polysaccharide Gum

Degraded Carrageenan: Degraded carrageenan (from *Eucheuma spinosum*; degraded by acid hydrolysis). 4 groups of 30 malesand 30 female rats 8fed a diet containing 0 (control), 1 %, 5 %, or 10% degraded carrageenan. Colorectal squamous metaplasia in rats fed degraded carrageenan at concentrations of 10% (59 of 60 rats) and 5% (53 of 60 rats) in the diet. Additionally, colorectal tumors (12 squamous-cell carcinomas, 8 adenocarcinomas and 3 adenomas) found in 19 of 60 rats fed 10% degraded carrageenan in the diet, and these tumors (3 squamous-cell carcinomas, 1 adenocarcinoma and 8 adenomas) also found in 12 of 60 rats fed 5% degraded carrageenan. Neither squamous metaplasia nor colorectal tumors observed in the low-dose group or in controls.[92]

Degraded Carrageenan: Degraded carrageenan (5% in drinking water) administered to 20 male and 20 female rats for 15 months. Colorectal squamous metaplasia observed in all rats after 15 months. Colorectal tumors observed in 11 of 40 treated rats (4 squamous-cell carcinomas, 4 adenocarcinomas, 3 adenomas and 1 myosarcoma); these tumors not observed in control rats (15 males, 15 females).[201]

Degraded Carrageenan: Degraded carrageenan (1 or 5 g/kg body weight) administered by intragastric intubation (frequency of administration not specified) to groups of 15 male and 15 female rats for 15 months. Control rats (15 males, 15 females) dosed intragastrically with distilled water. Squamous colorectal metaplasia observed in all 29 rats in high-dose group and in 11 of 30 rats in low-dose group. Colorectal tumors were observed only in the high-dose group (8 of 29 rats; 5 adenocarcinomas and 4 adenomas).[202]

Degraded Carrageenan 10% degraded carrageenan (in diet that also contained 30% sulfate) fed to Fischer 344 rats. Three groups fed this diet for 2 months (39 rats, group 1), 6 months (42 rats, group 2), and 9 months (42 rats, group 3). Control group (46 rats) received the same diet without carrageenan, and the same was true for all other groups after cessation of feeding. 100% incidence of colorectal squamous metaplasia observed in all treatment groups. Tumors also observed in 5 of 39 rats in group 1 (3 squamous-cell carcinomas, 1 adenoma, 1 anaplastic carcinoma), 8 of 42 rats in group 2 (6 squamous-cell carcinomas, 1 adenocarcinoma, 1 adenoma) and in 17 of 42 rats in group 3 (14 squamous-cell carcinomas, 4 adenocarcinomas). Colorectal changes not observed in control rats.[92,203]

Table12. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Skin Irritation and Sensitization - Non-Human

Linear Polysaccharides and Their Salts

Algin: 2% algin. Rabbits (number not stated). 3 primary skin irritation experiments. Occlusive patches applied to the skin. Mean skin irritation score of < 0.5 = non-irritating; 0.5 to 2.0 = slightly irritating. Primary irritation index (PII) values calculated. PII of < 0.5 deemed satisfactory, but PII no greater than 1 is also acceptable. PII values of 0, 0, and 0.08 were reported in the 3 experiments, respectively.[61]

Algin: 2% algin. Rabbits (3 per experiment). Test substance (2 ml) applied to flanks 5 days per week for 6 weeks. Mean maximum irritation index (MMII) values calculated. Macroscopic and histological examinations of test sites performed. MMII values of 0.67, 0, and 0.67 were reported in 3 experiments, respectively. Daily application of test substance did not induce a severe reaction at either macroscopic or histological examination.[61]

Carrageenan: Food grade iota-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units). Guinea pigs (number not stated). Study details not included. No skin sensitization.[62]

Branched - Natural/Unmodified

Glucomannan (in konjac flour [mechanically ground]). Guinea pigs (number not stated). Application to skin according to the Buehler closed patch method. No sensitization.[151]

Branched - Modified

Corn Starch Modified: Corn starch modified in distilled water (30% solids). 10 Zealand White rabbits (5 males and 5 females). Application to skin (2,000 mg/kg); dose per cm^2 not stated. Dermal reactions either absent or classified as barely perceptible at 24-h and 48-h readings, and absent at the 74-h reading. Mild skin irritant (primary irritation index = 0.25).[66]

Corn Starch Modified: Corn Starch Modified (up to 30%). 20 guinea pigs (strain not stated; 10 males, 10 females). Maximization test (OECD protocol 406.) During induction,10% solution injected and 30% solution applied topically. Concentration per cm^2 was not stated. During challenge, application of 20% solution for 24 h. Reactions scored at 48 h and 72 h post-application. Control group (5 males, 5 females) tested with distilled water during induction and challenged with test substance. Reactions ranging from no erythema to moderate erythema observed after induction with the control or test substance. Erythema observed after challenge with test substance. However, rechallenge with same test substance concentration did not cause erythema. Not a sensitizer.[66]

Corn Starch Modified: 50% corn starch modified paste. 25 female Hartley guinea pigs. RIPT according to Buehler method (OECD protocol 4067). 10 guinea pigs treated with distilled water (control). Positive control (isoeugenol) tested in study performed within 6 months of current study. During induction, test material applied topically to shoulder area (~ 0.4 g on occlusive patch; area of application site not stated) . Topical challenge with 50% corn starch modified paste for 6 h. Challenge reactions scored at 24 h and 48 h post-application. No erythema or edema during induction or challenge. Non-sensitizer. Positive control induced sensitization.[63]

Carboxymethyl Inulin: Carboxymethyl inulin (1% to 100%). Groups of 2 adult Dunkin–Hartley albino guinea pigs. Test substance injected into clipped scapular region; reactions scored at 24 h and 48 h. Also, series of test article concentrations (0.5 ml) applied topically for 24 h to clipped external flank using Metalline patches secured with tape and an elastic bandage. Test material was removed after 24 h and signs of irritation recorded at 24 h and 48 h after treatment. Undiluted carboxymethyl inulin produced necrosis after intradermal injection, observed both after 24 h and 48 h; 20% to 50% did not cause necrosis, but grade 2 erythema was observed at either 24 h or 48 h. Signs of irritation were not observed at 24 h or 48 h at concentrations up to 100% in the patch tests.[156]

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs. Maximization test. Five female guinea pigs served as vehicle controls. No evidence of sensitization.[156]

Potato Starch Modified: 10 rats received single dose of potato starch modified (dose = 2 g/kg) dermally. Very slight to well-defined erythema and edema observed in all animals after 24 h. At 48 h, very slight erythema and very slight edema in 5 and 3 rats, respectively. All reactions had cleared by 72 h.[155]

Potato Starch Modified: Rats (10 males, 10 females). Dose of 2 g/kg body weight/day applied to the skin, under occlusive dressing, for 28 days . Neither erythema nor edema observed. However, small scabs observed on 5 males and 6 females, attributed to adhesion of test material to skin.[155]

Potato Starch Modified: Potato starch modified (18.5% aqueous suspension). 20guinea pigs. Buehler test (OECD 406 test guideline). Faint erythema (non-confluent) observed in 6 of 20 animals after second or third induction application. No evidence of sensitization.[155]

Potato Starch Modified: Potato Starch Modified (10% solids aqueous solution). 10 male and 10 female New Zealand albino rabbits (test animals)). Using non-occlusive patch, test substance (2 g/kg body weight) applied to the skin. The area of application and dose per cm^2 not stated. 20 control animals tested with distilled water under non-occlusive patch. Neither erythema nor edema observed in treated or control animals. No adverse morphologic effects on the skin.[70]

Potato Starch Modified: Potato starch modified (18.5% solids). 20 guinea pigs (10 males, 10 females). RIPT according to Buehler method (OECD 406 protocol). Concentration per cm^2 not stated. 10 control animals (5 males, 5 females) treated with distilled water. During induction, very faint erythema in 6 of 20 animals; reactions not observed in controls. Very faint erythema observed in 2 of 20 treated animals and in 2 of 10 controls during challenge phase. Non-sensitizer.[70]

Dextrin Myristate: 6 New Zealand white rabbits. Skin irritation study (test protocol not stated). Non-irritant.[67]

Dextrin Myristate: Guinea pigs (number and strain not stated). Magnusson-Kligman maximization test. No evidence of skin sensitization.[67]

Dextrin Palmitate: 3 New Zealand white rabbits. Skin irritation study (test protocol not stated). Non-irritant.[68,69]

Table12. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Branched - Modified

Dextrin Palmitate: Guinea pigs (number and strain not stated). Magnusson-Kligman maximization test (test concentrations not stated). No evidence of skin sensitization.[68,69]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate: Test Material: Material (corn starch modified) described as structurally similar to sodium hydrolyzed starch dodecenylsuccinate and as the calcium salt of the ester formed from the reaction of 3-(dodecenyl)dihydro-2,5-furandione and corn starch, in which the degree of substitution per glucose unit is less than 0.1. 6 New Zealand White rabbits. OECD 404 test protocol. 50% slurry of test material (1 ml) applied topically (on occlusive patch, area of application site not stated) for 24 h to intact and abraded skin sites on the back of each animal. Reactions scored for up to 72 h after patch application. Erythema observed at intact and abraded sites on one animal, and reactions had cleared by 48 h. Mildly irritating to the skin (primary irritation index = 0.09).[63,204]

Stearoyl Inulin: 6 Japanese white rabbits. Skin irritation potential evaluated (concentrations and test protocol not stated). Non-irritant.[71,72]

Stearoyl Inulin: Guinea pigs (number and strain not stated). Skin sensitization potential evaluated (concentrations not stated) according to adjuvant and patch method. Skin irritation classified as weak. Very low skin sensitization potential.[71,72]

Skin Irritation and Sensitization - Human

Linear Polysaccharides and Their Salts

Algin: 20% aqueous sodium alginate. 12 male subjects with no history of allergy. Patch-testing (Finn chambers) with 20% aqueous sodium alginate according to International Contact Dermatitis Research Group (ICDRG) recommendations. Area (cm^2) of application and dose per cm^2 not stated. Reactions scored at 2 and 3 days post-application. ± reaction observed in one subject on days 2 and 3. Results negative for skin irritation and allergic contact dermatitis.[205]

Linear - Modified

Hydrolyzed Furcellaran: Mixture containing 1.35% furcellaran powder and 1% phenoxyethanol. 10 adults. Mixture applied (under occlusive patch) for 48 h to back. Area (cm^2) of application and dose per cm^2 not stated. Non-irritant.[73]

Hydrolyzed Furcellaran: Mixture containing 1.35% furcellaran powder, 0.1% potassium sorbate, and 0.05% citric acid. 10 adults. Mixture applied (under occlusive patch) for 48 h to back. Area (cm^2) of application and dose per cm^2 not stated. Non-irritant and non-sensitizer.[73]

Hydrolyzed Furcellaran: Mixture containing 0.6% hydrolyzed furcellaran, 0.05% concentrate of sea water, 1% phenoxyethanol, and 98.35% water. 100 subjects. Mixture applied 9 times to each subject. Area (cm^2) of application and dose per cm^2 not stated. Non-irritant and non-sensitizer.[73]

Maltodextrin: Eye gel containing 2.45% maltodextrin. 103 subjects. HRIPT. Patch type, area (cm^2) of application, and dose per cm^2 not stated. Challenge patches applied to original and alternate sites, and challenge reactions scored at approximately 48 h and 96 h post-application. Five instances of erythema (grade 1) during induction. At 48-h challenge reading, a grade of 1 reported for alternate challenge site of one subject. Gel did not induce allergic contact dermatitis.[206]

Branched - Modified

Corn Starch Modified: 7.5% solution in distilled water. 26 female subjects. 21-day cumulative irritation study. Test material (0.2 ml per 24-h patch) applied topically. Area (cm^2) of application and dose per cm^2 not stated. Reactions ranged from no erythema to minimal erythema. Non-irritant. Distilled water (vehicle control) did not cause erythema. Sodium lauryl sulfate (positive control) induced marked erythema and papules.[66]

Corn Starch Modified: 7.5% solution in distilled water. 113 subjects (86 females, 27 males). HRIPT. Patch type, area (cm^2) of application, and dose per cm^2 not stated. Challenge eactions scored at 48 h and 96 h post-application. Test substance and distilled water caused slight erythema in 3 subjects. Test substance and distilled water classified as non-sensitizers.[66]

Dextrin: Rinse-off facial product containing 42.6919 % dextrin (1% aqueous; effective concentration ≈ 0.4%). 54 subjects (46 females, 8 males). HRIPT. During induction, product (0.1-0.15 g on occlusive patch) applied for 24 h to the back.. Dose/concentration per cm^2 not stated. Challenge patch applied to new test site and reactions scored at 24 h and 72 h post-application. Transient, barely perceptible erythema, in 1 subject, during induction. No reactions observed during challenge phase. No clinically significant skin irritation or evidence of allergic contact dermatitiss.[207]

Dextrin Myristate: Leave-on facial product containing 0.3% dextrin myristate. 51 subjects (40 females, 11 males). HRIPT. During induction, product (0.1-0.15 g on occlusive patch) applied for 24 h to the back.. Dose/concentration per cm^2 not stated. Challenge patch applied to new test site and reactions scored at 24 h and 72 h post-application. Skin reactivity was not observed during the induction or challenge phase. Product did not cause skin irritation or allergic contact dermatitis.[208]

Hydroxypropyltrimonium Hydrolyzed Corn Starch: 15% hydroxypropyltrimonium hydrolyzed corn starch. 47 male and female subjects. HRIPT. During induction, semi-occlusive patch (1" x 1") containing approximately 0.2 ml of test material applied for 24 h to upper back. 24-h challenge patch applied to new test site, adjacent to induction patch site. No reactions during study. No skin irritation or allergic contact sensitization potential.[209]

Calcium Starch Isododecenylsuccinate: Test material (powder) and a 50% w/v slurry of test material in baby oil tested. 23 subjects. Powder applied topically (0.2 g, moistened with distilled water; area of application site not stated) under occlusive conditions for 21 days. 50% w/v slurry applied acccording to same procedure. Powder caused dermal effects that ranged from no irritation to erythema and papules cumulative irritation score = 177). Superficial layer effects ranged from none to glazing with peeling and cracking. 50% w/v slurry caused milder reactions (cumulative irritation score = 50.6). Both test materials classified as probable mild irritants under normal use conditions.[63,64,210]

Branched - Modified

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate: Cleanser containing 10 wt% sodium hydrolyzed potato starch dodecenylsuccinate. 227 subjects (18 to 69 years old; 165 females, 62 males). HRIPT. During induction, occlusive patch containing ~ 0.2 g of the test material was applied to the back (area of application site not stated) for 24 h. week non-treatment period. Occlusive challenge patch containing the test material (~ 0.2 g) applied for 24 h to new site on back. Reactions were scored for up to 96 h post-application. Four subjects had low-level (±) reactions during induction, and 2 subjects had ± reactions during challenge phase. Non-sensitizer.[211]

Table12. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Unknown Structural Configuration

Algae Exopolysaccharides: 1% solution of algae exopolysaccharides. 50 subjects. HRIPT. During induction, occlusive patch containing test substance (0.2 ml or 0.2 g) applied for 24 h to infrascapular region of back. Dose per cm^2 not stated. Challenge dose (equivalent to induction application) of test substance applied once to new test site. Reactions scored at 24 h to 48 h post-application. No evidence of adverse reactions. Not a primary skin irritant or sensitizer.[212]

In Vitro

Branched - Modified

Hydroxypropyltrimonium Hydrolyzed Corn Starch: MatTek Corporation EpiDerm™ skin model *in vitro* toxicity testing system. Skin model consists of normal, human-derived epidermal keratinocytes (NHEK) that have been cultured to form a multilayered, highly differentiated model of the human epidermis. Test procedure utilizes a water-soluble, yellow tetrazolium salt MTT. In the mitochondria of viable cells, MTT is reduced by succinate dehydrogenase to an insoluble formazan derivative (purple color). Substances that damage this enzyme inhibit reduction of the tetrazolium salt. Undiluted test substance (100 µl) added to millicells containing EpiDerm™ samples; time at which % viability would be 50% (ET_{50}) estimated. Mild irritant (ET_{50} = 18.1h).[213]

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2015 FDA VCRP Data

Maltodextrin

01B - Baby Lotions, Oils, Powders, and Creams	1
01C - Other Baby Products	1
02A - Bath Oils, Tablets, and Salts	24
02C - Bath Capsules	1
02D - Other Bath Preparations	2
03B - Eyeliner	1
03C - Eye Shadow	6
03D - Eye Lotion	11
03F - Mascara	7
03G - Other Eye Makeup Preparations	17
04C - Powders (dusting and talcum, excluding aftershave talc)	17
04E - Other Fragrance Preparation	1
05A - Hair Conditioner	22
05B - Hair Spray (aerosol fixatives)	2
05C - Hair Straighteners	1
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	18
05G - Tonics, Dressings, and Other Hair Grooming Aids	25
05H - Wave Sets	1
05I - Other Hair Preparations	10
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	61
06C - Hair Rinses (coloring)	1
06D - Hair Shampoos (coloring)	1
06H - Other Hair Coloring Preparation	2
07A - Blushers (all types)	3
07B - Face Powders	5
07C - Foundations	11
07E - Lipstick	13
07F - Makeup Bases	5
07I - Other Makeup Preparations	5
10A - Bath Soaps and Detergents	18
10E - Other Personal Cleanliness Products	22
11G - Other Shaving Preparation Products	2
12A - Cleansing	25
12C - Face and Neck (exc shave)	53
12D - Body and Hand (exc shave)	39
12F - Moisturizing	50
12G - Night	8
12H - Paste Masks (mud packs)	13
12I - Skin Fresheners	5
12J - Other Skin Care Preps	25
13A - Suntan Gels, Creams, and Liquids	2
13B - Indoor Tanning Preparations	3

13C - Other Suntan Preparations	1
Total	**542**

Acacia Catechu Gum	**NR**
Acacia Farnesiana Gum	**NR**

Acacia Senegal Gum

Acacia Seyal Gum	**NR**

Agar

02B - Bubble Baths	1
03G - Other Eye Makeup Preparations	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
05I - Other Hair Preparations	1
07A - Blushers (all types)	2
07B - Face Powders	3
07C - Foundations	8
07G - Rouges	6
07I - Other Makeup Preparations	1
10A - Bath Soaps and Detergents	4
12A - Cleansing	6
12C - Face and Neck (exc shave)	12
12D - Body and Hand (exc shave)	2
12F - Moisturizing	7
12G - Night	1
12H - Paste Masks (mud packs)	7
12J - Other Skin Care Preps	1
Total	**67**

Agarose

10B - Deodorants (underarm)	9
12G - Night	1
Total	**10**

Algae Exopolysaccharides	**NR**

Algin

01B - Baby Lotions, Oils, Powders, and Creams	4
02A - Bath Oils, Tablets, and Salts	1
03A - Eyebrow Pencil	8
03C - Eye Shadow	1
03D - Eye Lotion	5
03E - Eye Makeup Remover	1
03F - Mascara	6
03G - Other Eye Makeup Preparations	19
05F - Shampoos (non-coloring)	2
05I - Other Hair Preparations	1

06G - Hair Bleaches	1
07B - Face Powders	8
07C - Foundations	1
07F - Makeup Bases	1
07I - Other Makeup Preparations	2
08G - Other Manicuring Preparations	1
10A - Bath Soaps and Detergents	1
10E - Other Personal Cleanliness Products	1
11E - Shaving Cream	5
11F - Shaving Soap	1
11G - Other Shaving Preparation Products	1
12A - Cleansing	15
12C - Face and Neck (exc shave)	59
12D - Body and Hand (exc shave)	13
12F - Moisturizing	24
12G - Night	10
12H - Paste Masks (mud packs)	103
12I - Skin Fresheners	1
12J - Other Skin Care Preps	26
13B - Indoor Tanning Preparations	3
13C - Other Suntan Preparations	1
Total	**326**

Alginic Acid

03B - Eyeliner	2
03G - Other Eye Makeup Preparations	1
07I - Other Makeup Preparations	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	3
12F - Moisturizing	1
12J - Other Skin Care Preps	2
Total	**13**

Ammonium Alginate **NR**

Amylodextrin

07C - Foundations	1
12D - Body and Hand (exc shave)	1
Total	**2**

Amylopectin **NR**

Amylose **NR**

Aphanothece Sacrum Polysaccharide **NR**

Arabinoxylan **NR**

Astragalus Gummifer Gum

05A - Hair Conditioner	1
05I - Other Hair Preparations	1
06G - Hair Bleaches	1
12F - Moisturizing	3
12J - Other Skin Care Preps	1
Total	**7**

Avena Sativa (Oat) Starch

04C - Powders (dusting and talcum, excluding aftershave talc)	1
12F - Moisturizing	2
12H - Paste Masks (mud packs)	2
Total	**5**

Calcium Starch Isododecenylsuccinate **NR**

Calcium Starch Octenylsuccinate **NR**

Calcium Alginate

07B - Face Powders	1
07C - Foundations	1
07F - Makeup Bases	3
12C - Face and Neck (exc shave)	1
12D - Body and Hand (exc shave)	1
12F - Moisturizing	1
12J - Other Skin Care Preps	1
Total	**9**

Calcium Carrageenan **NR**

Carrageenan

01A - Baby Shampoos	1
02A - Bath Oils, Tablets, and Salts	4
02C - Bath Capsules	1
03B - Eyeliner	1
03C - Eye Shadow	4
03D - Eye Lotion	6
03F - Mascara	2
03G - Other Eye Makeup Preparations	5
05F - Shampoos (non-coloring)	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	4
05H - Wave Sets	1
05I - Other Hair Preparations	5
07A - Blushers (all types)	3
07B - Face Powders	4
07C - Foundations	8

07I - Other Makeup Preparations	1
08B - Cuticle Softeners	1
08E - Nail Polish and Enamel	1
09A - Dentifrices	17
09B - Mouthwashes and Breath Fresheners	5
09C - Other Oral Hygiene Products	3
10A - Bath Soaps and Detergents	4
10E - Other Personal Cleanliness Products	1
11A - Aftershave Lotion	9
12A - Cleansing	20
12C - Face and Neck (exc shave)	39
12D - Body and Hand (exc shave)	24
12E - Foot Powders and Sprays	2
12F - Moisturizing	31
12G - Night	8
12H - Paste Masks (mud packs)	8
12I - Skin Fresheners	5
12J - Other Skin Care Preps	18
Total	**249**

Cassia Augustifolia Seed Polysaccharide

03C - Eye Shadow	3
07A - Blushers (all types)	2
07B - Face Powders	6
07C - Foundations	4
07E - Lipstick	3
11A - Aftershave Lotion	2
12C - Face and Neck (exc shave)	7
12D - Body and Hand (exc shave)	1
12F - Moisturizing	6
12G - Night	1
12H - Paste Masks (mud packs)	1
Total	**36**

Cichorium Intybus (Chicory) Root Oligosaccharides

12C - Face and Neck (exc shave)	2
Total	**2**

Corn Starch Modified

01B - Baby Lotions, Oils, Powders, and Creams	1
01C - Other Baby Products	1
02C - Bath Capsules	1
03C - Eye Shadow	2
03D - Eye Lotion	1
03F - Mascara	4
04C - Powders (dusting and talcum, excluding aftershave talc)	1

04E - Other Fragrance Preparation	4
05B - Hair Spray (aerosol fixatives)	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	10
05I - Other Hair Preparations	3
06H - Other Hair Coloring Preparation	4
07B - Face Powders	2
07C - Foundations	1
07D - Leg and Body Paints	1
07E - Lipstick	1
07I - Other Makeup Preparations	4
09C - Other Oral Hygiene Products	1
10E - Other Personal Cleanliness Products	3
12A - Cleansing	1
12C - Face and Neck (exc shave)	8
12D - Body and Hand (exc shave)	4
12E - Foot Powders and Sprays	3
12F - Moisturizing	13
12G - Night	1
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	5
13B - Indoor Tanning Preparations	1
Total	**86**

Croscarmellose	**NR**

Cyclodextrin

02A - Bath Oils, Tablets, and Salts	1
03A - Eyebrow Pencil	8
03D - Eye Lotion	4
03G - Other Eye Makeup Preparations	7
04E - Other Fragrance Preparation	1
05F - Shampoos (non-coloring)	5
06G - Hair Bleaches	2
06H - Other Hair Coloring Preparation	1
07C - Foundations	5
07I - Other Makeup Preparations	2
09B - Mouthwashes and Breath Fresheners	2
10E - Other Personal Cleanliness Products	1
12A - Cleansing	12
12C - Face and Neck (exc shave)	17
12D - Body and Hand (exc shave)	5
12F - Moisturizing	28
12G - Night	8
12H - Paste Masks (mud packs)	3
12I - Skin Fresheners	1
12J - Other Skin Care Preps	8
13A - Suntan Gels, Creams, and Liquids	1

13B - Indoor Tanning Preparations	6
Total	**128**

Cyclodextrin Hydroxypropyltrimonium Chloride **NR**

Cyclodextrin Laurate

03D - Eye Lotion	2
12C - Face and Neck (exc shave)	1
12F - Moisturizing	1
12G - Night	1
Total	**5**

Cyclotetraglucose **NR**

Dextrin

03C - Eye Shadow	1
03D - Eye Lotion	9
03G - Other Eye Makeup Preparations	11
05A - Hair Conditioner	1
05I - Other Hair Preparations	1
06G - Hair Bleaches	2
07B - Face Powders	1
07C - Foundations	15
07E - Lipstick	1
07H - Makeup Fixatives	1
07I - Other Makeup Preparations	1
08E - Nail Polish and Enamel	2
08G - Other Manicuring Preparations	2
10A - Bath Soaps and Detergents	2
11A - Aftershave Lotion	1
11G - Other Shaving Preparation Products	1
12A - Cleansing	5
12C - Face and Neck (exc shave)	36
12D - Body and Hand (exc shave)	7
12F - Moisturizing	39
12G - Night	9
12H - Paste Masks (mud packs)	7
12I - Skin Fresheners	4
12J - Other Skin Care Preps	18
Total	**177**

Dextrin Behenate **NR**

Dextrin Isostearate **NR**

Dextrin Laurate **NR**

Dextrin Myristate **NR**

Dextrin Palmitate

03C - Eye Shadow	4
03D - Eye Lotion	1
03F - Mascara	7
03G - Other Eye Makeup Preparations	1
07A - Blushers (all types)	2
07C - Foundations	3
07E - Lipstick	37
07G - Rouges	6
07I - Other Makeup Preparations	4
10E - Other Personal Cleanliness Products	1
12A - Cleansing	4
12C - Face and Neck (exc shave)	4
12G - Night	1
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	1
Total	**77**

Dextrin Palmitate/Ethylhexanoate

07E - Lipstick	2
07I - Other Makeup Preparations	1
12F - Moisturizing	1
Total	**4**

Dextrin Palmitate/Stearate	**NR**
Dextrin Stearate	**NR**
Echinacin	**NR**

Galactoarabinan

03B - Eyeliner	3
03C - Eye Shadow	1
03D - Eye Lotion	4
03E - Eye Makeup Remover	1
03F - Mascara	10
03G - Other Eye Makeup Preparations	2
05A - Hair Conditioner	5
05F - Shampoos (non-coloring)	3
05I - Other Hair Preparations	1
07C - Foundations	6
07E - Lipstick	2
07F - Makeup Bases	2
07G - Rouges	1
10A - Bath Soaps and Detergents	3
11A - Aftershave Lotion	6
11E - Shaving Cream	1
11G - Other Shaving Preparation Products	1

12A - Cleansing	5
12C - Face and Neck (exc shave)	7
12D - Body and Hand (exc shave)	4
12F - Moisturizing	9
12G - Night	1
12H - Paste Masks (mud packs)	5
12J - Other Skin Care Preps	14
Total	**97**

Ghatti Gum **NR**

Glyceryl Alginate **NR**

Glyceryl Dimaltodextrin **NR**

Glyceryl Starch

12A - Cleansing	1
Total	**1**

Hydrogenated Potato Starch **NR**

Hydrogenated Starch Hydrolysate

03G - Other Eye Makeup Preparations	1
04E - Other Fragrance Preparation	4
05F - Shampoos (non-coloring)	10
07C - Foundations	2
07E - Lipstick	1
10A - Bath Soaps and Detergents	1
11E - Shaving Cream	1
12A - Cleansing	4
12C - Face and Neck (exc shave)	11
12D - Body and Hand (exc shave)	4
12F - Moisturizing	13
12G - Night	1
12H - Paste Masks (mud packs)	3
12J - Other Skin Care Preps	4
Total	**60**

Hydrolyzed Carrageenan **NR**

Hydrolyzed Corn Starch Hydroxyethyl Ether **NR**

Hydrolyzed Corn Starch Octenylsuccinate

07I - Other Makeup Preparations	1
10B - Deodorants (underarm)	3
12A - Cleansing	2
12C - Face and Neck (exc shave)	2
12F - Moisturizing	2

12G - Night	3
Total	**13**

Hydrolyzed Furcellaran	**NR**

Hydrolyzed Pectin	
03D - Eye Lotion	1
07C - Foundations	1
12A - Cleansing	2
12C - Face and Neck (exc shave)	5
12D - Body and Hand (exc shave)	1
12F - Moisturizing	1
12G - Night	3
Total	**14**

Hydrolyzed Soy Starch	**NR**
Hydrolyzed Starch	**NR**
Hydrolyzed Triticum Spelta Starch	**NR**

Hydrolyzed Wheat Starch	
02B - Bubble Baths	3
02D - Other Bath Preparations	1
03D - Eye Lotion	1
03F - Mascara	4
03G - Other Eye Makeup Preparations	1
05A - Hair Conditioner	37
05B - Hair Spray (aerosol fixatives)	6
05C - Hair Straighteners	3
05D - Permanent Waves	1
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	40
05G - Tonics, Dressings, and Other Hair Grooming Aids	54
05H - Wave Sets	3
05I - Other Hair Preparations	41
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	21
06C - Hair Rinses (coloring)	5
07I - Other Makeup Preparations	1
10A - Bath Soaps and Detergents	26
10E - Other Personal Cleanliness Products	17
12A - Cleansing	2
12C - Face and Neck (exc shave)	4
12D - Body and Hand (exc shave)	1
12F - Moisturizing	1
Total	**274**

Hydroxyethyl Cyclodextrin	**NR**

Hydroxypropyl Cyclodextrin

03A - Eyebrow Pencil	4
03D - Eye Lotion	5
03F - Mascara	1
03G - Other Eye Makeup Preparations	3
04E - Other Fragrance Preparation	4
05I - Other Hair Preparations	2
07I - Other Makeup Preparations	1
10B - Deodorants (underarm)	1
12C - Face and Neck (exc shave)	21
12F - Moisturizing	4
12G - Night	4
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	2
Total	**53**

Hydroxypropyltrimonium Hydrolyzed Corn Starch

05A - Hair Conditioner	5
05F - Shampoos (non-coloring)	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	3
Total	**11**

Hydroxypropyltrimonium Hydrolyzed Wheat Starch

10A - Bath Soaps and Detergents	8
Total	**8**

Hydroxypropyl Oxidized Starch **NR**

Hydroxypropyl Starch

03D - Eye Lotion	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	6
12A - Cleansing	1
12J - Other Skin Care Preps	1
Total	**9**

Hydroxypropyltrimonium Maltodextrin Crosspolymer **NR**

Inulin

01B - Baby Lotions, Oils, Powders, and Creams	1
03F - Mascara	1
05A - Hair Conditioner	4
05F - Shampoos (non-coloring)	12
05I - Other Hair Preparations	2
10A - Bath Soaps and Detergents	2
10E - Other Personal Cleanliness Products	2

11E - Shaving Cream	3
12A - Cleansing	4
12F - Moisturizing	7
12G - Night	1
12J - Other Skin Care Preps	2
Total	**41**

Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch

10E - Other Personal Cleanliness Products	6
Total	**6**

Magnesium Alginate **NR**

Mannan

05A - Hair Conditioner	1
05I - Other Hair Preparations	1
12C - Face and Neck (exc shave)	4
12D - Body and Hand (exc shave)	1
12F - Moisturizing	3
12G - Night	2
12H - Paste Masks (mud packs)	2
12I - Skin Fresheners	1
12J - Other Skin Care Preps	4
Total	**19**

Methyl Cyclodextrin

04A - Cologne and Toilet waters	8
04B - Perfumes	2
05I - Other Hair Preparations	1
10B - Deodorants (underarm)	3
11A - Aftershave Lotion	6
Total	**20**

Natto Gum

Palmitoyl Inulin **NR**

Pectin

01C - Other Baby Products	1
03C - Eye Shadow	2

03D - Eye Lotion	1
03G - Other Eye Makeup Preparations	1
05A - Hair Conditioner	7
05D - Permanent Waves	7
05F - Shampoos (non-coloring)	11
05G - Tonics, Dressings, and Other Hair Grooming Aids	5
07C - Foundations	1
10E - Other Personal Cleanliness Products	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	9
12F - Moisturizing	6
12G - Night	2
12H - Paste Masks (mud packs)	27
12J - Other Skin Care Preps	2
13B - Indoor Tanning Preparations	3
Total	**87**

Phaseolus Angularis Seed Starch	**NR**
Phaseolus Radiatus Seed Starch	**NR**
Pisum Sativum (Pea) Starch	**NR**

Polianthes Tuberosa Polysaccharide

12C - Face and Neck (exc shave)	2
Total	**2**

Potassium Alginate

12C - Face and Neck (exc shave)	1
12H - Paste Masks (mud packs)	36
Total	**37**

Potassium Carrageenan	**NR**
Potassium Dextrin Octenylsuccinate	**NR**
Potassium Undecylenoyl Alginate	**NR**
Potassium Undecylenoyl Carrageenan	**NR**

Potato Starch Modified

05A - Hair Conditioner	17
05F - Shampoos (non-coloring)	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
05I - Other Hair Preparations	28
06D - Hair Shampoos (coloring)	1
07C - Foundations	2
12A - Cleansing	1
12C - Face and Neck (exc shave)	3
12F - Moisturizing	2
12J - Other Skin Care Preps	1
13B - Indoor Tanning Preparations	2

Total	**61**
Propylene Glycol Alginate	
03D - Eye Lotion	1
03G - Other Eye Makeup Preparations	1
05I - Other Hair Preparations	1
07F - Makeup Bases	3
12C - Face and Neck (exc shave)	2
12F - Moisturizing	5
12G - Night	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	1
Total	**16**
Prunus Persica (Peach) Gum	**NR**
Pueraria Lobata Starch	**NR**
Sodium Algin Sulfate	**NR**
Sodium Carboxymethyl Inulin	**NR**
Sodium Carboxymethyl Starch	
03C - Eye Shadow	1
05I - Other Hair Preparations	1
06G - Hair Bleaches	8
12J - Other Skin Care Preps	1
Total	**11**
Sodium Carrageenan	
09A - Dentifrices	2
12C - Face and Neck (exc shave)	1
Total	**3**
Sodium Dextrin Octenylsuccinate	**NR**
Sodium Hydroxypropyl Oxidized Starch Succinate	**NR**
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate	
05F - Shampoos (non-coloring)	2
Total	**2**
Sodium Oxidized Starch Acetate/Succinate	
02B - Bubble Baths	1
05A - Hair Conditioner	2
05F - Shampoos (non-coloring)	2
10A - Bath Soaps and Detergents	1
12F - Moisturizing	1
Total	**7**

Sodium Starch Octenylsuccinate

03F - Mascara	1
05A - Hair Conditioner	7
05F - Shampoos (non-coloring)	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
05I - Other Hair Preparations	1
06G - Hair Bleaches	1
10B - Deodorants (underarm)	4
10E - Other Personal Cleanliness Products	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	6
12D - Body and Hand (exc shave)	7
12F - Moisturizing	2
Total	**35**

Sodium/TEA-Undecylenoyl Alginate **NR**

Sodium/TEA-Undecylenoyl Carrageenan **NR**

Solanum Tuberosum (Potato) Starch

05F - Shampoos (non-coloring)	1
12F - Moisturizing	1
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	1
Total	**4**

Starch Acetate

05A - Hair Conditioner	10
05I - Other Hair Preparations	1
Total	**11**

Starch Acetate/Adipate **NR**

Starch Diethylaminoethyl Ether

10A - Bath Soaps and Detergents	1
Total	**1**

Starch Hydroxypropyltrimonium Chloride

01A - Baby Shampoos	2
05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	12
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
10A - Bath Soaps and Detergents	2
Total	**18**

Starch Laurate **NR**

Starch Tallowate **NR**

Stearoyl Inulin

03C - Eye Shadow	3
03D - Eye Lotion	1
03G - Other Eye Makeup Preparations	3
07C - Foundations	2
Total	**9**

Sterculia Urens Gum	**NR**
Tamarindus Indica Seed Gum	**NR**

Tapioca Starch

01B - Baby Lotions, Oils, Powders, and Creams	1
02A - Bath Oils, Tablets, and Salts	2
03F - Mascara	12
03G - Other Eye Makeup Preparations	1
04C - Powders (dusting and talcum, excluding aftershave talc)	8
05A - Hair Conditioner	4
05F - Shampoos (non-coloring)	11
05G - Tonics, Dressings, and Other Hair Grooming Aids	3
06B - Hair Tints	8
07A - Blushers (all types)	1
07B - Face Powders	4
07I - Other Makeup Preparations	3
10A - Bath Soaps and Detergents	1
10E - Other Personal Cleanliness Products	1
11A - Aftershave Lotion	5
11G - Other Shaving Preparation Products	1
12C - Face and Neck (exc shave)	14
12D - Body and Hand (exc shave)	13
12E - Foot Powders and Sprays	1
12F - Moisturizing	40
12G - Night	3
12H - Paste Masks (mud packs)	2
12J - Other Skin Care Preps	12
13B - Indoor Tanning Preparations	2
13C - Other Suntan Preparations	1
Total	**154**

Tapioca Starch Crosspolymer	**NR**
TEA-Alginate	**NR**
TEA-Dextrin Octenylsuccinate	**NR**

Triticum Vulgare (Wheat) Starch

02A - Bath Oils, Tablets, and Salts	1
03C - Eye Shadow	5

05A - Hair Conditioner	1
07A - Blushers (all types)	2
07B - Face Powders	8
07F - Makeup Bases	1
09A - Dentifrices	1
09C - Other Oral Hygiene Products	1
10E - Other Personal Cleanliness Products	3
12A - Cleansing	2
12C - Face and Neck (exc shave)	1
12H - Paste Masks (mud packs)	1
Total	**27**

Undecylenoyl Inulin	**NR**
Xyloglucan	**NR**

Mannan

Glucomannan

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: July 1, 2015

SUBJECT: Comments on the Tentative Report: Safety Assessment of Polysaccharide Gums as Used in Cosmetics

Key Issues

The NICNAS assessment of Sodium Hydrolyzed Potato Starch Dodecenylsuccinate (STD/1511; included in the supplementary data provided before the June 2015 CIR Expert Panel meeting http://www.cir-safety.org/sites/default/files/Data_Supplement_W2.pdf) uses the CAS number 194810-88-3 for analogue 4, which is the INCI named material Calcium Starch Isododecenylsuccinate. Calcium Starch Isododecenylsuccinate is another ingredient included in this report. Rather than putting the information on analogue 4 (which is the same information provided directly to CIR from Akzo-Nobel) under Sodium Hydrolyzed Potato Starch Dodecenylsuccinate described as structurally similar to sodium hydrolyzed starch dodecenylsuccinate, the information should be presented under Calcium Starch Isododecenylsuccinate. This change needs to be made in the following locations in this report:

- Ocular Irritation, Non-Human, Sodium Hydrolyzed Potato Starch Dodecenylsuccinate and Corn Starch Modified - the study described in this section is the same as the eye irritation study of analogue 4 (Calcium Starch Isododecenylsuccinate) in the NICNAS assessment of Sodium Hydrolyzed Potato Starch Dodecenylsuccinate.
- Summary - Acute oral rat study of "DDDSA-modified starch; eye irritation study; skin irritation study; Buehler test; 21-day cumulative irritation study in 23 human subjects; check the genotoxicity assay as NICNAS indicates one assay on Sodium Hydrolyzed Potato Starch Dodecenylsuccinate, not an assay on analogue 4, Calcium Starch Isododecenylsuccinate
- Discussion - It is not clear what is meant by "relevant data have been included on analogous polysaccharide ingredients." If this is just referring to analogue

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4, Calcium Starch Isododecenylsuccinate, this is actually an ingredient in this report. If this is the only "analogous" compound, the Discussion should be revised.

Table 7 - The heading Sodium Hydrolyzed Potato Starch Dodecenylsuccinate needs to be corrected to Calcium Starch Isododecenylsuccinate.

Table 10 - Please check the information received from AkzoNobe. Were there really two genotoxicity studies (one on Sodium Hydrolyzed Potato Starch Dodecenylsuccinate and one on the analogue, Calcium Starch Isododecenylsuccinate)? The NICNAS assessment only includes one genotoxicity study on Sodium Hydrolyzed Potato Starch Dodecenylsuccinate. If both studies are left in Table 10, please indicate that the structurally similar compound is Calcium Starch Isododecenylsuccinate. What were the results of the study on the analogue? Currently, the Results column contains the same information as found in the Dose column.

Table 12, analogue of Sodium Hydrolyzed Potato Starch Dodecenylsuccinate - NICNAS describes the same human subject test on 23 subjects for analogue 4 identified as Calcium Starch Isododecenylsuccinate. Please identify this material as Calcium Starch Isododecenylsuccinate rather than "as structurally similar to sodium hydrolyzed starch dodecenylsuccinate and corn starch modified."

Please delete the word "Natural" used in the "Branched Natural/Unmodified" subheadings. The use of the word "Natural" in these headings suggests that the linear unmodified and unknown composition ingredients are not "natural". If "natural" is not deleted from the branched subheadings, for consistency "natural" should be added to the linear and unknown structural configuration subheadings.

It is not clear why Potassium Undecylenoyl Carrageenan is considered a linear modified compound, while Potassium Undecylenoyl Alginate is considered a branched modified compound. Both Algin and Carrageenan are in the linear polysaccharides category. It is not clear why the same modification of these compounds results in one being placed in the linear, modified category and one being placed in the branched, modified category.

Conclusion - Xyloglucan, which is in Table 1, is not in the conclusion. It should be in the Branched/Unmodified group.

Additional Comments

The CIR report on mono- and disachharides should also be mentioned in the Introduction.

The addition of *vide supra* is not helpful because the information presented above, including the information in the Introduction is essentially the same as in the paragraph ending with *vide supra*.

Cosmetic Use, Summary, Discussion - The 9.5% concentration of Avena Sativa (Oat) Starch was reported in a perfume product. This product may not be a spray.

Reproductive and Developmental Toxicity, Genotoxicity, Carcinogenicity - Please include references in the text of these sections.

Ocular Irritation, In Vitro, Maltodextrin - Please correct "dimethylthizol-2-yl" (missing an "a")

Mucous Membrane Irritation and Sensitization, Non-Human, Human - It is not necessary to state the identity of the antigen in konjac flour twice on the same page.

Miscellaneous Studies, Endocrine Function and Vitamin D Absorption, Glucomannan - Please correct: "glucomanna"

Antifungal Activity - It is not necessary to describe how the inhibitory rate was calculated.

Inflammation - It is not clear why there is a separate section on Inflammation. The study on Carrageenan should be presented with the studies on Allergenicity/Immune System Effects. Carrageenan injected into the rodent foot is a well-known model of inflammation that could be more clearly acknowledged in this report.

Summary - The descriptions of the repeated dose exposure studies that list the doses of all the compounds followed by the results is not helpful. The dose should be with the results of the study.

Summary - The Summary should note that a protein, rather than Glucomannan, is considered the allergen in konjac flour.

Summary - It is not clear what is meant by "inconsistent effects on reproduction and development." The information provided in Table 9 does not clarify this statement further.

Discussion - The information on Hydrolyzed Carrageenan in the Discussion is redundant. There are three paragraphs in a row that state that the data are insufficient for Hydrolyzed Carrageenant and that information on composition and method of manufacture is needed.

Discussion - Is the CIR Expert Panel really concerned about pesticide residues in "alkylating and other agents"?

Conclusion - TEA-Dextrin Octenylsuccinate has been placed in the middle of Sodium Hydrolyzed Potato Starch Dodecenylsuccinate.

Table 1 - Rather than include "Other source" in an individual ingredient description, it would be more efficient to state in the title of the table that references are provided when information is from a source other than the Dictionary.

Carrageenan - The spelling of "Rodophyceae" has been corrected in the definition of Carrageenan in the Dictionary data base; it should be corrected to "Rhodophyceae" in Table 1.

Triticum Vulgare (Wheat) Starch still needs to be moved to the Branched/Unmodified section of Table 1 with the other Starch ingredients (where it is found in the Conclusion).

Table 3 - Sodium Hydroxypropyl Oxidized Starch Succinate - The meaning of the oxygen under the structure is not clear.

Starch Hydroxypropyltrimonium Chloride - Please delete Ref 51.

Cassia Angustifolia Seed Polysaccharide - Please correct "9.66 x 104 Da"

Table 7 - The title of reference 151 says "konjac flour" not Glucomannan. If konjac flour was tested, the description of the study should say "konjac flour".

Table 8, Algin - The results of the Starch Acetate study should not be mentioned under Algin. Although more than one compound may have been studied in reference 162, the summary of the Algin study does not need to state "per test substance."

Carrageenan (second) - Delete Ref 71

Carrageenan (fourth) - Correct "hamatological"

Cyclodextrin - A dog study with 40 dogs per dose group is unbelievably large. Therefore, the reference (44) was checked. There were actually 8 dogs (4 male and 4 female) in each group. This needs to be corrected in Table 8

Cyclic - It is not clear why this subheading needs to be in Table 8 twice.

Dermal, Non-Human, Potato Starch Modified - Rat is the species - species should be "strain".

Table 9 - The results section should indicate whether or not maternal toxicity was observed, as some may not consider a developmental toxicity study adequate unless some maternal toxicity was observed at the highest tested dose.

In the description of the results of the rat study on Calcium Carrageenan, it is not clear what is meant by "Inconsistent effects on reproduction and development."

Glucomannan (reference 106) - Please correct "All pregnant female females..."

Table 10 - As genotoxicity potential was determined in bacteria, the host-mediated assays (references 178 and 153) should be moved to the Bacterial Assays section of Table 10.

Table 11, Agar - Did this study really look at "either" male or female mice? It is more likely the study included 50 rats and 50 mice of <u>each</u> sex.

As all the information under the heading "Degraded Polysaccharide Gum" is on degraded carrageenan, the heading should be changed to "Degraded Carrageenan".

Table 12, Potato Starch Modified - OECD 406 is a guideline for guinea pig sensitization tests include the Buehler test. Therefore, if it is known that OECD 406 was followed, it is known that this is a guinea pig study; "(species not stated)" should be deleted.

Dextrin Palmitate - What doses or concentrations were tested in the Magnusson-Kligman maximization test of Dextrin Palmitate?