Safety Assessment of Polysaccharide Gums as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	February 20, 2015
Panel Date:	March 16-17, 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.

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: February 20, 2015
Subject: Draft Tentative Report on Polysaccharide Gums

At the December 8-9, 2014 CIR Expert Panel meeting, the draft tentative report was tabled, pending reorganization of the report and to allow sufficient time for industry to provide additional data. The reorganized safety assessment (draft tentative report) is identified as *plpogu032015rep* in the pdf document.

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. Furthermore, 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. Additional information on the alkylating and other agents, such as epoxides, anhydrides, and chlorinated compounds that are used to modify polysaccharide gums was also requested.

To date, the data requested have not been received. However, use concentration data on glucomannan were received from the Council, and have been added to Table 3 of the draft tentative report. The structure of galactoarabinan from the published literature (Figure 3) is also included.

Included in this package for your review is the Draft Tentative Report on Polysaccharide Gums (plpogu032015rep pdf file), the CIR report history (plpogu032015hist pdf file), Literature search strategy (plpogu032015strat pdf file), Ingredient Data profile (plpogu032015prof pdf file), 2014 FDA VCRP data (plpogu032015FDAdata pdf file), December 2014 Panel meeting minutes (plpogu032015min pdf file) and use concentration data on glucomannan (plpogu032015data1 and data2 pdf files).

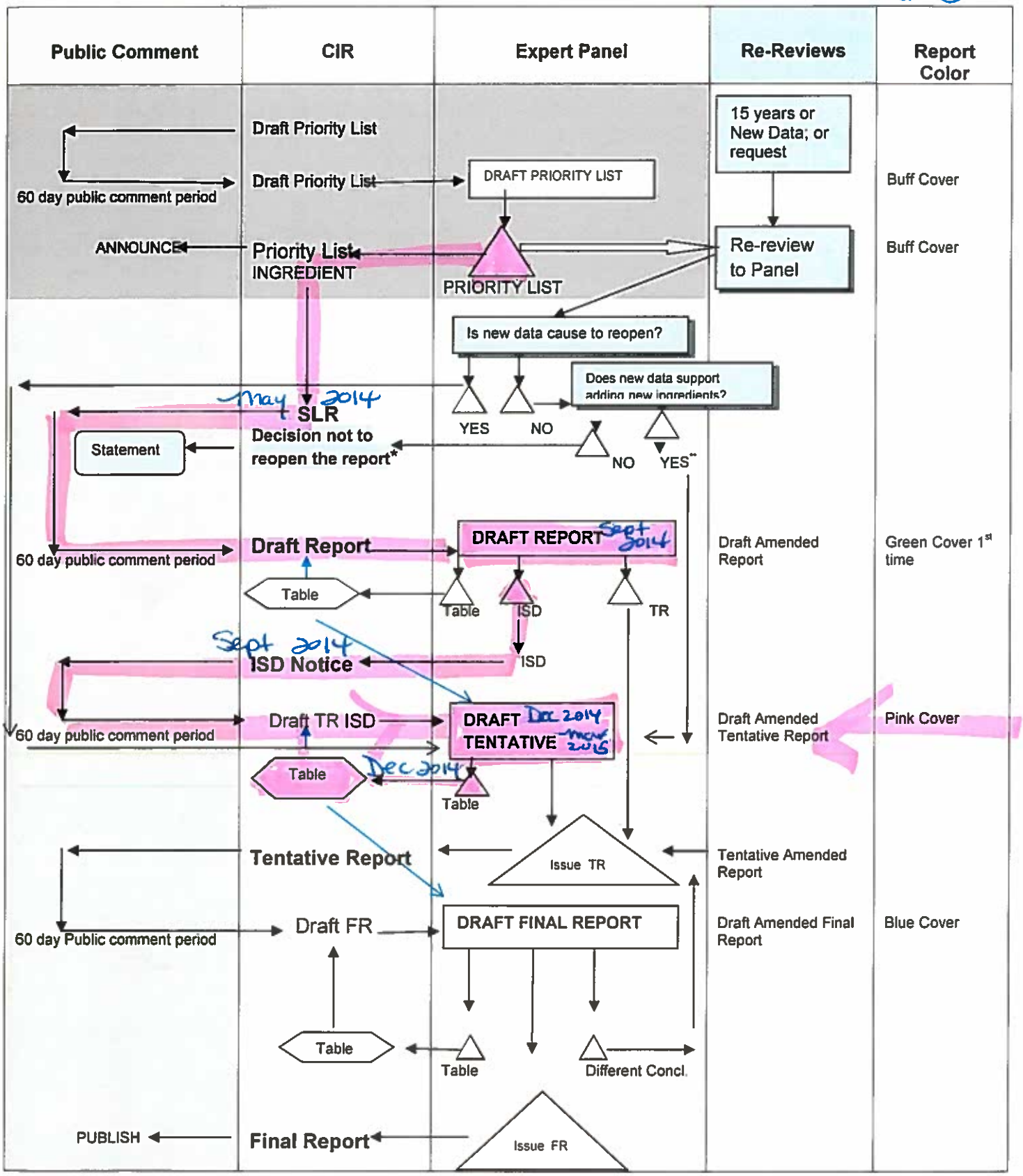
After considering the data included in this safety assessment, the Panel will need to determine whether a tentative report with an insufficient data conclusion should be issued, or whether the available data are sufficient for issuing a tentative report with a safe as used, safe with qualifications, or unsafe conclusion on these ingredients.

1620 L Street, NW Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

Polyacrylamide Gums

SAFETY ASSESSMENT FLOW CHART

Mar 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: March 16-17, 2015

Polysaccharide Gums Check List for March, 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 March, 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									carrageenan			
Pueraria Lobata Starch																				

Polysaccharide Gums Check List for March, 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 March, 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 (196 - Review)
Glucomannan **(Search performed on 9/19/2014)**

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

Day 1 of the December 8-9, 2014 CIR Expert Panel Meeting – Dr. Belsito's Team

Polysaccharide Gums

DR. BELSITO: Okay. So, our first one is polysaccharide gums. And at the September meeting, we issued an insufficient data announcement for polysaccharide gums. They were algal and plant derived. They're viscosity increasing agents, primarily rinse-offs up to about 50 percent leave-ons -- actually, to about the same percentage.

We're looking for methods of manufacturing impurity data on each of the ingredients, particularly concerned about the hydrolyzed polysaccharides and other modified polysaccharide gums. I thought we had put in a request to divide the report into the ingredients by these groupings. If it was, I had a hard time following it, because there were no subheadings in the report, and we had asked that it be divided into linear, branch, cyclic and unknown structures, and also in the introduction, that a stronger justification be made for placing these four groups together. And I didn't really get a sense that that was really done, at least to my satisfaction.

We did get a lot of data, both in the report and in wave 2, and I guess the question is, is it sufficient. I have a lot of comments throughout the manuscript, but my general comment to the panel is that I'm totally confused; that I don't know if we got all of the data that we had asked for, because I just spent an incredible amount of time trying to look and see what group this data belonged to and finally, quite honestly, gave up. So, I've got a long comment here.

So, from my standpoint, I think they're safe as used in terms of contact dermatitis, allergic and irritant, but I remain concerned about the kojic acid data, the carrageenans that we had asked about information for, and basically, I'm turning it over to the rest of my team to try and help me out here.

DR. LIEBLER: Well Don, I show you -- I share your surprise that the report wasn't organized in the way I thought it would be in terms of structural features of the polysaccharide gums as we discussed last time. They seem to be, instead, just simply laid out in some order. I didn't look to see if it was alphabetical or what, but it was -- so maybe, there is some underlying organization, but it's more subtle than we were able to pick up on. I don't know. Wilbur, is there -- how did you approach that?

MR. JOHNSON: Basically, we, in the introduction section of the report, you know, established the rationale for grouping, because at the last meeting, the decision was made not to reorganize the report. You know, organizing each section according to those (inaudible) --

(Discussion off the record)

MR. JOHNSON: Not to organize the report in such a way that the groupings were, you know, apparent in the subheadings, but rather, to state the rationale for grouping in the introduction section of the report. And also, table 1 contains those ingredients as organized into the groups as requested.

DR. LIEBLER: Okay. I mean, it's such a big group of ingredients. I suppose if they're not grouped throughout all the sections of the report. On the other hand, what doesn't come through is whether there's any kind of insight that the groupings provide us in helping us evaluate these compounds. It's true that you do indicate that these compounds can be grouped into these four categories that we discussed, but there's nothing that follows from that. There's no, you know, logical value to the report beyond that point. And the table, of course, comes after you've read it. And so --

So, I think that I agree with Don, overall. I think we actually did get much of the data that we asked for. One of the things that I think is still missing, unless I missed it, is a very clear literature or reference supported accounting for the polygenin, or the so-called degraded carrageenan. That's one issue that I thought would be pretty easy to put to bed, and we whiffed on it, I think, or we don't have any literature data where we can actually cite it.

And there's several places -- a couple of places in the report where I indicate how and where we could have dealt with that effectively. So, that's still hanging out there, unless I missed something. Nobody else saw it either?

(No response heard)

DR. LIEBLER: Okay.

(Pause)

DR. BELSITO: And you know, the other aspect that concerned me -- the only thing that I picked up on is, you know, when we get into the respiratory aspects, you know, we us our usual respiratory boilerplate. But then, we have this data from kojic acid --

DR. LIEBLER: I think it's konjac flour. Is that it?

DR. BELSITO: Konjac flour.

(Simultaneous discussion)

DR. LIEBLER: Konjac and not kojic acid. Right.

DR. BELSITO: Where these workers have respiratory problems. So, if these particular matters are not respirable to the point where they create issues, why do workers in that industry have problems?

(No response heard)

DR. LIEBLER: So I mean, again, I was -- and for irritation, allergic contact dermatitis, I don't have a problem. For respiratory, you know, I'm just not sure. And I guess I interpreted what we asked for quite differently. I thought we asked not only that they be given a table of grouping, but the data be presented by group, so I could easily understand what we had asked for and we had been able to tick off each group. And again, I tried, starting to do that with your table and just -- it was just taking way more time than I thought I needed to spend on this report.

The other issue that I would point out is, on PDF page 45, while these are large molecules and don't really appear to be absorbed through intact skin, per se, when you tape strip the skin and make skin look like mucous membranes, and these are used in lip products, 24 percent of the amount applied was absorbed. So, for mucous membrane products, these may be in the issue, if you're concerned about internal toxicology.

DR. LIEBLER: But this one, this was the cyclodextrin. This was the one that's the much smaller molecule --

DR. BELSITO: Right.

DR. LIEBLER: -- than any of the rest. And we debated whether this should even be included in the report last time. But I think Ron Hill and I both sort of agreed it was okay to keep it in. But this is a caveat with it. You're going to get -- if you do things like absorption studies with this, you're going to get data that's not really representative of the rest of the group at all.

DR. BELSITO: Okay. Just wanted to point that out, because we have been working, I think, on the assumption that they would not be absorbed.

DR. LIEBLER: I think that's true. This is the exception that proves the rule, as they say.

DR. SADRIEH: Can I ask -- I mean, I guess it's -- but just sort of to understand fundamentally, and it applies to this and probably --

DR. LIEBLER: You have blanket approval to ask any questions you want with any preamble of apology (Laughter).

DR. SADRIEH: That's right. So, with respect to the inhalation, I guess, the lack of data, does that -- you know, does that -- that is not proof of safety. Right? I mean, how does the committee you know, look at lack of data to make a conclusion about safety of an ingredient?

DR. BELSITO: In many cases, what we have done is, we have this respiratory boilerplate that is on the web site, that basically, to summarize, states that the particulate size that comes out of aerosol sprays would not really be respirable down to the alveolar area, and therefore, unless absorption in systemic toxicology was an issue in terms of pulmonary toxicology, we weren't concerned because of the size of the particles.

DR. SADRIEH: Okay. So, I guess my second question kind of maybe is related to that, and that's with respect to absorption, generally speaking. My understanding is the committee looks at particle sizes and size -- molecular size of ingredients, you know, sometimes permeability, I guess, of the ingredient. But the actual formulation is not taken into consideration.

The formulation is really what would drive something to get through, and so my question from a general perspective is, how do we account for you know, lack of -- or absorption, when there are ingredients there such as penetration enhancers that might actually cause -- I think you just raised the issue of the one ingredient that you thought would not be absorbed, and that it

is. And you know, I think it was mentioned that that's the exception, that probably --

DR. LIEBLER: Well, it's also backwards.

DR. BELSITO: It's on tape stripped skin.

DR. LIEBLER: Yeah.

DR. BELSITO: But as a panel, we really can't begin to look at how these ingredients may be formulated. How we handle that is whenever -- and you'll see in this report, there are several -- whenever we're dealing with a group of chemicals that are penetration enhancers, what we'll say is that care should be taken when used with chemicals that were found safe because of their lack, kind of, of absorption.

So, we'll put the onus back on the manufacturer to understand that they're adding something that may enhance the penetration of a chemical where we had raised concerns about its relative lack of absorption. And if absorbed, we were concerned about these specific types of toxicities. So, it's really impossible for us to understand how these will be formulated. In the final product, essentially, it's up to the manufacturer to assure that that product is safe.

And so, it's a little bit more of a backwards approach. We'll say that you know, this is safe. We have no concerns if it's absorbed. You know, it's a rather banal chemical. Or we'll say, you know, we were concerned about the effects when this was fed at you know, a kilo per gram -- or a gram per kilo, or when it was whatever. But as used in cosmetics, that's not going to happen, because it doesn't penetrate the skin. Well, the manufacturer is seeing that caveat in our discussion, and then, using an ingredient where we pointed out it can be a penetration enhancer. Then, it's up to them to assure that it's not enhancing the penetration of that chemical that we had concerns about.

DR. SADRIEH: Thank you.

DR. BELSITO: Does that make sense?

DR. SADRIEH: Yeah. I mean, you know, I --

DR. BELSITO: Because we're not looking at formulations. We're just looking at the --

(Simultaneous discussion)

DR. SADRIEH: Right. I know. I know.

DR. BELSITO: -- different chemicals.

DR. SADRIEH: I mean, yeah, I come from the world where we look at --

DR. BELSITO: Right.

DR. SADRIEH: -- formulations.

DR. BELSITO: Right.

DR. SADRIEH: And you know, formulations are made to deliver a product, you know, or an ingredient. And here, the ingredient is just looked at in isolation, not considering the formulation, which has a very big impact on whether something gets through intact or non-intact skin.

DR. BELSITO: Precisely.

DR. SADRIEH: And so --

DR. LIEBLER: It's not that we're not considering it all. I mean, we are considering the context in which these ingredients are used in products. I mean, we do consider, for example, if the -- first of all, if they're leave-on or rinse-off type products. We also consider if they're applied to certain areas where they're likely to have more concentrated exposure with greater chance of absorption like underarm deodorants, for example.

DR. SADRIEH: Mm-hmm.

DR. LIEBLER: We can't get into the specifics of formulations of individual products, because that's beyond our purview, and beyond our information resources.

DR. SADRIEH: No, no, I certainly understand that, because you know, yes, that would be difficult to do. But I'm just wondering, is there a way to sort of maybe exclude certain types of ingredients to be formulated with it, in conjunction with certain types of ingredients that may have, you know, excipients, basically, that might have certain physical, chemical characteristics that would drive the penetration of something into the skin.

And you know, this is maybe a philosophical discussion. You know what I mean? Just from my perspective, this was something that, you know, occurred to me, general speaking, as these ingredients are reviewed, that that aspect is not taken into consideration, and

there might be a good reason for it. I'm just saying that I just had that question, and I didn't know.

DR. LIEBLER: Well, I think as we go through the day and then in future meetings, you'll get a better feel for how we approach these issues. It's not that we can't or don't deal with them at all. We basically have to focus on the safety of the ingredient in the context of use.

DR. SADRIEH: Mm-hmm.

DR. LIEBLER: And if there are things that potentially go outside of the scope of our deliberations, we either note those things in the discussion when they can be reasonably anticipated, or they would need to be inferable from the content of our report by industry.

DR. SADRIEH: Mm-hmm. And because for example, I see a statement that's made, you know, safe if formulated to be non-irritating. For example, I've seen that. I'm just wondering, you know, if one could potentially say, you know, safe if it's not to be penetrating (Laughter)? You know what I mean? That's basically sort of the perspective that I have.

DR. KLAASEN: Well, one of the things that we do, and you'll see in some of these today that we note that some of these chemicals are penetration enhancers. So, we point that out in the discussion, that they are penetration enhancers. So, if this chemical is "mixed" with a chemical that if you enhanced its penetration, you'd better be careful, in essence.

DR. SADRIEH: Mm-hmm.

DR. KLAASEN: So, we approach those things, but maybe not maybe as specific as you can with a drug, per se, that you may be more used to.

DR. SADRIEH: Thank you.

DR. HOOGEVEST: My name is Peter Hoogevest. I'm here from Lipoid from Germany. My special interest is phosphatidylcholine, which we will discuss later on. So, in order to address your issue regarding formulation, this also plays a role in that particular draft report. But I think what should be done is when findings are reported with respect to compounds which are on lipids and certain formulations are being used, that these formulations have to be specifically mentioned in the statement, because what you said is absolutely correct. The formulation may influence the penetration rate.

So, reporting without mentioning which formulation has been used is, in my opinion, not correct. So, that's my recommendation, to always mention to which formulation this is related.

DR. BELSITO: Excuse me. We don't have the formulations. We have the types of products that are used. We have the range of ingredients. We have the range of the concentration of the ingredient used in a particular type of product, but we are not looking at company X's eye cream and saying this formulation is okay. We're saying that this chemical could potentially be used up to this concentration in company X's eye cream.

So, we're not looking at final formulations. We're looking at chemicals, for lack of a better word, in the abstract as they're used in cosmetics. So, we don't have any of that data.

DR. HOOGEVEST: Sorry. I disagree with that, because you also --

DR. BELSITO: You can't disagree with it, sir, because the purview of this committee is to look at the safety of a particular chemical.

DR. HOOGEVEST: Yeah, but he also cites literature from --

DR. BELSITO: Of course --

DR. HOOGEVEST: -- scientific literature which is certainly mentioning which formulation is being used, and referring not to products, but to scientific publications.

DR. BELSITO: But as part of trying to get to the safety of the chemical, we refer -- because oftentimes, the data we have is from companies who have looked at a particular product that they're manufacturing, and that's the only data we're getting. But we are not looking at that particular product, nor as I read your letter, are we looking at the particular brand of product your company is making. We're looking at lecithin, not the lecithin you're making.

We're looking at you know, svingo(?), whatever, not the particular product you're making. So, in the list of our dictionary, we're not going to mention your trade names. Your trade name may be in a separate part where we look at lecithin -- can be manufactured under these trade names. But in our safety report, your particular trade name will not be mentioned, unless you gave us data that allowed us to contribute to our safety report.

So, we are looking purely at ingredients. We are using data from commercial

preparations to help us with our safety, but we are not looking at the safety of commercial preparations. That's not the purview of this panel.

DR. SADRIEH: I just wanted to add one thing. I certainly agree with you. It would be impossible to look at, you know, all of the formulations, and I wasn't, you know, sort of suggesting that one would look at all of the formulations. It was more sort of in the generic way, if there are certain types of ingredients that may somehow, you know, interact with the skin to cause potential penetration.

I was just saying that one would maybe -- looking at the tox data, you know, if there were to be some areas of concern, one would want to assume that the formulation would contain penetration enhancers, not knowing what it's going to contain, and that in those situations, one would want to caution manufacturers to sort of say, you know, you really should know what you're formulating with your ingredient. In this case, while the ingredient itself does not seem to have characteristics that would allow it to get through the skin, One cannot say that in the presence of other excipients or ingredients, I guess you call them, it would not actually, you know --

DR. BELSITO: Again --

DR. SADRIEH: -- penetrate. And so, you really need to formulate it in such a way that it actually does not penetrate the skin. That was what I was referring --

DR. BELSITO: You will see that coming up, because there are a couple of reports where there is reported penetration enhancement in those ingredients, and you'll see how we handle that in a discussion.

DR. SADRIEH: Thank you.

DR. BELSITO: Okay. So, moving --

DR. EISENMANN: I have a couple of comments. On table one, the category that concerned me is the one at the end that's not necessarily polysaccharides. EG maybe primarily something other than polysaccharides.

DR. BELSITO: What page are you on?

DR. EISENMANN: I'm on the last section of table one. I don't have a PDF in front of me, so --

DR. LIEBLER: It's PDF 87.

DR. BELSITO: Okay.

DR. EISENMANN: This includes carrageenan.

DR. BELSITO: Yes.

DR. EISENMANN: A few other -- if this is a report -- I didn't quite understand that category. And I didn't necessarily see it discussed earlier in the report.

DR. BELSITO: Right. And I put a note, not sure what we mean by this. If they're not necessarily polysaccharides, why are we reviewing them here.

DR. EISENMANN: That's what I thought, too.

DR. BELSITO: Right.

DR. HILDRETH: All right. So, the idea of this last little section here on the table was, Wilbur went through the literature and what was submitted from industry, and there were certain ingredients where it became clear that they were resins, and they were not polysaccharides and we removed those from the report. But we still -- after Wilbur went through that process, we still had a number of ingredients where we didn't have a clear indication whether it was truly a polysaccharide or if it was more along the lines of a resin.

The definition in the dictionary didn't make it a hundred percent clear to us, and the data we received didn't clarify that, either. So, we put those there not to say that these are a problem and that there's a safety concern here. It's that we don't have enough information to say that for sure, there are polysaccharides. Or we're hoping that someone will provide information with it, or if the panel feels uncomfortable looking at these ingredients, because we don't know what they are, they could be listed as insufficient or be deleted, based on your decision.

DR. LIEBLER: I think you could simply call these modified polysaccharides.

DR. HILDRETH: I mean, but that was our concern. We weren't sure that they were polysaccharides.

DR. LIEBLER: Well, hydrolyzed carrageenan is carrageenan that's been hydrolyzed. Okay? So, you're starting with a polysaccharide .

DR. HILDRETH: Okay.

DR. LIEBLER: Okay? So that one's modified. And so potassium undecylenoyl carrageenan, that's a chemically modified carrageenan. Right? And then sodium TEA derivative is also a differently modified carrageenan. It may have other stuff in it. It could have byproducts of the modification chemistry, but they're basically modified carrageenans. All three of those guys are modified carrageenans. So, I think that fits, and it's easier to have a more straightforward label modified.

And we may choose to keep them or not for other reasons, but you know, I think having the not necessarily just -- you know, I mean, with some of these others, you don't know entirely, you know, if they have no other contaminant you know, protein. For example, it's in the impurities. There's some residual protein or other materials in these. So, in that respect, these are no different than the others.

DR. HILDRETH: Okay. Then we can certainly change them to a different category. If you'll notice in the previous iteration, there were a lot of other ingredients that are no longer in that listing --

DR. LIEBLER: Yeah.

DR. HILDRETH: -- because we did get the information to find out that they were actually --

DR. LIEBLER: Okay, good.

DR. HILDRETH: -- resins or something other than pure polysaccharide.

DR. LIEBLER: Yeah. Very good.

DR. HILDRETH: So we can easily move those.

DR. LIEBLER: Thank you.

DR. BELSITO: So, we're keeping them.

DR. HILDRETH: Yes.

DR. BELSITO: Under just chemical polysaccharides, chemical structure unknown?

(No response heard)

DR. BELSITO: I mean, I'm fine.

DR. LIEBLER: No, I wouldn't say --

DR. BELSITO: I'm just asking you a question.

DR. LIEBLER: It's not chemical structure unknown. It's modified polysaccharides.

DR. BELSITO: Okay.

DR. SNYDER: So, let's go back to your original question, Don, about the organization of the report. I thought the report was going to be organized into modified and --

DR. BELSITO: That's what I thought.

DR. SNYDER: -- and unmodified. And then within those, we were going to have branch, linear, cyclic. Different readings.

DR. BELSITO: That was my understanding.

DR. SNYDER: And so -- because we mentioned those two in the introduction, where we talk about categories, and you put in there linear, branch, macrocyclic, modified and unmodified. And so to me, the issue is in the modified, because we don't have any issues with the unmodified. It seems like only when it becomes hydrolyzed or the degraded carrageenan.

And so for me, in my mind, it made it easier for me to think about, are there any unique toxicities that could be potentially there? And so, I was a little -- difficult to delineate that as a current format of the report.

DR. HILDRETH: So, is it the consensus of this team then, that Wilbur should re-order the tox data that's within this report as a modified group, and then an unmodified group?

DR. BELSITO: That's what I thought was going to be done.

DR. EISENMANN: Yes, I think that would be better.

DR. BELSITO: Also, I mean, just to get back to the introduction and the reason for grouping, I mean, the only reasoning that I see here is that it says regardless of how they're structured, all the (Inaudible) that comprise the molecular structures are polymers comprised of monosaccharides. But usually, when we give reasonings, it's not only that there's a similar grouping, but they have similar metabolism, similar uses, similar -- other similar characteristics that would allow them to be grouped. And I'm not seeing that in the introduction. Does anyone

else feel that way?

I mean, I just thought there should be a stronger basis of why we're grouping all these. But maybe it's not necessary. Maybe cyclic, linear, modified doesn't really matter, but from our discussions before, I thought that it did; that you guys were very concerned about, particularly about hydrolyzed fractions.

DR. LIEBLER: Well, there was the one hydrolyzed product that -- or one hydrolyzed carrageenan that is apparently -- at least we were told it is not a cosmetic ingredient. It's a laboratory artifact that's produced in -- but it's not the same material that's used -- that data supporting that assertion was promised to us, and we don't have it, still.

And Ron Shank proposed in the last meeting -- if you read the transcript of the second day, Ron proposed basically two groups; the unmodified materials, which were all pretty straightforward in terms of their safety, and then the modified, which presented some challenges. And we had instead suggested -- I think in our discussion with Bart during our first day session last time, we came up with the idea of having these grouped, but on a more structural basis.

I think you know, grouping these on a structural basis is fine, although it hasn't been done in the report. It would mean that all the tox and other data would be organized differently. It would be really a matter of regrouping the thing, but the report would probably largely be the same, although I'm not averse to you know, doing it modified and unmodified, either. But I think that --

DR. BELSITO: Do you mean writing two separate reports?

DR. LIEBLER: No, no, no.

SPEAKER: No, no.

DR. LIEBLER: Grouping -- making the grouping simpler. Doing unmodified and chemically modified forms. So, I would support either of those. The table one organization is a little bit complicated, and it's just not useful in framing the rest of the report. That's the problem. I mean, the way we see it, of course, table one is at the end.

The way a reader would see it later on, table one would be in the middle or near the beginning of the report, but the organization of the rest of the report doesn't fit table one. So, I don't know. I mean, how do the rest of you guys feel? Would you rather have this organized by some structural features, grouping as we talked about last time, or just modified and unmodified?

DR. BELSITO: I was under the impression it would be under structural groups.

DR. LIEBLER: That's what we ended up agreeing.

DR. BELSITO: I'm not a toxicologist, and from a toxicological standpoint, I think it should be organized in whatever way that makes it easier for you to assess whether all the data needs have been met.

DR. SNYDER: I think it goes back to the unmodified or almost all GRAS. Okay? And so it's only when it becomes modified that we then raised some concerns, and that was only because of an unnatural product, glucomannan or carrageenan hydrolyzed or whatever that was.

DR. BELSITO: Hydrolyzed carrageenan.

DR. SNYDER: But we put that to bed, to rest, last time, because we were told there was a seven year monkey study --

DR. BELSITO: Which is not in here.

DR. SNYDER: -- which is not in here. I couldn't find it.

MR. JOHNSON: It's in the report, but it's not on hydrolyzed carrageenan.

SPEAKER: Yeah.

MR. JOHNSON: It's on the naked carrageenan.

DR. SNYDER: Okay, but that's the one that's important to us, because we can put it to rest in the discussion, because carrageenan is not degraded naturally.

MR. JOHNSON: Right.

DR. SNYDER: It has to be done only in the laboratory. So, we can put that to rest --

MR. JOHNSON: Yes.

DR. SNYDER: -- that it's not an issue, and that's how we were going to put that to rest. We haven't done that very well in this report, and I kind of highlighted that in my comments on the report.

DR. BELSITO: Yeah.

DR. SNYDER: So, I think that that's the reason why we wanted it modified and unmodified. And then the chemical structure, I'm less concerned with, unless there's something that Dan or Kurt or Ron Hill come up with to tell us there could be some unique toxicities related to chemical structure.

DR. BELSITO: Right. While we're looking at ingredients and how to place them in the report, I just had a question, particularly since we're looking at this group here, is why have we put avenous sativo, oat starch -- granted it's polysaccharide, but why have we carved that out from the avena report and not included that with the avena report? Is there a specific reason?

DR. HILDRETH: I don't remember (Inaudible). It's just for structural purpose.

DR. BELSITO: But we're looking at other ingredients in the avena report that are polysaccharides, as well.

DR. HILDRETH: I mean, typically for the botanical reports, we're not looking at discreet chemicals. We're looking at you know, a leaf extract or a leaf oil or a peel oil.

DR. BELSITO: Okay.

DR. HILDRETH: Whereas here, we have -- although it's a large polymer, we have some discreet chemical information about it.

DR. BELSITO: We don't have a chemical structure. We just have -- it's a starch obtained from oats, as we have from for most of the botanicals, where it's oil obtained from lemon peel.

DR. HILDRETH: Right. But if it's a starch, we know that it's compromised of a certain group of polysaccharides. You have the different amylose and different monosaccharide sugars that give it some chemically distinct structure. We don't have the exact structure laid out before us, but we have similar structures.

DR. BELSITO: Okay.

DR. HILDRETH: That's why we put it in here. I mean, we can certainly move it, if you feel it's more appropriate from a safety assessment --

DR. BELSITO: It just soft stood out to me as being --

DR. LIEBLER: It's only because we're just doing, you know, Avena sativa. But this is a starch -- I mean, this is a polysaccharide report.

DR. BELSITO: Okay.

DR. LIEBLER: And it belongs here. I agree.

DR. SADRIEH: I mean, I agree with your comment, that it's a bit confusing to have the same ingredient, you know, listed in two separate reports.

DR. LIEBLER: It's not the same ingredient. It's the same source plant, but it's a different ingredient. So, the other report is the oat stuff. It's the oat stuff except for this one starch product. Okay? So, this one starch ingredient goes in here with the other polysaccharides.

DR. SADRIEH: So, it's not included in the other report at all?

DR. LIEBLER: Right. Yeah. We don't double dip.

DR. BELSITO: Okay. Wilbur?

MR. JOHNSON: Thank you, Dr. Belsito. Yes, on page 88, there is a table with the ingredient functions and the various groupings are apparent in that table. Is that table okay? And also, the tables, you know, containing the various groupings are -- even though they don't appear at the beginning of the report, they are introduced at the beginning of the report.

DR. BELSITO: No, I understand that.

MR. JOHNSON: Mm-hmm.

DR. BELSITO: My problem was, I printed out that table, and I made a note of, you know, what were the ones we wanted data on, and then as I'm going through the report, I had to keep going back to the table. And finally, quite frankly, after two hours and looking, that I still had lots of pages to go through, I said from a skin standpoint, I'm not concerned. I'm going to let the tox people figure this out, because in my dermatologic brain, I could not keep remembering what chemical grouping this particular ingredient belonged to.

So it would, just for me, have been easier to say, okay, I'm looking at linear modified, I'm looking at cyclic modified. We needed the data on the modified, and this is the data I'm getting. And I just couldn't wrap my hands around it the way the report was given. The tables were fine, but I had to just -- as I was looking at the data, I had to keep going back to the table, and

it was just to me --

DR. KLAASEN: I think what Wilbur's maybe asking is the categorization that he did in this table 88, if we like that --

DR. BELSITO: Yes.

DR. KLAASEN: -- that then, he could do --

DR. BELSITO: The tox data that way.

DR. KLAASEN: -- the tox data using that outline.

DR. HILDRETH: Yes.

DR. BELSITO: Yes.

DR. KLAASEN: And I would say that's great, for me, because it contains -- well, it says both if it's modified or non modified. It also includes if it's branched or straight chain or cyclic or what have you. So, it should keep everybody happy.

DR. BELSITO: Dan, comments?

DR. LIEBLER: I mean, it's okay to do that. You know, I realize that we discussed this last time, and we thought that it might be a good idea to organize these by chemical structures. I think it will simply make the report have more subheadings. That's the main result of that organizational change (Laughter).

It won't make it easier to understand. It won't make it come together in any -- you know, logical, useful way, I don't think. I don't object to doing it, but I don't think it will help us that much.

DR. BELSITO: Okay.

DR. LIEBLER: This is a very heterogeneous group of ingredients. And in fact, if you look at table 2, which is you know, PDF page 88 on the next few pages, and you look at the uses of the different structures, they're completely overlapping. So, these ingredients -- the fact that they have somewhat different structures is, I suppose, chemically interesting. But it doesn't really guide us in terms of understanding their safety based properties.

DR. BELSITO: Okay.

DR. LIEBLER: What I would suggest is that this is this table -- these last two not necessarily categories, we need to resolve those, because they really do belong elsewhere, even if it's only in the unknown structural configuration in a couple of cases.

DR. BELSITO: And how would you suggest we do that, since you're our wing man for these things?

DR. LIEBLER: Yeah. I don't -- see, for example, the carrageenans which are in the not necessarily just polysaccharides, may be primarily something other than polysaccharides, I thought the carrageenans were polysaccharides.

DR. BELSITO: Okay.

DR. LIEBLER: Yeah. I mean, so, I'm not sure why they're under that heading. Is there something that I'm missing here?

DR. HILDRETH: I mean, you can extract something and get the pure polysaccharide, depending on the conditions of the extraction. If we don't know the manufacturing details, we don't know if something else got extracted with it.

DR. LIEBLER: So it's an impurities issue.

DR. HILDRETH: It's possibly a purity issue. I mean, we can extract a polysaccharide from a resin.

DR. LIEBLER: Mm-hmm.

DR. HILDRETH: You know, even though that resin can contain a lot of other --

DR. LIEBLER: Right.

DR. HILDRETH: -- materials that we might have allergenicity issues with. But these ones that we've had in this category were ones that we didn't have -- the information that we needed to know that (Inaudible).

DR. LIEBLER: So, this category is just a little bit misleading, though.

DR. HILDRETH: Sure.

DR. LIEBLER: Because it suggests that there's something unique about these. We're grouping everything chemically, and then we're putting these in a pail that basically says, well, we don't know what else is in them. But that's not a structural organization issue. It's an

impurities issue, and that can be dealt with through assessing impurities.

DR. BELSITO: Okay.

DR. LIEBLER: So, I would suggest that these go back into the categories that they chemically correspond to from a polysaccharide structure standpoint. And I think almost all of these except for the peach gum are the carrageenans, so they go right back in with -- we're trying to remember exactly where carrageenans fall chemically, but that's where they would go.

DR. BELSITO: Okay.

DR. LIEBLER: Okay?

DR. HILDRETH: Should we then have something to denote that we don't have any data on the manufacturing or on the purity of these particular --

DR. BELSITO: Under manufacturing and impurities.

DR. LIEBLER: Right, exactly.

DR. HILDRETH: To come out and really say, you know --

(Simultaneous discussion)

DR. BELSITO: Yeah.

DR. HILDRETH: -- they put data on these --

DR. LIEBLER: Right. It's not a chemistry issue. It's not a basic structure issue. It's our standard issues of method and manufacturing impurities.

DR. BELSITO: Okay.

DR. HILDRETH: Does that make sense, Wilbur?

(No response heard)

DR. BELSITO: As we're going through the report, just a few general comments. On page 70 of the PDF, where we're talking about that degraded carrageenan, which is a non-issue now, I realize that. And maybe these sentences will come out of the report. But we're expressing concern about it used as a cosmetic ingredient, you know, because of that colonic carcinogenicity.

But then, above, we're talking about granuloma formulation, and two -- I think it's two paragraphs above, we talk about granuloma formation when it's injected intradermally. And then, we say well that's not an issue, because it's not going to get absorbed. So, if it doesn't get absorbed through the skin and cause dermal granulomas, then why are we concerned about it getting -- even if this were a cosmetic product, which it's not, why would we be concerned about getting absorbed and causing colonic issues?

DR. LIEBLER: We're not concerned.

DR. BELSITO: Right. So --

DR. LIEBLER: We're not concerned. But if you search the literature on carrageenan, there are these data where in mouse models of colorectal carcinogenesis, that --

DR. BELSITO: Right, I understand.

DR. LIEBLER: -- co-feeding carrageenan gives you an enhanced --

DR. BELSITO: Right.

DR. LIEBLER: -- tumor condition.

DR. BELSITO: But I would shorten that sentence and say, first of all, this is not a cosmetic ingredient. It's not found in nature. It's a lab abnormality. And P.S., even if it were, it wouldn't get absorbed, and so it's not an issue, rather than -- you know, I think we spend too much time saying that it's about the fact that it's not a cosmetic ingredient.

It just seemed to me to be contradictory. We're spending all this time saying why we're concerned about not causing colon cancer, because it's not there to begin with. And then, we suddenly dismiss granuloma formation by saying it's simply not absorbed. So, it's not an issue for using cosmetics.

DR. LIEBLER: Yeah. I think there are two issues here. One is the so-called degraded carrageenan or polygeenan. That is what's referred to in these two paragraphs in the summary on PDF page 70.

DR. BELSITO: Mm-hmm.

DR. LIEBLER: But the top paragraph on that page ends with a sentence in a co-carcinogenicity study, carrageenan, 15 percent in the diet. Not the hydrolyzed or degraded carrageenan, but carrageenan enhanced incidents of colon tumors in F344 rats injected with azoxy methane and NMU. So, this is not about the degraded carrageenan. It's a result that was obtained,

apparently, with regular carrageenan in this model. It's still not, I think, a concern to us. If necessary, we can handle it in the discussion. But it's not the hydrolyzed carrageenan artifact.

DR. BELSITO: Okay. And then, just to go back to the konjac dust lung issues. So, just help me out with this glucomannan, because it's not a cosmetic ingredient. It's a portion of many of these polysaccharides. Is that it? I mean --

DR. EISENMANN: Actually, glucomannan is a cosmetic ingredient. The concentration of use survey is still under way. I have just recently gotten a response from a company that says they are using it. I'm trying to get them to provide me some information, but so far, I haven't gotten anything more.

DR. BELSITO: Because it wasn't listed in any of the tables.

DR. EISENMANN: I think he's added it. I mean, it was in the dictionary. It was not in the report at the last meeting.

DR. BELSITO: I didn't see it listed in the report (Inaudible).

DR. EISENMANN: And then my other question, is there a difference between the glucomannan that's a cosmetic ingredient and konjac flour? What's the purity? So, I'm trying to get more information, but I don't have a supplier, so I have to work with this company who has just recently reported they are using it.

DR. HILDRETH: Right. The speaker we had at the last panel meeting made it sound like konjac flour and glucomannan was synonymous. And that may be trued outside of the cosmetic industry, but within the cosmetic industry, that is absolutely false. Konjac flour is a separate ingredient altogether of pure glucomannan. It's a different structure. It's a different beast, and I think that's created a lot of confusion.

DR. LIEBLER: And Carol is trying to get the documentation for that, though.

DR. EISENMANN: Right.

DR. LIEBLER: So, okay. What about the degraded carrageenan? Can we get anything on it? Because I'm not comfortable just to say we exclude that from the report because somebody said something at the last meeting. Without literature, we can't do that.

DR. BELSITO: And they promised that we would get that data.

DR. LIEBLER: Right. Yeah.

DR. EISENMANN: You know, I don't know. There's an ingredient called hydrolyzed carrageenan in the dictionary.

DR. LIEBLER: Right.

DR. EISENMANN: I'm not sure it was ever the same as degraded carrageenan.

DR. LIEBLER: Right.

DR. EISENMANN: But there's no supplier anymore for hydrolyzed, and so far, I have not heard anybody say that they're using it. So, if you keep that as insufficient on down the road, I think that would be acceptable, because we don't really know what they were selling. But the company that was selling it -- I think a long time ago, I had a conversation with them, and they kept telling me it's not the same. But they -- obviously, they're not supplying it anymore, so it must not have -- never gotten the market for it.

DR. LANGE: And I think last time, the woman who had the reference didn't work for that company anymore. She was just aware of the student.

DR. LIEBLER: I see. Okay. Okay. Well, I suppose -- I'm trying to think. If we could deal --

SPEAKER: I thought that she was the lead author on that. She said that the monkey study, that she thought that she was on --

MR. JOHNSON: No, that would be a respiratory sensitization study.

SPEAKER: Oh, okay.

MR. JOHNSON: She was the lead author on it.

SPEAKER: Thank you.

DR. LIEBLER: So, I'm wondering if we could deal with the hydrolyzed/degraded carrageenan issue by removing that ingredient from this report.

DR. BELSITO: We don't need to remove it. Carol said we can go insufficient for further information about its chemical structure, and any other issues you want with it.

DR. LIEBLER: There's no uses and no producer anymore.

(Simultaneous discussion)

DR. BELSITO: But it's in the dictionary.

DR. LIEBLER: Yeah, it's in the dictionary (Laughter).

DR. BELSITO: And then we get slammed for not reviewing something that's in our dictionary.

DR. HILDRETH: So then if you go insufficient on it, since there's no uses, it will immediately go into the zero use category.

DR. LIEBLER: Uh-huh. Okay. So, it's better to actually go insufficient.

DR. BELSITO: Yes.

DR. LIEBLER: Okay.

DR. BELSITO: Because then, after two years --

DR. HILDRETH: They won't beat the clock. Since it's not in use, it immediately goes into the zero use category.

DR. BELSITO: Okay.

DR. LIEBLER: Okay.

DR. BELSITO: So, where are we with this? Do we want to table it for Carol to get the information on konjac flour and how that might relate to hydrolyzed carrageenan -- or how it relates to glucomannan, and get information on this degraded carrageenan and how that relates to hydrolyzed carrageenan, and get more information, or at least put the monkey study where we think it belongs?

Because I missed that as well, Dan. I was looking for it with the degraded carrageenan when we were talking about that. Or, do we think that there are still data needs? Where are we? Again, from my standpoint, from a purely skin sensitization and irritation, I'm okay with this whole group. I mean, I don't like the way the report is written, but I'm okay with the group.

DR. LIEBLER: So, I agree with you on that, and I think the report can be reorganized a little bit more along the lines that we discussed. I think it's sounds like we can go insufficient for method of manufacture and impurities on hydrolyzed carrageenan, and we go can go insufficient for method of manufacturing, impurities on the glucomannan.

DR. EISENMANN: But if you want the report reorganized, it would probably be good to give Wilbur a little bit of time to do that and table it, because if it goes tentative, he needs to have the report back in a couple of weeks or something.

DR. BELSITO: Okay. That's fair. So, table it. Now, normally, with a table, we don't make requests. But as a P.S. --

DR. EISENMANN: I will put the request is, yes.

DR. BELSITO: -- take industry -- we would say that unless we get further information, the hydrolyzed carrageenan and the glucomannan will go insufficient, and they'll go insufficient for method of manufacture and impurities.

DR. KLAASEN: And then, in regard to the discussion, I think there are two things that really need to be clarified that aren't clarified. One is the --

DR. BELSITO: Page number?

DR. KLAASEN: We're now on page 70, I guess, of the draft discussion. I mean, it's two areas that really need to be clarified better. One is the cancer business, and especially the cancer of the colon. And that can be done, you know, without doing experiments, et cetera. We can just talk about that. The other is the whole respiration thing needs to bring into -- all of the information that we do have in here.

And I think that also, the monkey study that has been done should be incorporated somewhere into the discussion. You know, that's a seven year study in monkeys. In fact, this is the first time ever.

DR. SNYDER: So Don, I think in the report -- Wilbur, in the introduction and in the discussion, both sections, you start off with, are each naturally derived materials. And so I think that we need to take that -- because they're not naturally derived, because some of them are modified. Right?

(No response heard)

DR. SNYDER: And so we had them unmodified, which are largely GRAS, and then we have the modified ingredients. And it's when they become modified, that then we start to have some --

DR. BELSITO: I guess naturally derived, they're derived from plant.

DR. SNYDER: But like the carrageenan, it's not --

DR. BELSITO: Algae.

DR. SNYDER: -- it's not degraded naturally. It has to be done only in the laboratory.

DR. BELSITO: Right. So if we're only considering naturally derived, well, that's (Inaudible) report, because that's not a natural derived ingredient. So, that's --

DR. LIEBLER: I think natural is just so imprecise -- the term naturally is so imprecise.

DR. KLAASEN: Should we use the word green (Laughter)?

DR. LIEBLER: Let's just use something -- no, let's just use something more specific; that these are derived from plant and algae. Because naturally just means different things to different people, and it's a source of confusion. It's natural that we should be confused.

MR. JOHNSON: Dr. Belsito, I know the panel had expressed concern that the introduction doesn't sufficiently establish the basis for grouping of these ingredients and inclusion of all of those in the same safety assessment. The draft discussion, the last, I think two or three sentences, should that information be added to the introduction?

DR. BELSITO: Give me a page, Wilbur, please?

MR. JOHNSON: That's on page 70.

DR. KLAASEN: Which sentences did you say, Wilbur?

MR. JOHNSON: The last two in the first paragraph of the discussion.

DR. BELSITO: First paragraph.

DR. KLAASEN: Thus during cosmetic use in a --

MR. JOHNSON: Okay, now that needs to be revised. But that should begin with these ingredients are unlikely. That was an error in the discussion.

DR. KLAASEN: Okay, these ingredients are unlikely to have significant systemic accessibility, and any major decomposition products are likely to be simple saccharides.

DR. BELSITO: So now, but you're talking about the sentence before? For the sake of clarity and organization, these ingredients can be subdivided? Is that what you're talking about?

MR. JOHNSON: Yeah, that one as well as the one that Dr. Klaasen read.

DR. BELSITO: Yeah, I mean, I think that that makes it clearer that you know, the unifying -- but again, I would you know -- decomposition are likely to be simple saccharides. I guess that takes into my point that with metabolism, if there is metabolism, they're going to end up as the types of molecules with the same functions and activities. So yeah, I mean, I think that adds a little bit more clarity to the document.

DR. LIEBLER: And the only metabolism we're going to be dealing with is probably with the cylcodextrin. And it's going to be a limited extent dermal metabolism if that happens at all, because it's the only one absorbed. Everything else doesn't get to see an enzyme, because these are very large molecules that aren't going to be absorbed at all.

DR. HILDRETH: So, do you have any specific grouping verbiage for (Inaudible) for that introduction? I know that that seems to be something that everybody thinks is missing. Do you have something that would be useful there?

DR. KLAASEN: Well first of all, I would say the last half of that sentence could be just eliminated. That might not be what you're asking. And any major decomposition products. I just don't think that's important to hear. I mean, we're not talking about metabolism. We're talking about these things. I mean, it's amazing how long we can talk about these (Laughter) chemicals that are about the size of a semi-truck getting through your skin causing toxicity. It is kind of the big picture here, I think we're kind of forgetting. Nothing is going to happen.

DR. BELSITO: Okay, so we're going ahead, just so Wilbur has his -- and we all have our understanding of where we're going, we're going to recommend that this be tabled; that all the data be reorganized under headings of at least unmodified and modified. And then do we do further headings under modified, unmodified of linear, branch, cyclic or not?

DR. LIEBLER: So, to get back to Bart's question, Bart, do you mean guidance for Wilbur for writing the introduction section of the report?

DR. BELSITO: Or writing the whole report?

DR. LIEBLER: Well, no, but Bart's question was about the introduction. Is that correct?

DR. HILDRETH: Yes, yes.

DR. LIEBLER: So, the current introduction, the second paragraph starts to do this, but it's -- So it says based on chemical similar -- so on PDF page 33, based on chemical similarities relevant down on the following are included for use in evaluation safety.

This doesn't lay out the ingredients. It lays out other ingredients that are included in our evaluation of safety. So, I think probably in a paragraph before this or a paragraph after this -- I would say a paragraph before this, perhaps. So, the first paragraph, you simply lay out the broad features of this class of material -- of compounds, and then a new second paragraph could introduce that these fall into broad structural categories.

They basically include, you know, you could -- I think it would be best to first say they include extracted polysaccharides and they're chemically modified forms. But the panel also felt that it would be useful to view these as falling into four broad categories, which are the ones that we have in table one. And that these categories help to group chemically similar species together for further consideration. The panel felt it would be useful to review the safety data on this basis.

And then, you go onto the next paragraph, based on chemical similarities, relevant data are included for these other things. And since you do mention their structural features, it falls right in line with the previous paragraph. So, does that help for guidance, Wilbur?

MR. JOHNSON: Yes, it does.

DR. LIEBLER: It makes sense? Okay.

DR. BELSITO: Okay. So, we're going to table it. The introduction is going to be strengthened a little bit more as to rationale for grouping. And if I heard you, Dan, suggesting a new second paragraph about the broad categories, including the polysaccharides, modified and unmodified. And within these broad categories, there are sub-groupings of linear, branch, cyclic and unknown. But in the end, they're all polysaccharides and would be metabolized to shorter saccharides.

DR. LIEBLER: I would not emphasize metabolism in this introduction.

DR. BELSITO: Okay.

DR. LIEBLER: Because there's almost no metabolism of the ingredients in this report. The one exception would be the cyclodextrin. I think that could be mentioned, perhaps, in the discussion, if at all. I mean, there is a little metabolism data anyway, and it's the only one with any percutaneous absorption, as well.

DR. BELSITO: Okay. And then after that, in terms of organization of the toxicity data, we're going to have broad headings of unmodified and modified. Within those broad headings, are we going to again break the data down into linear, branch, cyclic?

DR. LIEBLER: No. What I suggest is you start by saying that these include ingredients that are extracted and not modified and others that are modified. And then, period. Okay? And then, say that the panel also noted that these fall into structural groupings, and this forms the basis for the way that the report is arranged; that the structural groupings -- as opposed to grouping them as modified and unmodified, because that's still too broad.

DR. BELSITO: Okay. So then with structural groupings, under linear, we would have all of the linear modified unmodified, for example.

DR. LIEBLER: Correct.

DR. BELSITO: Okay.

DR. SNYDER: I think this one is just a little bit more difficult, because on our normal ingredient list, we talk about the salts and esters, and that's easy to deal with. Those are simple modifications. But here, the modifications aren't quite so simple, so I think that's what we're trying to do. And we're trying to use our normal thought process, and it's for some reason, not working very well.

DR. SADRIEH: I just had a question about -- since the cyclodextrin is a bit different, would it warrant a separate report for itself or not?

DR. LIEBLER: We considered that last time. It is different in one notable way, but that's not enough to conclude that it doesn't belong with the rest of these. There are a number

of ways in which it does belong with these. Chemical structure, even though it's the small one -- but chemical structure it fits. Uses it fits and so forth. So you know, there are reasons.

And it's -- for practical purposes, it's a real pain to have a separate report on one ingredient that could easily be incorporated into a larger report. So, for economy of scale and efficiency of our overall, you know, procedure, we do things like that.

DR. SADRIEH: Thanks. And with respect to the title, do you think it may be kind of like indicating you know, the fact that you have the different categories sort of as a parentheses in the title that might help? Or normally, that would not?

DR. LIEBLER: Simple titles are good titles.

DR. SADRIEH: Okay (Laughter).

DR. BELSITO: Okay. So let me then recoup again. So, we're going to table it. We're going to make a slightly stronger rationale for the grouping and the introduction, particularly as Dan suggested, with a second paragraph. We're going to point out there are modified and unmodified. For all of the tox data, though, we're just going to break it into groupings of linear, branch, cyclic, not as to whether they're -- we'll know whether they're modified or unmodified, but we're going to do the tox data based upon that type of structure, not whether they've been modified or not modified.

And as we're looking at it now, once that's done and it comes back to us, we're thinking that we will have a safe as used, except for hydrolyzed carrageenan and glucomannan, where we want method of manufacture and impurities, and we want the data on the seven and a half year monkey study tweaked a little bit more in the discussion. And for glucomannan, we want method of manufacture and impurities and how that differs from konjac flour.

(Begin Track 3)

DR. BELSITO: Carrageenan, two Rs, two Es. Anything else that I'm missing here, since I think I'm the lucky guy who gets to report on this? (Laughter)

(No response heard)

DR. BELSITO: Is that it?

(No response heard)

DR. BELSITO: Okay.

MS. FIUME: Dr. Belsito?

DR. BELSITO: Yes.

MS. FIUME: Can I just ask a question, because I'm coming in a little bit late on the discussion? So, I understand it needs a lot of reorganization based on what you said. But if you're going to list -- have a list for IDA, can it go out as an insufficient (inaudible) not tentative, so that the next time it comes back, if it's reorganized the way you want it, then (Inaudible)?

DR. BELSITO: Well, Carol was concerned that if we do that, it gives Wilbur only a limited time to reorganize the report, and there's too much reorganization that needs to be done.

MS. FIUME: Well, okay, because it wouldn't be publicly announced. It would just be reorganized as it would be coming back next time. If it's an insufficient announcement --

DR. EISENMANN: It was already an insufficient data announcement. So, if you want to do a second insufficient data announcement, that's fine.

MS. FIUME: Okay, so the list that you read was already the list of the insufficient data announcement from last time? The list of needs that were just given?

DR. BELSITO: Let me go back and look. So, method of manufacturing and impurities, we had asked for each of the ingredients. Now, we're basically down to the hydrolyzed carrageenan; how that differs from the degraded laboratory carrageenan, and basically, how glucomannan differs from konjac flour that created respiratory issues in these Japanese workers. So, we're down to those two, rather than saying we want them for all.

MS. FIUME: Okay, so it's not new need. This is just sort of reorganizing.

DR. BELSITO: It's reorganizing and still asking for the same data, except that we're asking only for two specific ingredients now, rather than the general give us all.

MS. FIUME: All right, thank you.

MR. JOHNSON: So my question is, are you tabling or are you just going to issue --

DR. BELSITO: I think --

MR. JOHNSON: -- an insufficient data announcement?

DR. BELSITO: I think we're tabling it. No? Would you like to -- I would like to be able to wrap my head around this a little bit better, even though I'm really not responsible for the tox end, and I just really had a hard time with this document. I really did. I don't know. How do you guys feel?

DR. LIEBLER: Well, the reason to table it was to give you more time to reorganize; tell us what you need.

MR. JOHNSON: That's fine with me.

DR. LIEBLER: I know (Laughter). We table.

DR. BELSITO: Okay. Anything else?

SPEAKER: No.

DR. BELSITO: Okay.

Day 1 of the December 8-9, 2014 CIR Expert Panel Meeting – Dr. Marks' Team

Polysaccharide Gums

DR. MARKS: We have a draft tentative report on the polysaccharide gums. Ron Shank hasn't changed his position it's good to know. "Conclusion; the ingredients listed on Page 42 and 43 under non-cosmetic uses are grass, food additives too large to penetrate the stratum corneum; therefore, safe as used. For the hydrolyzed and modified polysaccharides we need method of manufacture, impurities and contaminants and molecular weight ranges."

And actually Wave 2, Ron doesn't say if he had wave 2; but, boy, we have a lot of methods of manufacture there, and more toxicology in terms of irritation sensitization; some acute oral tox too, so --

DR. SLAGA: I had safe as used.

DR. MARKS: Interesting. All?

DR. HILL: All of them, because the wave 2 had additional data unmodified and unhydraulized.

DR. MARKS: And with that then you don't feel like we need -- you know those discussions that even in the first sentence, that Wilbur has a memo about dividing them by chemical structure. That's unnecessary if they're all safe.

DR. SLAGA: I think Wilbur did a very good job on a very difficult group of material.

MR. JOHNSON: Well, thank you. I was a rough one all right.

DR. MARKS: Did you have any issues with the dietary degraded carrageenan? That was in the second paragraph there.

MR. JOHNSON: The carrageenan was in the laboratory when it's broken down, and it becomes carcinogenic but there is no indication that really occurs.

DR. MARKS: Okay. That's what -- I wanted to confirm that. It's interesting. I have also in my notes, second a safe conclusion. Ron Hill, do you feel that it's safe? These ingredients are safe, all these gums?

DR. HILL: The gums, themselves, I think, yes. The method of manufacture data, it's happy to get, but yet I think there are some new questions raised because they are using things like acylating agents to do the modification on some of these gums. So we have information that they're using it; but then we don't have corresponding typical impurity ranges. And I guess we can use the same kind of approach as we use for dioxane and ethylene oxide.

For example in -- I don't remember what the language is that we use in the boilerplate, but basically refers, I think, to CGMP and best practices to keep those levels minimized, but yet these particular ones, for example, haloethyl -- I mean pro-prionic acid is one, octenylsuccinate in hybrid. I think it's written wrong but -- in what they supplied but that's -- I think what they mean; 3 Core02 hydroxypropyltrimethylammonium chloride.

So there were these things that raised concern much more so than the gums themselves; because I thought, you know, pretty much for the gums what I see sensitization is where all the action, and if --

DR. MARKS: Yes. (Inaudible). To me I'm concerned about sensitization.

DR. HILL: And if it occurred, it seemed like to me if it's not oral exposure, then it would probably be related to some of these residual impurities. We don't have clear information. But maybe we can craft language in the discussion that talks about that without changing any conclusions here.

DR. MARKS: Well, we are still -- Crystals' Draft Report. This is really not even gone about -- It is s a draft tentative report; so we would issue a tentative report. So do you feel comfortable moving forward with a safe conclusion, and not dividing it up?

DR. HILL: Amazingly -- I think amazingly I do provided, again, we have language in there about -- and actually what we used in one of the polymer reports I thought was quite good; one, a couple meetings ago about that.

DR. MARKS: Okay.

DR. BERGFELD: Could you repeat?

DR. HILL: Yes. I need to go back and -- and this is unhelpful for whoever; but

one of polymer reports that we used we had some very nice language in there. It was either the one we put to bed at the last meeting or the meeting before that; I'll figure out which one it is I can find it. And it discussed issues with low molecular weight, reactive impurities, is basically what this was about; because that really was my only unresolved concern, because they provided us method of manufacturer on most of these that I -- if not all of these that I asked about. But then it raised this other issue.

DR. MARKS: Okay. So --

DR. HILL: So my comment was; I don't honestly see how one gets around the need sensitization testing for each and every one of these ingredients. That's kind of how I feel, and probably should have gone.

DR. MARKS: So I'll move tomorrow that we issue a tentative report with a conclusion of, safe as used, but no provisos in there in terms of -- Okay. Any other comments about this or these ingredients? Okay. Next we are on the centella asiatica, which is Indian pennywort. All right, let me close this. And let's see here. So this is the first time that we've seen this report. And as always, what we need to do is decide, are the ingredients okay and what are the needs moving forward? Let me see what Ron Shank said, "Need more information on the chemistry of the extracts. The madecassoside is large molecular weight at 9.75 and has several hydroxyl groups. This compound should be water soluble and penetrate the stratum corneum only, slowly, if at all. It's a sycophant; and is it --

DR. HILL: Which one? I'm sorry, can you -- Oh, yes. Yes. The madecassoside.

DR. MARKS: Yes; madecassoside. We need skin penetration data, but that's difficult to mix for -- is it representative of all the components of the extract, was the question. The only serious toxicity noted in the report is male reproductive system toxicity, but this was seen in rat studies using oral doses high relative to use concentration. Similar tox for the leaf extract, but use concentration; need HRIPT data case reports are insufficient. So, Tom, and then Ron, (inaudible)?

DR. SLAGA: The only data we have is from the extract and leaf extract. And I was a little confused; we had this term used before in one other --

DR. MARKS: So I had the same. I had the extract and leaf extract with --

DR. SLAGA: What's the difference between the leaf and the leaf cell culture extract? That's putting the cells from the leaf in culture and growing it for awhile, in endemic -- you see, I don't know what that is. Obviously when you put stuff into culture it's not like normal cells anymore. So I'm kind of concerned about what that really means. We have -- in another group we had a meristem cell culture too, and I wasn't sure what that was.

DR. MARKS: And we declared that insufficient.

DR. SLAGA: But if you eliminate those three, then it could be dealt with, you know, very simple logged concerns for data needs.

DR. MARKS: I agree. I thought the callus meristem, flower leaf stem extract and root was insufficient, I would put. And we need the method of manufacturer, impurities, compositions, systemic and skin tox.

DR. SLAGA: Wilbur, do you know what the cell part means? They're actually grown in culture for awhile then extracted?

MR. JOHNSON: You know, the definition, I'm referring to PDF Page 18; and the definition is rather vague in terms of, you know, exactly what that is. The centella asiatica meristem cell stem culture?

SPEAKER: Mm-hmm.

MR. JOHNSON: Yes, that's the only definition, that we, you know, are knowledgeable of.

DR. MARKS: It's the same for the callus --

SPEAKER: Mm-hmm.

DR. BERGFELD: The question I have, when you talk about what you have and what you don't have, you have the extract of the whole plant. And then you have extracts of certain parts of the plant. Wouldn't the whole plant stand for the rest of the plant?

DR. MARKS: No. I think the --

DR. SLAGA: We would have some of the -- all of it.

DR. BERGFELD: Yes.

DR. SLAGA: I mean what is there besides flower, leaf and stem? Root.

MR. JOHNSON: Root, yes.

DR. ANSELL: Fruit.

DR. BERGFELD: Well, you have --

DR. SLAGA: Well flower in this case.

DR. BERGFELD: So it's the whole plant.

DR. MARKS: It says it there. But in method of manufacture I thought it said just the leaf. Where do we go? Let me go back under there, kind of stop -- yes. Stalks and leaves. So that is -- that's on page 8, so that's I limited it to --

DR. BERGFELD: Stalks and leaves?

DR. MARKS: Yes. Stalks and leaves, so that is -- that's on Page 8. So that's why I limited it to this. So I guess the question is, which is right, the table with the whole plant, or is it just the stalks and leaves? Do you see under --

DR. BERGFELD: Yes, I see it. And does it have a flowering portion? Most plants do, but does it?

DR. MARKS: I don't know. That was one of the ingredients, was it not? I was not going to -- Yes, there was a flower/leaf/stem extract and the reason I would put that in the insufficient is, in the past when we've had different plant parts; you know, if it were an extract of the whole plant then I agree with you, but I guess, which is right, in the table or in the method of manufacture.

DR. GILL: Then when it talks about the components of the whole plant, the (inaudible) and so the largest I may have (inaudible) in the plant. I'm having trouble with those?

DR. MARKS: Since its first pass at this, we could do an insufficient data notice --

DR. SLAGA: It asks for a definition.

DR. MARKS: -- and get these sorts of things that we are asking. So I think that's one we need to reconcile what really is the extract. Is it the whole plant, or is it just the stem and the leaf? Let me write some of these down here. The other thing; yes, I thought the irritation sensitization it was perfectly fine for the extra and the left extract.

DR. SLAGA: Mm-hmm. And then what actually meant by the leaf cell culture extract, the meristem cell culture, the meristem cell culture extract, more of a definition to what --

DR. MARKS: Okay. Define other ingredients. Did you have a different approach, Ron Hill, than going out at this point with an insufficient?

DR. HILL: No. My bottom line conclusions were, I thought that the extract, the leaf extract and the leaf stem extract should be okay, and I was looking for something about the method of manufacture for the leaf/flower/stem, insufficient for sure for the root, meristem cell culture; and then there were some other puzzle ones actually.

And I didn't know how to think about the reproductive or developmental toxicology issue simply because we had -- in respect of (inaudible) production, but it was really high doses and maybe just known species of rat. Don't know have anything about the effects of lower doses. We don't have any teratogenicity data. I'm just not familiar with this plant and there are some unusual -- some unusual-looking components in here, but we don't really have a good handle on the levels.

So sketchy information, but not solid information in each of these extracts. Still, I thought leaf -- the plant extract, leaf extract and leaf stem extract probably were okay.

DR. MARKS: So that's others -- manufacturing purities composition systemic in skin tox?

DR. HILL: Yes.

DR. MARKS: Okay. Well a couple other questions I had; talks about the pharmacologic activity of a triterpenoid.

DR. HILL: Yes.

DR. MARKS: Triterpenoid?

DR. HILL: Tricyclic triterpenoid is the --

DR. SLAGA: Triterpenoid.

DR. MARKS: Oh. They left that -- supponents; did you have any comments

about that? I wonder what was meant by the pharmacologic activity. Once you start saying, its pharmacologic activity, then I say, what is it? And is that a potential toxic? So I guess, what is -- that was to me, when I read that, what do you mean by pharmacologic activity? Did you have this --

DR. ANSELL: Well it has a --

DR. MARKS: Huh?

DR. ANSELL: It has ancient use as a dietary supplement.

DR. MARKS: Page 9 is where the --

DR. HILL: Yes. I mean there are medicinal uses for this plant; and what puzzled me a little bit was, in some cases they are standardizing on -- in fact, in 10 or 11, and in some cases they say, the main cassiaside is the main bioactive supponent. And then in another place right next to there they were monitoring asiatica acids, not madecassic acid. So I was not sure what the story was there.

DR. MARKS: So how would you --

DR. HILL: I don't know.

DR. MARKS: Wilbur, did they say, in your reference there, what the pharmacologic activity was? Are we concerned, like --

MR. JOHNSON: Well I know there are reports in the literature of effects on learning and memory.

DR. MARKS: Oh!

DR. HILL: Positive effects; positive effects.

MR. JOHNSON: And there are also -- and there's wound healing.

DR. HILL: Yes. That's a (inaudible)

MR. JOHNSON: Yes. Mm-hmm.

DR. MARKS: That's a whole another -- Yes. Okay.

SPEAKER: And the key is defining the pressure.

DR. MARKS: So Ron Hill, do you think just defining that, or do you think just leave the sentence as it is? To me I was thinking, okay what does this stuff do pharmacologically? Is it a clotting inhibiter? What is it?

DR. HILL: So, you know, in our shop the limb- healing assays being used extensively for an indication of compounds that have antiproliferative effects. So if it's positive in wound healing, there is -- proliferative effects -- excuse me -- that doesn't necessarily mean tumor-promoting, or cancer-causing, or anything of the sort because we need to be able to heal a wound.

So, yes; I mean if they are being used for wound healing it would be nice if we could determine whether there's any additional knowledge of the pharmacology beyond that. I suspect there may not be, but then again; it didn't bother me from a sense of safety review here.

DR. MARKS: Okay. And then (inaudible) you had the discussion. On Page 16, Wilbur, you say it's widely used for this wound healing, and I think that's what the reference -- I guess -- I wasn't aware of it being used.

DR. BERGFELD: I think it's homeopathic use.

MR. JOHNSON: In Europe in particular. Mm-hmm.

DR. MARKS: Okay. So maybe you could put that in there, I would; because in the U.S. when I looked at this, I didn't talk to my surgeon friend, but I wasn't aware of it being used widely. Okay. Or you could just delete the "widely" and just and put, it is used.

MR. JOHNSON: Okay.

DR. MARKS: I mean that's fine. And then what did I have on collagen? Pre-cell proliferation; collagen fiber -- Oh, I know what it was. So if we go on Page 14.

DR. SLAGA: We had -- the other name for it is gotu kola. It's used in dermatology in treatment, dermatological conditions in Asia.

DR. MARKS: How in Asia?

DR. BERGFELD: No. It's an Asian drug. It's one of the Chinese or Asian homeopathic plants.

DR. MARKS: So on Page 14, the second paragraph under scintilla asiatica extract; that says, "A history of use in keloid management; that is anti-scar activity." And then the whole rest of it talks about how it stimulates collagen and fibronectin synthesis, and increased cellular hyperplasia in collagen. And to me, it just didn't -- I mean, if that's how it's used, it's

counter intuitive if you are trying to treat excessive scar formation with an extract that increases collagen and fibronectin.

I couldn't put the two together. But I don't know, Wilbur, I'm going to -- Was I the only one that was questioning that? Because to me that's -- I had no problems with all the rest of it. I just don't know why you use it for keloids.

DR. HILL: There are definitely disconnects in here.

DR. MARKS: Okay. So, Wilbur and I can go into the next -- well I presume we'll be doing an insufficient data notice. And maybe you can kind of reconcile those two if you would.

DR. BERGFELD: Why would you do that? I mean what difference does that make?

DR. MARKS: Well --

DR. BERGFELD: I mean just for interest; I understand.

DR. MARKS: Yes. Okay. To me I wouldn't want to put its use for keloids in the --

DR. BERGFELD: Maybe that's the medical treatment for it.

DR. MARKS: Yes. That's true.

DR. BERGFELD: We could clarify a bit.

DR. MARKS: Yes. That's so I -- Okay. So, it had a huge point obviously, and the safety assessment here. I just was questioning how it could be used to decrease scars when it has a high proliferative effect.

DR. BERGFELD: I mean, with the mechanism of keloid, we don't fully understand. Maybe there's some component.

DR. MARKS: Yes, who knows? Maybe by stimulating, stimulating the right collagen, and the right fibronectin, and the -- but at any rate.

DR. HILL: Well, that actually goes with -- what is this -- let's see, individuals with varicosities. I know that's something different; 30 milligram, total triterpenoids fraction twice daily for 3 months had significantly reduced levels of serum enzymes involved in mucopolysaccharide metabolism. The beta-glucuronidase beta- N-acetylglucosaminidase, and arylsulfatase. So I didn't know exactly what to make of that, but it seemed it's doing beneficial things, it's doing --

DR. MARKS: And then maybe I missed this, Wilbur, but in the -- or am I in the wrong place -- centilia. Yes, I that's -- I think that's it.

DR. HILL: And how about Table 2, let's see, table 2,did we get all the concentrations of use? Because I wrote down in big letters, NEED CONCENTRATIONS OF USE; something to do with Table 2 -- No, I see. There are no concentrations of use for the leaf extract at all, lots of uses and no concentrations.

DR. MARKS: I have, uses 0.5 percent.

DR. HILL: That's for asiatica extract; but the leaf extract --

DR. MARKS: I guess I didn't -- I wasn't too concerned since the extract included the leaf and stem based on its manufacturer. So I was willing to give the leaf extract a pass since the use is for the -- you are right. I mean if the irritation sensitization up to 30 percent, I guess you would say that the leaf extract was greater than that.

DR. HILL: That's what I was getting at. Absolutely!

DR. MARKS: So, see if we can find that.

DR. BERGFELD: I guess it's important to know if the whole plant extract is the whole plant.

DR. MARKS: Yes.

DR. BERGFELD: That would solve everything.

DR. MARKS: Perhaps.

DR. BERGFELD: Yes.

DR. MARKS: It would help.

DR. HILL: Because the method of manufacturing says it is not.

DR. BERGFELD: Yes.

DR. MARKS: Correct. Okay. So tomorrow I'm going to move that we have an insignificant data notice. That we need manufacture, impurities composition, systemic and skin

tox on the callus, the meristem flower/leaf/stem extract from the root. And that it would appear that the extract -- the whole extract or what's the extract and leaf extract are going to be safe as long as we get that concentration of use.

MR. JOHNSON: Dr. Marks, would you mention those ingredients names again, since (inaudible)?

DR. MARKS: Callus.

MR. JOHNSON: Callus?

DR. MARKS: Everything other than the extract and the leaf extract basically.

MR. JOHNSON: Okay.

DR. MARKS: Tom, Ron, sounds good?

DR. SLAGA: Mm-hmm.

DR. HILL: Yes, sir.

DR. MARKS: Okay.

MR. JOHNSON: Dr. Marks, let me just mention this; Dr. Eisenman provided us with a link to a report by the European Medicines Agency, an assessment report on centella asiatica. And in the absence of carcinogenicity data in this safety assessment, there is one study in that report, actually a dermal carcinogenicity study on asiatica side which is a supponent. And I'm wondering whether or not you would want that study summarized in this safety assessment.

DR. SLAGA: Yes.

DR. BERGFELD: Is this the major one?

DR. HILL: But they didn't find anything comparable on the madecassic side? The madecassic side, maybe find out how that's (inaudible).

MR. JOHNSON: I didn't -- I did not see a carcinogenicity study on that particular component in this assessment report.

DR. HILL: Most of what they are showing is actually anti-cancer, and so it's interesting because it promotes wound healing but, yes, if look at, at least the sketchy data that they have on cancer cell lines; it's toxic to all the cancer cell lines, but not the normal correctly lines. So it's an interesting -- interesting preparation.

MR. JOHNSON: Yes. It was actually in that study they are reporting skin papillomas, in that study.

DR. HILL: They were reporting increased skin papillomas?

MR. JOHNSON: Yes; mm-hmm.

DR. SLAGA: Yes. I definitely would include it.

DR. HILL: Yes. So we need to get the dose response, whatever they are getting on that.

DR. BERGFELD: Who is that from, (inaudible)?

MR. JOHNSON: It's in this -- that's what it is, and you see the length of this report.

DR. BERGFELD: European analysis?

MR. JOHNSON: Yes.

DR. GILL: And that just came in -- when was it -- last Thursday, or so.

MR. JOHNSON: Despite the (inaudible) --

DR. MARKS: So we do want to include it?

SPEAKER: Mm-hmm.

DR. MARKS: And there were no toxicologic concerns from that report?

MR. JOHNSON: Well, for example, you know, relating to the asiatica side, the dermal papillomas; and other than that, most of the studies related to a clinical efficacy.

DR. MARKS: Okay. Any other comments? So, move into patient data notice. You already know that the parts of this centella asiatica, we are splitting it out by the different parts of the plant and cells. Okay.

MR. JOHNSON: We are -- to the skin papillomas.

DR. BERGFELD: Animals? That's animals?

MR. JOHNSON: Yes. Mm-hmm.

DR. MARKS: I tell you what, that's going to appear in the next since it's insufficient.

DR. BERGFELD: You know, I just wondered what the skin papillomas and the

(inaudible) does? Works by (inaudible), skin tag?

DR. SLAGA: It's actually a precursor to (inaudible).

DR. BERGFELD: Is it?

DR. SLAGA: Mm-hmm. In the model.

DR. BERGFELD: Okay. Thank you; thank you.

DR. MARKS: Okay. So that's going to be important to begin here. I'm going to let you, Tom, take another look at this obviously.

DR. SLAGA: Is there any more anticarcinogenic due to the activity of this; in the anti additional studies?

MR. JOHNSON: I think that there may be some in here. I'm look and see whether or not there are any additional studies on that in here.

DR. HILL: Well, that's the interesting thing about that asiatica side because you are isolating one component. It's probably important to know about that biology. But then when you get to plant extracts you've got multiple components. So you can envision case where, is that sort of a Yin and Yang for its balancing out in a way that's beneficial. We are cutting new ground here.

DR. MARKS: Okay. We'll get to see this again as a tentative report.

MR. JOHNSON: Just to answer your question, there's at least one study relating to antimutagenic effects, and you have antitumoral activity, effects of the methanolic crude extract of centella asiatica. So, yes, we have antitumoral activity and antimutagenic studies in here.

DR. HILL: That's in here already, right?

MR. JOHNSON: No. No.

DR. HILL: No? In there?

MR. JOHNSON: Right. Mm-hmm.

DR. BERGFELD: It's in this -- it's in this newer document.

DR. SLAGA: I would put that in here too, so we can compare the two.

DR. HILL: Because we had something that was done with methanolic extract in here a year ago.

DR. SLAGA: That's for delete?

DR. HILL: The centalla asiatica extract, what's supposedly the whole plant, but then this is probably a research study, right, so -- because none of the cosmetic ingredients report methanol.

DR. LORETZ: Are you on the one that was just above carcinogenic; but because it says, aqueous edible parts.

DR. HILL: No. I'm looking right above the irritation and sensitization section near the bottom of Page 14 or some other page -- no, near the top of Page 14.

DR. LORETZ: The top of 14.

DR. HILL: It's where they are looking at induction of hepatosis and cancer cell lines. If I ever see another MCF-7, or (inaudible), it's too soon; but anyway, yes.

DR. MARKS: Okay. Any other comments about these plant ingredients?

DR. SLAGA: Well, it will be interesting seeing the next version of this, making it finally.

Day 2 of the December 8-9, 2014 CIR Expert Panel Meeting – Full Panel

Polysaccharide Gums

So, moving on to the next group, polysaccharide gums. Dr. Marks?

DR. MARKS: So, in September the panel issued an insufficient data announcement for this large group of polysaccharide gums, which has over three pages of ingredients. There was quite a bit of discussion as to this large number how to divide them up, whether you use modified/unmodified as Dr. Ron Shank suggested, the unmodified are grass ingredients and could easily be moved on into a safe conclusion.

We asked for method of manufacturing (inaudible) as the insufficient data, and we actually received lots of information in wave two.

We felt that we could actually go with one report. We didn't have to divide these ingredients out either by modified/unmodified or by chemical structure, such as linear blanch cycling. So, with that in mind, our team felt we could move forward with a tentative report having a conclusion of safe for all these ingredients.

DR. BERGFELD: So, a motion's been made. Belsito team?

DR. BELSITO: Well, again it was hard to grapple with these because it was our understanding that they were going to be grouped into the linear and the cyclic and the other groups and they weren't, so some of us on our team, particularly myself, had problems going through to see if all of our data needs were met.

We're also still concerned that the idea of the in-laboratory hydrolyzed (inaudible) had not been totally addressed and we're also concerned about the glucomannan and respiratory sensitization and so we -- I hope I'm remembering this right because I didn't write it down -- I think we had suggested that it be tabled, that the report be reorganized in the way that we had expected it to be reorganized, and we request a little bit more information from industry on this hydrolyzed caradenin and the seven and a half year monkey study be placed in a position when we're talking about that so it's quite clear that when fed this material that's not hydrolyzed in the same fashion in the gut, and again that we get a little more information about the glucomannan and the respiratory sensitization.

So, we're requesting that it be tabled.

DR. HILL: And we said insufficient for the --

DR. BELSITO: Insufficient for those two -- as a head's up to industry, but I think the idea was that since we wanted to reorganize, if we didn't table it, it would require that Wilber essentially spend all of his time reorganizing this document for the March meeting and we didn't think that that would be necessarily feasible, so we ended up with the idea of tabling it but giving industry a head's up that we wanted this information.

DR. BERGFELD: So, you're going to have a motion to table and then have a request to industry for specific information?

DR. BELSITO: Table, reorganize the report into the linear -- the --

DR. BERGFELD: Yeah, the structural.

DR. BELSITO: -- right, the structurals, and then a head's up to industry that we want a little bit more data on the hydrolyzed carrageenan and glucomannan in respiratory sensitization.

DR. BERGFELD: Ron Hill, you had your hand up.

DR. HILL: The other thing we briefly discussed yesterday that came to light is that in the modified polysaccharides, the reactive materials that are used for modification were specifically acylating agents, so they're either epoxides, in one case an anhydride, probably not such a big deal, but also chlorinated compounds that are used and I was looking for some sort of -- that raised the issue of some sort of language to indicate, in the absence of full characterization, that the typical levels that are out there in the manufactured product, some language about the approach that's taken to minimize the levels of those reactive substances in the marketed products.

So, that wasn't there until we got the most recent wave of information that had all of these, and I have a list, there are really only four or five that I noted, but I'm not sure that it's exhaustive, you know, the modified polysaccharides, and there's also the other reason is because there's always the possibility that somebody -- okay, we have a high molecular weight substance,

it's applied to the skin, but if we have a substantial amount of residual -- of the low molecular weight modifying agent, somebody could sensitize to that.

If we haven't seen it in prior testing, it may be those are high quality sources of materials, and as long as it stays that way, the problem won't happen. But some reference in the discussion to these reactive re-agents that are used in the process, and we've taken a similar approach in some of our polymeric reviews and I was going to provide (inaudible) -- I was going to provide him with that particular one that we did some time within the last year where I thought they did that very well.

DR. BERGFELD: And your opinion on tabling?

DR. HILL: I think that would provide us also time to make sure that that's well covered before we see the report again, so I'm happy with tabling.

DR. BERGFELD: Tom, do you have an opinion?

DR. SLAGA: (inaudible) substance, but, you know, to get specific data related to how the laboratory researched hydrolytes (inaudible) why it's carcinogenic, we have not looked at that specific publication. We were told we would be --

DR. ANSELL: Tom, I think that hydrolytes (inaudible) is in the -- it's on the ingredient list, it's in the dictionary, so in addition to -- so, it appeared from the discussion we had --

DR. SLAGA: But that's a different thing than what the laboratory does.

DR. ANSELL: Exactly, so --

DR. BELSITO: We don't know how it's different.

DR. ANSELL: We don't know how it's different. So, there's no documentation. That was sort of promised to us verbally at the last meeting, nothing showed, so we basically got this hydrolyzed carrageenan on the list, we've got sort of verbal assurance that this thing that caused the colon tumors in the animal model was a laboratory artifact, but we have no proof of anything.

So, nothing to hang our hat on on that, so -- that was one of the things we would basically -- yeah.

And in terms of the reorganization, the suggestion that we came up with was in the introduction, a new second paragraph that started out by laying out that these groups basically consist of the sort of naturally -- or the extracted products and then modified products, and that they can further be rationalized as belonging to broad structural groupings, and that, essentially, introduces the rationale for how the groupings would be reorganized, but that would be a sort of a paragraph -- second paragraph in the introduction that sort of eases the reader into understanding our approach to this.

So, that was the only specific of the reorganization other than them taking those groupings and using that to organize the rest of the data off the report.

DR. MARKS: So, on pages six through nine where all the ingredients are listed, we suggest Wilber re-do that table and add it as linear straight-chained or modified/unmodified grass --

DR. ANSELL: I think it's table two or table one already does that, but there's a couple of basket categories at the end, like, you know, not really, maybe, and those can be actually separated into the other four groups, satisfactorily, so --

DR. MARKS: I withdraw my motion and second Belsito's motion that this -- these groups of ingredients be tabled.

DR. BERGFELD: There's no discussion on the table, so we'll call the vote. All those in favor of tabling this group of ingredients? Thank you. This ingredient group is tabled.

I would like now to hear the list of what you think industry should give you. What are your needs?

DR. BELSITO: Well, basically we want to know what hydrolyzed carrageenan is used in cosmetics is and how structurally it differs from this hydrolyzed carrageenan that caused colon cancers and we do have a seven and a half year monkey study and that's nice, but was that done on the material that is cosmetic hydrolyzed carrageenan, and that we don't know. We haven't been provided with that data.

And then we still remain a little bit concerned about the respiratory sensitization with glucomannan and we want a little bit further clarification for that.

DR. BERGFELD: And I think I heard again something about reactive forms --

DR. HILL: Right, if we have any modified polysaccharides we're missing the re-agents that are used -- the reactive re-agents that might be used to modify. To me, that's an important piece of information to know because then we have a list of what we need industry to work to minimize.

DR. BERGFELD: Dan.

DR. ANSELL: Although -- I mean, I respect your point, Ron, I agree with it. We may not get, you know, the levels of all of the residual modifying agents and I think we can deal with that in the discussion.

UNIDENTIFIED: I'm not asking for medicals, I was looking for identities.

DR. ANSELL: Correct.

DR. BERGFELD: Okay, anything else --

DR. ANSELL: Method of manufacturing and impurities.

UNIDENTIFIED: Correct.

DR. BERGFELD: So, we're adding method of manufacturing and impurities to the list. Anything else? Wilbur?

MR. JOHNSON: In terms of the reorganization, you're just talking about unmodified and modified as subcategories or do you want them to be further organized based upon the four groupings, you know, linear --

DR. BELSITO: I believe that Dan asked that they be categorized by the four groupings with the modified and unmodified included under that same grouping.

DR. ANSELL: Just like in the table. The only reason I brought up modified and unmodified is because it was the original suggestion that Ron Shank made at our last meeting of a possible grouping. That didn't carry the day for whatever reason and we ended up sort of accepting the idea of having these sort of structure oriented groupings.

And in that introductory paragraph, Wilbur, I simply suggested that you could begin that paragraph by pointing out broadly that you have the unmodified and modified forms, but that then they break down into these four structural groupings and that will be the organizational basis for the remainder of the report.

DR. BERGFELD: Wilbur, are you in need of any other guidance?

MR. JOHNSON: No, I think that that's sufficient.

DR. BELSITO: Dan was going to draft that second paragraph, right, Dan?

DR. ANSELL: No, that was another one.

DR. BERGFELD: I think that we've settled this. We've tabled this group of ingredients and we've gotten our needs in a list form that both Lillian seems to be typing and Wilbur, so we can move on to the next ingredient in these reports advancing, and that's the benzotriazolyl with Dr. Belsito.

Safety Assessment of Polysaccharide Gums as Used in Cosmetics

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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.

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

INTRODUCTION

The safety of 102 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. As a group they 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.

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 cylic. Regardless of how they are structured, all of the "moieties" that comprise the molecular structures of these ingredients are polymers composed of monosaccharides.

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 subgroup will be subdivided into Linear Polysaccharides and Salts Thereof, 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; pectin-derived acidic oligosaccharides (mixture of linear oligomers and small polymers of galacturonic acid) - for safety assessment of pectin, which consists chiefly of partially methoxylated polygalacturonic acids; and carboxymethyl inulin - for safety assessment of sodium carboxymethyl inulin. 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.

In addition, the Cosmetic Ingredient Review (CIR) Expert Panel has issued "safe as used" conclusions for the following cosmetic ingredients which are 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

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] 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. 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 from additional sources are included below.

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.

Linear Polysaccharides and Salts Thereof

Algin

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.[14]

Ammonium Alginate, Calcium Alginate, Magnesium Alginate, Potassium Alginate, Propylene Glycol Alginate, Sodium/TEA-Undecylenoyl Alginate, and TEA Alginate

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.[15] 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.

According to another source, 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.[16] 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

Starch is composed of two polysaccharides, amylose and amylopectin.[17] Amylose is a complex α-glucan. It is an essentially linear polymer made up of α(1-4)-linked glucopyranose units.

Carrageenan

Carrageenan is a high-molecular-weight sulfated polygalactan derived from several species of red seaweeds of the class *Rhodophyceae*.[18] 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).[19] 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.[20] 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).

Inulin

Inulin has been identified as a fructan, a general term that is used to refer to naturally occurring plant oligo- and polysaccharides.[21] 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.[21]

Linear - Modified

Hydrolyzed Furcellaran

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*.[22]

Branched Natural/Unmodified

Amylopectin

Amylopectin is a complex α-glucan.[17] 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.

According to another source, amylopectin consists of numerous short chains of α(1→4)-linked D-glucopyranosyl residues with a chain length of approximately 6 to 35 units.[23] 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.

Arabinoxylan

Arabinoxylan is a non-starch polysaccharide, and is also described as a pentosan.[24] 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.[25,26] Moreover, acetic acid, hydroxycinnamic acids, ferulic acid, and p-coumaric acid are linked with xylose residues in arabinoxylan.[27,28] The attached moieties are partly or wholly lost when arabinoxylan is extracted from cereal or cereal subfractions using alkaline extraction.[24,29,30]

Ghatti Gum

Ghatti gum has been defined as the dried exudate of *Anogeissus latifolia*.[31] Degradation studies have shown that ghatti gum is a polysaccharide that consists of a backbone of galactose units to which other sugars are attached.[32] The side chains can consist of arabinose residues and aldobiuronic acids.

Glucomannan

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.[33] 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.[34]

Sterculia Urens Gum

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.[35] Karaya gum is composed of the sugars galactose, rhamnose, and galacturonic acid.

Xyloglucan

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.[36]

Branched - Modified

Propylene Glycol Alginate and Sodium/TEA-Undecylenoyl Alginate

The information on alginates stated earlier in this section also relates to these two branched - modified polysaccharide gums.

Starch Hydroxypropyltrimonium Chloride

Sensomer™ CI-50 Polymer, a starch hydroxypropyltrimonium chloride trade name material, is an aqueous solution of a naturally derived cationic polysaccharide produced from food grade potato starch.[37]

Cyclic

Cyclodextrin

Cyclodextrins are cyclic amylose-derived oligomers composed of a varying number of α-1-4-linked glucose units.[38] Cyclodextrins contain 6, 7, or 8 glucose units. β-Cyclodextrin is a carbohydrate consisting of seven glucose units.[39]

Unknown Structural Configuration

Cassia Angustifolia Seed Polysaccharide

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*.[40]

Physical and Chemical Properties

Linear Polysaccharides and Salts Thereof

Carrageenan

Food-grade carrageenan has an average molecular weight greater than 100,000 Da, with a low percentage of smaller fragments.[18]

The stability of native carrageenans in aqueous solution over a pH range has been established for various types of carrageenans extracted from single seaweed sources.[41] The carrageenans were in their sodium ion form without co-gelling cations. The carrageenans included κ-carrageenan from *Euchema cottonii*, ι-carrageenan from *Eucheuma spinosoum*, a κ/λ mixture extracted from *Chondrus crispus*, and a κ/λ hybrid carrageenan from *Gigartina radula*. Results indicated that the 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. 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. These data illustrate the susceptibility of carrageenans, particularly κ-carrageenan, to acid hydrolysis at elevated temperature in formulations having a pH below 4. 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.[18]

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. The rate of depolymerization is strongly influenced by both pH and temperature.[41]

Branched Natural/Unmodified

Arabinoxylan

The molecular weight of water-extractable wheat arabinoxylan, obtained by sedimentation, ranged from 65 to 66 kDa.[42] In comparison, estimations of molecular weight via gel filtration yielded results in the range of 800–5000 kDa[43] and 70-l000 kDa.[44] High molecular weight arabinoxylan forms rigid cross-linked hydrogels, owing to their greater water-holding capacities.[45]

Ghatti Gum

Ghatti gum has a molecular weight of approximately 8.94 x 10^7 Da.[46]

Glucomannan

The average molecular weight of glucomannan is 1 million daltons, and commercial samples have a molecular weight range between 200,000 and 2 million daltons.[47] Glucomannan forms a biphasic liquid crystal phase in water at 7 weight% concentration and becomes completely anisotropic above 10 weight% concentrations. It forms a thermally stable gel in the presence of an alkaline coagulant.[34] Glucomannan begins to decompose at approximately 250˚C, and decomposition is complete at 350˚C.[47]

Branched Modified

Dextrin Myristate

The following physical and chemical properties have been reported for dextrin myristate:[48]

- Physical state: powder or particles
- Color: white to pale yellow
- Odor: odorless or characteristic
- Melting point/freezing point: 50 ~ 150˚C
- Flash point: 210˚C
- Solubility: insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride

Dextrin Palmitate

Physical and chemical properties of dextrin palmitate are as follows:[49,50]

- Physical state: powder or particles
- Color: white to pale yellow
- Odor: odorless or characteristic
- Melting point/freezing point: 50 ~ 130˚C; 100 ~ 130˚C
- Flash point: 200 ~ 250˚C
- Solubility: insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride

Dextrin Palmitate/Ethylhexanoate

Dextrin palmitate/ethylhexanoate has the following physical and chemical properties:[51]

- Physical state: powder or particles
- Color: white to pale yellow
- Odor: odorless or characteristic
- Melting onset temperature: 120°C
- Flash point: 216°C
- Specific gravity (relative density): 0.45-0.60
- Solubility: insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride

Dextrin Isostearate

Physical and chemical properties of dextrin isostearate are as follows:[52]

- Physical state: soft solid
- Color: colorless to pale yellow

- Odor: odorless or characteristic
- Melting point/freezing point: 60 ~ 70°C
- Flash point: > 200°C
- Solubility: insoluble in water, methanol and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

The solubility of sodium hydrolyzed potato starch dodecenylsuccinate in water is > 100 g/L (149.5 – 158.2 g/L).[53]

Starch Hydroxypropyltrimonium Chloride

Typical physical and chemical properties of starch hydroxypropyltrimonium chloride are as follows:[37]

- Molecular weight: 2,000,000
- Appearance: clear to slightly hazy liquid (clear in 1:5 water solution)
- Odor: very mild; slightly sweet
- Color, Gardner: ≤ 2.5
- % Dry substance: 31-33
- pH @ 20°C: 3.5-4.5

Stearoyl Inulin

The following physical and chemical properties have been reported for stearoyl inulin:[54,55]

- Physical state: powder or particles
- Color: white to pale yellow
- Odor: odorless or characteristic
- Melting onset temperature: 64˚C; 68.2˚C
- Flash point: 210˚C; 214˚C
- Solubility: insoluble in water, methanol, and ethanol

Cyclic

Cyclodextrin

β-Cyclodextrin, a cyclic oligosaccharide, has been described as having low aqueous solubility (1.85 g/100mL).[56]

Unknown Structural Configuration

Cassia Angustifolia Seed Polysaccharide

The average molecular weight of cassia angustifolia seed polysaccharide is 9.66 x 10^4 Da. The intrinsic viscosity of this purified seed galactomannan is 209 mL/g.[57]

Method of Manufacture

Linear Polysaccharides and Salts Thereof

Inulin

The food industry can use three plant species for large-scale production of inulin: agave (*Agave azul tequilana*), Jerusalem artichoke (*Helianthus tuberosus*), and chicory (*Cichorium intybus*).[21] Commercial production is by extraction from the roots of *Cichorium intybus.*[58]

Linear - Modified

Amylodextrin

The linear dextrin, amylodextrin, has been prepared from waxy maize by enzymatic hydrolysis with pullulanase.[59]

Hydrolyzed Furcellaran

The manufacturing process for hydrolyzed furcellaran is presented in Figure 1.[60] The polymer furcellaran (a carrageenan [Kappa type]) obtained from *Furcellaria lumbricallis* is depolymerized by supercritical CO_2 without any solvent, and the product is an opalescent liquid.[22]

Maltodextrin

Maltodextrin is prepared as a white powder or concentrated solution by partial hydrolysis of corn starch, potato starch, or rice starch with suitable acids and enzymes.[61]

Branched Natural/Unmodified

Cichorium Intybus (Chicory) Root Oligosaccharides

It should be noted that the commercial production of inulin is by extraction from the roots of *Cichorium intybus.*[58]

Glucomannan

Glucomannan is obtained by a dry milling process of thin tuber (*Amorphophallus konjac*) slices.[33] Additionally**,** glucomannan can be obtained from monocot storage organs other than tubers, such as leaves, bulbs, roots, or seeds.[47] Specifically, 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.

Branched - Modified

Carboxymethyl Inulin

Carboxymethyl inulin has been synthesized by incorporation of carboxymethyl groups into the inulin framework; by reacting inulin with the sodium salt of monochloroacetic acid in the presence of sodium hydroxide.[62]

Corn Starch Modified

Corn starch modified is produced by an aqueous corn starch slurry reaction with 3-(dodecenyl) dihydro-2,5-furandione.[63,64] The degree of substitution per glucose was determined to be ≈ 0.01-0.08.

Dextrin

According to one method of production of dextrin**,** dilute acid (e.g. HNO_3) is added to native starch, and the starch is pre-dried.[65] 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.

Another production method begins with the suspension of starch in water and adjustment of the pH to between 6 and 8.[65] 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.

Dextrin Palmitate, Dextrin Myristate,
Dextrin Palmitate/Ethylhexanoate, and Stearoyl Inulin

A common method of manufacture has been reported for the following ingredients: dextrin palmitate, dextrin myristate, dextrin palmitate/ethylhexanoate, and stearoyl inulin.[66] 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.

Dextrin Isostearate

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.[67]

Glyceryl Dimaltodextrin

The 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.[68]

Hydroxypropyl Starch

Sodium sulfate (Na_2SO_4) and sodium hydroxide (NaOH) are dissolved in water, and starch and propylene oxide are added, and heated to 38°C to 42°C.[65] After the reaction is finished, the slurry is neutralized by acid (H_2SO_4). 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.

Potato Starch Modified

In the production of potato starch modified, an aqueous potato starch slurry is reacted with haloethylaminopropionic acid.[69] This reaction is followed by washing, filtration, and drying.

Sodium Dextrin Octenylsuccinate

Three methods of production of sodium dextrin octenylsuccinate are as follows:[65] 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.

Dextrin solution and octenylsuccinic anhydrate 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.

Dextrin solution and octenylsuccinic anhydrate are esterified, whereby the pH value is adjusted between 7 and 8 with sodium hydroxide solution. The solution is then dried.[65]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

Sodium hydrolyzed potato starch dodecenylsuccinate results from the reaction of a hydrolyzed starch with dodecenylsuccinic anhydride.[70]

Sodium Hydroxypropyl Oxidized Starch Succinate

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.[71,72] The substituent groups of a partially substituted starch derivative are distributed among the the 3 groups (C-2, C-3, and C-6) of the hydroglucose units of the starch molecule. Ether-, ester-, and cationic groups are attached mainly to C-6 of the anhydroglucose units. Modifications with different ether-, alkyl-, or cationic groups are possible as long as unreacted free hydroxyl groups are available.

Reactions leading to the production of sodium hydroxypropyl oxidized starch succinate are presented below:[71]

<u>Reaction to form oxidized 2-hydroxypropyl starch</u>

Starch, Oxidized + Propylene Oxide → Starch 2-Hydroxypropyl Ether, Oxidized

ST-OH CH_3-CH-CH_2-O ST-O-CH_2-CH-CH_3OH

Reaction to form 2-hydroxypropyl, oxidized starch succinate

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

$ST\text{-}O\text{-}CH_2\text{-}CH(O)\text{-}CH_3OH$ $C_4H_4O_3CH_2$ $ST\text{-}O\text{-}(C\text{-}CH_3)_x\text{-}(C_4H_4O)_y$

Sodium Starch Octenylsuccinate

Starch is suspended in water, and octenylsuccinic anhydride is added.[65] 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 (H_2SO_4). 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.

Starch Hydroxypropyltrimonium Chloride

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). The reaction to form cationic starch ether appears below:[72]

Reaction to form cationic starch ether

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

ST-OH $CH_2\text{-}CH\text{-}CH_2\text{-}N(CH_3)_3\ CL$ $ST\text{-}O\text{-}CH_2\text{-}CH\text{-}CH_2N(CH_3)_3\text{-}Cl$

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.[73] This reaction is followed by washing with isopropanol/water, and the material is then filtered and dried.

Unknown Structural Configuration

Algae Exopolysaccharides

Microalgae is grown in fermenters under conditions that promote the production of the exopolysaccharide, which is secreted by the microalgae.[74] 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 $(C_{27}H_{44}O_{27}S)_n$. Additionally, it was noted that this is the CAS number for D-galactopyranose.

Unknown Structural Configuration – Modified

Hydrolyzed Starch

The method of manufacture of 2 hydrolyzed starch trade name materials is presented in Figure 2.[75,76]

Composition/Impurities/Specifications

Linear Polysaccharides and Salts Thereof

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.[14]

Carrageenan

The low-molecular-weight forms of carrageenan are <5% of the total composition of the commercial product.[18]

Twenty-nine samples of food-grade refined carrageenan were analyzed using high-performance liquid gel permeation chromatography directly connected to vacuum-ultraviolet, inductively coupled plasma-atomic emission spectrometry. Each sample had no obvious peak of poligeenan (defined as degraded carrageenan, detection limit ≈ 5%).[77] 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 approximately 15,000 Da.[18] According to another source, the molecular weight of poligeenan is in the range of 10,000 to 20,000 Da.[78]

Inulin

According to the *Food Chemicals Codex*, inulin should contain no more than the following:[58] 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.

Linear - Modified

Hydrolyzed Furcellaran

Composition data on hydrolyzed furcellaran trade name mixtures that are sold to the cosmetics industry are as follows:[22,79]

- I09-112 - hydrolyzed furcellaran (0.6%), concentrate of sea water (0.05%), phenoxyethanol (1%), and water (98.35%)
- I08-216 - hydrolyzed furcellaran (1.35%), phenoxyethanol (1%), and water (97.65%)
- I08-295 - hydrolyzed furcellaran (1.90%), citric acid (0.05%), potassium sorbate (0.10%), and water 97.95%)

The following impurities data are on hydrolyzed furcellaran trade name mixtures:[22]

- I09-112 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).
- I08-295 contains heavy metals at a concentration < the limit of quantification, except for Cr (0.162 mg/kg) and Pb (0.08 mg/kg).
- I09-112 and I08-295 contain research pesticides at a concentration < the limit of quantification (i.e., 10 ng/g).
- I09-112 contains PCB at a concentration < the limit of quantification (i.e., 2 µg/kg).
- I08-295 contains PCB at a concentration < the limit of quantification (i.e.,10 µg/kg).
- I09-112 contains iodine at a concentration < the limit of quantification (i.e., 1 ppm).
- I08-295 contains iodine at a concentration < the limit of quantification (i.e., 9 ppm).

The following composition data are on 3 mixtures containing hydrolyzed furcellaran that were tested in studies summarized in this safety assessment:[80]

I08-216	I08-295	(I09-112)
97.65% water	97.95% water	98.35% water
1% phenoxyethanol	1.90% hydrolyzed furcellaran	1% phenoxyethanol
1.35% hydrolyzed furcellaran	0.10% potassium sorbate	0.60% hydrolyzed furcellaran
	0.05% citric acid	0.05% sea salt

Maltodextrin

According to the *Food Chemicals Codex*, maltodextrin should contain no more than the following:[58] 0.5 mg/kg lead, 0.0025% sulfur dioxide, 1% maltodextrins produced from high-amylose starches, and 0.5% all other types of maltodextrins.

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.[81]

Glucomannan

Glucomannan consists of the following: carbohydrates (as water-soluble fiber, ~75% of glucomannan composition), protein (2-8%), fat (<1%), ash (3-5%), and moisture (<15%).[33]

Starch Hydroxypropyltrimonium Chloride

Starch hydroxypropyltrimonium chloride consists of approximately 30% solids, and is preserved with food grade sodium benzoate.[37]

Stearoyl Inulin

The typical composition of stearoyl inulin is as follows:[82]

- Stearoyl inulin (> 95%)
- Moisture, based on loss on drying (< 1%)
- Stearic acid (< 5%)
- 3-Methylpyridine (beta-picoline) (< 300 ppm)
- DMF (< 5 ppm, detection limit)
- Methanol (< 5 ppm, detection limit)

Starch Hydroxypropyltrimonium Chloride

Starch hydroxypropyltrimonium chloride consists of approximately 30% solids, and is preserved with food grade sodium benzoate.[37]

Sterculia Urens Gum

Commercial sterculia urens gum contains 19%-21% of rhamnose and similar proportions of galactose and galacturonic acid.[83] Nitrogen content (probably non-protein in nature) of 0.07% has also been reported.[84]

Branched - Modified

Dextrin Myristate

Dextrin myristate has the following typical compostion:[85]

- Dextrin myristate (> 95%)
- Moisture, based on loss of drying (< 1%)
- Myristic acid (< 5%)
- 3-Methylpyridine (beta-picoline) (< 300 ppm)
- DMF (< 5 ppm, detection limit)
- Methanol (< 5 ppm, detectioin limit)

Dextrin Palmitate

The typical composition of dextrin palmitate is as follows:[86,87]

- 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)
- Methanol (< 5 ppm, detection limit)

Dextrin Palmitate/Ethylhexanoate

Dextrin palmitate/ethylhexanoate has the following typical composition:[88]

- 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)
- Methanol (< 5 ppm, detection limit)

Dextrin Isostearate

The typical composition of dextrin isostearate is as follows:[89]

- Dextrin isostearate (> 95%)
- Isostearic acid (< 5%)
- 3-Methylpyridine (beta-picoline) (< 300 ppm)
- Heptane (< 200 ppm)
- Methanol (< 5 ppm, detection limit)

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

A sodium hydrolyzed starch dodecenylsuccinate powder contains the following heavy metals:[90]

- 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)
- Mercury (< 0.1 mg/kg)

Starch Hydroxypropyltrimonium Chloride

Starch hydroxypropyltrimonium chloride consists of approximately 30% solids, and is preserved with food grade sodium benzoate.[37]

Impurities/residuals data on starch hydroxypropyltrimonium chloride include:[73] diol levels (< 2%), enol levels (< 1.5%), and quaternizing agent (< 0.1%).

Stearoyl Inulin

The typical composition of stearoyl inulin is as follows:[82]

- Stearoyl inulin (> 95%)
- Moisture, based on loss on drying (< 1%)
- Stearic acid (< 5%)
- 3-Methylpyridine (beta-picoline) (< 300 ppm)
- DMF (< 5 ppm, detection limit)
- Methanol (< 5 ppm, detection limit)

Unknown Structural Configuration

Cassia Angustifolia Seed Polysaccharide

The purified seed galactomannan contains mannose:galactose in a ratio of 2.90:1.[57]

Unknown Structural Configuration – Modified

Hydrolyzed Starch

Composition/Properties data on hydrolyzed starch are presented in Table 4.[75,76]

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, the following 55 polysaccharide gums are being used in cosmetic products and maltodextrin has the highest reported use frequency:[91,92,93]

maltodextrin
agar
agarose
align
alginic acid
amylodextrin
avena sativa (oat) starch
carrageenan
cassia angustifolia seed polysaccharide
cichorium intybus (chicory) root oligosaccharides
corn starch modified
cyclodextrin
cyclodextrin laurate
dextrin
dextrin myristate
dextrin palmitate
dextrin palmitate/ethylhexanoate
dextrin palmitate/stearate
galactoarabinan
glucomannan
glyceryl starch
hydrogenated starch hydrolysate
hydrolyzed corn starch octenylsuccinate
hydrolyzed pectin
hydrolyzed starch
hydrolyzed wheat starch
hydroxyethyl cyclodextrin
hydroxypropyl cyclodextrin
hydroxypropyltrimonium hydrolyzed corn starch
hydroxypropyltrimonium hydrolyzed wheat starch
hydroxypropyl starch
hydroxypropyltrimonium maltodextrin crosspolymer
inulin
laurdimonium hydroxypropyl hydrolyzed wheat starch
mannan
methyl cyclodextrin
pectin
polianthes tuberosa polysaccharide
potassium alginate
potato starch modified
propylene glycol alginate
pueraria lobata starch
sodium carboxymethyl starch
sodium carrageenan
sodium hydrolyzed potato starch dodecenylsuccinate
sodium oxidized starch acetate/succinate
sodium starch octenylsuccinate
solanum tuberosum (potato) starch
starch acetate
starch diethylaminoethyl ether
starch hydroxypropyltrimonium chloride
stearoyl inulin
sterculia urens gum
tamarindus indica seed gum
tapioca starch

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).[91,93] Frequency of use/use concentration data for polysaccharide gums are summarized in Table 3.

Cosmetic products containing polysaccharide gums may be applied to the skin and hair or, incidentally, may come in contact with the eyes and mucous membranes. 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 concentratiions 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.[94,95,96,97] 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.[94,95] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[95] 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):[98,99]

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
Starch Acetate
Tapioca Starch
Hydroxypropyl Starch
Propylene Glycol Alginate
Carrageenan
Ghatti Gum
Sterculia Urens Gum

Linear Polysaccharides and Salts Thereof

Algin

The viscosity of blood substitutes is among the important determinants in restoring microcirculation.[100] 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.[101]

Carrageenan

κ-Carrageenan (thickening agent) stabilizes milk proteins and is widely used in dairy products.[31]

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.[102] 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.[103]

Cyclic

Cyclodextrin

Cyclodextrins have been used to solubilize drugs in aqueous vehicles as guest-host complexes.[104]

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.[31]

Sterculia Urens Gum

Sterculia urens gum has the following uses in food: formulation aid, stabilizer and thickener, and emulsifier and emulsifier salt.[105] World Health Organization (WHO) reports affirming the safety of karaya gum as a food additive are available.[106,107]

TOXICOKINETICS

Non-Human

Linear Polysaccharides and Salts Thereof

Carrageenan

Carrageenan is not degraded or absorbed in the gastrointestinal tracts of rodents, dogs, and non-human primates.[18]

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.[108] 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.[108]

An aqueous suspension containing the drug piroxicam and carboxymethylcellulose (0.5%) or piroxicam β-cyclodextrin was administered to male Wistar rats (number/group not stated).[109] Each drug suspension (single dose of 10 mg/kg) was administered by gavage at a constant volume of 5 ml/kg. Blood samples were collected from the jugular vein for up to 22 h after drug administration. Lymph samples were collected by cannulation of the thoracic duct for up to 20 h after drug administration. When Cp (peak concentration) values for plasma piroxicam in the 2 groups were compared, there was no significant difference between the group treated with free piroxicam versus the group treated with piroxicam β-cyclodextrin. However, C_p was reached sooner in the free piroxicam group. Piroxicam β-cyclodextrin reduced total clearance, having increased the half-life of elimination and the area under the curve. The lymph profile of piroxicam was similar in the 2 groups, and the pharmacokinetic parameters were not significantly different. Bioavailablity in the plasma was greater in the piroxicam β-cyclodextrin group, whereas bioavailability in the lymph was greater in the free piroxicam group.

Branched Natural/Unmodified

Sterculia Urens Gum (a.k.a. Karaya 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, glactose 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.[83]

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).[110] 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 (a.k.a. Karaya 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.[35] 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.[111] 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 within a 1 to 2 min interval. 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.[112] 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.

TOXICOLOGY

Cyclic

Cyclodextrin

A toxicity profile of β-cyclodextrin is available from the WHO.[113] The toxicity profile of cyclodextrins can differ depending on the route of administration. For example, β-cyclodextrin administered orally induces limited toxicity.[114,115] 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.[116] 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.[116,117] In another study (rats), s.c. administration of β-cyclodextrin (≥ 450 mg/kg) induced similar changes in kidney proximal tubules.[118]

Acute Toxicity

Inhalation

Branched Natural/Unmodified

Glucomannan

An acute inhalation toxicity study on glucomannan was performed using male and female rats (number and strain not stated). An LC_{50} of > 0.0015 mg/l was reported.[119]

Oral

Branched Natural/Unmodified

Glucomannan

In an acute oral toxicity study on glucomannan involving male and female mice (number and strain not stated), an LD_{50} of > 2,800 mg/kg body weight was reported. None of the animals dosed with 2,800 mg/kg died, and there were no abnormalities with respect to the following: appearance, behavior, body weight changes, occult blood in the urine and feces, or macroscopic findings.[120] In another study**,** an LD_{50} of > 5,000 mg/kg body weight was reported for glucomannan in a study involving male and female rats (number and strain not stated).[119]

Sterculia Urens Gum

The acute oral toxicity of sterculia urens gum (in corn oil) was evaluated using 5 fasted male Sprague-Dawley rats.[121] Oral dosing with 10,000 mg/kg body weight did not cause death. Except for transient depression for a few hours (time not specified) after dosing, no toxic effects were observed.

Branched – Modified

Corn Starch Modified

Corn starch modified was administered orally (in distilled water, 2,000 mg/kg) to 5 male and 5 female Wistar albino rats according to the Organisation for Economic Co-operation and Development (OECD) 401 protocol.[63] Dosing was followed by a 14-day observation period. None of the animals died, and each was in good health throughout the study. Alopecia was observed in one animal during the study. The oral LD_{50} was > 2,000 mg/kg.

Dextrin Myristate

Rats (number and strain not stated) were dosed orally with 2,000 mg/kg dextrin myristate. None of the animals died.[48]

Dextrin Palmitate

In an oral toxicity study involving rats (number and strain not stated), none of the animals dosed with 2,000 mg/kg dextrin palmitate died.[49,50]

Potato Starch Modified

The acute oral toxicity of potato starch modified was evaluated according to the OECD 401 protocol using albino rats (5 males, 5 females).[69,122] The test substance (5,000 mg) was administered orally in a 30% aqueous solution, and dosing was followed by a 14-day observation period. Soft stool was reported for 1 female, and no other signs were reported for the duration of the study. Body weight changes at necropsy were normal. The LD_{50} was > 5,000 mg/kg.

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate and Corn Starch Modified

A material described as structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn starch modified was evaluated for acute oral toxicity in a study involving 5 male and 5 female Wistar albino rats.[123,124,125] The OECD Guideline 401 test protocol was used. Each animal received an oral dose of 5,000 mg/kg, and dosing was followed by a 14-day observation period. All of the animals survived, and no abnormal systemic signs were noted during the observation period. The LD_{50} was > 5,000 mg/kg body weight.

Stearoyl Inulin

In acute oral toxicity studies involving rats (number and strain not stated), none of the animals dosed with 2,000 mg/kg stearoyl inulin died.[54,55]

Dermal

Branched Natural/Unmodified

Glucomannan

An acute dermal LD_{50} of > 2,000 mg/kg body weight was reported in an acute dermal toxicity study on glucomannan involving male and female rabbits (number and strain not stated).[119]

Branched – Modified

Carboxymethyl Inulin

The sensitization potential of 31.1% aqueous carboxymethyl inulin was evaluated in a maximization test using 10 adult Dunkin–Hartley albino guinea pigs (4 weeks old).[145] Five female guinea pigs served as vehicle controls. No mortality occurred and no clinical signs of systemic toxicity were observed. Body weights and weight gains were considered similar when treated and control groups were compared.

Corn Starch Modified

Corn starch modified (Amaze® [28-1890]) in distilled water (30% solids) was applied to the skin of 5 male and 5 female New Zealand White rabbits according to the OECD 402 protocol.[63] The animals received a dose of 2,000 mg/kg, and dosing was followed by a 14-day observation period. Nine of 10 rabbits survived; one animal was killed due to a spinal column fracture that was unrelated to test substance administration. The dermal LD_{50} was > 2,000 mg/kg.

Dextrin Myristate

Using an occlusive dressing technique, dextrin myristate was evaluated for acute dermal toxicity in a study involving rats (number and strain not stated). Details relating to the test protocol were not included. Dosing with 2,000 mg/kg did not cause death.[48]

Dextrin Palmitate

The acute dermal toxicity of dextrin palmitate was evaluated in rats (number and strain not stated) using an occlusive dressing technique. Details relating to the test protocol were not included. Dermal administration of the test substance at a dose of 2,000 mg/kg did not cause death.[49,50]

Potato Starch Modified

The acute dermal toxicity of potato starch modified in 10 rats (strain not specified) was evaluated,[122] in accordance with the OECD 402 test guideline. Details relating to the test protocol were not included. An LD_{50} of > 2,000 mg/kg body weight was reported. Results relating to skin irritation potential are included in the section on Skin Irritation and Sensitization.

The acute dermal toxicity of potato starch modified was evaluated according to the OECD 402 protocol using 10 New Zealand White rabbits (5 males and 5 females).[69] An 18.5% solids aqueous potato starch modified solution was applied (dose of 2,000 mg solids/kg body weight) to intact skin using a semi-occlusive patch. The dose per cm^2 was not stated. Initially, very slight to slight erythema/edema was observed at the application sites of all animals, but reactions had cleared by 72 h. The authors noted that signs of local irritation included only mild erythema/edema, which may have been due to mechanical trauma. The LD_{50} was > 2,000 mg/kg.

Intravenous

Linear Polysaccharides and Salts Thereof

Iota (ι)-Carrageenan and Potassium Carrageenan

Groups of 5 female MF1 mice were injected i.v. (lateral tail vein) with ι-carrageenan or potassium carrageenan (2 mg in phosphate-buffered saline [PBS]).[126] Controls were injected with PBS (0.3 ml). The animals were killed 1 h and 24 h post-injection, and tissues were prepared for microscopic examination. 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 were observed. Carrageenan persisted for at least 6 months in the livers and kidneys. This contact with tissues did not appear to cause adverse effects in hepatocytes, but resulted in chronic renal damage. The authors noted that ι-carrageenan was less toxic to mouse liver and kidney compared to the potassium carrageenan, which was less pure than the ι-carrageenan.

Groups of 9 to 15 female CAF_1 mice (Balb/c x A/He) were injected i.v. (0.5 ml or 1 ml injection) with potassium or iota (ι)-carrageenan in saline (0.5 ml or 1 ml injection) and studied for 7 or 14 days, respectively, thereafter.[127] Treatment with either compound induced anemia, granulocytosis, and early profound thrombocytopenia. Treatment with ι-carrageenan

resulted in an early lymphocytosis, and both compounds induced lymphopenia by 18 h post-treatment. Additionally, 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. Potassium carrageenan and ι-carrageenan induced splenomegaly, and ι-carrageenan-treated mice developed hypoplasia of the thymus by 18 h post-injection. There was also a sustained increase in the numbers of colony-forming cells in the spleen after treatment with each compound. The authors noted that ι-carrageenan had a profound effect on hematopoiesis.

Intrapleural

Linear Polysaccharides and Salts Thereof

λ-Carrageenan

Groups of 6 adult female Balb/c mice (6 to 7 weeks old) received single intrapleural injections of λ-carrageenan.[128] Animals of one group each received a single intrapleural injection of 0.1 ml sterile saline (0.9% NaCl) and λ-carrageenan (1%; solvent not stated), which induced pleurisy. The lungs were not examined microscopically. Animals of another group each received a single intrapleural injection of 1% λ-carrageenan (0.1 ml) only. The 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 in these animals.

In another study involving groups of 10 mice, the injection of 2% λ-carrageenan in saline (200 mg/kg) into the pleural cavity induced pleurisy.[129] This acute reaction was characterized by marked accumulation of fluid and the migration of leukocytes to the site of inflammation in the lung.

Transbronchial

Linear Polysaccharides and Salts Thereof

Carageenan

A study involving male albino rabbits was performed to describe the morphological sequences of the pulmonary injuries caused by transbronchial administration (single injection) of carrageenan.[130] Transbronchial injection of 0.75% carrageenan in physiological saline induced pneumonia, followed by emphysema in the insulted lung. The surving 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. 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. Therefore the lungs (mild to severe erythema observed) of the remaining 5 animals injected with carrageenan and of 5 control rabbits killed at 4 months were prepared for morphometric analysis. In the stages of pneumonia, scattered infiltration of polymorphonuclear leukocytes was observed throughout the affected lobe, and was subsequently replaced by the accumulation of carrageenan-laden macrophages, which lasted for 1 to 2 months. The enlargement of alveoli and alveolar ducts was observed at 2 weeks to 2 months post-injection, and pulmonary emphysema was observed at 4 months. The lobes that were not injected with carrageenan were normal in appearance throughout the study.

Repeated Dose Toxicity

Oral

Non-Human

Linear Polysaccharides and Salts Thereof

Algin

A chronic feeding study was carried out in mice with sodium alginate (also known as algin) and starch acetate (a chemically modified potato starch).[131] Two groups of mice (75 males and 75 females per test substance) were fed sodium alginate and starch acetate in the diet, respectively, for 89 weeks. At week 87, half of the surviving male and female mice in each test group were placed on control diet (containing 55% pregelatinized potato starch). During the dosing period, the dietary levels of the test substances were gradually increased until the diets contained (by weight) 55% starch acetate or 25% sodium alginate. All survivors were killed during weeks 89 to 92. Sodium alginate and starch acetate caused increased water

consumption, distinct caecal and colonic enlargement, and a slightly increased incidence of intratubular nephrosis. Sodium alginate caused slightly lower body weights. An increased incidence of gastric trichobezoars was observed in mice fed starch acetate. The occurrence of concretions in the 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 was regarded as an effect of little, if any, toxicological significance.

Sodium alginate at 25% (w/w) in the diet was nephrotoxic to mice, as manifested by extremely high water consumption, high urine production, urinary incontinence, high pH and low specific gravity of the urine, increased level of blood urea nitrogen, increased kidney weights, distension of the renal calyx and high incidence of dilated distal tubules. Caecal and colonic enlargement and changes in urinalysis results were found to be reversible, completely or largely disappearing within 2-5 weeks of the cessation of the treatment (in week 87). The incidence of intratubular calcinosis or concretions in the pelvic space was not reduced during the recovery period. Study results are also included in the section on Carcinogenicity.[131]

Carrageenan

Groups of Fischer 344 rats (20/sex/group) received control or treated diets at levels of 0, 25,000 or 50,000 ppm kappa carrageenan with a molecular weight range of 196,000–257,000 Da for 90 days.[132] The low molecular weight tail (LMT) ranged between 1.9% and 12.0%, < 50 kDa (mean 7%), based on the results of a program initiated to develop a validated analytical method to measure the LMT. Clinical examinations were performed daily. Individual food consumption/body weight measurements were made weekly. Ophthalmic exam was conducted prior to and at the end of treatment. Hematology/serum chemistry and urinalysis evaluations were done at necropsy, and the same was true for organ weight determinations for adrenals, brain, heart, kidneys, liver, ovaries, spleen, testes and thyroid (with parathyroids). Full histopathological evaluation of paraffin-embedded rolled colon was performed. Clinical signs were limited to soft feces in high dose rats, and to a lesser extent, in low dose rats. There were no treatment-related effects on body weights, urinalysis, hematology or clinical chemistry parameters, or on organ weights or ophthalmic, macroscopic or microscopic findings. The gastrointestinal tract appeared normal in detailed histopathological evaluation using the Swiss roll technique. The NOAEL was 50,000 ppm in the diet (mean calculated test material consumption of 3394 ± 706 mg/kg/day in males and 3867 ± 647 mg/kg/day in females).

Lifetime administration of *kappa/lambda*-carrageenan from *C. crispus* or *G. mamillosa* at concentrations of 0, 0.1, 5, 15, or 25% in the diet to groups of five male and five female mice of 2 unidentified strains had no adverse effect.[133] The lifetime administration of *kappa/lambda*-carrageenan at the same dietary concentrations in groups of 5 male and 5 female rats of 2 unidentified strains resulted in evidence of hepatic cirrhosis, only at the 25% concentration, with no effect on mortality.

Groups of 15 male and female Sprague-Dawley rats were given extracts of *kappa*-carrageenan from *Hypnea musciformis* or *Irideae crispata* at a concentration of 1% or 5% in the diet for one year.[133] Weight loss ($p = 0.05$) was observed in all treated rats as compared with the control group, which received alphacel. The livers of rats at 1% were normal on gross and microscopic examination. Gross and microscopic examinations of the livers of rats given 5% *kappa*-carrageenan from *H. musciformis* were normal, except for nodules in 2 of 12 livers. Gross observation of the livers of rats receiving 5% *kappa*-carrageenan from *I. crispata* showed decreased size, rough surface, and vascularization in 10/13 rats, which was probably related to treatment. Microscopically, these livers were normal, except for focal necrosis in 1 of 10 livers. There was no evidence of storage of carrageenan-like material (metachromatic) in the liver cells of any of the treated rats, and no fibrillar material was observed by electron microscopy. No changes were observed in the stools of rats receiving 1% of either carrageenan, but female rats given 5% *kappa*-carrageenan from *I. crispata* and males given either carrageenan at the 5% concentration had loose stools. Blood was found sporadically in the stools, but the frequency was not significant.

Groups of 19 male and 21 female rhesus monkeys were fed 0, 50, 200, or 500 mg/kg body weight *kappa/lambda*-carrageenan by gavage daily on 6 days per week for five years, and carrageenan incorporated into the diet for an additional 2.5 years.[133] Loose stools, chronic intestinal disorders, poor appetite, and emaciation were seen in an apparently random distribution. Stool consistency was decreased in a dose-related trend over the entire 7.5 years of the study, and findings of faecal occult blood were increased in a similar fashion. Mean survival time was similar in all groups, and no gross or microscopic changes were detected in the tissues examined. Sporadic differences in body weight from controls were seen randomly; females had significant body-weight depression in the last 2.5 years of the study, which did not appear to be dose-related. No consistent, statistically significant changes occurred in haematological or clinical chemical values, absolute organ weights, or organ-to-body weight ratios after 7.5 years of feeding carrageenan. Cytochemical and ultrastructural observations revealed no storage of carrageenan-like material in livers, obtained at biopsy or in other organs obtained at necropsy, from monkeys given carrageenan, and no dose-related gross or microscopic changes in other tissues.

At the June 2014 meeting of the 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.[102] The discussion on which this determination was based is summarized as follows: "The margins of exposure (MOEs) between the NOAEL of 430 mg/kg bw per day (2250 mg/kg formula), the highest dose tested, from a neonatal pig study and human infant exposures at 2–4 weeks of age range from 2 to 12 on a body weight basis and from 2 to 8 on a concentration basis. The Committee noted that although the MOEs are small in magnitude, they are derived from a neonatal pig study in which the highest dose tested was without adverse effects on the gut or on immune parameters, supported by a neonatal minipig study. These new studies allay the earlier concerns that carrageenan, which is unlikely to be absorbed, may have a direct effect on the immature gut. The Committee also took account of the previous toxicological database on carrageenan, which did not indicate other toxicological concerns. It also noted that at carrageenan concentrations higher than 2500 mg/kg, formula becomes highly viscous, which adversely affects palatability and growth."

Inulin

Test results on inulin are included in the repeated dose oral toxicity study on arabinoxylan, summarized below.[134]

Branched Natural/Unmodified

Arabinoxylan

The repeated dose oral toxicity of wheat bran extract (~ 80% arabinoxylan oligopeptides) was evaluated using groups of 20 Wistar rats of the Crl:(WI)BR strain (10 males/group, 10 females/group).[134] The 3 test groups were fed 0.3%, 1.5%, and 7.5% wheat bran extract in the diet, respectively. These concentrations corresponded to average intakes of 0.2 g/kg, 0.9 g/kg, and 4.4 g/kg wheat bran extract per day. A basal diet control group and a 7.5% inulin control group were included in the study. The exposure duration was 13 weeks. There was no evidence of adverse macroscopic or microscopic findings considered to be test-substance related. However, on histopathological examination, minimal bilateral hypertrophy of the renal cortical tubules was observed in males and females, particularly in the highest-dose group. These findings were not accompanied by degenerative changes or changes in kidney weight, and were, therefore, considered to be suggestive of an adaptive response rather than a toxic effect. There were no remarkable findings in the control animals. The no-observed-adverse effect level (NOAEL) for wheat bran extract was 4.4 g/kg/day, the highest dose administered.

Ghatti Gum

Groups of Sprague-Dawley rats (10 males/group, 10 females/group) were given ghatti gum at concentrations of 0, 0.5, 1.5 and 5% in the diet (AIN-93M diet) for at least 90 days.[135] Ghatti gum intake at the 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. Incidentally, 2 of 10 females of the 5% ghatti gum group had a single colon ulcer, with associated acute inflammation. The ulcers were considered to be sporadic occurrences, possibly attributable to the basal diet. The authors noted that this explanation for the occurrence of ulcers is speculative, and that it was not proven that ulcer formation was related to the AIN-93M diet. The 5% dietary concentration was the NOAEL. NOAELs for males and females were estimated to be 3044 and 3309 mg/kg/day, respectively.

In a second study, groups of 20 female Sprague-Dawley rats were given ghatti gum in the diet (AIN-93M or NIH-07 diet) at concentrations of 0 and 5% for at least 90 days. A single colon ulcer, with associated acute inflammation, occurred in 1 of 20 control females given the AIN-93M basal diet. Again, the colon ulcer was considered to be sporadic, possibly attributable to the basal diet. A few statistically significant alterations in clinical chemistry were observed and considered sporadic and unrelated to treatment. Feed consumption among treated and control groups was similar for each sex. Specifically, feed consumption was measured weekly and showed that the amount of test substance consumed in this second study (females only) was equivalent to the amount consumed in the 5% dose group (males and females) in the preceding study. The 5% dietary concentration was the NOAEL. NOAELs for females were estimated to be 3670 and 3825 mg/kg/day for the AIN-93M and NIH-07 diets, respectively.[135]

Glucomannan

Groups of four male Sprague-Dawley rats were fed either 5% cellulose (control), 10% pectin, or 10% konjac (plant consisting mostly of glucomannan) for 28 days. At the end of treatment, the rats were fasted for 24 h and then fed 5 g/kg body weight brown rice and killed 5 h later. There was no no indication of toxicity resulting from the intake of konjac.[136,137]

Groups of 12 five-week-old Sprague-Dawley rats of each sex were fed either a normal basal diet, a hypercholesterolaemic diet (control diet containing 1% cholesterol), or one of three test diets containing 2.5, 5, or 10% refined konjac meal.[138] Refined konjac meal contains ~ 80% glucomannan. Thus, the highest dietary concentration of glucomannan was ~ 8%. Four animals of each sex from each group were killed after 4, 8, and 12 weeks of treatment. The livers were removed and subjected to gross and microscopic examination. Histological examination of the livers of rats fed 1% cholesterol showed spreading fatty degeneration with focal necrosis and a nonspecific inflammation reaction. Similar changes were seen in the 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.

Groups of 15 Sprague-Dawley rats of each sex were fed basal diet or basal diet in which 1% of the cornstarch was replaced with refined glucomannan, for 18 months.[136] Body weights were measured weekly for 3 months and monthly thereafter. At the end of treatment, the animals were killed and the brain, liver, aorta, kidney, spleen, and heart were removed and examined by electron microscopy. At microscopic examination, the livers of treated rats contained smaller, more lightly stained nuclei and reduced bile-duct proliferation in the portal area. The endothelial cells in the aorta of treated animals were smaller and there was less thickening of the aortic wall. The authors concluded that these changes were related to less senescence in the treated than in the control group. There was no evidence of treatment-related pathological changes. The NOAEL was 1% konjac meal, equivalent to an intake of 500 mg/kg body weight per day.[139,140,141,142]

Pectin and Solanum Tuberosum (Potato) Starch

A repeated dose oral toxicity study involved F_1 rats (from outbred strain of Wistar rats (Crl:WI(WU)) administered a test diets containing pectin-derived acidic oligosaccharides (pAOS) (±7 g/kg body weight/day) and control diets for 13 weeks.[143] The ±7 g/kg body weight/day dose was defined as higher, when compared to the maximum recommended limit dose for the micronucleus tests of 1 g/kg body weight/day for treatments longer than 14 days. The authors noted that F_1 rats were produced in a reproductive toxicity study summarized in the section on Reproductive and Developmental toxicity. There were two control groups. 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. Two experimental groups received the standard diet supplemented with 5% or 10% pAOS. 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. No treatment- related clinical signs were observed, and none of the rats died during the study. Ophthalmoscopic examination did not reveal any treatment-related ocular changes. Neurobehavioral examination and motor activity assessment did not indicate any neurotoxic potential. There were no relevant differences in body weight, growth rate and feed intake.

Macroscopic examination of the F_1 rats 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. These changes were characterized by thickening of the transitional epithelial layer of the urinary bladder (diffuse simple urothelial hyperplasia). The changes were slightly more prominent in males than in females. 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. Slight diffuse hyperplasia of the epithelial layer of the urinary bladder was suggested to be attributable to the concurrently elevated urinary sodium that, in turn, can be explained by the high sodium content of the pAOS and elevated urinary pH. In contrast, in rats fed pAOS in combination with NH_4Cl, an acidifying agent, the reduced urinary pH was associated with the absence of urothelial hyperplasia. The authors noted that hyperplasia induced by this mechanism in rats is considered not relevant to humans. It was concluded that 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.[143]

Starch Acetate

Test results on starch acetate are included in the preceding repeated dose oral toxicity study on algin that is summarized earlier in this section.[131]

Sterculia Urens Gum

In a study involving 5 non-fasted male Sprague-Dawley rats, the animals were intubated daily for 5 days with sterculia urens gum (5 g/kg/day).[121] No adverse effects were observed.

Transmission electron microscopy was used to study the ultrastructure of albino Wistar rat (rats housed 3 per cage; number tested not stated) jejunum, ileum, and cecum after dietary supplementation with 7% (w/w) sterculia urens gum [15 micrographs analyzed] for 45 days.[144] Analyses of micrographs revealed no abnormalities in any of the organelles.

Branched - Modified

Carboxymethyl Inulin

Repeated dose oral toxicity was investigated in groups of rats that received carboxymethyl inulin (31.1% aqueous), by gavage, at doses of 0, 50, 150 and 1000 mg/kg/day for 4 weeks.[145] Groups of five male and five female Wistar Crl rats approximately 6 weeks of age were included in each test group. No treatment-related effects were observed with respect to body weight, feed consumption, mortality, hematology, clinical blood chemistry, organ weights or gross or microscopic pathology up to the highest dose (1000 mg/kg/day) tested. Motor activity, as observed in a functional observation battery, was increased in high-dose females, but was not considered to be toxicologically significant.

Cyclic

Cyclodextrin

A 52-wk oral toxicity (dietary administration) study on β-cyclodextrin, a starch derivative, was performed using CrI:CD (SD) BR Sprague-Dawley rats and pure-bred Beagle dogs.[115] Concentrations of 0 (control), 12, 500, 25,000 and 50,000 ppm were selected for the rat study, and 0 (control), 6200, 12,500 and 50,000 ppm were selected for the dog study. The liver and kidney were identified at histopathological examination as target organs for toxicity in the rat 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. In the dog study, there was 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 results of these studies, therefore, indicate that the "non-toxic dietary inclusion level" of β-cyclodextrin was 12,500 ppm in the rat (equivalent to 654 or 864 mg/kg/day for males or females, respectively) and 50,000 ppm in the dog (equivalent to 1,831 or 1,967 mg/kg/day for males or females, respectively).

The oral toxicity of γ-cyclodextrin was examined in a 13-week feeding study in which four groups of four male and four female Beagle dogs received γ-cyclodextrin in the diet at concentrations of 0 (control), 5%, 10%, or 20%.[146] No treatment-related changes were noted in behavior or appearance of the dogs and no mortalities occurred. There were no treatment-related differences with respect to ophthalmoscopic examinations, hematological parameters, clinochemical analyses of the plasma, and semiquantitative urine analyses. Relative ovary weights were significantly increased in the 10% and 20% concentration groups, but the authors noted that 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 abnormalities were seen at necropsy that were attributable to treatment. At microscopic examination, no treatment-related effects were observed in any of the various organs and tissues. It was concluded that 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) was tolerated with no toxic effects observed.

Human

Branched Natural/Unmodified

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

The ingestion of karaya gum (10.5 g in diet) by 5 male volunteers (30 to 56 years old) daily for 21 days did not cause toxicity.[147] No significant effects on plasma biochemistry, hematological indices, or urinalysis parameters were noted.

Branched - Modified

Propylene Glycol Alginate

Following a 7-day control period, 5 male volunteers consumed an amount of propylene glycol alginate equal to 175 mg/kg body weight during the first 7 days of the test period.[148] 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. The ingestion of propylene glycol alginate had 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. Therefore, the results of this study indicated that the ingestion of propylene glycol alginate at a high level for 23 days caused no adverse dietary or physiological effects. Particularly, the enzymatic and other sensitive indicators of toxicological effects remained unchanged.

Dermal

Branched - Modified

Carboxymethyl Inulin

The sensitization potential of 31.1% aqueous carboxymethyl inulin was evaluated in a maximization test using 10 adult Dunkin–Hartley albino guinea pigs (4 weeks old).[145] Five female guinea pigs served as vehicle controls. No mortality occurred and no clinical signs of systemic toxicity were observed. Body weights and weight gains were considered similar when treated and control groups were compared.

Potato Starch Modified

A 28-day, repeated dose dermal toxicity study in rats (10 males, 10 females) was performed according to the OECD 410 test guideline.[122] Potato starch modified (2 g/kg body weight/day) was applied, under an occlusive dressing, to the skin of rats. Sporadic gains and losses of body weight were observed in males and females. When compared to the vehicle control group, a statistically significant (p value not stated) decrease in body weight gain was observed in treated females during weeks 1 and 4. The authors noted that the lower body weight gain could have been due to stress associated with the dosing procedure, whereby adhesion of the test material to the skin and dressings was a problem. Clinical biochemical test results indicated a statistically significant (p value not stated) decrease in serum triglycerides and a 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. A decrease in organ weights and differences in hematologic test parameters were also reported, but these findings were within historical control ranges for this species of rat. Signs of systemic toxicity were not observed at gross examination of treated animals. Thus, the NOAEL was considered to be $\geq$ 2,000 mg/kg body weight/day. Results relating to skin irritation potential are included in the Skin Irritation and Sensitization section.

The repeated dose toxicity of potato starch modified (28-1808) was studied using 10 male and 10 female New Zealand albino rabbits (test animals) and 20 rabbits (controls).[69] Using a non-occlusive patch, the test substance (2 g/kg bodyweight) was applied to the skin as a 10% solids aqueous solution. The area of application and concentration/dose per cm^2 were not stated. The control animals were tested with distilled water under a non-occlusive patch. Evaluations for signs of systemic toxicity, mortality, or morbidity occurred daily, and the animals were necropsied on day 28. The following were considered within normal parameters: body weights, food consumption, gross pathology, and histopathology. Minor differences in organ weight and clinical chemistry changes were observed, but considered irrelevant. It was concluded that potato starch modified was without significant toxic effect in rabbits.

Ocular Irritation

Non-Human

Linear Polysaccharides and Salts Thereof

Algin

The ocular irritation potential of algin (2%) was studied in 3 experiments using rabbits (number not stated).[149] 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 was not irritating to unrinsed eyes of rabbits and was minimally irritating to rinsed eyes.[133]

Branched – Modified

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).[63] 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.[48]

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.[49,50]

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.[69] 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.

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate 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.[123,124,150] 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.

Stearoyl Inulin

The ocular irritation potential of steraroyl inulin (test concentrations and protocol not stated) was evaluated using 8 Japanese white rabbits per test substance. Each test substance was classified as practically non-irritating.[54,55]

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.[22] 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.[22]

Maltodextrin

The ocular irritation potential of maltodextrin was evaluated using the *in vitro* bovine corneal opacity and permeability assay.[151] 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.[152] 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-dimethylthizol-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).[153] 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

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.[154] 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.

Skin Irritation and Skin Sensitization

Non-Human

Linear Polysaccharides and Salts Thereof

Algin

In 3 primary skin irritation experiments, occlusive patches containing 2% algin were applied to the skin of rabbits (number not stated) using adhesive tape.[149] Regarding the interpretation of mean skin irritation scores, a score of less than 0.5 was classified as non-irritating and scores ranging from 0.5 to 2.0 were classified as slightly irritating. A primary irritation index (PII) was calculated. It was noted that a PII of < 0.5 is deemed satisfactory, but that a PII of no greater than 1 is also acceptable. PII values of 0, 0, and 0.08 were reported in the 3 experiments, respectively.

The cumulative skin irritation potential of algin was evaluated in 3 experiments in which 2% algin (2 ml) was applied to the flanks of rabbits (3 per experiment) 5 days per week for 6 weeks.[149] A cumulative irritation index (CII) and then a mean maximum irritation index (MMII) were calculated. Macroscopic and histological examinations of test sites were performed. MMII values of 0.67, 0, and 0.67 were reported in the 3 experiments, respectively. Daily application of the test substance did not induce a severe reaction at either macroscopic or histological examination.

Carrageenan

Food grade *iota*-carrageenan was not sensitizing to the skin of guinea pigs.[133] Additional study details were not included.

Branched Natural/Unmodified

Glucomannan

The application of mechanically ground konjac flour to the skin of guinea pigs according to the Buehler closed patch method did not produce skin sensitization reactions.[119] Additional study details were not included.

Branched - Modified

Corn Starch Modified

In an acute dermal toxicity study, corn starch modified in distilled water (30% solids) was applied to the skin of 5 male and 5 female New Zealand White rabbits.[63] The animals received a dose of 2,000 mg/kg. The dose per cm^2 was not stated. Results relating to skin irritation potential were reported in this study, and results relating to acute dermal toxicity are included in that section of the safety assessment. Dermal reactions were either absent or classified as barely perceptible at 24-h and 48-h readings, and were absent at the 74-h reading. The test substance was classified as a mild skin irritant (primary irritation index = 0.25).

The skin sensitization potential of corn starch modified was evaluated in the maximization test, according to OECD protocol 406, using 20 guinea pigs (strain not stated; 10 males, 10 females).[63] During induction, a 10% solution of the test substance was injected and a 30% solution was applied topically. The concentration per cm^2 was not stated. Following induction, the challenge phase involved application of a 20% solution of the test substance for 24 h. Reactions were scored at 48 h and 72 h post-application. The control group (5 males, 5 females) was tested with distilled water during induction and challenged with the test substance. Reactions ranging from no erythema to moderate erythema were observed after induction with the control or test substance. Erythema was also observed after challenge with the test substance. However, rechallenge with the same test substance concentration did not induce erythema. It was concluded that the test substance did not induce sensitization in guinea pigs.

Carboxymethyl Inulin

The skin irritation potential of carboxymethyl inulin (1% to 100%) was studied using groups of 2 adult Dunkin–Hartley albino guinea pigs (4 weeks old).[145] The test substance was injected into the clipped scapular region, and reactions were scored at 24 h and 48 h. Additionally, a series of test article concentrations was topically applied to the clipped external flank of two guinea pigs using Metalline patches secured with tape and an elastic bandage. Two different concentrations were applied (0.5 ml each) per animal. 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.

The sensitization potential of 31.1% aqueous carboxymethyl inulin was evaluated in the maximization test using 10 adult Dunkin–Hartley albino guinea pigs (4 weeks old).[145] Five female guinea pigs served as vehicle controls. No evidence of dermal sensitization was observed.

Potato Starch Modified

In an acute dermal toxicity study involving 10 rats dosed with potato starch modified (2 g/kg), very slight to well-defined erythema and edema were observed in all animals after 24 h. At 48 h, very slight erythema and very slight edema were observed in 5 and 3 rats, respectively. All reactions had cleared by 72 h.[122] In a 28-day, repeated dose dermal toxicity study in rats (10 males, 10 females), a dose of 2 g/kg body weight/day was applied to the skin under an occlusive dressing.[122] Neither erythema nor edema was observed at treatment sites. However, small scabs were observed on 5 males and 6 females, and this observation was attributed to adhesion of the test material to the skin. The authors noted that, in both toxicity tests, removal of the test substance was difficult because of adhesion to the skin and dressing. Thus, some of the slight local irritation observed may have been due to mechanical trauma.

The skin sensitization potential of potato starch modified (18.5% aqueous suspension) in animals (species not stated) was evaluated in the Buehler test (OECD 406 test guideline).[122] Faint erythema (non-confluent) was observed in 6 of 20 animals after the second or third induction application. However, there was no evidence of sensitization.

The repeated dose toxicity of potato starch modified was studied using 10 male and 10 female New Zealand albino rabbits (test animals) and 20 rabbits (controls).[69] Results relating to skin irritation potential were reported, and other results relating to systemic toxicity/histopathological examination are included in the Repeated Dose Toxicity – Dermal section of the safety assessment. Using a non-occlusive patch, the test substance (2 g/kg body weight) was applied to the skin as a 10% solids aqueous solution. The area of application and concentration/dose per cm^2 were not stated. The control animals were tested with distilled water under a non-occlusive patch. Neither erythema nor edema was observed in treated or control animals, and there were no adverse morphologic effects on the skin or internal tissues. However, mechanical trauma from adherence of the test substance to the skin resulted in minimal to slight acanthosis at necropsy.

The skin sensitization potential of potato starch modified was evaluated according to the Buehler method (OECD 406 protocol) using 30 guinea pigs (15 males, 15 females).[69] The strain of animals tested was not stated. Twenty animals (10 males, 10 females) were treated topically with 18.5% solids potato starch modified, and 10 control animals (5 males, 5 females) were treated with distilled water. The concentration per cm^2 was not stated. The induction phase consisted of a 6-h topical application 3 times per week for 3 weeks. Reactions were scored at 24 h post-application. Following a 1-week non-treatment period, both the control and treated animals were challenged with a topical application of the test substance for 6 h. Reactions were scored at 24 h and 48 h post-application. During induction, very faint erythema was observed in 6 of 20 animals treated with the test substance; reactions were not observed in controls. Very faint erythema was also observed in 2 of 20 treated animals and 2 of 10 controls during the challenge phase. These challenge reactions were not classified as indicative of skin sensitization, and the test substance was classified as a non-sensitizer.

Dextrin Myristate

Dextrin myristate was evaluated for skin irritation potential in a study involving 6 New Zealand white rabbits (test protocol not stated). Skin irritation was not observed.[48]

The skin sensitization potential of dextrin myristate in guinea pigs (number and strain not stated) was studied using the Magnusson-Kligman maximization test. There was no evidence of skin sensitization.[48]

Dextrin Palmitate

The skin irritation potential of dextrin palmitate was studied using 3 New Zealand white rabbits per test substance (test protocol not stated). Skin irritation was not observed.[49,50]

In a Magnusson-Kligman maximization test on dextrin palmitate involving guinea pigs (number and strain not stated), there was no evidence of skin sensitization.[49,50]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate and Corn Starch Modified

A material (corn starch nmodified]) described as structurally similar to sodium hydrolyzed starch dodecenylsuccinate was evaluated for skin irritation potential in a study involving 6 New Zealand White rabbits.[123,155] This material has the following definition: 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.[156] The OECD 404 test protocol was used. A 50% slurry of the test material (1 ml) was 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 were scored for up to 72 h after patch application. All animals appeared healthy during the test. Erythema was observed at intact and abraded sites on one animal, and reactions had cleared by 48 h. The test material was classified as mildly irritating to the skin (primary irritation index = 0.09).

The skin sensitization potential of a 50% corn starch modified paste was evaluated according to the Buehler method (OECD protocol 4067) using female Hartley guinea pigs.[123,124,157] Twenty-five females were treated with the paste and 10 were treated with distilled water (control). The positive control (isoeugenol) was tested in a study performed within 6 months of the current study. During induction, the test material was applied topically to the shoulder area (~ 0.4 g on occlusive patch; area of application site not stated) for 6 h, 3 times per week for 6 weeks. After a 1-week non-treatment period, the animals were challenged topically for 6 h with the same concentration. Challenge reactions were scored at 24 h and 48 h post-application. The 50% 73-8050 paste did not induce erythema or edema during the induction or challenge phase, and was classified as a non-sensitizer. The positive control induced sensitization.[123]

Stearoyl Inulin

Skin irritation studies on stearoyl inulin (concentrations and test protocol not stated) were performed using 6 Japanese white rabbits per test substance. Skin irritation was not observed.[54,55]

The skin sensitization potential of stearoyl inulin (concentrations not stated) in guinea pigs (number and strain not stated) was evaluated according to the adjuvant and patch method. The skin reactions observed were estimated to have been very weak, and it was noted that each test substance possibly had a very low sensitization potential.[54,55]

Human

Linear Polysaccharides and Salts Thereof

Algin

Twelve male subjects with no history of allergy were patch-tested (using Finn chambers) with 20% aqueous sodium alginate according to International Contact Dermatitis Research Group (ICDRG) recommendations.[158] Reactions were scored at 2 and 3 days post-application. A ± reaction was observed in one subject on days 2 and 3. Results were negative for skin irritation and allergic contact dermatitis in this study.

Linear - Modified

Hydrolyzed Furcellaran

A mixture containing 1.35% furcellaran powder and 1% phenoxyethanol was applied (under occlusive patch) for 48 h to the backs of 10 healthy adults. The mixture was classified as a non-irritant.[22] In another skin irritation study involving

10 healthy adults, a mixture containing 1.35% furcellaran powder, 0.1% potassium sorbate, and 0.05% citric acid was applied to the back according to the same procedure. The product did not cause skin irritation.[22]

The skin irritation and sensitization potential of a mixture containing 0.6% hydrolyzed furcellaran, 0.05% concentrate of sea water, 1% phenoxyethanol, and 98.35% water was evaluated using 100 subjects. The mixture was applied 9 times to each subject. Additional details relating to the test protocol were not included. The mixture was considered non-irritating and non-sensitizing.[22]

Maltodextrin

A human repeat insult patch test (HRIPT) on an eye gel containing 2.45% maltodextrin was performed using 103 subjects. [159] The volume of gel applied and the patch site location and area of application were not stated. During induction, patches (type not stated) were applied 9 times at approximately 48-h to 72-h intervals. Reactions were scored at approximately 48 h to 72 h after each application. Challenge patches were applied to original and alternate sites at 12 to 24 days after application of the last induction patch. Reactions at challenge were scored at approximately 48 h and 96 h post-application. Five instances of erythema grades 1 were observed during induction. At the 48-h challenge reading, a grade of 1 was reported for the alternate challenge site of one subject. It was concluded that the gel did not induce allergic contact dermatitis.

Branched – Modified

Corn Starch Modified

Corn starch modified was evaluated in a 21-day human cumulative irritation study involving 26 female subjects.[63] A 7.5% solution of the test substance in distilled water (0.2 ml per patch) was applied topically for 21 days. The concentration per cm^2 was not stated. The scoring of reactions for cumulative irritation was performed every 24 h immediately prior to reapplication or until excessive irritation was observed. No adverse events were reported during the study. Application of the test substance produced reactions ranging from no erythema to minimal erythema. Based on these results, the test substance was classified as a non-irritant in this study. Distilled water (vehicle control) did not produce any significant evidence of erythema. Sodium lauryl sulfate (positive control) produced marked erythema and papules.

The skin sensitization potential of corn starch modified was evaluated in an HRIPT involving a non-exclusive panel of 113 subjects (86 females, 27 males).[63] A 7.5% solution of the test substance was applied to the skin for a total of nine 24-h induction applications, followed by a single challenge. Reactions were scored at 48 h or 72 h after the induction application and 48 h and 96 h after the challenge. Both the test substance and distilled water caused slight erythema in 3 subjects. It was concluded that neither the test substance nor the negative control (distilled water) caused sensitization reactions in human subjects.

Dextrin

A rinse-off facial product containing 42.6919 % dextrin (1% aqueous; effective concentration ≈ 0.4%) was evaluated using 54 subjects (46 females, 8 males; 21 to 69 years old) in an HRIPT.[160] The product (0.1-0.15 g) was placed on an occlusive patch that was applied for 24 h to the back of each subject, between the scapulae and waist (adjacent to the spinal midline). The dose/concentration per cm^2 was not stated. This procedure was repeated for a total of 9 induction applications. Following a 2-week non-treatment period, a challenge patch was applied to a new test site and reactions were scored at 24 h and 72 h post-application. Transient, barely perceptible erythema, observed in 1 subject, was the only induction reaction observed. Reactions were not observed during the challenge phase. It was concluded that the test substance, diluted to 1% aqueous, did not induce clinically significant skin irritation or any evidence of allergic contact dermatitis in human subjects.

Dextrin Myristate

The skin irritation and sensitization potential of a leave-on facial product containing 0.3% dextrin myristate was evaluated using 51 subjects (40 females, 11 males) in an HRIPT.[161] Testing was performed according to the HRIPT procedure on dextrin immediately above. An occlusive patch containing the product was applied; the dose/concentration per cm^2 was not stated. Skin reactivity was not observed during the induction or challenge phase. It was concluded that the product did not induce skin irritation or allergic contact dermatitis.

Hydroxypropyltrimonium Hydrolyzed Corn Starch

In an HRIPT, 47 male and female subjects (17 to 74 years old) were tested with 15% hydroxypropyltrimonium hydrolyzed corn starch.[162] A semi-occlusive patch (1" x 1") containing approximately 0.2 ml of the test material was applied for 24 h to the upper back, between the scapulae. This procedure was repeated 3 times per week for a total of 9 induction applications. Following a non-treatment period of approximately 2 weeks, a challenge patch was applied to a new test site that was adjacent to the original induction patch site. Reactions were to have been scored at 24 h and 72 h post-application. However, reactions were not observed during the study, and it was concluded that the test substance did not have skin irritation or allergic contact sensitization potential.

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate and Corn Starch Modified

A material described as structurally similar to sodium hydrolyzed starch dodecenylsuccinate and corn starch modified was evaluated for cumulative skin irritation potential in a study involving 23 human subjects (≥ 18 years old).[123,124,163] The powder was applied topically (0.2 g, moistened with distilled water; area of application site not stated) under occlusive conditions for 21 days. The following other materials were also applied topically according to the same procedure: a 50% w/v slurry of the test material in baby oil, saline and baby oil (negative controls), and 0.1% sodium lauryl sulfate (positive control). Scoring for cumulative irritation was performed every 24 h. Cumulative applications of the moistened 73-8050 powder caused dermal effects that ranged from no irritation to erythema and papules. Superficial layer effects ranged from none to glazing with peeling and cracking. A cumulative irritation score of 177 was reported for the moistened powder. Milder dermal reactions were observed after application of the 50% w/v slurry of the test material (cumulative irritation score = 50.6). Both test materials were classified as probable mild irritants under normal use conditions.

A RIPT on a cleanser containing 10 wt% sodium hydrolyzed potato starch dodecenylsuccinate was perfomed using 227 subjects (18 to 69 years old; 165 females, 62 males).[164] During induction, an occlusive patch containing ~ 0.2 g of the test material was applied to the back (area of application site not stated) for 24 h, and a total of 9 induction patch applications was made to each subject during the 3-week induction period. The challenge phase was initiated after a 2-week non-treatment period. An occlusive challenge patch containing the test material (~ 0.2 g) was applied for 24 h to a new site on the back. Reactions were scored for up to 96 h after patch application. Four subjects had low-level (±) reactions during induction, and 2 subjects had ± reactions during the challenge phase. It was concluded that the cleanser did not induce sensitization.

Unknown Structural Configuration

Algae Exopolysaccharides

The skin irritation and sensitization potential of a 1% solution of algae exopolysaccharides was evaluated using 50 human subjects. [165] An occlusive patch containing the test substance (0.2 ml or 0.2 g) was applied for 24 h to the infrascapular region of the back (to the right or left of midline) of each subject. The dose per cm^2 was not stated. This procedure was repeated for a total of 9 consecutive induction applications during 3 consecutive weeks. Following a 10- to 14-day non-treatment period, a challenge dose of the test substance was applied once to a new test site. The challenge dose was equivalent to any one of the original 9 induction applications. Reactions were scored at 24 h to 48 h after patch application. There was no evidence of adverse reactions in any of the subjects during the study, and it was concluded that 1% algae polysaccharides was a non-primary irritant and non-primary sensitizer.

In Vitro

Branched - Modified

Hydroxypropyltrimonium Hydrolyzed Corn Starch

The skin irritation potential of hydroxypropyltrimonium hydrolyzed corn starch (undiluted) was evaluated using the MatTek Corporation EpiDerm™ skin model *in vitro* toxicity testing system.[166] This 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. The 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 the reduction of the tetrazolium salt. The undiluted test substance (100 µl) was added to millicells containing the EpiDerm™ samples, and the time at which the % viability would be 50% (ET_{50}) was estimated. The test substance was classified as mildly irritating (ET_{50} = 18.1h).

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.[167] 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.

Respiratory 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:[168]

- 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)
- Copper (0.08 mg)

Prior to initiation of the following study, a sensory irritation study on konjac flour (primary polysaccharide component is glucomannan) was performed using ND4 Swiss Webster mice (number not stated).[169] 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.[169] 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.[169]

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.[170]

Clinical Trials

Linear Polysaccharides and Salts Thereof

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.[171] 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 Salts Thereof

Calcium Alginate

A 50-year-old woman was referred for treatment after the discovery of adenoid cystic carcinoma in an excised left submandibular gland.[172] 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.[173] 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.[174] 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:[175] 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.

Allergenicity/Immune System Effects

Non-Human

Linear Polysaccharides and Salts Thereof

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.[176] Pretreatment (intraperitoneal [i.p.] injection) with ANK-102 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).[177] 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).[84] 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.).[178] 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.[148] 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 Salts Thereof

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.[179] 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.

Cytotoxicity

Calcium Alginate

Linear Polysaccharides and Salts Thereof

In a cytotoxicity assay, calcium alginate fibers were introduced into human embryonic kidney cells and human fibroblasts.[180] These cells were in their exponential growth phase, and were incubated for 48 h. Calcium alginate fibers were not cytotoxic.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity data on polysaccharide gums are summarized in Table 5. 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 6. 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/HYPERPLASIA

Linear Polysaccharides and Salts Thereof

Agar

The carcinogenicity of agar, isolated from Pterocladia and used as a gelling agent in foods and pharmaceuticals, was evaluated using groups of 50 F344 rats and 50 B6C3F_1 mice of either sex.[181] The animals were fed diets containing 25,000 ppm or 50,000 ppm agar for 103 weeks. Groups of untreated mice and rats served as controls. No test substance-related effects on survival, feed consumption, or clinical signs of toxicity were observed. When compared to controls, an increased incidence of adrenal cortical adenomas (not statistically significant) was reported for female rats fed 50,000 ppm agar in the diet. In male mice, the incidence of hepatocellular adenomas in the 50,000 ppm group was significantly increased ($p = 0.007$) when compared to the control group. However, the incidence of total liver tumors did not differ statistically among

the control, 25,000 ppm and 50,000 ppm groups. The increased incidences of adrenal cortical adenomas and liver tumors were not considered test substance-related. It was concluded that the agar isolated from Pterocladia was not carcinogenic in F344 rats or $B6C3F_1$ mice.

Algin

A chronic feeding study of sodium alginate (also known as algin) and starch acetate (a chemically modified potato starch) was performed.[131] Two groups of mice (75 males and 75 females per test substance) were fed sodium alginate and starch acetate in the diet, respectively, for 89 weeks. At week 87, half of the surviving male and female mice in each test group were placed on control diet (containing 55% pregelatinized potato starch). The dietary levels of the test substances were gradually increased until the diet contained (by weight) 55% starch acetate or 25% sodium alginate. The study did not find any evidence of carcinogenicity of dietary sodium alginate or starch acetate exposure.

Carrageenan

Groups of 16 Fischer 344 rats were fed a basal diet supplemented with 5% ι-carrageenan for up to 91 days in a study evaluating the proliferative response of the colonic epithelium to ι-carrageenan.[182] Proliferating cell nuclear antigen (PCNA) served as a marker of cell proliferation. Immunohistochemical staining for PCNA-positive cells in the distal colon was performed. Rats fed carrageenan for 91 days had an intact layer of epithelial cells lining the mucosa. The epithelial layer was composed of increased numbers of goblet cells. Few resident leukocytes were present in the lamina propria or submucosa. There was no evidence of alterations in the muscular layers (tunica muscularis) of the colon. An 8-fold increase in the number of labeled cells in the upper third of the crypt was reported. PCNA-positive cells were not found at the luminal surface. Rats fed the control diet for 91 days had an intact layer of columnar epithelial cells lining the mucosa. The lamina propria and submucosa had few resident lymphocytes and macrophages.

A second experiment (dose-response experiment) evaluating the proliferative response of the colonic epithelium to ι-carrageenan involved groups of 4 F344 rats. Thymidine kinase enzymatic activity and PCNA served as markers of cell proliferation. Immunohistochemical staining for PCNA-positive cells in the distal colon was performed. The groups were fed ι-carrageenan in the diet at concentrations of 0.5%, 1.5%, and 5% for 28 days. Another group was fed control diet. There was no increase in PCNA-positive cells in the upper third of the crypt. Increased thymidine kinase levels were observed only in the 5% ι-carrageenan dietary group, which corresponded to a 4-fold increase in colonic cell proliferation resulted. In a third experiment in which F344 rats were fed ι-carrageenan in the diet for 64 days, followed by a 28-day recovery period, proliferating cells returned to a location and level similar to those in rats fed the control diet during the 28-day recovery period. The authors noted that the results suggest that the quantitative changes in cell proliferation were probably adaptive, and would not contribute to an increased risk of colon neoplasia.[182]

In another study, groups of 5 male and 5 female mice of two strains were administered carrageean at concentrations of 0, 0.1, 5, 15, and 25% in the diet for their lifespan, without evidence of adverse effects or carcinogenicity.[183] Likewise, 0, 1, 5, 15, and 25% carrageenan was administered in the diet, for up to 24 months, to groups of 5 male and 5 female rats of two strains without evidence of carcinogenicity or other adverse effects, except for the suggestion of hepatic sclerosis at the 25% concentration.

A long-term carcinogenicity study on κ-carrageenan (from *C. crispus*) was performed using rats and hamsters.[184] Seven-week-old MRC outbred rats and randomly bred Syrian golden hamsters from the Eppley colony were fed *kappa* carrageenan at concentrations of 0.5, 2.5, and 5% in the diet. The average daily intake of carrageenan at the highest dose in rats was estimated to be 4022 mg/kg/day and, in hamsters, the estimate was 3719 mg/kg/day. Each dose group consisted of 30 females and 30 males of each species. Untreated controls received the same pelleted diet without added carrageenan, and there were 100 females and 100 males in each control group. These diets were administered for the lifetime of the animals, approximately 150 weeks for rats and 110 weeks for hamsters. There was no evidence of increased mortality, weight gain, clinical signs of toxicity, or incidences of gross or microscopic lesions, including tumors. The only abnormality found was occasional soft stool consistency in some of the animals, particularly during the initial phase of the experiment. There was no increased incidence of erosion or ulcerations of the gastrointestinal tract mucosa.

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.[19] IARC also concluded that experiments in rats with doses of degraded carrageenan comparable to those used to test native carrageenan provide sufficient evidence for the carcinogenicity of degraded carrageenan in rats, and noted that no human data were available. Both native carrageenan and degraded carrageenan are defined in the Chemistry section.

Carrageenan (Degraded)

A series of experiments with degraded carrageenan (from *Eucheuma spinosum*; degraded by acid hydrolysis) was performed using male and female Sprague-Dawley rats. [19,185,186] In one experiment, four groups of 30 males and 30 females were fed a diet containing 0 (control), 1 %, 5 %, or 10% degraded carrageenan. Animals in each group were killed at 6, 12, 18 and 24 months. Colorectal squamous metaplasia occurred 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) were 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) were also found in 12 of 60 rats fed 5% degraded carrageenan. Neither squamous metaplasia nor colorectal tumors were observed in the low-dose group or in controls.

In the second experiment, degraded carrageenan (5% in drinking water) was administered to 20 male and 20 female rats for 15 months. Colorectal squamous metaplasia was observed in all rats after 15 months. Colorectal tumors were observed in 11 of 40 treated rats (4 squamous-cell carcinomas, 4 adenocarcinomas, 3 adenomas and 1 myosarcoma); these tumors were not observed in control rats (15 males, 15 females). In the third experiment, degraded carrageenan (1 or 5 g/kg body weight) was 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) were dosed intragastrically with distilled water. Squamous colorectal metaplasia was observed in all 29 rats in the high-dose group and in 11 of 30 rats in the low-dose group. Colorectal tumors were observed only in the high-dose group (8 of 29 rats; 5 adenocarcinomas and 4 adenomas).[19,185,186]

Fischer 344 rats were maintained on a diet containing 10% degraded carrageenan (degraded by acid hydrolysis; also contained 30% sulfate).[19,187] Three groups were fed this diet for 2 months (39 rats, group 1), 6 months (42 rats, group 2), and 9 months (42 rats, group 3). The control group (46 rats) received the same diet without carrageenan, and the same was true for all other groups after cessation of carrageenan feeding. None of the animals died during the study, and all were killed after 18 months of feeding. A 100% incidence of colorectal squamous metaplasia was observed in all treatment groups. Tumors were 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 were not observed in control rats.

Inulin

Groups of 10 to 15 Min/+ mice were fed a control diet or an inulin-enriched diet (10% w/w) from the ages of 5 weeks to 8 or 15 weeks.[188] This animal model of colon cancer, multiple intestinal neoplasia in the Min/+ mouse, has a heterozygous mutation in the *Apc* gene, resulting in the truncated Apc protein and development of numerous intestinal adenomas.[189,190] Animals were killed at 8 or 15 weeks of age. Additionally, the wild-type littermates were fed the same diets until the age of 8 weeks, to determine whether similar changes occur in wild-type and Min/+ mice. The mucosa without adenomas was collected and fractionated to produce nuclear, cytosolic, and membrane pools. The levels of β-catenin, cyclin D1 and E-cadherin were determined by Western blotting at 8 and 15 weeks, and immunohistochemical staining was done for 8- week-old mice. The promotion of adenoma growth by inulin (week 15: 1.3-fold increase [$p = 0.0004$]) was associated with accumulation of cytosolic and nuclear β-catenin, and increased amounts of cytosolic cyclin D1 (1.5-fold increase, $p = .003$) in the normal-appearing mucosa of the Min/+ mice. Furthermore, inulin feeding reduced the membranous pools of β-catenin and E-cadherin. Also, in the wild-type mice, the decrease in membranous β-catenin was clear ($p = 0.015$), and a subset of crypts had enhanced nuclear β-catenin staining. These data indicate that dietary inulin can activate the normal-appearing mucosa β-catenin signaling, which, in the presence of Apc mutation, induces adenoma growth.

Branched Natural/Unmodified

Pectin

The effects of pectin on the morphological parameters of the small intestine were investigated.[191] Male Wistar rats (groups of 4) were fed an elemental diet containing 2.5% pectin for 14 days. Pectin feeding induced a statistically significant increase in the villus height and crypt depth, indicating that feeding with pectin caused mucosal hyperplasia in the small intestine.

Starch Acetate

Results for starch acetate are included in the chronic feeding study on algin, summarized earlier in this section .[131]

Cyclic

Cyclodextrin

The carcinogenicity of β-cyclodextrin was examined using Fischer 344 (F344) rats. Groups of 50 males and 50 females were given the compound in their diets at concentrations of 0 (control), 2.5%, or 5% for 104 weeks.[39] Surviving rats were then given a basal diet for an additional 5 weeks. The animals were killed at 109 weeks. Dose-dependent inhibitory effects of β-cyclodextrin on growth were observed in both sexes of the treated groups. There were no significant differences in mean survival times between control and treatment groups. A variety of tumors developed in all groups, including the control group, but all of the neoplastic lesions were histologically similar to those known to occur spontaneously in this strain of rat, and no statistically significant increase in the incidence of any tumor was 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.

Fifty Fischer 344 rats and 52 CD-1 outbred mice of each sex were assigned, respectively, to 4 treatment groups and one control group in carcinogenicity studies.[192] The four groups received β-cyclodextrin in the diet at doses of 25, 75, 225, and 675 mg/kg per day, respectively. Another group of rats or mice received a control diet. Termination of the rat oncogenicity study occurred at week 122 (males) and between weeks 129 and 130 (females). The mouse study was terminated at week 93 (males) and between weeks 104 and 105 (females). Chronic feeding of β-cyclodextrin to Fischer 344 rats and CD-1 mice did not cause any treatment-related carcinogenic effects. The only toxic effect reported was observed in mice, and was described as macroscopic distension of the large intestine. This finding was histologically associated with mucosa (covered by mucous secretion containing exfoliated cells), mucosal flattening, and intestinal gland atrophy. However, there were no differences between control and treated groups in mortality, clinical observations, or body weight and food consumption.

Co-carcinogenicity

Linear Polysaccharides and Salts Thereof

Carrageenan

The co-carcinogenicity of undegraded (native) carrageenan in the presence of azoxymethane (AOM) or *N*-nitrosomethylurea (NMU) in weanling female Fischer 344 rats was evaluated.[193] The treatment groups were as follows: 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). At 7 weeks of age, rats were dosed with AOM or NMU; animals were killed 40 weeks after the initial injection of AOM or 30 weeks after the initial injection of NMU. The following data indicate that 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%).

Branched Natural/Unmodified

Pectin

The effect of low-methoxylated pectin and high-methoxylated pectin on 1,3-dimethylhydrazine initiation of colon cancer was investigated using groups of 30 Sprague-Dawley rats.[194] Two groups were fed a basic diet containing 5% low-methoxylated pectin and high-methoxylated pectin, respectively. The control group was fed the basic diet only. The diets were fed during the entire initiation period as follows: the 4 weeks of acclimation, the 12-week period of 1,2-dimethylhydrazine (DMH) injections, and for another 2 weeks. During the last 10 weeks (promotion period), the rats were given standard rat pellets *ad libitum*. Both kinds of pectin increased the multiplicity of colon tumors.

Tumor Promotion

Linear Polysaccharides and Salts Thereof

Carrageenan

Initiation and promotion of cancer were assessed using the aberrant crypt focus (ACF) assay.[195] In the initiation experiment, 24 rats were randomly allocated to 3 groups: 9 rats were given carrageenan (as a 10% jelly, replacing water for eight days), 9 rats were given pure water (negative controls), and 6 rats received an AOM injection (5 mg/kg i.p., positive controls). The animals were killed 1 month later. In the promotion experiment, 30 rats received a single AOM injection (20 mg/kg i.p.) to initiate colon cancer. They were randomly allocated 7 days later to three groups of 10 rats. A control group was given pure water. Two other groups were given water supplemented with 0.25% (liquid) or 2.5% carrageenan (solid gel) for 100 days. Initiation was assessed by the number of ACF at 30 days. Promotion was assessed by the multiplicity of ACF at 100 days, i.e. the mean number of crypts/ACF.

No ACF was found in any of the negative controls or in carrageenan-fed rats (ingested dose: 27.4 g/day/ kg body weight for 8 days). A mean number of 6 ACF was found in positive controls given AOM. No ulceration was detected by macroscopic examination of the colon. The administration of liquid 0.25% carrageenan reduced the number of ACF/rat, and did not change the ACF multiplicity when compared to controls. In contrast, the administration of carrageenan jelly (2.5%) for 100 days promoted the growth of aberrant crypt foci ($P = 0.016$). Thus, carrageenan jelly did not initiate colon tumors. However, the long-term administration of carrageenan jelly enhanced intestinal tumor growth in rats.[195]

The initiation and promotion effects of κ-carrageenan were studied using 54 conventional female Fischer 344 (F-344) rats (harboring a normal rat flora) and 52 germ-free female F-344 rats maintained in isolators.[196] The intiating effect of κ-carrageenan was studied by comparing the number ACF in the colon of rats given pure water or κ-carrageenan (as a 10% gel in tap water) for 8 days. The promoting effect of κ-carrageenan was studied by comparing the 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. Study results indicated that κ-carrageenan 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 ($p < 0.02$). The 0.25% κ-carrageenan gel did not promote ACF.

A second study was performed using 20 human flora-associated (HFA) rats. The rats, maintained in a single isolator, were randomized to 3 groups and treated according to the preceding test procedure. Eight HFA rats were given κ-carrageenan and an additional 8 rats were given water. Four rats received an AOM injection. Administration of the 2.5% κ-carrageenan gel to HFA rats did not produce a promotion effect as follows: $2.81 \pm 0.1$and 2.78 ± 0.38 crypts/ACF in control and treated rats, respectively ($p = 0.80$). It was noted that the specific microflora of rats, but not the human gut flora, might be involved in colon tumor enhancement by κ-carrageenan.[196]

The modifying effects of carrageenan administration on colon carcinogenesis were investigated using male F344/DuCrj rats.[197] The animals were allocated to 8 groups (18 rats for groups 1 to 5; 6 rats for groups 6 to 8). Rats in groups 1 to 5 were injected s.c. with DMH (in saline; dose = 20 mg/kg body weight 4 times per week) as an initiator. Beginning at 4 weeks later, the rats were administered diet containing carrageenan at dietary levels of 0 (control), 1.25%, 2.5%, and 5.0%, or 0.2% cholic acid (reference group) for 32 weeks. Animals in groups 6 to 89 received saline and were then treated with 0% and 5.0% carrageenan or 0.2% cholic acid. All survivors were killed and examined for preneoplastic and neoplastic lesion development in the colon at week 36. No treatment-related changes in clinical signs and body weights were found. Detailed histopathological examination did not demonstrate any carrageenan-induced enhancement of carcinogenesis with respect to the incidence of lesions in the colon. These results demonstrate that carrageenan did not possess any promoting activity for colorectal carcinogenesis at the highest dietary level of 5.0%.

Antitumor Activity

Branched Natural/Unmodified

Arabinoxylan

The antitumor activity of wheat bran arabinoxylan was investigated using groups of 10 ICR male mice.[198] The 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. All three doses of arabinoxylan (100, 200, and 400 mg/kg body weight) 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. Treatment with the positive control, cyclophosphamide, conferred the highest inhibitory rate (78.4%) on S180 sarcomas transplanted in mice ($p < 0.01$). Dosing with arabinoxylan also remarkably promoted thymus and spleen indexes, splenocyte proliferation, natural killer cell and macrophage phagocytosis activity, interleukin 2 production, and delayed-type hypersensitivity reaction. Additionally, it increased peripheral leukocyte count and bone-marrow cellularity in tumor-bearing mice. Arabinoxylan did not have any effect on the growth of K562 and HL-60 cells *in vitro*. The authors stated that arabinoxylan can be considered to be an antitumor agent with immunomodulatory activity.

Anticarcinogenicity

Linear Polysaccharides and Salts Thereof

Inulin

Thirty Sprague-Dawley rats (4 months old) were experimentally treated s.c. with the procarcinogen, DMH to induce colon cancer.[199] The rats were randomly assigned to the following 3 groups: control group, group treated s.c.with DMH, and a group given DMH and inulin in the diet. The effects of inulin on the activities of bacterial glycolytic enzymes, short-chain fatty acids, coliform and lactobacilli counts, cytokine levels, and cyclooxygenase-2 (COX-2) and transcription nuclear factor kappa beta (NFκB) immunoreactivity were measured. Inulin significantly decreased coliform counts ($p <0.01$), increased lactobacilli counts ($p < 0.001$), and decreased the activity of β-glucuronidase ($p < 0.01$). Butyric acid and propionic acid (both short-chain fatty acids) concentrations were decreased in the DMH only group. Dosing with inulin increased the concentration of inulin that had been reduced by DMH. Also, when compared to the DMH only group, inulin also decreased the numbers of COX-2- and NFκB-positive cells in the *tunica mucosae* and *tela submucosae* of the colon. The expression of IL-2, TNFα, and IL-10 was also diminished. The results of this 28-week study indicated that dietary intake of inulin prevented preneoplastic changes and inflammation that promote colon cancer development.

The effect of inulin (in basal diet) on the growth of intramuscularly transplanted mouse tumors, belonging to 2 tumor lines (TLT and EMT6), was investigated using groups of 20 to 22 young Balb/c mice.[200] Inulin (15 g) was added to the basal diet (85 g) fed for 7 days prior to tumor implantation. After tumor transplantation, the basal or experimental diet was consumed up to the end of the experiment (day 46 after tumor implantation). The results were evaluated by tumor measurements, using a vernier caliper. The mean tumor surface in the experimental groups was compared with that in animals of the control group fed the basal diet. The growth of both tumor lines was significantly inhibited by supplementing the diet with inulin.

Branched Natural/Unmodified

Arabinoxylan

Two types of preneoplastic lesions (ACF and mucin-depleted foci [MDF]) were detected in the colon of 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) (15 rats in each group).[201] Thirteen weeks after DMH treatment, MDF counts were significantly lower in the 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 [$p = 0.05$]). Although the number of ACF in the entire colon was not significantly different between control and arabinoxylan-oligosaccharides fed rats, 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.

Glucomannan

A diet containing konjac mannan (a.k.a. glucomannan) was evaluated for its effects on the incidence of spontaneous liver tumors in C3H/He mice; these tumors generally occur in 60-70% of 1-year-old mice of this strain. At 7 weeks of age, groups of 30 male mice were fed either a powdered commercial diet (control group) or the same diet, to which 10% glucomannan had been added. At 1 year of age, all animals were necropsied and the number and size of liver tumor nodules were determined. There was a slight decrease in the number of animals with liver tumors in the konjac flour 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; glucomannan: 0.5). However, mean tumor size was not

altered. Weight gain in the 10% glucomannan dietary group was lower ($p<0.05$) than that in the control dietary group throughout the experiment, but there was no change in total feed intake between the control and glucomannan-treated mice. While feed efficiency was decreased in glucomannan-treated mice when compared to controls (control: 2.9%; konjac flour: 2.3%), the decrease was not statistically significant. In this study, spontaneous liver tumors in C3H/He mice were inhibited by maintaining the mice on a diet containing 10% glucomannan, although animals maintained on this diet consumed approximately 10% fewer calories per day when compared to control animals.[202]

In another study, the effect of a diet containing 5% konjac mannan (glucomannan) on the incidence of colon tumors induced by DMH in rats was studied.[203] Five-week old male Fisher 344 rats (20/group) were fed either a commercial diet (414 kcal/100 g) or a similar diet containing 5% glucomannan. At 6 weeks of age, and weekly thereafter for a total of 13 weeks, all rats were injected i.p. with 20 mg DMH/kg body weight. Feed consumption was measured weekly for 20 weeks (duration of the study was approximately 27 weeks). Rats were necropsied 13 weeks after the last injection of DMH; the intestine (small and large) and other organs (unspecified) were examined grossly and microscopically for the numbers and types of tumors. Throughout the study, body weights of glucomannan-fed rats were significantly lower than those of rats fed the control diet; however, there was no significant difference in feed efficiency between glucomannan-fed and control rats. The incidence of DMH-induced colon tumors was significantly lower in the glucomannan-fed group (39%) when compared to the control group (75%). The number of colon adenocarcinomas per rat was also significantly lower in glucomannan-fed rats (0.22) than in control rats (0.75). However, the mean diameter of colon tumors was not significantly different in the two groups of rats (glucomannan-fed rats: 5.8 ± 1.3 mm; control rats: 6.9 ± 3.6 mm).

In contrast to the effects reported for colon tumors, dietary glucomannan had no significant effect on the incidence of tumors of the small intestine, all of which were adenocarcinomas in this study (control: 45%; glucomannan: 33%); mean diameters of adenocarcinomas of the small intestine were not significantly different in the two groups (control: 8 ± 4 mm; konjac flour: 6 ± 2 mm). Dietary glucomannan did not appear to have a significant effect on the incidences of ear duct or pancreatic tumors in rats in this study.[203]

Epidemiology

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.[204] 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.[204]

OTHER EFFECTS

Endocrine Function and Vitamin D Absorption

Branched Natural/Unmodified

Glucomannan

The effect of glucomannan on the absorption of vitamin D was measured in a double-blind trial on the efficacy of konjac flour (identified as glucomannan) in the treatment of pediatric obesity.[205] 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 a-lipoprotein and increased pre-b-lipoprotein and triglyceride. Serum vitamin D levels were similar in the two groups at the beginning and end of the study.

Antifungal Activity

Linear Polysaccharides and Salts Thereof

Calcium Alginate

The antifungal properties of calcium alginate fiber were studied using *Candida albicans*.[180] 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.

Inflammation

Linear Polysaccharides and Salts Thereof

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).[206] 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 Salts Thereof

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.[207] 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 each naturally derived materials that comprise polysaccharides obtained from plants or algae. As a group they comprise polymers of simple saccharide monomers. 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, 55 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 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 DDDSA-modified starch (considered structurally similar to sodium hydrolyzed potato starch dodecdenylsuccinate 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 DDDSA-modified starch (considered structurally similar to sodium hydrolyzed potato starch dodecdenylsuccinate 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 DDDSA-modified starch (considered structurally similar to sodium hydrolyzed potato starch dodecdenylsuccinate 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% DDDSA-modified starch (considered structurally similar to sodium hydrolyzed potato starch dodecdenylsuccinate and corn-starch modified) was not a sensitizer in guinea pigs. ι-Carrageenan and konjac flour (glucomannan is primary polysaccharide component) 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 a modified starch (considered structurally similar to sodium hydrolyzed potato starch dodecdenylsuccinate 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 inconsistent effects on reproduction and development, with no relationship to dose.

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, DDDSA-modified starch (considered structurally similar to sodium hydrolyzed potato starch dodecdenylsuccinate and corn-starch modified), and a sodium hydrolyzed potato starch dodecdenylsuccinate trad name material (PS-111 Hydrophobically Modified Starch Powder) . 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.

DRAFT DISCUSSION

The polysaccharide gums comprise polysaccharides obtained from plants or algae. Their substantial molecular sizes suggest that skin penetration of these ingredients 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. 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 are unified as each being polymeric materials from simple saccharide monomers. 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 either equivocal or they 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. However, the Panel was informed by industry that degraded carrageenan is manufactured in the laboratory by acid hydrolysis of a certain type of seaweed, is not available commercially, and, thus, is not a cosmetic ingredient. 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. With this in mind, the Panel determined that method of manufacture and impurities data on the hydrolyzed, modified, and substituted polysaccharide gums 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. 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.

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.

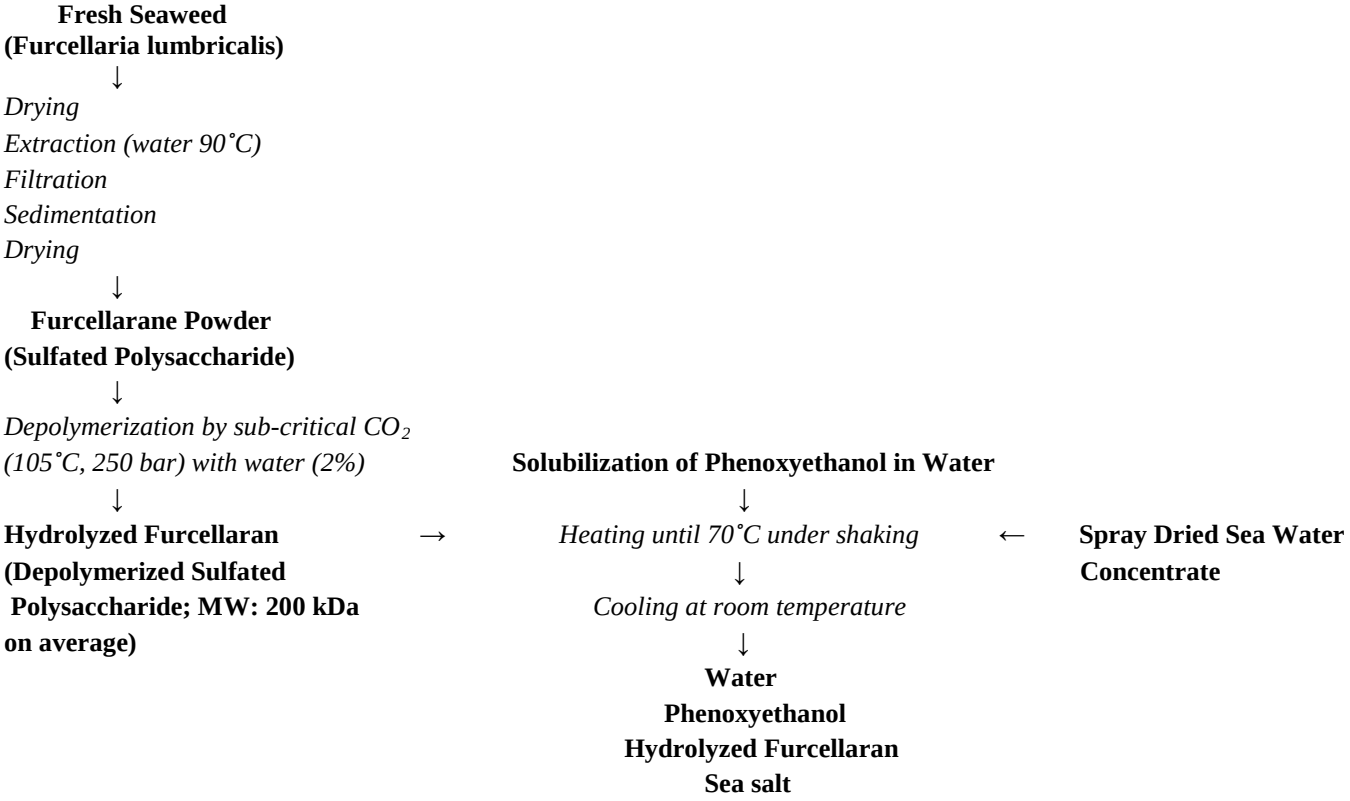


Figure 1. Manufacturing Process for Hydrolyzed Furcellaran.[60]

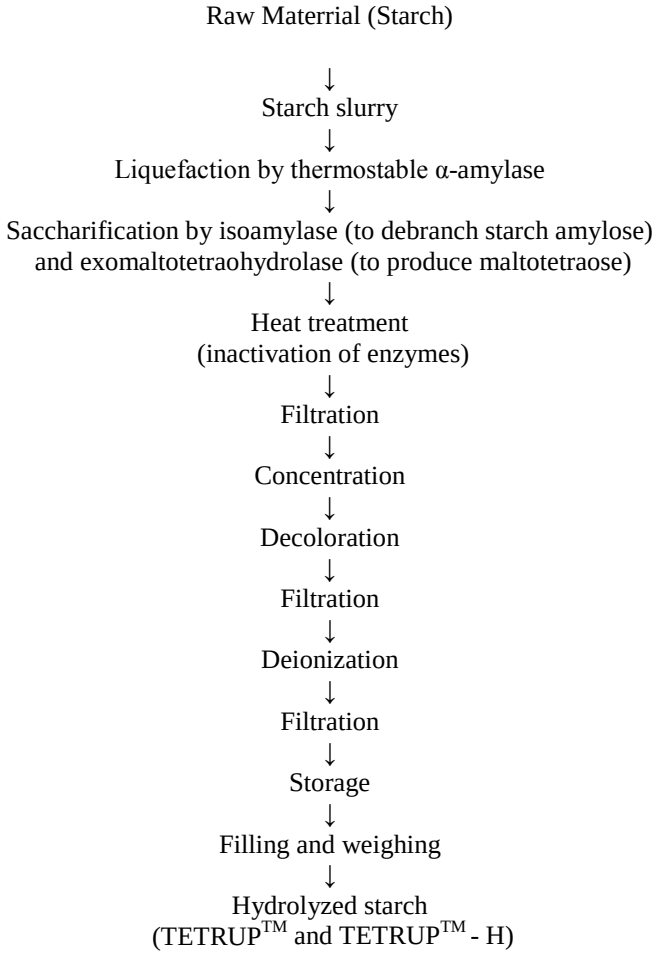
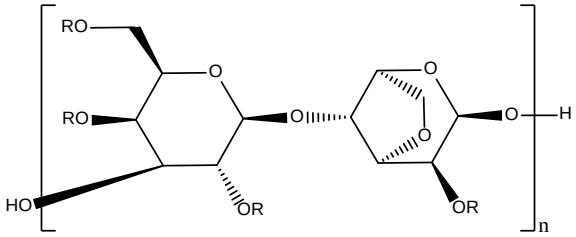
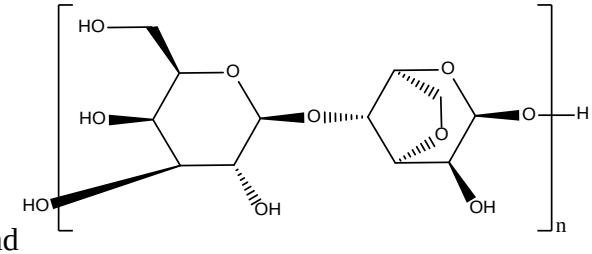
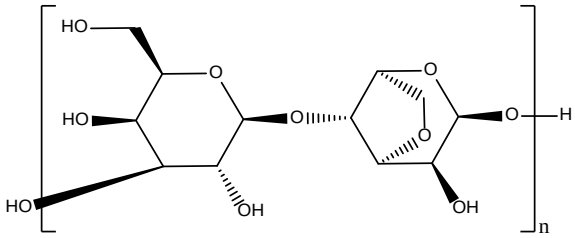
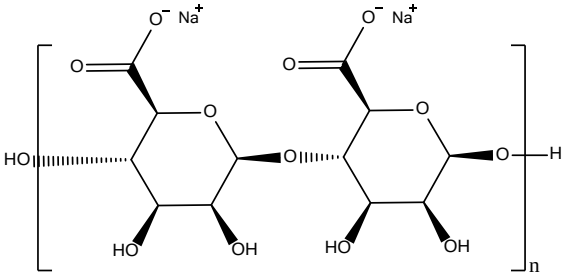
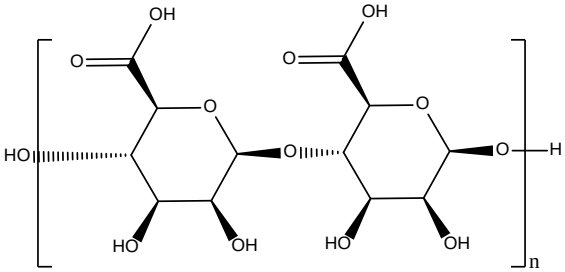
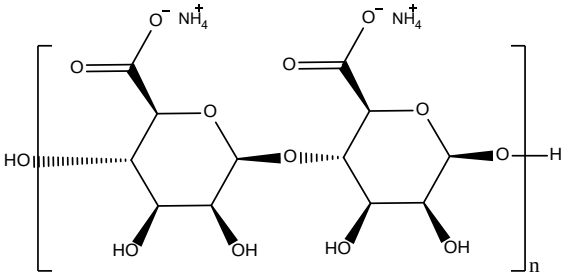
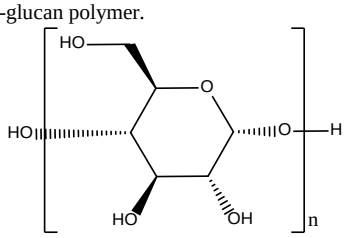
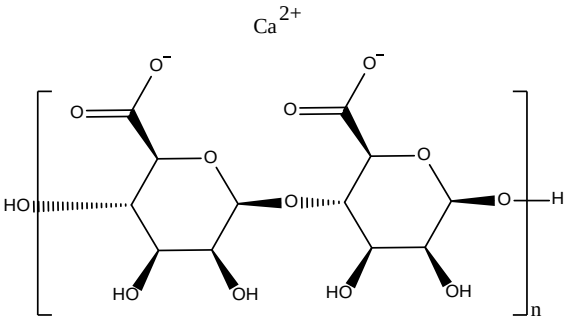
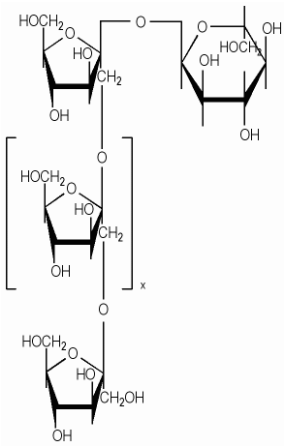
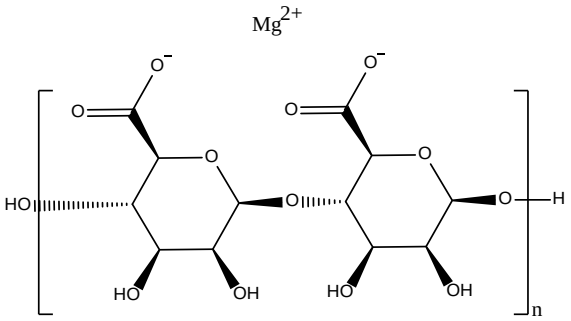
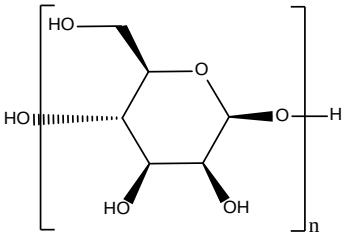
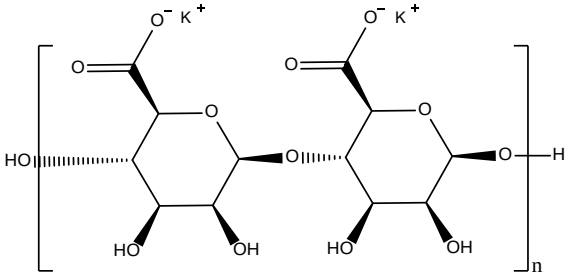
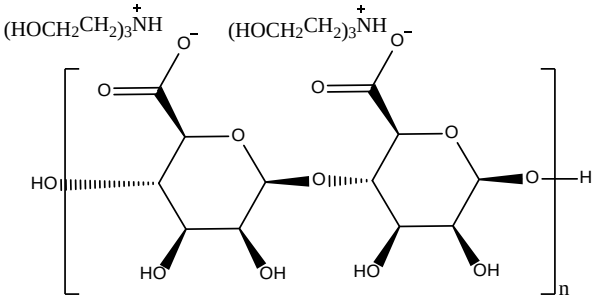


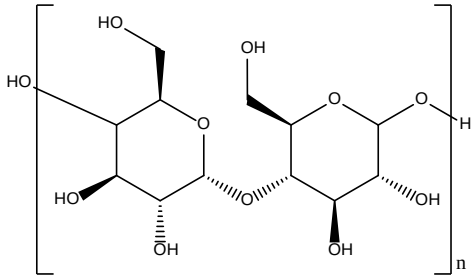
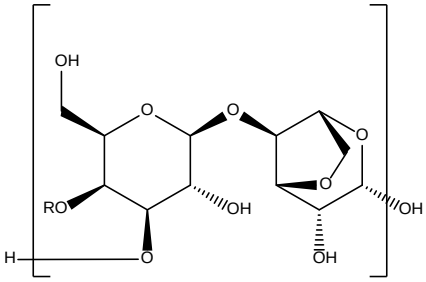
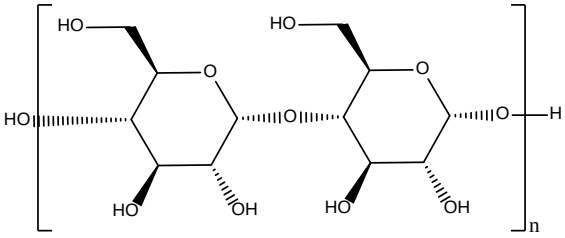
Figure 2. Manufacturing Flow Chart for Hydrolyzed Starch (TETRUP™ and TETRUP™ – H).[75,76]

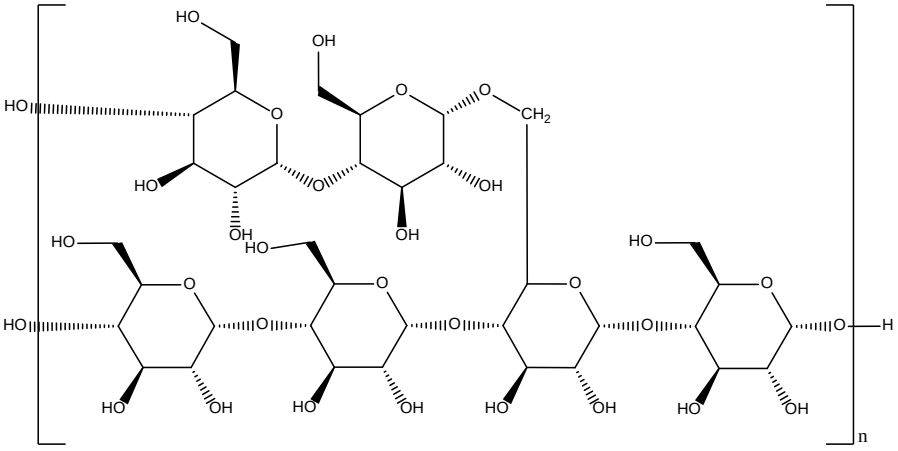
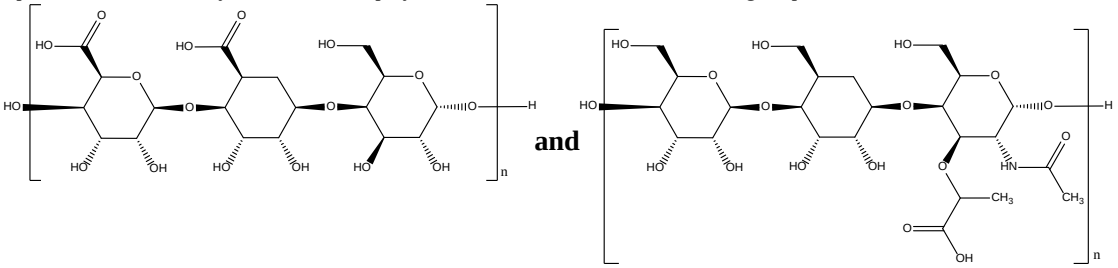
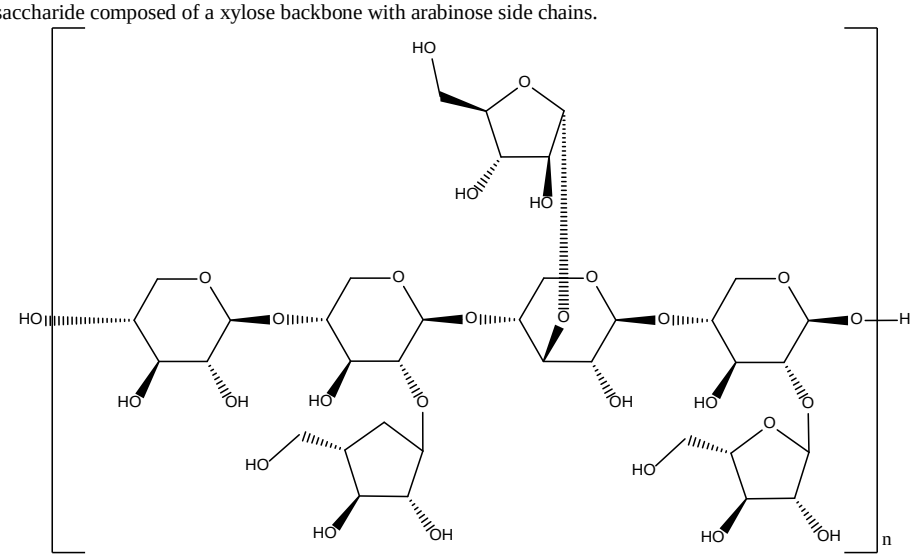
Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Plant Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

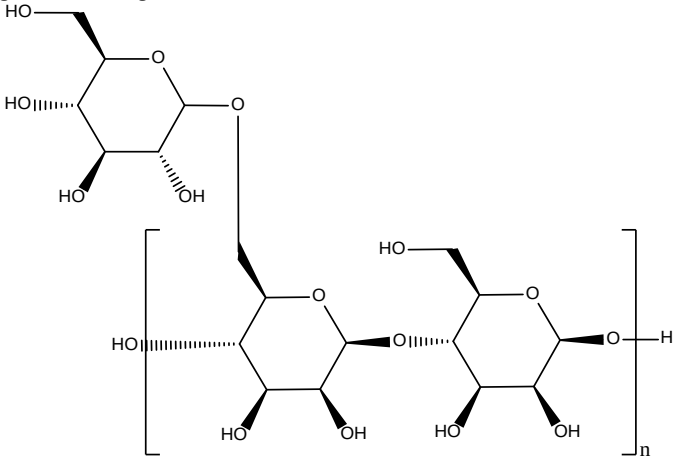
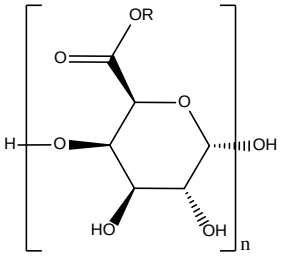
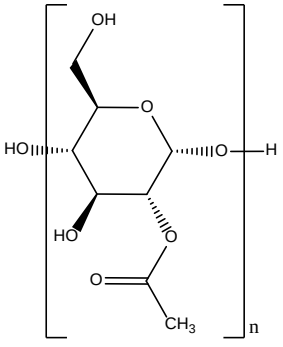
Ingredient CAS No.	Definition	Formula/structure
Linear polysaccahrides and salts thereof		
Agar 9002-18-0	Agar is the dried, hydrophilic, colloidal polygalactoside derived from various Gelidium species or closely related red alga. *Agar is typically a mixture of agarose and agaropectin.*[208]	 and  wherein R is hydrogen, sulfate, or pyruvate
Agarose 9012-36-6	Agarose is the polysaccharide extracted from the red seaweed Gracilaria.	
Algin ~~57606-04-9~~ 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.*	
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.*[209]	

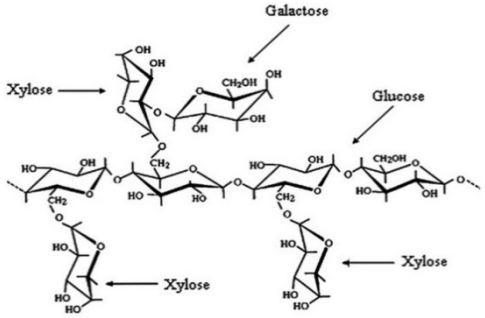
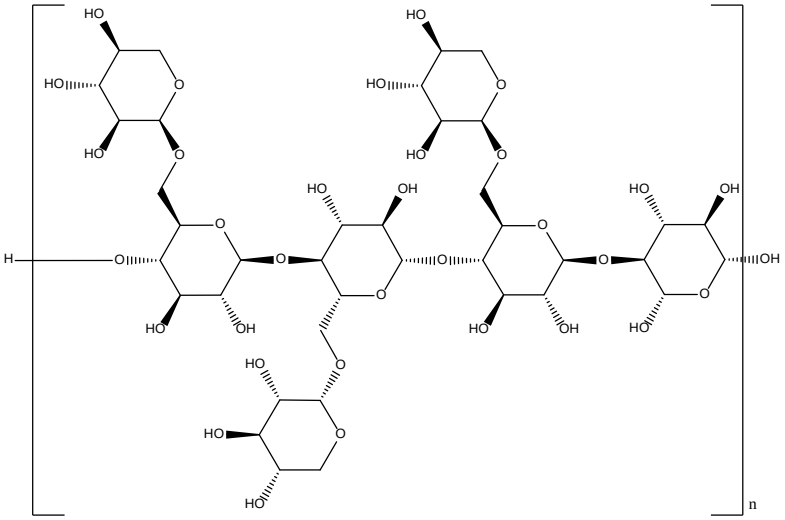
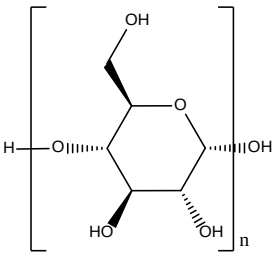
Ingredient CAS No.	Definition	Formula/structure
Ammonium Alginate 9005-34-9	Ammonium Alginate is the ammonium salt of Alginic Acid. *Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.*	
Amylose 9005-82-7	Amylose is the carbohydrate stored by plants that consists of a linear (1→4)-(structure)-D-glucan polymer.	
Astragalus Gummifer Gum	Astragalus Gummifer Gum is a dried resinous exudate obtained from Astragalus gummifer. *is a complex polysaccharide composed of D-galacturonic acid, D-galactose, D-xylose, and L-arabinose, with associated calcium, and potassium cations.*(JACT1987)	
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, *Rodophyceae*.	
Inulin 9005-80-5	Inulin is the polysaccharide that conforms to the formula:	

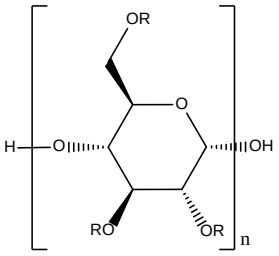
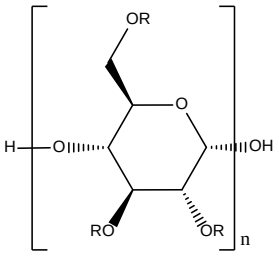
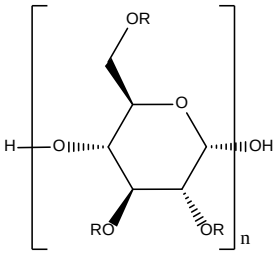
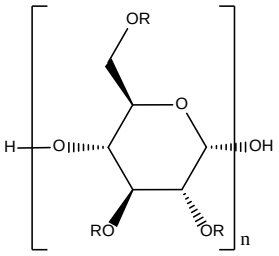
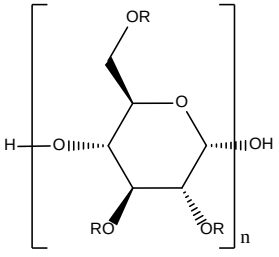
Ingredient CAS No.	Definition	Formula/structure
Magnesium Alginate 37251-44-8	Magnesium Alginate is the magnesium salt of Alginic Acid.	
Mannan 9036-88-8 51395-96-1	Mannan is a natural polysaccharide consisting of a polymer of Mannose.	
Polianthes Tuberosa Polysaccharide	Polianthes Tuberosa Polysaccharide 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.	
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.	
Triticum Vulgare (Wheat) Starch 9005-25-8 (generic)	Triticum Vulgare (Wheat) Starch is a starch obtained from wheat, *Triticum vulgare.*	

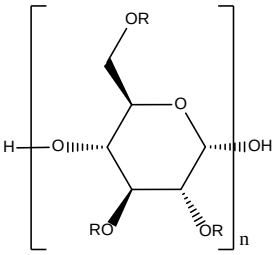
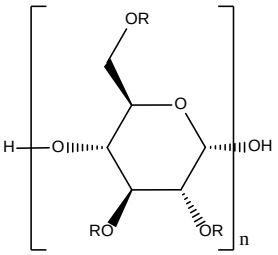
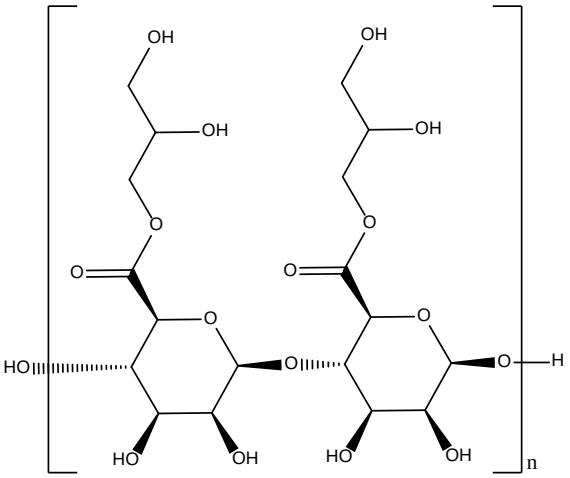
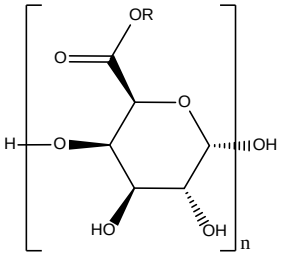
Ingredient CAS No.	Definition	Formula/structure
Linear - modified		
Amylodextrin 9005-84-9	Amylodextrin is the product obtained by treating potato or corn starch with dilute hydrochloric acid.	
Hydrolyzed Carrageenan 53973-98-1	Hydrolyzed Carrageenan is the hydrolysate of Carrageenan derived by acid, 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-sulphate.*	 where R is hydrogen or SO_3
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.*[210] *The term "maltodextrin" can be applied to any starch hydrolysis product that contains fewer than 20 dextrose (glucose) units linked together.*	
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.	

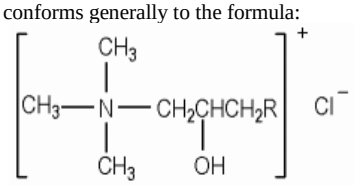
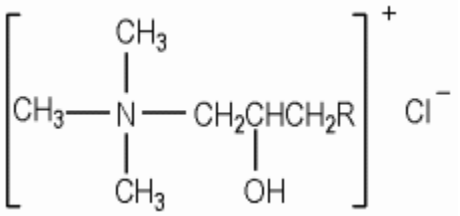
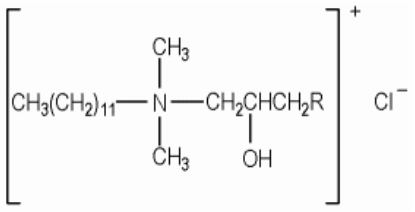
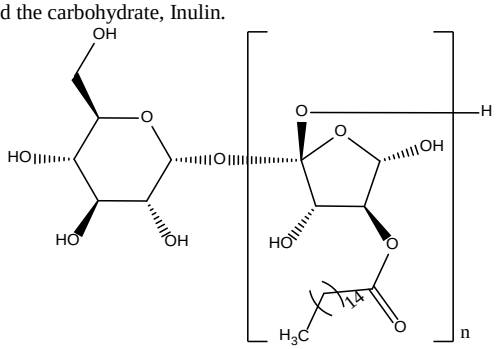
Ingredient CAS No.	Definition	Formula/structure
Branched – natural/unmodified		
Amylopectin 9037-22-3	Amylopectin is the branched chain polysaccharide portion of starch.	
Aphanothece Sacrum Polysaccharide	Aphanothece Sacrum Polysaccharide is the polysaccharide fraction isolated from the alga, Aphanothece sacrum.	
Arabinoxylan 9040-27-1	Arabinoxylan is a polysaccharide composed of a xylose backbone with arabinose side chains.	
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.*	
Ghatti Gum 9000-28-6	Ghatti Gum is the dried, gummy exudate obtained from the stems and bark of *Anogeissus latifolia.*	

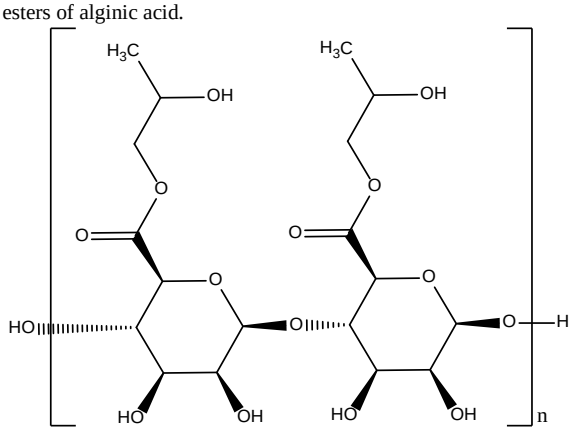
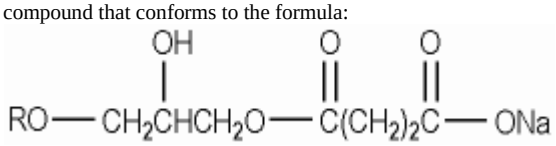
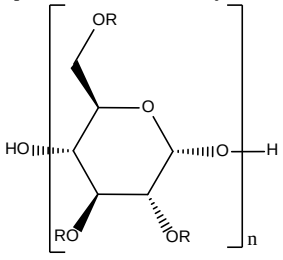
Ingredient CAS No.	Definition	Formula/structure
Glucomannan 37220-17-0 11078-31-2 76081-94-2	Glucomannan is the polymer of mannose containing side chains of glucose.	
Pectin 9000-69-5	Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus 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.*	
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.*	

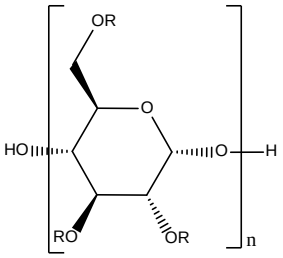
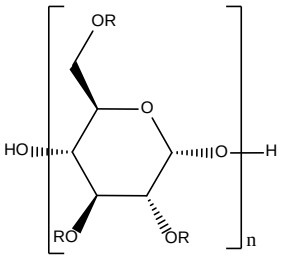
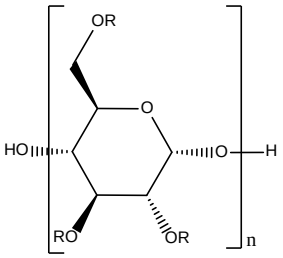
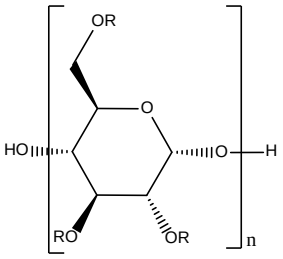
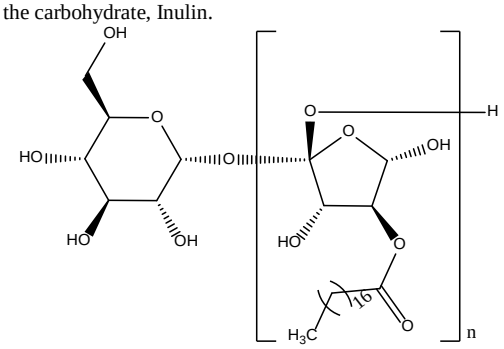
Ingredient CAS No.	Definition	Formula/structure
Tamarindus Indica Seed Gum 39386-78-2	Tamarindus Indica Seed Gum is the gum obtained from the seeds of *Tamarindus indica.*	
Tapioca Starch 9005-25-8	Tapioca Starch is the starch obtained from the roots of *Manihot esculenta.* It consists primarily of amylose and amylopectin.	
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.	
***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.	
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.	

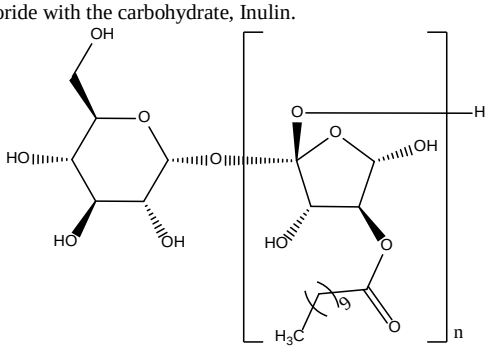
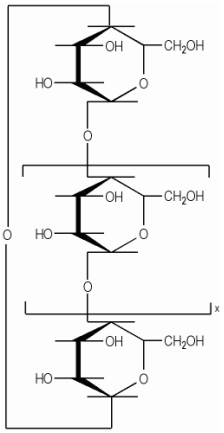
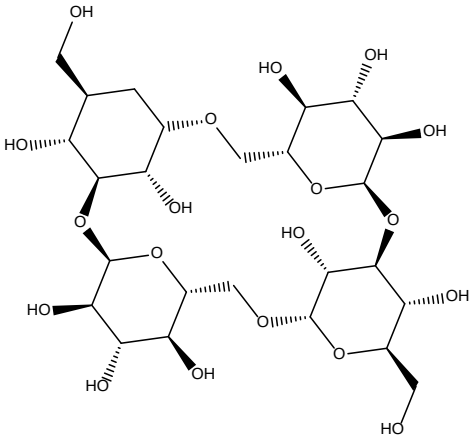
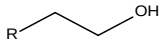
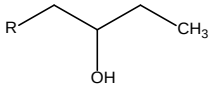
Ingredient CAS No.	Definition	Formula/structure
Dextrin Behenate 112444-74-3	Dextrin Behenate is the ester of Dextrin and Behenic Acid.	 wherein R is the residue of behenic acid
Dextrin Isostearate	Dextrin Isostearate is the ester of Dextrin and Isostearic Acid.	 wherein R is the residue of isostearic 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
Dextrin Palmitate 83271-10-7	Dextrin Palmitate is the palmitic acid ester of Dextrin.	 wherein R is the residue of palmitic acid

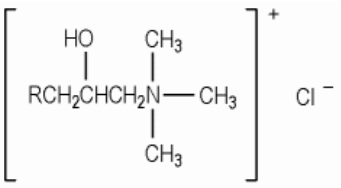
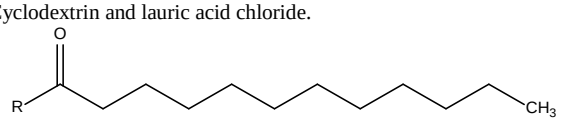
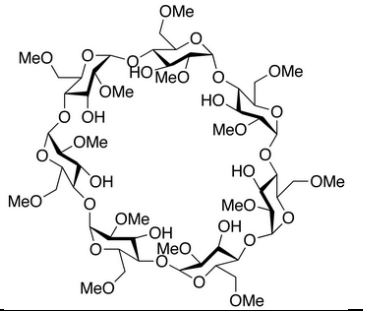
Ingredient CAS No.	Definition	Formula/structure
Dextrin Palmitate/Ethylhexanoate 183387-52-2	Dextrin Palmitate/Ethylhexanoate is the mixed ester of Dextrin with palmitic and ethylhexanoic acids.	 wherein R is the residue of palmitic or ethylhexanoic acid
Dextrin Stearate 37307-33-8	Dextrin Stearate is 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.	
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

Ingredient CAS No.	Definition	Formula/structure
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.
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.	

Ingredient CAS No.	Definition	Formula/structure
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.	
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

Ingredient CAS No.	Definition	Formula/structure
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.	 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
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.	

Ingredient CAS No.	Definition	Formula/structure
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.	
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:	 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.

Ingredient CAS No.	Definition	Formula/structure
Cyclodextrin Hydroxypropyltrimonium Chloride	Cyclodextrin Hydroxypropyltrimonium Chloride is the organic compound that conforms to the formula:	 where R represents the Cyclodextrin polymer.
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 are exopolysaccharides produced and secreted by various species of microalgae of the divisions, Rhodophyta and Chlorophyta.	
Cassia Angustifolia Seed Polysaccharide	Cassia Angustifolia Seed Polysaccharide is the polysaccharide fraction derived from the seed of Cassia angustifolia.	
Echinacin 8001-18-1	Echinacin is a polysaccharide fraction derived from the dried rhizome and roots of *Echinacea pallida*.	
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.	

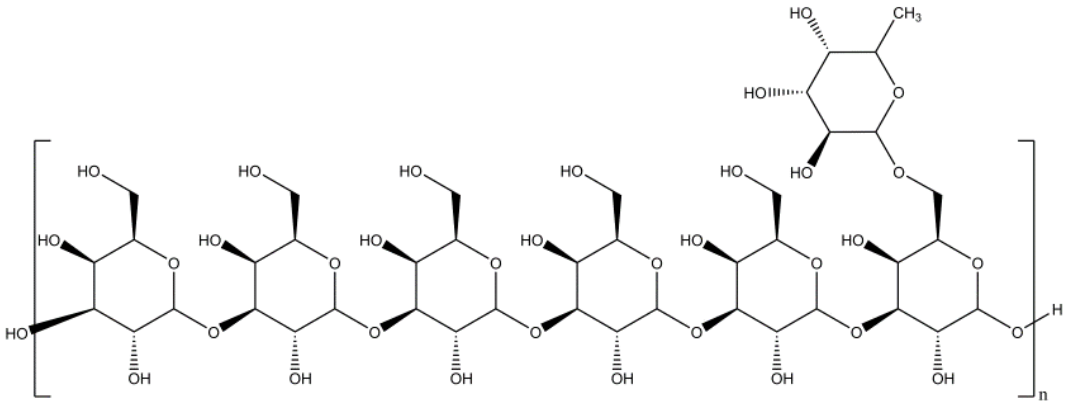


Figure 3. Structure of Galactoarabinan (Branched – Natural/Unmodified).[211]

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

Linear polysaccahrides and salts thereof	
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
Inulin	Skin-Conditioning Agents - Humectant
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
Triticum Vulgare (Wheat) Starch	Abrasives; Absorbents; Binders; Bulking Agents; 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
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

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

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
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
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

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

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
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
Cassia Angustifolia Seed Polysaccharide	Skin-Conditioning Agents - Emollient
Echinacin	Not Reported
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. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[91,92,93]

	Maltodextrin		**Acacia Senegal Gum**		**Agar**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	509	0.00001-4	422	0.0001-11	68	0.002-1
Duration of Use						
Leave-On	305	0.00001-3	345	0.0001-11	49	0.002-1
Rinse off	180	0.00006-3	76	0.001-1	18	0.0043-0.015
Diluted for (bath) Use	24	0.22-4	1	NR	1	NR
Exposure Type						
Eye Area	40	0.001-2.5	201	0.002-6	2	1
Incidental Ingestion	10	0.00075-0.6	11	0.018-11	NR	NR
Incidental Inhalation- Sprays	173	0.00012-0.38	85	0.0001-0.1	25	0.0075-1*
Incidental Inhalation- Powders	163	0.005-1	97	0.6	26	0.0075**
Dermal Contact	354	0.00001-4	219	0.0003-4.8	65	0.002-1
Deodorant (underarm)	NR	0.0045-0.12	NR	0.0003	NR	NR
Hair - Non-Coloring	75	0.00012-2	17	0.0001-1	3	1
Hair-Coloring	65	0.0001-0.0033	NR	NR	NR	NR
Nail	NR	0.0015-3	NR	0.001	NR	NR
Mucous Membrane	72	4	72	0.0075-11	6	NR
Baby Products	2	NR	1	NR	NR	NR
	Agarose		**Algin**		**Alginic Acid**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	10	0.2-0.7	317	0.001-50	13	NR
Duration of Use						
Leave-On	10	0.2-0.7	187	0.001-18	12	NR
Rinse off	NR	NR	129	0.01-50	1	NR
Diluted for (bath) Use	NR	NR	1	0.1	NR	NR
Exposure Type						
Eye Area	NR	NR	39	0.025-0.75	2	NR
Incidental Ingestion	NR	NR	NR	1.1	NR	NR
Incidental Inhalation- Sprays	1	NR	105	0.001-0.025	6	NR
Incidental Inhalation- Powders	1	NR	113	0.025	7	NR
Dermal Contact	10	0.2-0.7	306	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	10	NR	5	0.1-9.5
Duration of Use						
Leave-On	2	NR	8	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	6	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	5	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 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[91,92,93]

	Calcium Alginate		**Carrageenan**		**Cassia Angustifolia Seed Polysaccharide**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	8	0.01-3	241	0.003-15.7	35	0.002-0.75
Duration of Use						
Leave-On	8	0.01-3	174	0.003-15.7	34	0.002
Rinse off	NR	0.01	62	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	17	0.2-3.7	3	NR
Incidental Ingestion	NR	NR	25	1-1.1	3	0.002
Incidental Inhalation- Sprays	2	0.016-1	115	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	8	0.01-3	203	0.003-3.7	32	0.0025-0.025
Deodorant (underarm)	NR	0.016-1	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	9	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	NR	NR	NR	NR
	Cichorium Intybus (Chicory) Root Oligosaccharides		**Corn Starch Modified**		**Cyclodextrin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	1	NR	79	0.0062-45.7	135	0.000025-4
Duration of Use						
Leave-On	1	NR	72	0.12-45.7	103	0.000025-4
Rinse off	NR	NR	6	0.0062-3	31	0.0042-1.6
Diluted for (bath) Use	NR	NR	1	9	1	NR
Exposure Type						
Eye Area	NR	NR	6	0.9-8	18	0.05-0.25
Incidental Ingestion	NR	NR	2	0.4	1	0.1
Incidental Inhalation- Sprays	1	NR	48	0.45-45.7*	70	0.08-2.5
Incidental Inhalation- Powders	1	NR	33	0.44**-15	60	0.2
Dermal Contact	1	NR	58	0.0062-15	119	0.0005-4
Deodorant (underarm)	NR	NR	NR	0.12	NR	2.5-4
Hair - Non-Coloring	NR	NR	16	0.45-45.7	12	0.000025-1.6
Hair-Coloring	NR	NR	NR	NR	3	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	6	0.0062-9	3	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	4	0.0035	174	0.000008-43	NR	0.05-19
Duration of Use						
Leave-On	4	0.0035	153	0.000008-30	NR	0.094-19
Rinse off	NR	NR	21	0.001-43	NR	0.05-7
Diluted for (bath) Use	NR	NR	NR	5	NR	NR
Exposure Type						
Eye Area	2	NR	22	0.000008-30	NR	0.094-19
Incidental Ingestion	NR	NR	NR	0.008	NR	7-15
Incidental Inhalation- Sprays	2	NR	91	0.00037-2.8	NR	0.099-18
Incidental Inhalation- Powders	2	0.0035**	92	0.0044-2.8	NR	0.3**-16**
Dermal Contact	4	0.0035	162	0.000008-43	NR	0.05-19
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	6	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	2	0.008-5	NR	7-15
Baby Products	NR	NR	NR	NR	NR	NR

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[91,92,93]

	Dextrin Palmitate		Dextrin Palmitate/Ethylhexanoate		Dextrin Palmitate/Stearate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	93	0.0001-16.8	11	NR	NR	0.1-18
Duration of Use						
Leave-On	87	0.0001-16.8	11	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	11	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	49	0.0001-13	9	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	91	NR	NR	0.5	1	4
Duration of Use						
Leave-On	70	NR	NR	0.5	NR	4
Rinse off	21	NR	NR	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	18	NR	NR	NR	NR	NR
Incidental Ingestion	2	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	20	NR	NR	NR	NR	NR
Incidental Inhalation- Powders	20	NR	NR	0.5**	NR	4**
Dermal Contact	73	NR	NR	0.5	1	4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	8	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	4	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	56	0.00007-3.8	13	0.06-0.67	14	NR
Duration of Use						
Leave-On	40	0.00007-0.75	11	0.06	12	NR
Rinse off	16	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	3	0.065-3.8	NR	NR	NR	NR
Incidental Inhalation- Sprays	30	3.8*	7	NR	10	NR
Incidental Inhalation- Powders	26	0.0007**-0.54**	7	NR	10	NR
Dermal Contact	46	0.00007-0.75	13	0.06-0.67	14	NR
Deodorant (underarm)	NR	NR	3	NR	NR	NR
Hair - Non-Coloring	7	0.13	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	5	0.065-3.8	NR	0.67	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[91,92,93]

	Hydrolyzed Starch		**Hydrolyzed Wheat Starch**		**Hydroxyethyl Cyclodextrin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	NR	0.000013-0.00046	259	0.000003-0.31	NR	1.2
Duration of Use						
Leave-On	NR	0.00046	107	0.00005-0.31	NR	1.2
Rinse off	NR	0.000013	148	0.000003-0.25	NR	NR
Diluted for (bath) Use	NR	NR	4	0.000003	NR	NR
Exposure Type						
Eye Area	NR	NR	4	0.03-0.038	NR	1.2
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	0.00046*	63	0.00005-0.02	NR	NR
Incidental Inhalation- Powders	NR	NR	6	0.0002**-0.06**	NR	NR
Dermal Contact	NR	NR	52	0.000003-0.06	NR	1.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.00046	179	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	41	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	77	0.00001-2	7	0.19-0.65	6	NR
Duration of Use						
Leave-On	76	0.00001-2	1	0.24-0.65	NR	NR
Rinse off	1	0.02-0.1	6	0.19-0.43	4	NR
Diluted for (bath) Use	NR	NR	NR	NR	2	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	34	0.34-1	1	0.24*	NR	NR
Incidental Inhalation- Powders	30	0.1-2	NR	NR	NR	NR
Dermal Contact	74	0.00001-2	NR	0.65	6	NR
Deodorant (underarm)	24	0.34-2	NR	NR	NR	NR
Hair - Non-Coloring	2	1	7	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	6	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	6	0.25-8.2	NR	0.00045	38	0.0005-3
Duration of Use						
Leave-On	5	0.25-8.2	NR	0.00045	11	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	NR	NR	NR	NR	NR	0.0005
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	5	0.25-0.88	NR	NR	8	NR
Incidental Inhalation- Powders	NR	8.2**	NR	NR	9	0.0008**-2.5**
Dermal Contact	1	0.5-8.2	NR	0.00045	20	0.0005-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	5	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 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[91,92,93]

	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	25	4-5
Duration of Use						
Leave-On	NR	NR	16	0.01-0.25	25	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	17	5
Incidental Inhalation- Powders	NR	NR	11	0.01**	NR	NR
Dermal Contact	6	0.017	17	0.01-0.25	24	4-5
Deodorant (underarm)	NR	NR	NR	NR	NR	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	84	0.0001-9	1	0.001-0.1	37	1
Duration of Use						
Leave-On	30	0.001-0.05	1	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	2	NR	NR	NR	NR	NR
Incidental Ingestion	NR	0.09-9	NR	NR	NR	NR
Incidental Inhalation- Sprays	22	0.05	1	0.001-0.1*	1	NR
Incidental Inhalation- Powders	15	NR	1	0.001-0.05**	1	NR
Dermal Contact	54	0.05	1	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	41	0.3-1.3	16	0.00001-0.15	NR	NR
Rinse off	20	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	10	1.3*	9	0.005-0.03*	NR	NR
Incidental Inhalation- Powders	6	0.3**	9	0.00001**-0.15**	NR	NR
Dermal Contact	12	0.3-1.3	15	0.00001-0.15	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	48	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 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[91,92,93]

	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	NS
Duration of Use						
Leave-On	11	1.9-4.7	1	NR	NR	NS
Rinse off	NR	0.05-2.5	2	NR	2	NS
Diluted for (bath) Use	NR	NR	NR	NR	NR	NS
Exposure Type						
Eye Area	1	4.7	NR	NR	NR	NS
Incidental Ingestion	NR	NR	2	NR	NR	NS
Incidental Inhalation- Sprays	8	NR	1	NR	NR	NS
Incidental Inhalation- Powders	NR	NR	1	NR	NR	NS
Dermal Contact	2	0.05-4.7	1	NR	NR	NS
Deodorant (underarm)	NR	NR	NR	NR	NR	NS
Hair - Non-Coloring	9	1.9	NR	NR	2	NS
Hair-Coloring	NR	2.5	NR	NR	NR	NS
Nail	NR	NR	NR	NR	NR	NS
Mucous Membrane	NR	NR	2	NR	NR	NS
Baby Products	NR	NR	NR	NR	NR	NS
	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)	4	0.05	4	0.048	NR	NR
Hair - Non-Coloring	NR	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	19	0.002-1.2
Duration of Use						
Leave-On	1	NR	NR	NR	2	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	2	0.05-1.2*
Incidental Inhalation- Powders	NR	NR	NR	NR	1	0.02**
Dermal Contact	NR	NR	1	NR	3	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 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[91,92,93]

	Stearoyl Inulin		**Sterculia Urens Gum**		**Tamarindus Indica Seed Gum**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	6	0.44-4.8	NR	0.2-0.7	NR	0.01-0.3
Duration of Use						
Leave-On	6	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	5	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	6	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**		**Glucomannan**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	139	0.45-33	27	0.01-6	NR	0.3-17
Duration of Use						
Leave-On	112	0.5-33	17	0.01-6	NR	NR
Rinse off	25	0.45-15	9	0.03-3.6	NR	0.3-17
Diluted for (bath) Use	2	0.86-32	1	NR	NR	NR
Exposure Type						
Eye Area	10	NR	5	NR	NR	17
Incidental Ingestion	NR	NR	2	0.01	NR	NR
Incidental Inhalation- Sprays	68	1-15*	1	NR	NR	NR
Incidental Inhalation- Powders	77	3.7-33	9	NR	NR	NR
Dermal Contact	107	0.5-33	24	0.03-6	NR	0.3-17
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	15	0.45-15	1	NR	NR	NR
Hair-Coloring	8	3.6	NR	3.6	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	3	0.86-32	6	0.01	NR	NR
Baby Products	1	NR	NR	NR	NR	NR

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on 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 4. Composition/Properties Data on Hydrolyzed Starch.[75,76]

TETRUP™	TETRUP™ -H
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 5. Reproductive and Develpmental 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.[133]
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.[133]
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.[133]
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.[133]
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	Inconsistent effects on reproduction and development, with no relationship to dose.[133]
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.[133]
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.[133]
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.[133]
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.[133]
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).[212]
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).[213]

Ingredient	Animals	Procedure	Results
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.[214]
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.[215]
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 female females completed lactation and a normal gestation period. No adverse effect on mean birth weight or mean litter size.[33]
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.[143]
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.	Not teratogenic.[216]
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.[216]
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.[216]
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.[216]
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.[217]
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.[217]

Table 6. 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.[134]
Carboxymethyl inulin	Same as above	Ames test	Same as above	Not genotoxic.[145]
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.[218]
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.[133]
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.[218]
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.[63]
Dextrin myristate (Rheopearl MKL2)	*Salmonella typhimurium* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[48]
Dextrin palmitate (Rheopearl KL2 and Rheopearl TL2)	*Salmonella typhimurium* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[49,50]
Dextrin isostearate (Unifilma HVY)	*Salmonella typhimurium* and *E. coli* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[52]
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.[219]
Glucomannan	*Salmonella typhimurium* (5 strains, not stated)	Ames test	With and without metabolic activation (doses not stated)	Not genotoxic.[119]

Table 6. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
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.[22]
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.[143]
Material (DDSA-modified starch [73-8050]) structurally similar to Sodium Hydrolyzed Potato Starch Dodecenylsuccinate	*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	up to 5,000 µg/plate, with and without metabolic activation.[123]
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.[220]
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.[54,55]
	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.[134]
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.[145]
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.[218]
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.[218]
Ghatti gum	Chinese hamster ovary (CHO-WBL) cells	Chromosome aberrations assay	up to 6,000 µg/ml, with and without metabolic activation	Not genotoxic.[219]

Table 6. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
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.[219]
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.[136]
Glucomannan	CD-1 (ICR) mouse bone marrow cells	Micronucleus test	Mice dosed orally with 5,000 mg/kg body weight	Not genotoxic.[136]
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.[143]
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.[143]
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.[143]
Potato starch modified	Mice (strain not stated)	Mouse lymphoma assay. OECD 476 test guideline.	Not stated	Not genotoxic.[122]
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.[121]
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.[121]

Table 6. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
Sterculia urens gum	WI-38 human embryonic lung cells	Cytogenetic assay	up to 1,000 µg/ml	No effect on anaphase chromosomes.[121]
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.[121]

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2014 FDA VCRP Data

Maltodextrin

01B - Baby Lotions, Oils, Powders, and Creams	1
01C - Other Baby Products	1
02A - Bath Oils, Tablets, and Salts	21
02C - Bath Capsules	1
02D - Other Bath Preparations	2
03B - Eyeliner	3
03C - Eye Shadow	6
03D - Eye Lotion	11
03F - Mascara	5
03G - Other Eye Makeup Preparations	15
04C - Powders (dusting and talcum, excluding aftershave talc)	17
04E - Other Fragrance Preparation	1
05A - Hair Conditioner	21
05B - Hair Spray (aerosol fixatives)	2
05C - Hair Straighteners	1
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	15
05G - Tonics, Dressings, and Other Hair Grooming Aids	24
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)	2
07B - Face Powders	5
07C - Foundations	10
07E - Lipstick	10
07F - Makeup Bases	4
07I - Other Makeup Preparations	7
10A - Bath Soaps and Detergents	17
10E - Other Personal Cleanliness Products	21
11G - Other Shaving Preparation Products	2
12A - Cleansing	23
12C - Face and Neck (exc shave)	44
12D - Body and Hand (exc shave)	37
12F - Moisturizing	46
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	**509**

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

Acacia Senegal Gum

01B - Baby Lotions, Oils, Powders, and Creams	1
02D - Other Bath Preparations	1
03B - Eyeliner	7
03C - Eye Shadow	3
03D - Eye Lotion	6
03E - Eye Makeup Remover	1
03F - Mascara	175
03G - Other Eye Makeup Preparations	9
04C - Powders (dusting and talcum, excluding aftershave talc)	11
04E - Other Fragrance Preparation	1
05A - Hair Conditioner	2
05B - Hair Spray (aerosol fixatives)	1
05F - Shampoos (non-coloring)	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	7
05I - Other Hair Preparations	4
07A - Blushers (all types)	2
07B - Face Powders	10
07C - Foundations	4
07E - Lipstick	11
07I - Other Makeup Preparations	8
10A - Bath Soaps and Detergents	59
10E - Other Personal Cleanliness Products	1
12A - Cleansing	6
12C - Face and Neck (exc shave)	39
12D - Body and Hand (exc shave)	7
12F - Moisturizing	20
12G - Night	8
12H - Paste Masks (mud packs)	4
12I - Skin Fresheners	1
12J - Other Skin Care Preps	9
13B - Indoor Tanning Preparations	1
Total	**422**

Acacia Seyal Gum	**NR**

Agar

02B - Bubble Baths	1
03G - Other Eye Makeup Preparations	2
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	5
12A - Cleansing	6
12C - Face and Neck (exc shave)	11
12D - Body and Hand (exc shave)	4
12F - Moisturizing	7
12G - Night	1
12H - Paste Masks (mud packs)	7
12J - Other Skin Care Preps	1
Total	**68**

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	7
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	16
12C - Face and Neck (exc shave)	58

12D - Body and Hand (exc shave)	13
12F - Moisturizing	20
12G - Night	9
12H - Paste Masks (mud packs)	100
12I - Skin Fresheners	1
12J - Other Skin Care Preps	26
13B - Indoor Tanning Preparations	3
13C - Other Suntan Preparations	1
Total	**317**

Alginic Acid

01B - Baby Lotions, Oils, Powders, and Creams	1
03B - Eyeliner	1
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
05G - Tonics, Dressings, and Other Hair Grooming Aids	3
05I - Other Hair Preparations	1
06G - Hair Bleaches	1
12F - Moisturizing	3
12J - Other Skin Care Preps	1
Total	**10**

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
12D - Body and Hand (exc shave)	1
12F - Moisturizing	1
12J - Other Skin Care Preps	1
Total	**8**

Calcium Carrageenan	**NR**

Carrageenan

02A - Bath Oils, Tablets, and Salts	4
02C - Bath Capsules	1
03B - Eyeliner	1
03C - Eye Shadow	3
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	3
05H - Wave Sets	1
05I - Other Hair Preparations	2
07A - Blushers (all types)	2
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	10
12A - Cleansing	19
12C - Face and Neck (exc shave)	39
12D - Body and Hand (exc shave)	23
12E - Foot Powders and Sprays	2
12F - Moisturizing	31
12G - Night	8

12H - Paste Masks (mud packs)	9
12I - Skin Fresheners	4
12J - Other Skin Care Preps	18
Total	**241**

Cassia Angustifolia Seed Polysaccharide

03C - Eye Shadow	3
07A - Blushers (all types)	2
07B - Face Powders	6
07C - Foundations	4
07E - Lipstick	3
11A - Aftershave Lotion	1
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	**35**

Cichorium Intybus (Chicory) Root Oligosaccharides

12C - Face and Neck (exc shave)	1
Total	**1**

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	3
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	2
07B - Face Powders	2
07C - Foundations	1
07D - Leg and Body Paints	1
07E - Lipstick	1
07I - Other Makeup Preparations	3
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	**79**

Croscarmellose **NR**

Cyclodextrin

02A - Bath Oils, Tablets, and Salts	1
03A - Eyebrow Pencil	7
03D - Eye Lotion	4
03G - Other Eye Makeup Preparations	7
04E - Other Fragrance Preparation	1
05A - Hair Conditioner	2
05F - Shampoos (non-coloring)	9
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
06G - Hair Bleaches	2
06H - Other Hair Coloring Preparation	1
07C - Foundations	5
07I - Other Makeup Preparations	2
09B - Mouthwashes and Breath Fresheners	1
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	29
12G - Night	8
12H - Paste Masks (mud packs)	3
12I - Skin Fresheners	1
12J - Other Skin Care Preps	9
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	6
Total	**135**

Cyclodextrin Hydroxypropyltrimonium Chloride **NR**

Cyclodextrin Laurate

03D - Eye Lotion	2
12C - Face and Neck (exc shave)	1
12G - Night	1
Total	**4**

Cyclotetraglucose **NR**

Dextrin

03C - Eye Shadow	2
03D - Eye Lotion	8
03G - Other Eye Makeup Preparations	12
05A - Hair Conditioner	4
05F - Shampoos (non-coloring)	1
05I - Other Hair Preparations	1
06G - Hair Bleaches	2
07B - Face Powders	1
07C - Foundations	16
07H - Makeup Fixatives	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)	35
12D - Body and Hand (exc shave)	7
12F - Moisturizing	37
12G - Night	8
12H - Paste Masks (mud packs)	6
12I - Skin Fresheners	4
12J - Other Skin Care Preps	16
Total	**174**

Dextrin Behenate	**NR**
Dextrin Isostearate	**NR**
Dextrin Laurate	**NR**
Dextrin Myristate	**NR**

Dextrin Palmitate

03C - Eye Shadow	2
03D - Eye Lotion	1
03F - Mascara	7
03G - Other Eye Makeup Preparations	1
07A - Blushers (all types)	2
07C - Foundations	4
07E - Lipstick	37
07G - Rouges	24
07I - Other Makeup Preparations	3
10E - Other Personal Cleanliness Products	1
12A - Cleansing	4
12C - Face and Neck (exc shave)	4
12D - Body and Hand (exc shave)	1
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	1
Total	**93**

Dextrin Palmitate/Ethylhexanoate	**NR**
07E - Lipstick	2
07I - Other Makeup Preparations	8
12F - Moisturizing	1
Total	**11**

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

Galactoarabinan	
03B - Eyeliner	3
03D - Eye Lotion	4
03E - Eye Makeup Remover	1
03F - Mascara	8
03G - Other Eye Makeup Preparations	2
05A - Hair Conditioner	5
05F - Shampoos (non-coloring)	2
05I - Other Hair Preparations	1
07C - Foundations	7
07E - Lipstick	2
07F - Makeup Bases	2
07G - Rouges	1
10A - Bath Soaps and Detergents	2
11A - Aftershave Lotion	6
11E - Shaving Cream	1
11G - Other Shaving Preparation Products	1
12A - Cleansing	4
12C - Face and Neck (exc shave)	5
12D - Body and Hand (exc shave)	5
12F - Moisturizing	9
12G - Night	1
12H - Paste Masks (mud packs)	5
12J - Other Skin Care Preps	14
Total	**91**

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)	7
07C - Foundations	2
07E - Lipstick	3
10A - Bath Soaps and Detergents	1
10E - Other Personal Cleanliness Products	1
11E - Shaving Cream	1
12A - Cleansing	4
12C - Face and Neck (exc shave)	10
12D - Body and Hand (exc shave)	4
12F - Moisturizing	11
12G - Night	1
12H - Paste Masks (mud packs)	2
12J - Other Skin Care Preps	4
Total	**56**

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	2
03G - Other Eye Makeup Preparations	1
05A - Hair Conditioner	36
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	51
05H - Wave Sets	2
05I - Other Hair Preparations	39
06A - Hair Dyes and Colors (all types requiring caution statem	21
06C - Hair Rinses (coloring)	5
07I - Other Makeup Preparations	1
10A - Bath Soaps and Detergents	20
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	**259**

Hydroxyethyl Cyclodextrin **NR**

Hydroxypropyl Cyclodextrin **NR**

03A - Eyebrow Pencil	4
03D - Eye Lotion	4
03F - Mascara	1
03G - Other Eye Makeup Preparations	4
04E - Other Fragrance Preparation	4
05I - Other Hair Preparations	2
07I - Other Makeup Preparations	1
10B - Deodorants (underarm)	24
12C - Face and Neck (exc shave)	19
12F - Moisturizing	4
12G - Night	7
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	2
Total	**77**

Hydroxypropyltrimonium Hydrolyzed Corn Starch

05A - Hair Conditioner	4
05F - Shampoos (non-coloring)	2

05G - Tonics, Dressings, and Other Hair Grooming Aids	1
Total	**7**

Hydroxypropyltrimonium Hydrolyzed Wheat Starch

02D - Other Bath Preparations	2
10A - Bath Soaps and Detergents	4
Total	**6**

Hydroxypropyl Oxidized Starch **NR**

Hydroxypropyl Starch

05G - Tonics, Dressings, and Other Hair Grooming Aids	5
12A - Cleansing	1
Total	**6**

Hydroxypropyltrimonium Maltodextrin Crosspolymer **NR**

Inulin

01B - Baby Lotions, Oils, Powders, and Creams	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	**40**

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	16
04B - Perfumes	1
05I - Other Hair Preparations	1
11A - Aftershave Lotion	7
Total	**25**

Natto Gum

03D - Eye Lotion	1
03G - Other Eye Makeup Preparations	2
07C - Foundations	1
12C - Face and Neck (exc shave)	13
12D - Body and Hand (exc shave)	5
12F - Moisturizing	3
Total	**25**

Palmitoyl Inulin **NR**

Pectin

01C - Other Baby Products	1
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	2
07F - Makeup Bases	1
10E - Other Personal Cleanliness Products	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	7
12F - Moisturizing	6
12G - Night	2
12H - Paste Masks (mud packs)	27
12J - Other Skin Care Preps	2
13B - Indoor Tanning Preparations	2
Total	**84**

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

Polianthes Tuberosa Polysaccharide

12C - Face and Neck (exc shave)	1
Total	**1**

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	16
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)	4
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
12F - Moisturizing	1
Total	**19**
Starch Laurate	**NR**
Starch Tallowate	**NR**
Stearoyl Inulin	
03C - Eye Shadow	1
03D - Eye Lotion	1
03G - Other Eye Makeup Preparations	3
07C - Foundations	1
Total	**6**
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	9
03G - Other Eye Makeup Preparations	1
04C - Powders (dusting and talcum, excluding aftershave talc)	8
05A - Hair Conditioner	4
05F - Shampoos (non-coloring)	9
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
06B - Hair Tints	8
07A - Blushers (all types)	1
07B - Face Powders	4

07I - Other Makeup Preparations	3
10E - Other Personal Cleanliness Products	1
11A - Aftershave Lotion	5
11G - Other Shaving Preparation Products	1
12C - Face and Neck (exc shave)	12
12D - Body and Hand (exc shave)	12
12E - Foot Powders and Sprays	1
12F - Moisturizing	36
12G - Night	3
12H - Paste Masks (mud packs)	2
12J - Other Skin Care Preps	12
13B - Indoor Tanning Preparations	2
Total	**139**

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

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**

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: January 5, 2015

SUBJECT: Concentration of Use by FDA Product Category: Glucomannan

Concentration of use by FDA Product Category – Glucomannan

Product Category	Maximum Concentration of Use
Other eye make up preparations Rinse-off	17%
Other skin care preparations Rinse-off	0.3%

Information collected in 2014

Table prepared December 23, 2014