Safety Assessment of Polysaccharide Gums as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	May 22, 2015
Panel Date:	June 15-16, 2015

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

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 22, 2015
Subject: Draft Tentative Report on Polysaccharide Gums

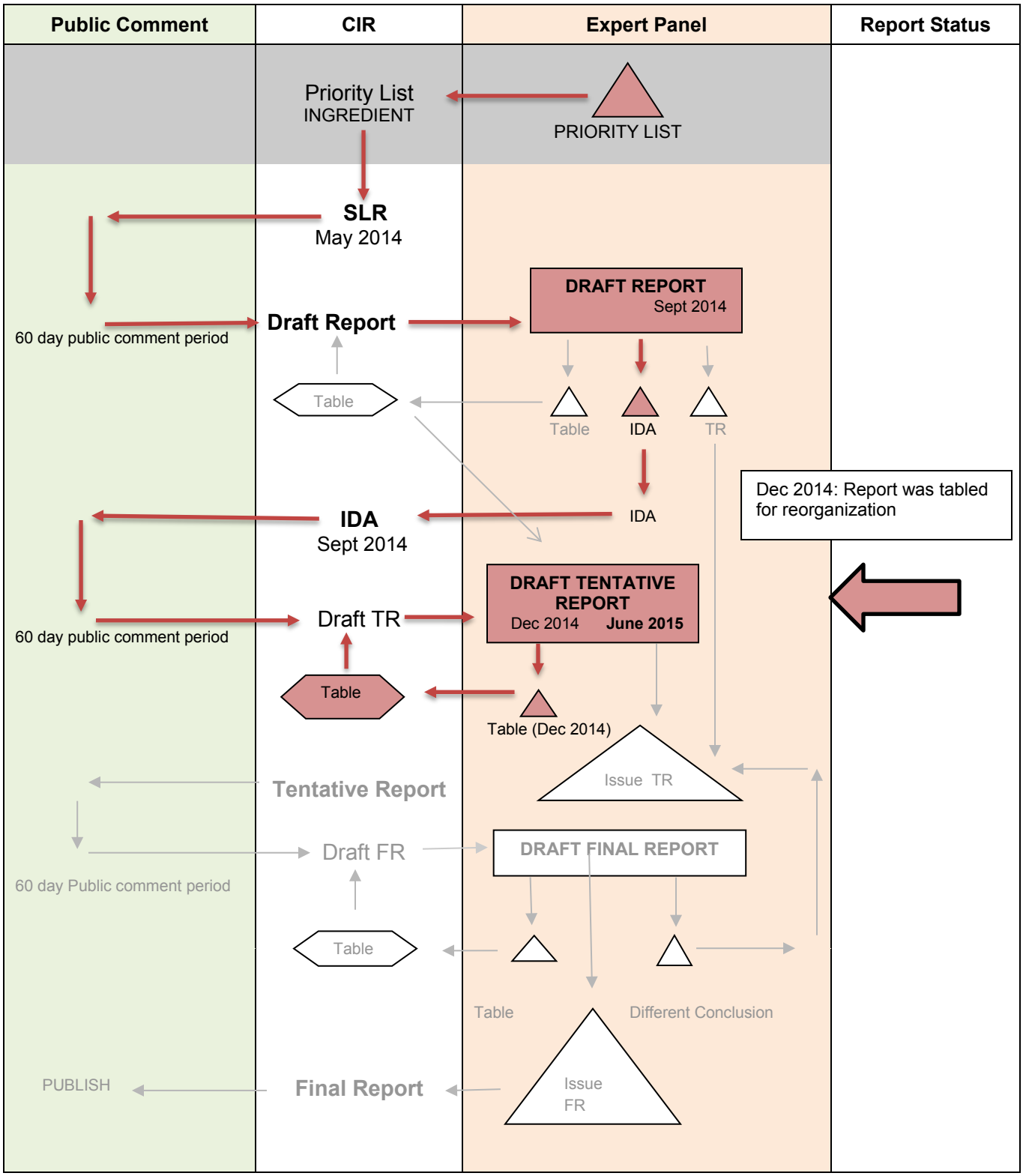
At the December 8-9, 2014 CIR Expert Panel meeting, the draft tentative report was tabled, pending reorganization of the report and to allow sufficient time for industry to provide additional data. The reorganized safety assessment (draft tentative report) is identified as *plpogu062015rep* in the pdf document. Comments received from the Council (*plpogu062015pcpc1)* will be addressed prior to the Panel meeting.

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 5 of the draft tentative report. The structure of galactoarabinan from the published literature is also included.

Included in this package for your review is the Draft Tentative Report on Polysaccharide Gums (plpogu062015rep*)*, the CIR report history (plpogu062015hist), Literature search strategy (plpogu062015strat), Ingredient Data profile (plpogu062015prof), 2015 FDA VCRP data (plpogu062015FDAdata), December 2014 Panel meeting minutes (plpogu062015min) and use concentration data on glucomannan and sodium hydrolyzed potato starch dodecenylsuccinate (plpogu062015data1, plpogu062015data2, and plpogu062015data3).

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.


Public Comment
CIR
Expert Panel
Report Status
Priority List
INGREDIENT
PRIORITY LIST
SLR
May 2014
60 day public comment period
Draft Report
DRAFT REPORT
Sept 2014
Table
Table
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Sept 2014
Dec 2014: Report was tabled for reorganization
60 day public comment period
Draft TR
DRAFT TENTATIVE REPORT
Dec 2014 June 2015
Table
Table (Dec 2014)
Issue TR
Tentative Report
Draft FR
DRAFT FINAL REPORT
60 day Public comment period
Table
Table
Different Conclusion
PUBLISH
Final Report
Issue
FR

CIR History of:

Plant Polysaccharide Gums

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Polysaccharide Gums Check List for June, 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 June, 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.

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ABSTRACT

The CIR Expert Panel (Panel) reviewed the safety of 102 polysaccharide gums, many of which function as viscosity increasing agents in cosmetic products. The Panel reviewed relevant data relating to the safety of these ingredients. 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.

INTRODUCTION

The safety of 102 polysaccharide gums (see Tables 1) as used in cosmetics is reviewed in this safety assessment. The polysaccharide gums are each naturally derived materials that comprise polysaccharides obtained from plants or algae. Based on the different chemical structures that are associated with polysaccharide gums, these ingredients can be subdivided into categories such as modified, unmodified, linear, branched, and cylic. Regardless of how they are structured, all of the "moieties" that comprise the molecular structures of these ingredients are polymers composed of monosaccharides.

Although these ingredients could be categorized in multiple ways, all of these ingredients fall into two predominate categories, modified and unmodified. The ingredients in the Modified subgroup have been further subdivided into Linear, Branched, Cyclic, and Unknown Structural Configuration. The ingredients in the Unmodified subgroup have been subdivided into Linear Polysaccharides and 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 (branched - natural/unmodified subgroup); pectin-derived acidic oligosaccharides (mixture of linear oligomers and small polymers of galacturonic acid) - for safety assessment of pectin (branched - natural/unmodified subgroup), which consists chiefly of partially methoxylated polygalacturonic acids; and carboxymethyl inulin - for safety assessment of sodium carboxymethyl inulin (branched - modified subgroup). Many of the polysaccharide gums reviewed in this safety assessment function as viscosity increasing agents in cosmetic products.[1] Other functions are listed in Table 2.

As a group 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.

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

CHEMISTRY

Definition and Structure

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

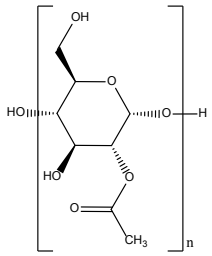


Figure 1. Starch Acetate – an example of a polysaccharide gum

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

Physical and Chemical Properties

Physical and chemical properties of polysaccharide gums are presented in Table 3.

Method of Manufacture

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

Linear – Modified

Hydrolyzed Furcellaran

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

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

→

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

←

Spray Dried Sea Water
Concentrate

Figure 1. Manufacturing Process for Hydrolyzed Furcellaran.[14]

Branched – Modified

Starch Hydroxypropyltrimonium Chloride

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

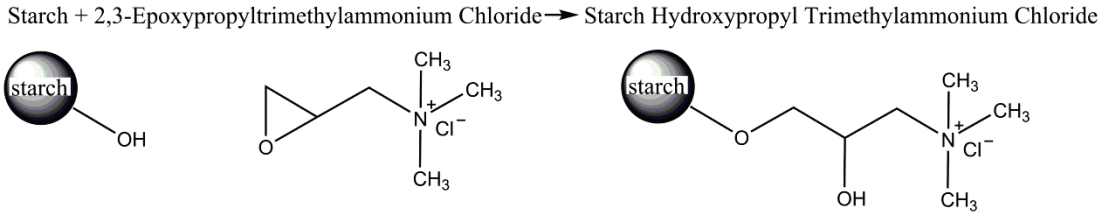


Figure 3. Reaction to form cationic starch ether.[15]

Composition/Impurities

Composition and impurities data on polysaccharide gums are presented in Table 4.

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, 55 of these polysaccharide gums are being used in cosmetic products and maltodextrin has the highest reported use frequency.[16,17,18,19]

The Council survey data also indicate that polysaccharide gums are being used in rinse-off cosmetic products at maximum ingredient use concentrations up to 50% (i.e., for algin in paste masks and mud packs), and in leave-on cosmetic products at maximum ingredient use concentrations up to 45.7% (i.e., for corn starch modified in tonics, dressings, and other hair grooming aids).[16,18] Frequency of use/use concentration data for polysaccharide gums are summarized in Table 5.

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.[20,21,22,23] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[20,21] There is

some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[21] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Non-cosmetic

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

Linear Polysaccharides and Salts Thereof

Algin

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

Alginates

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

Carrageenan

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

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

Inulin

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

Branched Natural/Unmodified

Ghatti Gum

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

Sterculia Urens Gum

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

Cyclic

Cyclodextrin

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

TOXICOKINETICS

Non-Human

Linear Polysaccharides and Salts Thereof

Carrageenan

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

Branched Natural/Unmodified

Sterculia Urens Gum (a.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.[36]

Cyclic

Cyclodextrin

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

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

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).[38] 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.

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).[39] 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.[40] 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.[41] 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.[42] The test material (100 µL on occlusive patch) was applied to dorsal skin (2 cm^2) for 24 h. Radioactivity in the patches, in the stratum corneum (collected by tape stripping), and in the epidermis and cutis of the skin (obtained by peeling off the treated portion) was measured using a scintillation counter. The percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin through intact skin was extremely low, i.e., ~ 0.02% of the amount applied to the skin. The absorption rate of ^{14}C-2-hydroxypropyl-β-cyclodextrin through skin from which the stratum corneum had been removed by tape stripping was approximately 24% of the amount applied to the skin. The latter finding suggests that the stratum corneum may act as a barrier to the percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin. Thus, the results of this study clearly demonstrate that 2-hydroxypropyl-β-cyclodextrin has low permeability through hairless mouse skin.

TOXICOLOGICAL STUDIES

A toxicity profile of β-cyclodextrin (a cyclic polysaccharide gum) is available from the WHO.[43] The toxicity profile of cyclodextrins can differ depending on the route of administration. For example, β-cyclodextrin administered orally induces limited toxicity.[44,45] 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.[46] 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.[46,47] In another study (rats), s.c. administration of β-cyclodextrin (≥ 450 mg/kg) induced similar changes in kidney proximal tubules.[48] Acute and repeated dose toxicity studies on polysaccharide gums (according to type of exposure) are summarized in Tables 7 and Table 8, respectively. The following acute toxicity studies (according to type of exposure) on polysaccharide gums are summarized in Table 7: inhalation, oral, dermal, intravenous, intrapleural, and transbronchial. Oral and dermal repeated dose toxicity studies on polysaccharide gums are summarized in Table 8.

Single Dose (Acute) Toxicity

The following acute toxicity studies on polysaccharide gums are summarized in Table 7: inhalation, oral, dermal, intravenous, intrapleural, and transbronchial.

Repeated Dose Toxicity

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

Cytotoxicity

Linear Polysaccharides and Salts Thereof

Calcium Alginate

In a cytotoxicity assay, calcium alginate fibers were introduced into human embryonic kidney cells and human fibroblasts.[49] These cells were in their exponential growth phase, and were incubated for 48 h. Calcium alginate fibers were not cytotoxic.

Allergenicity/Immune System Effects

Non-Human

Linear Polysaccharides and 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.[50] 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).[51] 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).[52] 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.).[53] 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.[54] 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.[55] This experimental model permitted the study of microvascular permeability, blood flow, vessel diameters and leucocyte adhesion to vessel walls intravitally, and leucocyte migration and mast cell degranulation histologically. Deionized water alone and potassium alginate with flavor and color mixed in saline was found to cause severe microvascular alterations, while potassium alginate, without flavor and color, mixed in saline and applied to the microvasculature resulted in a minor inflammatory reaction

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

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

GENOTOXICITY

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

CARCINOGENICITY

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.[56] 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) was performed.[57] A group of mice (75 males and 75 females) was fed sodium alginate in the diet for 89 weeks. At week 87, half of the surviving male and female mice was 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) 25% sodium alginate. The study did not find any evidence of carcinogenicity of dietary sodium alginate.

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.[58] 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.[58]

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.[59] 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.[60] 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.[61] 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. [61,62,63] 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).[61,62,63]

Fischer 344 rats were maintained on a diet containing 10% degraded carrageenan (degraded by acid hydrolysis; also contained 30% sulfate).[61,64] 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.[65] 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.[66,67] 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.

Thirty Sprague-Dawley rats (4 months old) were experimentally treated s.c. with the procarcinogen, DMH to induce colon cancer.[68] 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.[69] 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).[70] 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% konjac mannan 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 mannan group (control: 63% of 24 mice; konjac mannan: 48% of 23 mice) and a statistically significant decrease ($p<0.05$) in the mean number of tumor nodules per mouse in the konjac mannan group (control: 1.1; konjac mannan: 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 konjac mannan-treated mice. While feed efficiency was decreased in konjac mannan-treated mice when compared to controls (control: 2.9%; konjac mannan: 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% konjac mannan, although animals maintained on this diet consumed approximately 10% fewer calories per day when compared to control animals.[71]

In another study, the effect of a diet containing 5% konjac mannan on the incidence of colon tumors induced by DMH in rats was studied.[72] 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% konjac mannan. 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 konjac mannan-fed rats were significantly lower than those of rats fed the control diet; however, there was no significant difference in feed efficiency between konjac mannan-fed and control rats. The incidence of DMH-induced colon tumors was significantly lower in the konjac mannan-fed group (39%) when compared to the control group (75%). The number of colon adenocarcinomas per rat was also significantly lower in konjac mannan-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 (konjac mannan-fed rats: 5.8 ± 1.3 mm; control rats: 6.9 ± 3.6 mm).

In contrast to the effects reported for colon tumors, dietary konjac mannan had no significant effect on the incidence of tumors of the small intestine, all of which were adenocarcinomas in this study (control: 45%; konjac mannan: 33%); mean diameters of adenocarcinomas of the small intestine were not significantly different in the two groups (control: 8 ± 4 mm;

konjac mannan: 6 ± 2 mm). Dietary konjac mannan did not appear to have a significant effect on the incidences of ear duct or pancreatic tumors in rats in this study.[72]

Pectin

The effects of pectin on the morphological parameters of the small intestine were investigated.[73] 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

A chronic feeding study of starch acetate (a chemically modified potato starch)was performed.[57] A group of mice (75 males and 75 females) was fed starch acetate in the diet for 89 weeks. At week 87, half of the surviving male and female mice was placed on control diet (containing 55% pregelatinized potato starch). The dietary levels of the test substance were gradually increased until the diet contained (by weight) 55% starch acetate. The study did not find any evidence of carcinogenicity of dietary starch acetate.

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.[74] 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.[75] 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.[76] 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 1,2-dimethylhydrazine initiation of colon cancer was investigated using groups of 30 Sprague-Dawley rats.[77] 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.[78] 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.[78]

The initiation and promotion effects of κ-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units) 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.[79] 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.[79]

The modifying effects of carrageenan administration on colon carcinogenesis were investigated using male F344/DuCrj rats.[80] 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.[81] 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.

IRRITATION AND SENSITIZATION

Dermal Irritation and Sensitization

Skin irritation and sensitization studies on polysaccharide gums are summarized in Table 11.

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

Clinical Trial

Linear Polysaccharides and 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.[83] 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.[84] 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.[85] 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.[86] 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:[87] abdominal cramps, mild generalized pruritus, generalized urticaria, hypotension, transient loss of consciousness, chest tightness, wheezing, and cyanosis. A skin prick test for a component of the barium enema solution, 0.4% weight/volume sodium alginate, were positive (i.e., an 8 mm wheal diameter with surrounding flare). This is the only component of the barium enema solution that yielded a positive reaction.

Ocular Irritation

Non-Human

Linear Polysaccharides and Salts Thereof

Algin

The ocular irritation potential of algin (2%) was studied in 3 experiments using rabbits (number not stated).[88] Instillation of the test substance was followed by scoring after 1 h, 24 h, 2 days, 3 days, 4 days, and 7 days. Corneal opacity and ulceration or granulation were evaluated. Ocular irritation was graded on a scale of 0 to 110, and an ocular irritation index (OII) was calculated. It was noted that a compound does not provoke any significant injury to the mucous membrane of the eye when no opacity of the cornea occurs and when the ocular irritation index is less than 15. OII values of 3.00, 9.17, and 5.50 were reported in the 3 experiments, respectively. Pathological lesions of the ocular mucosa were not observed.

Carrageenan

Food grade *iota*-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units) was not irritating to unrinsed eyes of rabbits and was minimally irritating to rinsed eyes.[89]

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).[90] 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.[91]

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.[92,93]

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.[94] 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.[95,96,97] 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.[98,99]

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.[100] 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.[100]

Maltodextrin

The ocular irritation potential of maltodextrin was evaluated using the *in vitro* bovine corneal opacity and permeability assay.[101] 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.[102] 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).[103] Fertile White leghorn eggs were used. The chorioallantoic membrane (CAM) of the chick embryo responds to injury with a complete inflammatory reaction that is comparable to that induced in the rabbit ocular irritation test. The test substance (0.3 ml) was administered to the CAM at concentrations of 5%, 10%, and 15%. Results indicated that hydroxypropyltrimonium hydrolyzed corn starch would have practically no irritation potential *in vivo*. It was noted that the CAM results at 5%, 10%, and 15% are equivalent to Draize test results for the test substance at concentrations of 10%, 20%, and 30%.

Mucous Membrane Irritation and Sensitization

Non-Human

Branched Natural/Unmodified

Glucomannan

Konjac flour was evaluated in the following study, but the composition of konjac flour is not stated. However, according to one source, every 100 g of konjac flour contains the following:[104] glucomannan (79.37 mg), protein (1.64 g), fat (0.004 g), phosphorus (57 mg), iron (4.06 mg), zinc (123 mg), manganese (0.2 mg), chromium (0.25 mg), and copper (0.08 mg). Prior to initiation of the study, a sensory irritation study on konjac flour (primary polysaccharide component is glucomannan) was performed using ND4 Swiss Webster mice (number not stated).[105] 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.[105] 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.[105]

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.[106] After a single nasal administration of 2% randomly methylated β-cyclodextrin, only minor changes were observed in the appearance of the cilia and the apical cell membranes, and small amounts of mucus

were excreted into the nasal cavity. These effects were similar to those noted for control animals dosed with physiological saline (0.9% NaCl). Using confocal laser scanning microscopy, no changes in nasal epithelial cell morphology were observed after a single intranasal administration of 2% randomly methylated β-cyclodextrin, whereas 1 % sodium taurodihydrofusidate resulted in swelling of the cells and substantial mucus extrusion.

Human

Branched Natural/Unmodified

Glucomannan

The inhalation of konjac dust in factories producing konnyaku, a popular food in Japan made from konjac tubers, has been reported to produce allergic bronchial asthma (known as konnyaku asthma) in sensitized individuals.[107] Furtherhmore, bronchial asthma that was likely triggered by the inhalation of Maiko powder has been associated with residents near a konjac milling plant in Japan.[108] Konjac root is dried and ground into powder in the process of manufacturing the food known as knojac. Maiko is a fine konjac root powder that is blown by air pressure to obtain konjac powder for commercial use.

EPIDEMIOLOGY

Linear Polysaccharides and Salts Thereof

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.[109] 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.[109]

MISCELLANEOUS STUDIES

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.[110] 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*.[49] 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).[111] 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.[112] 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. 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. While, for the sake of clarity and organization, these ingredients can be subdivided into these categories, these moieties are unified as each being polymeric materials from simple saccharide monomers. Based on chemical similarities, relevant data have been included on analogous, polysaccharide ingredients. Therein, read-across may be appropriate from one ingredient to the next, and from one ingredient to one subgroup of polysaccahrides, of which that ingredient or analogue is a member.

The substantial molecular sizes of many of these polysaccharides suggest that skin penetration would be unlikely. Specifically, the percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin through intact hairless mouse skin was extremely low, i.e., approximately 0.02% of the amount applied to the skin. Thus, during cosmetic use, these ingredients are unlikely to have significant systemic bioavailability and decomposition products are likely to be simple saccharides.

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

Genotoxicity data for pectin-derived acidic oligosaccharides in mammalian assays were 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.

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

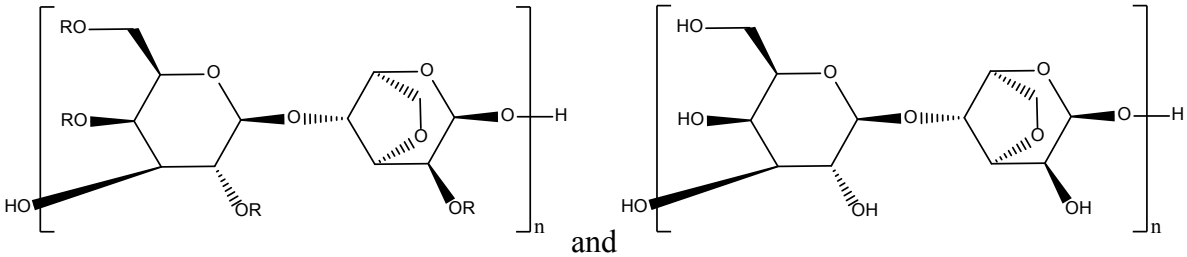
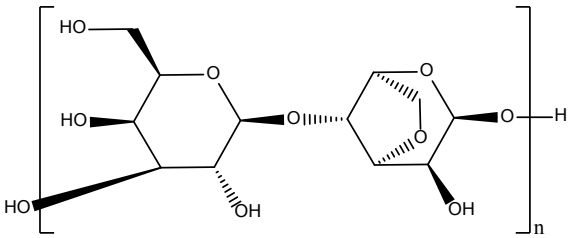
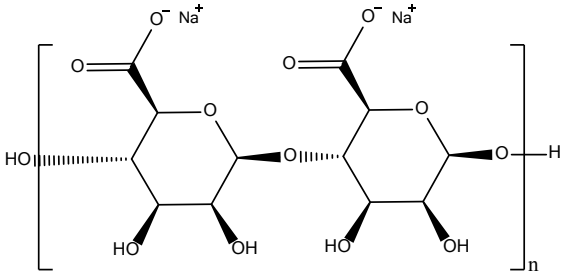
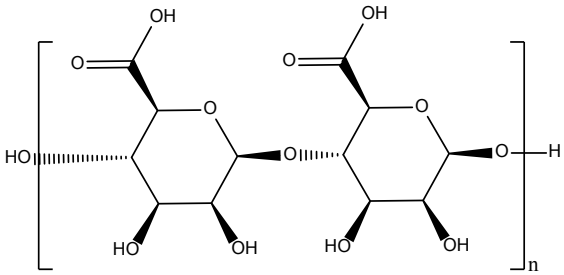
Ingredient CAS No.	Definition	Formula/structure
Linear polysaccahrides and salts thereof		
Agar 9002-18-0	Agar is the dried, hydrophilic, colloidal polygalactoside derived from various Gelidium species or closely related red alga. *Agar is typically a mixture of agarose and agaropectin.*[113]	 and wherein 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.* Other source: Algin is a linear polymer of anhydro-β-D-mannuronic acid. The main structural feature of this molecule is a chain of 1,4-linked-β-D-mannuronic acid residues.[114]	
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.*[115]	

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

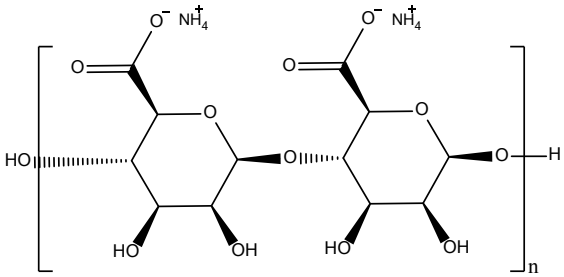
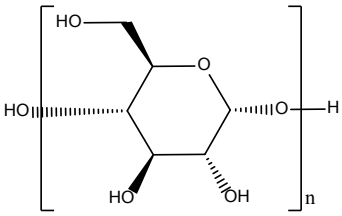
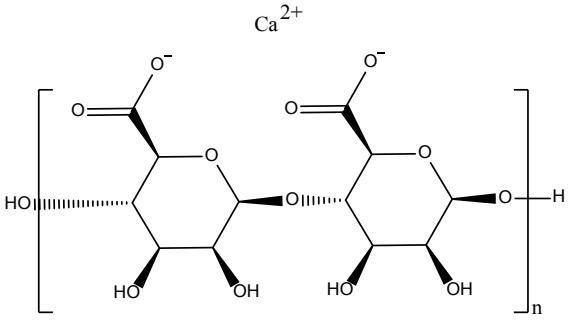
Ingredient CAS No.	Definition	Formula/structure
Ammonium Alginate 9005-34-9	Ammonium Alginate is the ammonium salt of Alginic Acid. *Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.* Other sources: Alginate, a term that refers to salts and derivatives of alginic acid, is a gelling polysaccharide and a structural component extracted from marine brown algae (*Phaeophyceae*), in which it is present in the cell wall as water-insoluble salts.[116] Alginates are polymers composed of β-1,4-D-mannuronic acid (M) and α-1,4-L-guluronic acid (G). Alginates have been determined to be true block copolymers, organized in homopolymeric blocks consisting of either mannuronate or guluronate, or mixed in heteropolymeric MG-block structures. Alginate, the monovalent salt form of alginic acid, is a non-repeating copolymer that contains two uronic acid monomers, 1,4- linked-β-D-mannuronic and α-L-guluronic acid.[117] These residues exist in linear polysaccharide chains that can dimerize to form hydrogels at room temperature in the presence of divalent ions such as calcium.	
Amylose 9005-82-7	Amylose is the carbohydrate stored by plants that consists of a linear (1→4)-(structure)-D-glucan polymer. Other source: Starch is composed of two polysaccharides, amylose and amylopectin.[118] Amylose is a complex α-glucan. It is an essentially linear polymer made up of α(1-4)-linked glucopyranose units.	
Astragalus Gummifer Gum	Astragalus Gummifer Gum is a dried resinous exudate obtained from Astragalus gummifer. *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*. Other sources: Carrageenan is a high-molecular-weight sulfated polygalactan derived from several species of red seaweeds of the class *Rhodophyceae*.[35] Native carrageenan is defined as a hydrocolloid isolated from red algae (seaweed) and consisting mainly of varying amounts (depending on the processing methods) of the ammonium, calcium, magnesium, potassium or sodium salts of sulfate esters of galactose and 3,6-anhydrogalactose copolymers (the two hexose units are alternately linked α-1,3 and β-1,4 in the polymer).[61] 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.[119] Kappa carrageenan is mostly the alternating polymer of D-galactose-4-sulfate and 3,6-anhydro-D-galactose. Iota carrageenan is similar, but with the 3,6-anhydro-D-galactose sulfated at the 2-hydroxyl. Between kappa and iota carrageenan, there is a continuum of intermediate compositions that differ only in the degree of sulfation at the 2-OH. Lambda carrageenan has alternating monomeric units composed mostly of D-galactose-2-sulfate (1,3- linked) and D-galactose-2,6-disulfate (1,4-linked).	

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

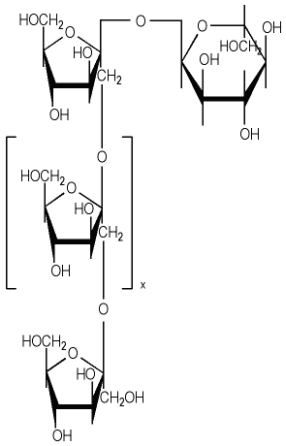
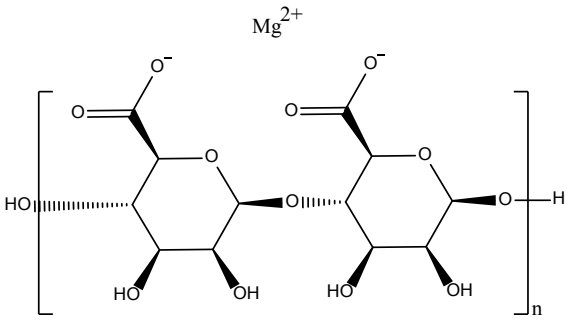
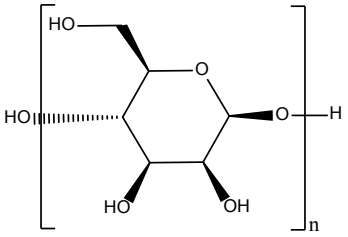
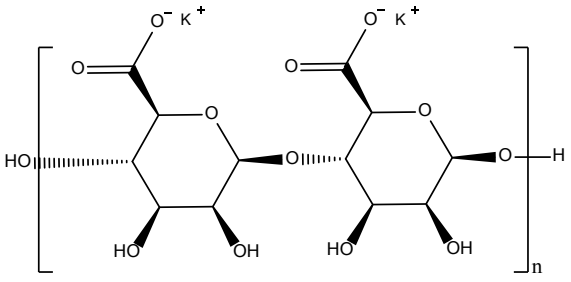
Ingredient CAS No.	Definition	Formula/structure
Inulin 9005-80-5	Inulin is the polysaccharide that conforms to the formula below. Other sources: Inulin has been identified as a fructan, a general term that is used to refer to naturally occurring plant oligo- and polysaccharides.[120] The term refers 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.[120]	
Magnesium Alginate 37251-44-8	Magnesium Alginate is the magnesium salt of Alginic Acid.	
Mannan 9036-88-8 51395-96-1	Mannan is a natural polysaccharide consisting of a polymer of Mannose.	
Polianthes Tuberosa Polysaccharide	Polianthes Tuberosa Polysaccharide is the polysaccharide fraction produced by the cultured cells of *Polianthes tuberosa.*	
Potassium Alginate 9005-36-1	Potassium Alginate is the potassium salt of Alginic Acid.	

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

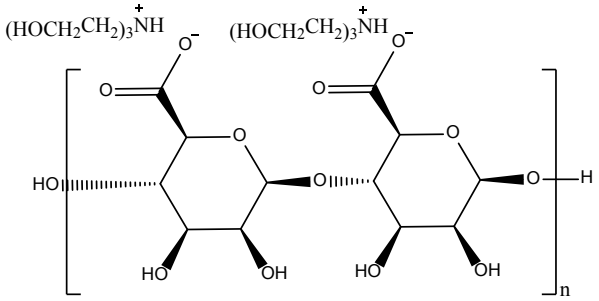
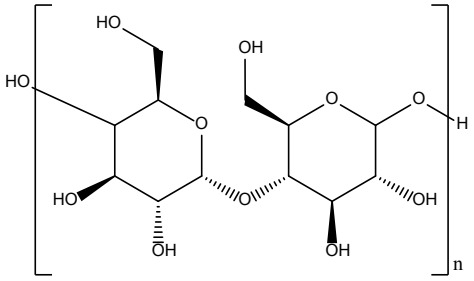
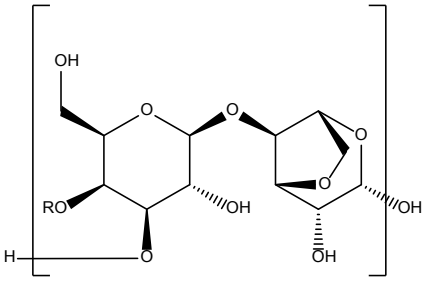
Ingredient CAS No.	Definition	Formula/structure
Potassium Carrageenan 64366-24-1	Potassium Carrageenan is the potassium salt of Carrageenan.	
Sodium Carrageenan 60616-95-7 9061-82-9	Sodium Carrageenan is the sodium salt of Carrageenan.	
TEA-Alginate	TEA-Alginate is the triethanolamine salt of Alginic Acid.	
Triticum Vulgare (Wheat) Starch 9005-25-8 (generic)	Triticum Vulgare (Wheat) Starch is a starch obtained from wheat, *Triticum vulgare.*	
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.* Other source: Information relating to the algal source of hydrolyzed furcellaran indicates that this ingredient is a carrageenan (Kappa type) that is obtained from red algae, *Furcellaria lumbricallis*.[100]	 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.*[121] *The term "maltodextrin" can be applied to any starch hydrolysis product that contains fewer than 20 dextrose (glucose) units linked together.*	

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

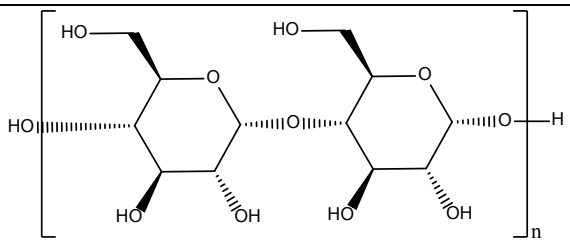
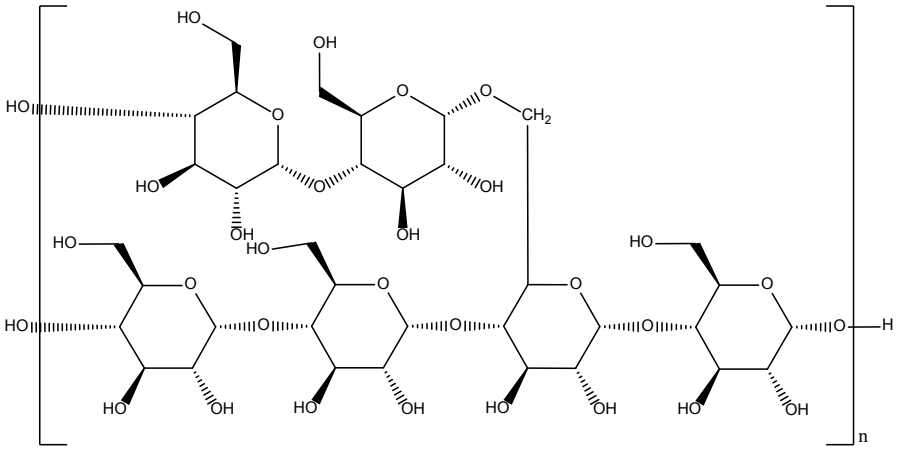
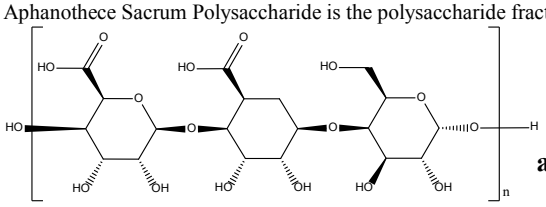
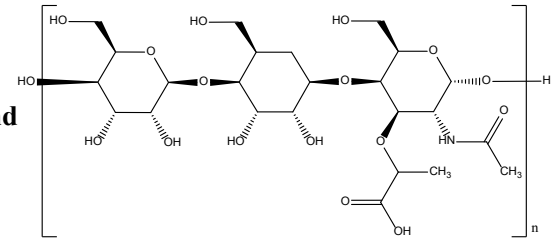
Ingredient CAS No.	Definition	Formula/structure
		
Potassium Undecylenoyl Carrageenan	Potassium Undecylenoyl Carrageenan is the potassium salt of the condensation product of undecylenic acid chloride and Carrageenan.	
Sodium Algin Sulfate 9010-06-4	Sodium Algin Sulfate is the sulfate ester of Algin.	
Sodium/TEA-Undecylenoyl Carrageenan	Sodium/TEA-Undecylenoyl Carrageenan is the mixed sodium and triethanolamine salt of the condensation product of undecylenic acid chloride and Carrageenan.	
Branched – natural/unmodified		
Amylopectin 9037-22-3	Amylopectin is the branched chain polysaccharide portion of starch. Other sources: Amylopectin is a complex α-glucan.[118] It is a highly branched polysaccharide composed of segments of linear α(1→4)-linked glucopyranose units joined at branching points via α(1→6) glycosidic linkages to give a structure that resembles a dendrimer. Amylopectin consists of numerous short chains of α(1→4)-linked D-glucopyranosyl residues with a chain length of approximately 6 to 35 units.[122] The chains are α(1→6)-linked into clusters defined as groups of chains, in which the internal chain length between the branches is less than 9 residues.	
Aphanothece Sacrum Polysaccharide	Aphanothece Sacrum Polysaccharide is the polysaccharide fraction isolated from the alga, Aphanothece sacrum.	 **and** 

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

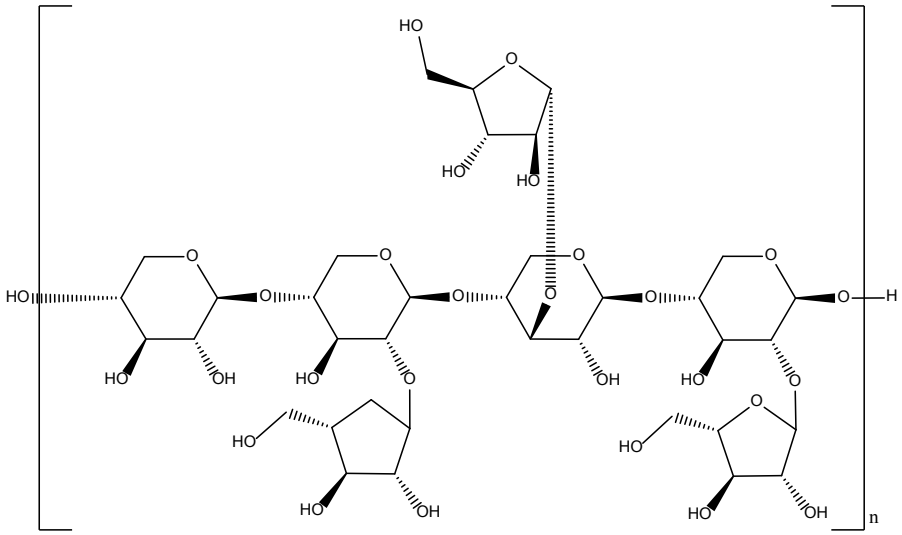
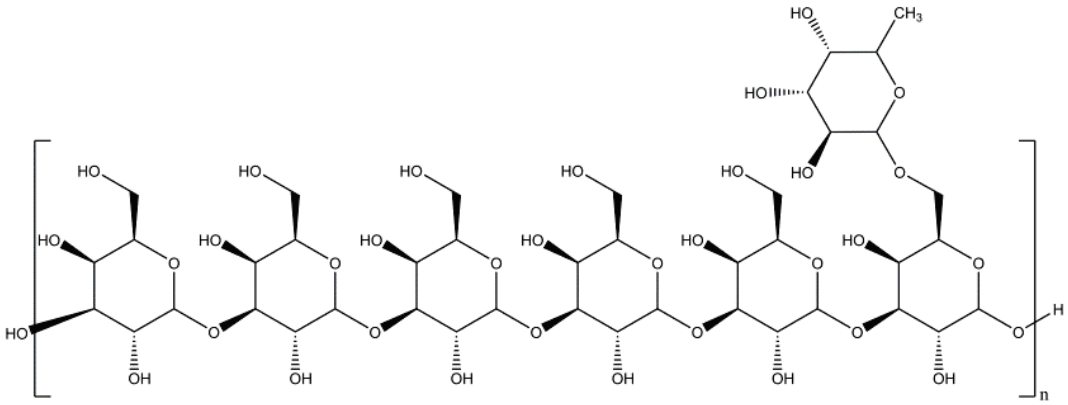
Ingredient CAS No.	Definition	Formula/structure
Arabinoxylan 9040-27-1	Arabinoxylan is a polysaccharide composed of a xylose backbone with arabinose side chains. Other sources: Arabinoxylan is a non-starch polysaccharide, and is also described as a pentosan.[123] It can also be sub-categorized as water-extractable arabinoxylan and water-unextractable arabinoxylan. Arabinoxylans consist of D-xylopyranosyl residues, connected together by β-(1/4) glycosidic bonds.[124,125] Moreover, acetic acid, hydroxycinnamic acids, ferulic acid, and p-coumaric acid are linked with xylose residues in arabinoxylan.[126,127] The attached moieties are partly or wholly lost when arabinoxylan is extracted from cereal or cereal subfractions using alkaline extraction.[123,128,129]	
Avena Sativa (Oat) Starch 9005-25-8 (generic)	Avena Sativa (Oat) Starch is a starch obtained from oats, Avena sativa.	
Cichorium Intybus (Chicory) Root Oligosaccharides	Cichorium Intybus (Chicory) Root Oligosaccharides is the carbohydrate fraction isolated from the roots of Chicorium intybus.	
Galactoarabinan 9036-66-2	Galactoarabinan is the polysaccharide obtained from the extraction of one or more species of the larch tree, *Larix.* The structure of galactoarabinan is:[130]	
Ghatti Gum 9000-28-6	Ghatti Gum is the dried, gummy exudate obtained from the stems and bark of *Anogeissus latifolia.* Other sources: Ghatti gum has been defined as the dried exudate of *Anogeissus latifolia*.[28] Degradation studies have shown that ghatti gum is a polysaccharide that consists of a backbone of galactose units to which other sugars are attached.[131] The side chains can consist of arabinose residues and aldobiuronic acids.	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
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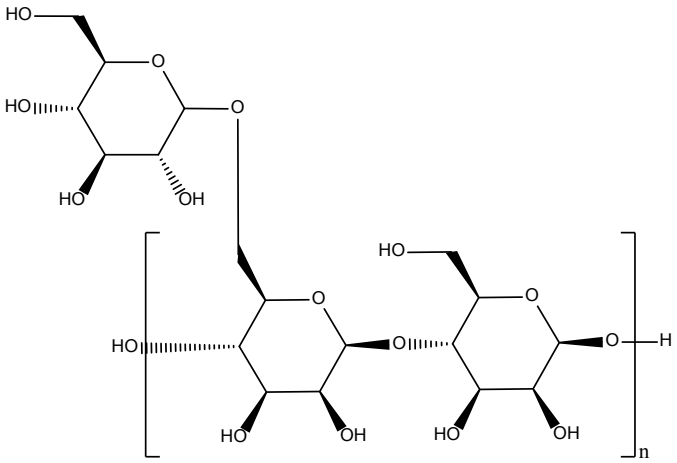
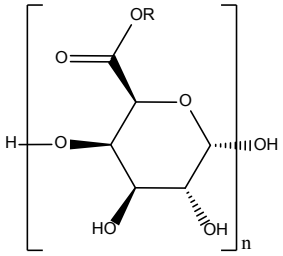
Ingredient CAS No.	Definition	Formula/structure
Glucomannan 37220-17-0 11078-31-2 76081-94-2	Glucomannan is the polymer of mannose containing side chains of glucose. Other sources: Glucomannan (a.k.a. konjac flour or konjac mannan) is a β-D-(1→4)-linked linear copolymer of glucose and mannose substituted with *O*-acetate every 9-19 sugar units.[132] 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.[133]	
Pectin 9000-69-5	Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.	 where R is hydrogen or methyl
Phaseolus Angularis Seed Starch	Phaseolus Angularis Seed Starch is a starch obtained from the bean, *Phaseolus angularis.*	
Phaseolus Radiatus Seed Starch	Phaseolus Radiatus Seed Starch is the starch obtained from the seeds of the bean, *Phaseolus radiatus.*	
Pisum Sativum (Pea) Starch	Pisum Sativum (Pea) Starch is a starch obtained from *Pisum sativum.*	
Pueraria Lobata Starch 9005-25-8 (generic)	Pueraria Lobata Starch is the starch obtained from the roots of *Pueraria lobota.*	
Solanum Tuberosum (Potato) Starch 9005-25-8 (generic)	Solanum Tuberosum (Potato) Starch is a polysaccharide obtained from the potato, *Solanum tuberosum.*	

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

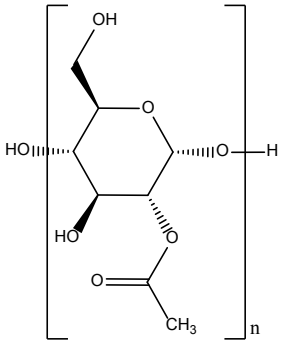
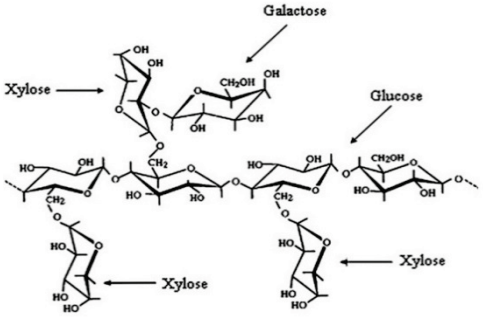
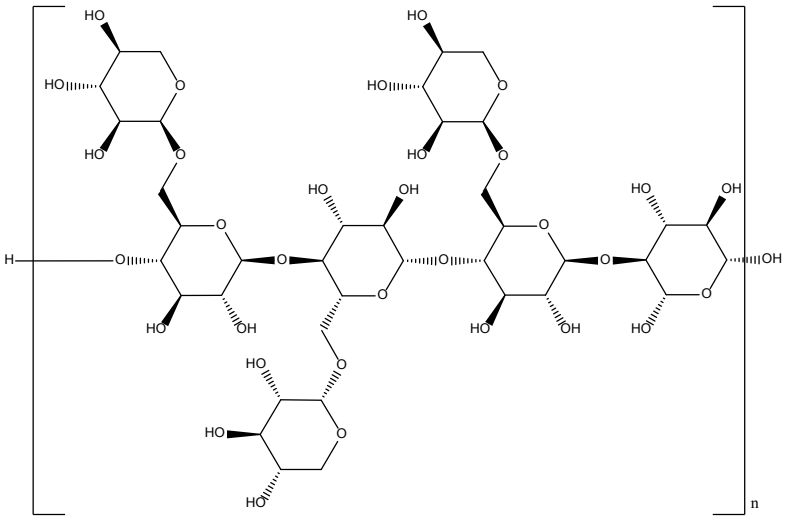
Ingredient CAS No.	Definition	Formula/structure
Starch Acetate 9045-28-7	Starch Acetate is the product obtained by the reaction of acetic acid with starch.	
Sterculia Urens Gum 9000-36-6 [VCRP name: Karaya Gum]	Sterculia Urens Gum is a dried exudate from the tree, *Sterculia urens*. Other source: Sterculia urens gum (a.k.a. karaya gum), the dried exudate of *Sterculia wens* Roxb. and other *Sterculia* spp. (fam. *Sterculiaceae),* is a complex, partially acetylated polysaccharide with a very high molecular weight.[40] Karaya gum is composed of the sugars galactose, rhamnose, and galacturonic acid.	
Tamarindus Indica Seed Gum 39386-78-2	Tamarindus Indica Seed Gum is the gum obtained from the seeds of *Tamarindus indica.*	
Tapioca Starch 9005-25-8	Tapioca Starch is the starch obtained from the roots of *Manihot esculenta.* It consists primarily of amylose and amylopectin.	
Xyloglucan 37294-28-3	Xyloglucan is an oligosaccharide containing a 1,4-β-glucan backbone with 1,6-α-xylosyl residues attached to the 6-position of β-glucosyl residues. Other source: The xyloglucan derived from tamarind seeds is composed of a (1-4)-β-glucan backbone chain, which has (1-6)-α-D-xylose branches that are partially substituted with (1-2)-β-D-galactoxylose.[134]	
***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.	

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

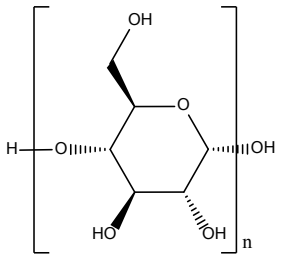
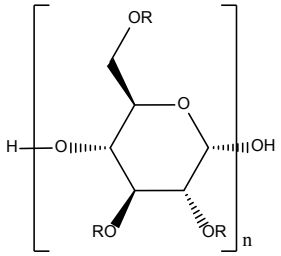
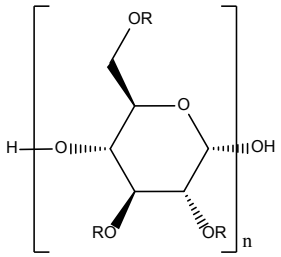
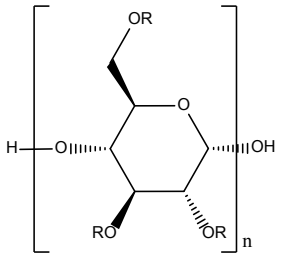
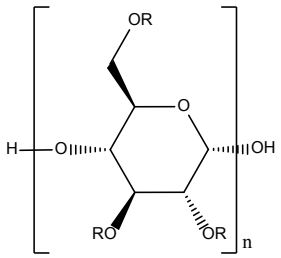
Ingredient CAS No.	Definition	Formula/structure
Corn Starch Modified	Corn Starch Modified is the calcium salt of the ester formed from the reaction of 3-(dodecenyl)dihydro-2,5-furandione and corn starch in which the degree of substitution per glucose unit is less than 0.1.	
Dextrin 9004-53-9	Dextrin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

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

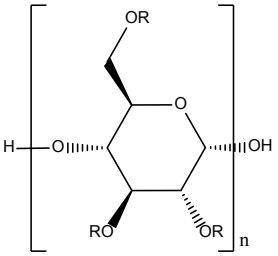
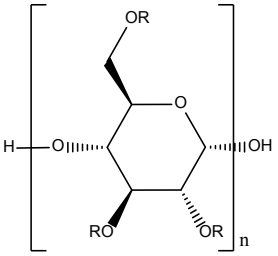
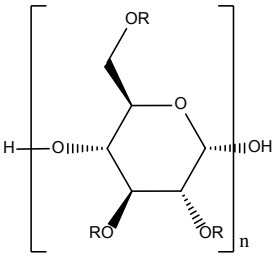
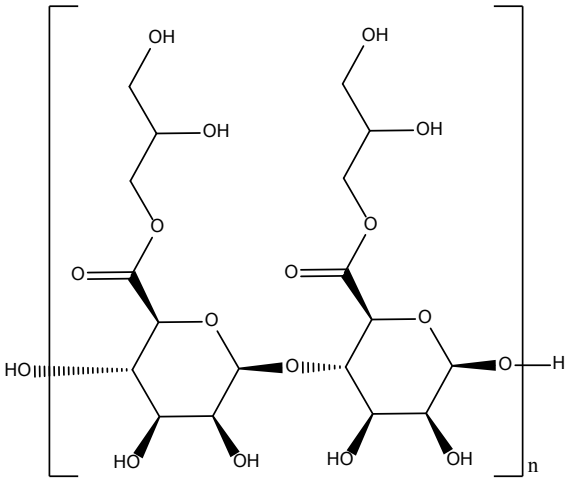
Ingredient CAS No.	Definition	Formula/structure
Dextrin Palmitate 83271-10-7	Dextrin Palmitate is the palmitic acid ester of Dextrin.	 wherein R is the residue of palmitic acid
Dextrin Palmitate/Ethylhexanoate 183387-52-2	Dextrin Palmitate/Ethylhexanoate is the mixed ester of Dextrin with palmitic and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

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

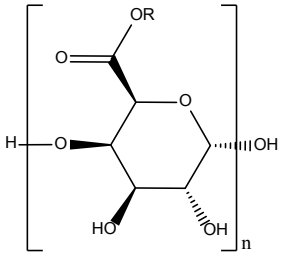
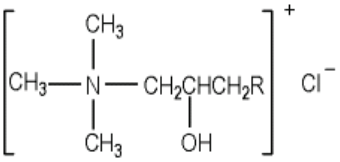
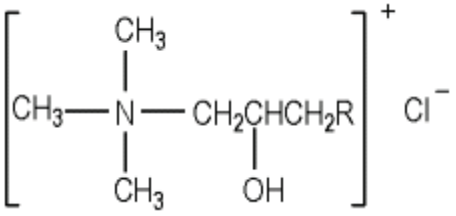
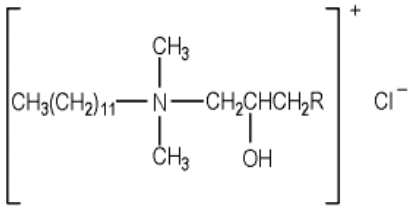
Ingredient CAS No.	Definition	Formula/structure
Hydrolyzed Pectin	Hydrolyzed Pectin is the hydrolysate of Pectin derived by acid, enzyme or other method of hydrolysis. *Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or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

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

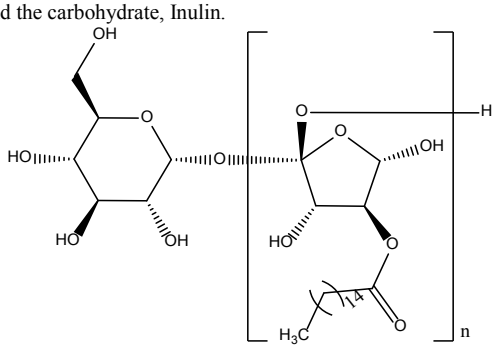
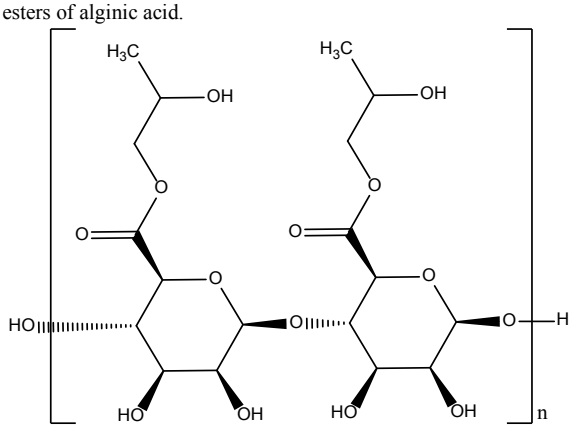
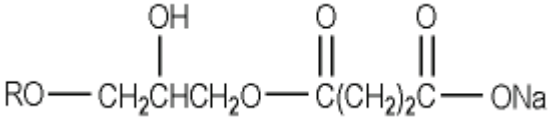
Ingredient CAS No.	Definition	Formula/structure
Palmitoyl Inulin	Palmitoyl Inulin is the condensation product of palmitic acid chloride and the carbohydrate, Inulin.	
Potassium Dextrin Octenylsuccinate	Potassium Dextrin Octenylsuccinate is the potassium salt of the reaction product of octenylsuccinic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

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

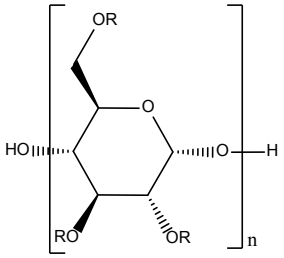
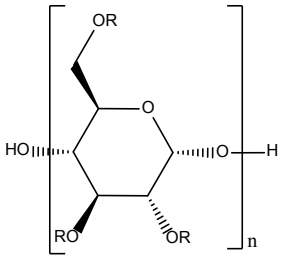
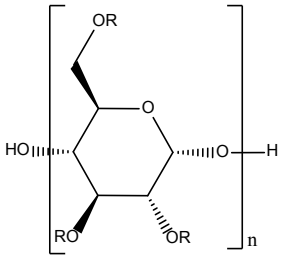
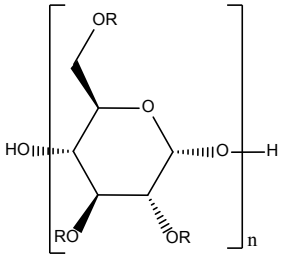
Ingredient CAS No.	Definition	Formula/structure
Sodium Starch Octenylsuccinate 52906-93-1 66829-29-6 70714-61-3	Sodium Starch Octenylsuccinate is the sodium salt of the reaction product of octenylsuccinic anhydride with Zea Mays (Corn) Starch.	
Sodium/TEA-Undecylenoyl Alginate	Sodium/TEA-Undecylenoyl Alginate is the mixed sodium and triethanolamine salt of the condensation product of undecylenic acid chloride and Alginic Acid.	
Starch Acetate/Adipate 63798-35-6	Starch Acetate/Adipate is the product obtained by the reaction of Zea Mays (Corn) Starch with Adipic Acid and acetic anhydride.	 where R is adipate or acetate
Starch Diethylaminoethyl Ether 9041-94-5	Starch Diethylaminoethyl Ether is the product obtained by conversion of some hydroxyl groups in starch to diethylaminoethyl ether groups.	 where R is hydrogen or constitutes, with the attached oxygen, diethylaminoethyl ether
Starch Hydroxypropyltrimonium Chloride 56780-58-6	Starch Hydroxypropyltrimonium Chloride is the quaternary ammonium compound formed by the reaction of starch with 2,3-epoxypropyltrimethylammonium chloride. Other source: One of the starch hydroxypropyltrimonium chloride trade name materials is defiuned as an aqueous solution of a naturally derived cationic polysaccharide produced from food grade potato starch.[135]	 where R is hydrogen or constitutes, with the attached oxygen, hydroxypropyltrimonium
Starch Laurate	Starch Laurate is the product obtained by the reaction of lauric acid with starch.	 where R is hydrogen or laurate

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

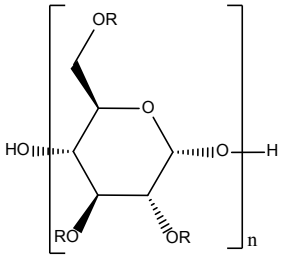
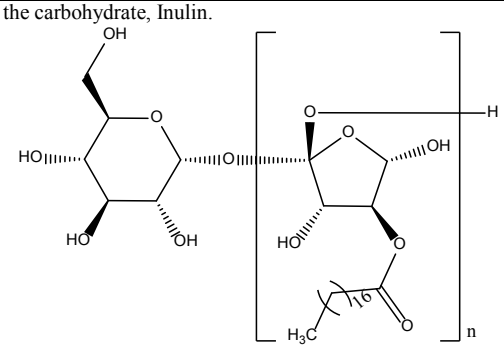
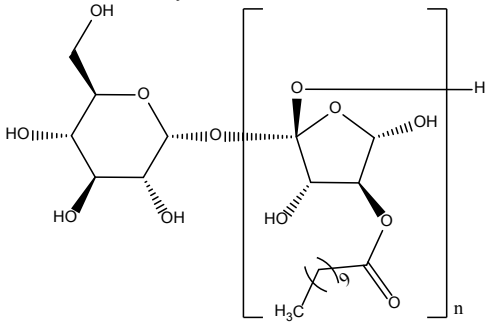
Ingredient CAS No.	Definition	Formula/structure
Starch Tallowate	Starch Tallowate is the ester of starch with the fatty acids derived from Tallow.	 where R is hydrogen or the residue of a fatty acid from tallow
Stearoyl Inulin	Stearoyl Inulin is the condensation product of stearic acid chloride with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

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

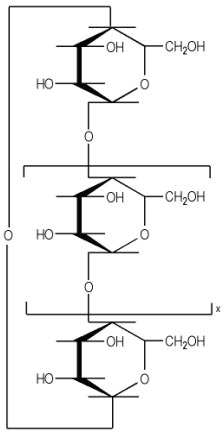
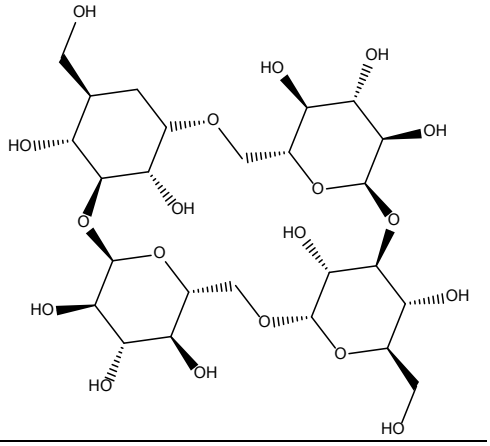
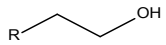
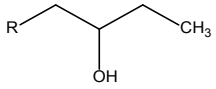
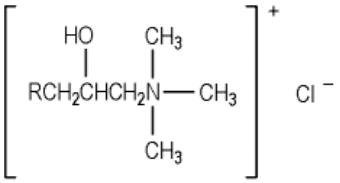
Ingredient CAS No.	Definition	Formula/structure
Cyclic		
Cyclodextrin 12619-70-4 7585-39-9	Cyclodextrin is a cyclic polysaccharide comprised of six to eight glucopyranose units. It conforms to the formula below: Other sources: Cyclodextrins are cyclic amylose-derived oligomers composed of a varying number of α-1-4-linked glucose units.[136] Cyclodextrins contain 6, 7, or 8 glucose units. β-Cyclodextrin is a carbohydrate consisting of seven glucose units.[74]	 where x may have values from 4 to 6.
Cyclotetraglucose 159640-28-5	Cyclotetraglucose is a cyclic polysaccharide comprised of four Glucose units.	
Cyclic - modified		
Hydroxyethyl Cyclodextrin	Hydroxyethyl Cyclodextrin is the hydroxyethyl ether of Cyclodextrin.	 where R represents the Cyclodextrin polymer.
Hydroxypropyl Cyclodextrin 128446-33-3 128446-35-5	Hydroxypropyl Cyclodextrin is a propylene glycol ether of Cyclodextrin.	 where R represents the Cyclodextrin polymer.
Cyclodextrin Hydroxypropyltrimonium Chloride	Cyclodextrin Hydroxypropyltrimonium Chloride is the organic compound that conforms to the formula:	 where R represents the Cyclodextrin polymer.

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

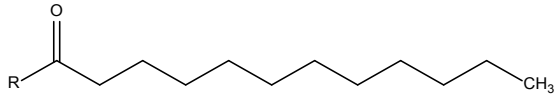
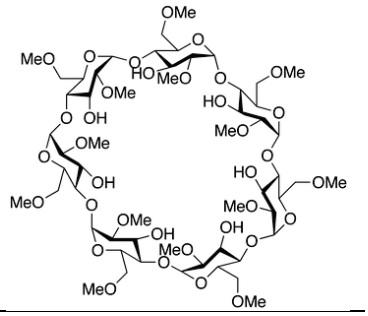
Ingredient CAS No.	Definition	Formula/structure
Cyclodextrin Laurate	Cyclodextrin Laurate is the product obtained by the reaction of Cyclodextrin and lauric acid chloride.	 where R represents the Cyclodextrin polymer.
Methyl Cyclodextrin 128446-36-6	Methyl Cyclodextrin is the product obtained by the methylation of Cyclodextrin.	
Unknown structural configuration		
Algae Exopolysaccharides	Algae Exopolysaccharides (Retired) are exopolysaccharides released by the fermentation of various species of microalgae of the divisions, Rhodophyta and Chlorophyta. The INCI Name, Algae Exopolysaccharides, originally published in 2010, was designated with a retired status in 2015. For an interim period of time, trade name assignments formerly published with the INCI Name Algae Exopolysaccharides will be retained in the retired monograph, and also published with the new name assignment based on the current genus and species name for the specific alga. For further information, consult the Introduction, Retired INCI Names.	
Cassia Angustifolia Seed Polysaccharide	Cassia Angustifolia Seed Polysaccharide is the polysaccharide fraction derived from the seed of Cassia angustifolia. Other source: Cassia angustofolia seed polysaccharide has been defined as a water-soluble galactomannan, consisting of D-galactose and D-mannose in the molar ratio of 3:2, isolated from the seeds of *Cassia angustifolia*.[137]	
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.	

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
Pectin	Binders; Emulsion Stabilizers; Oral Health Care Drugs; Viscosity Increasing Agents - Aqueous
Phaseolus Angularis Seed Starch	Absorbents
Phaseolus Radiatus Seed Starch	Abrasives; Bulking Agents

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

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
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

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

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. Properties and Method of Manufacture of Polysaccharide Gums

Linear Polysaccharides and Salts Thereof

Carrageenan

Average Molecular Weight: > 100,000 Da.[35] **Molecular Weight Range:** 196,000–257,000 Da.[138]

Stability: Data on carrageenans (in their sodium ion form without co-gelling cations) included κ-carrageenan from *Euchema cottoni*i, ι-carrageenan from *Eucheuma spinosoum*, a κ/λ mixture extracted from Chondrus crispus, and a κ/λ hybrid carrageenan from *Gigartina radula*. Reasonable stability to heating at 75˚C down to pH 4, and the rate of depolymerization increases dramatically as the pH decreases from 4 to 3. ι-Carrageenan is the most stable form, while κ-carrageenan has the greatest susceptibility to acid hydrolysis. The carrageenans from *Gigartina radula* and *Chondrus crispus* have intermediate stability.[139]

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.[139]

Inulin

Method of Manufacture: Extraction from the roots of *Cichorium intybus*.[140]

Linear - Modified

Amylodextrin

Method of Manufacture: Prepared from waxy maize by enzymatic hydrolysis with pullulanase.[141]

Hydrolyzed Furcellaran

Method of Manufacture: 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 **(See Figure 2)**.[100]

Maltodextrin

Method of Manufacture: Prepared as a white powder or concentrated solution by partial hydrolysis of corn starch, potato starch, or rice starch with suitable acids and enzymes.[142]

Branched Natural/Unmodified

Arabinoxylan

Molecular Weight: 65 to 66 kDa (obtained by sedimentation),[143] 800 - 5000 kDa (obtained by gel filtration),[144] and 70 - 1,000 kDa (obtained by gel filtration).[145]

Cichorium Intybus (Chicory) Root Oligosaccharides

Method of Manufacture: Extraction from the roots of Cichorium intybus.[140]

Ghatti Gum

Molecular Weight: ≈ 8.94 x 10^7 Da.[146]

Glucomannan

Average Molecular Weight: 1,000,000 Da; between 200,000 and 2,000,000 Da (commercial samples).[147]

Form: biphasic liquid crystal phase in water at 7 weight% concentration; becomes completely anisotropic at >10 weight%.[133]

Decomposition: Begins to decompose at approximately 250˚C; decomposition is complete at 350˚C.[147]

Method of Manufacture: Obtained by a dry milling process of thin tuber (Amorphophallus konjac) slices.[132] Can also be obtained from monocot storage organs other than tubers, such as leaves, bulbs, roots, or seeds.[147] 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.[147]

Branched - Modified

Carboxymethyl Inulin

Method of Manufacture: Synthesized by incorporation of carboxymethyl groups into the inulin framework. Also synthesized by by reacting inulin with the sodium salt of monochloroacetic acid in the presence of sodium hydroxide.[148]

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Corn Starch Modified

Method of Manufacture: aqueous corn starch slurry reaction with 3-(dodecenyl) dihydro-2,5-furandione.[90,149]

Dextrin

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

Dextrin Myristate

Form: Powder or particles.[91]

Color: White to pale yellow.[91]

Odor: Odorless or characteristic.[91]

Melting Point/Freezing Point: 50 ~ 150˚C.[91]

Flash Point: 210˚C.[91]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[91]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[151]

Dextrin Isostearate

Form: Soft solid.[152]

Color: Colorless to pale yellow.[152]

Odor: Odorless or characteristic.[152]

Melting Point/Freezing Point: 60 ~ 70°C.[152]

Flash Point: > 200°C.[152]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[152]

Method of Manufacture: The method of manufacture for dextrin isostearate begins with an esterification reaction involving 3-methylpyridine (beta-picoline) and n-heptane, followed by percolation, washing (methanol), drying, and filtration.[153]

Dextrin Palmitate

Form: Powder or particles.[92,93]

Color: White to pale yellow.[92,93]

Odor: Odorless or characteristic.[92,93]

Melting Point/Freezing Point: 50 ~ 130˚C; 100 ~ 130˚C.[92,93]

Flash Point: 200 ~ 250˚C.[92,93]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[92,93]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[151]

Dextrin Palmitate/Ethylhexanoate

Form: Powder or particles.[154]

Color: White to pale yellow.[154]

Odor: Odorless or characteristic.[154]

Melting Onset Temperature: 120°C.[154]

Flash Point: 216°C.[154]

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Dextrin Palmitate/Ethylhexanoate

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[154]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[151]

Glyceryl Dimaltodextrin

Method of Manufacture: Production of maltodextrins involves the obtention of products consisting of D-glucose units that are linked primarily by α(1→4) bonds and having dextrose equivalents less than 20.[155]

Hydroxypropyl Starch

Method of Manufacture: Sodium sulfate (Na2SO4) and sodium hydroxide (NaOH) are dissolved in water, and starch and propylene oxide are added, and heated to 38°C to 42°C. After the reaction is finished, the slurry is neutralized by acid (H2SO4). The starch is then dewatered, washed, and dried. The slurry of hydroxyl-propyl starch may also be degraded by an enzyme (e.g., liquefying-type amylase), purified by diatomite and active-carbon, and then dried.[150]

Potato Starch Modified

Method of Manufacture: An aqueous potato starch slurry is reacted with haloethylaminopropionic acid. This reaction is followed by washing, filtration, and drying.[94]

Sodium Dextrin Octenylsuccinate

Method of Manufacture: Method 1: The slurry of sodium starch octenylsuccinate is degraded by an enzyme (e.g., liquefying-type amylase), purified by diatomite and active-carbon, and dried. The dried starch film is crushed into a fine powder. **Method 2:** Dextrin solution and octenylsuccinic 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. **Method 3:** 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.[150]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

Solubility: Soluble in water (149.5 - 158.2 g/l).[156]

Method of Manufacture: Reaction of a hydrolyzed starch with dodecenylsuccinic anhydride.[157]

Sodium Hydroxypropyl Oxidized Starch Succinate

Method of Manufacture: Native starch (CAS No. 9005-25-8) and oxidized starch (CAS No. 065996-62-5) can be modified by reacting starch with etherifying and/or esterifying reagents in the presence of an alkaline catalyst.[15,158]

Reaction to form 2-hydroxypropyl, oxidized starch succinate

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

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

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

Sodium Starch Octenylsuccinate

Method of Manufacture: Starch is suspended in water, and octenylsuccinic anhydride is added. The slurry is heated to approximately 40°C, and the pH value is adjusted between 6 and 9 with dilute sodium hydroxide solution. The pH value of the solution is stable between 7 and 8, and the slurry is neutralized by acid (H2SO4). The starch is then dewatered, washed, and dried. Sodium starch octenylsuccinate may also be suspended in water and dried. The dried starch film is crushed into a find powder.[150]

Starch Hydroxypropyltrimonium Chloride

Molecular Weight: 2,000,000 Da.[135]

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Starch Hydroxypropyltrimonium Chloride

Form: Clear to slightly hazy liquid (clear in 1:5 water solution).[135]

Dry Substance (%) 31-33.[135]

Color, Gardner: ≤ 2.5.[135]

Odor: Very mild; slightly sweet.[135]

pH @ 20°C: 3.5-4.5.[135]

Method of Manufacture: The starting materials for the production of starch hydroxypropyltrimonium chloride are: oxidized starch and the cationic reagent 3-chloro-2-hydroxypropyltrimethylammonium chloride (CAS No. 3327-22-8).[158]
Ref 51 The reaction to form cationic starch ether appears below:[158]

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

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

According to another source, starch hydroxypropyltrimonium chloride is produced by an aqueous starch slurry reaction with 2,3-epoxypropyltrimethylammonium chloride in the presence of isopropanol. This reaction is followed by washing with isopropanol/water, and the material is then filtered and dried.[159]

Stearoyl Inulin

Form: Powder or particles.[98,99]

Color: White to pale yellow.[98,99]

Odor: Odorless or characteristic.[98,99]

Melting Onset Temperature: 64˚C; 68.2˚C.[98,99]

Flash Point: 210˚C; 214˚C.[98,99]

Solubility: Insoluble in water, methanol, and ethanol.[98,99]

Cyclic

Cyclodextrin

Solubility: Low aqueous solubility (1.85 g/100mL, β-Cyclodextrin).[160]

Unknown Structural Configuration

Algae Exopolysaccharides

Method of Manufacture: Microalgae is grown in fermenters under conditions that promote the production of the exopolysaccharide, which is secreted by the microalgae. The exopolysaccharides are removed from the cells via filtration or centrifugation, followed by precipitation with alcohol. The exopolysaccharide is then dried and ground to a fine powder. The supplier of this information stated that the CAS number for the ingredient produced (algae exopolysaccharides) is 1122611-69-1, and that the empirical formula for this ingredient is (C27H44O27S)n. Additionally, it was noted that this is the CAS number for D-galactopyranose.[161]

Cassia Angustifolia Seed Polysaccharide

Average Molecular Weight: 9.66 x 104 Da.[162]

Unknown Structural Configuration - Modified

Hydrolyzed Starch

Method of Manufacture: Raw Material (Starch) →Starch slurry→Liquefaction by thermostable α-amylase→Saccharification by isoamylase (to debranch starch amylose) and exomaltotetraohydrolase (to produce maltotetraose)→Heat treatment (inactivation of enzymes)→Filtration→Concentration→Decoloration→Filtration→Storage →Filling and weighing→Hydrolyzed starch.[163,164]

Table 4. Composition/Impurities Data on Polysaccharide Gums

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.[114]

Carrageenan

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

Twenty-nine samples of food-grade refined carrageenan were analyzed using high-performance liquid gel permeation chromatography. Each sample had no obvious peak of poligeenan (which is defined as degraded carrageenan, detection limit ≈ 5%).[165] Poligeenan is produced by a different manufacturing process of seaweed that involves intentional extensive acid hydrolysis, resulting in sulfated galactose polymers with a weight average molecular weight of ~ 15,000 Da.[35] Furthermore**,** according to another source, the molecular weight of poligeenan is in the range of 10,000 to 20,000 Da.[166]

Inulin

According to the *Food Chemicals Codex*, inulin should contain no more than the following: 1 mg/kg lead, 0.2% ash, and 15% (combined) of monosaccharides (as fructose and glucose) and disaccharides (as sucrose), calculated on the dried basis.[140]

Linear - Modified

Hydrolyzed Furcellaran (Mixtures).[100,167]

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

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

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

Maltodextrin

According to the *Food Chemicals Codex*, maltodextrin should contain no more than the following: 35 0.5 mg/kg lead, 0.0025% sulfur dioxide, 1% maltodextrins produced from high-amylose starches, and 0.5% all other types of maltodextrins.[140]

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.[168]

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%).[132]

Sterculia Urens Gum

Commercial sterculia urens gum contains 19%-21% of rhamnose and similar proportions of galactose and galacturonic acid.[36] Nitrogen content (probably non-protein in nature) of 0.07% has also been reported.[52]

Branched - Modified

Dextrin Myristate

Dextrin myristate contains: dextrin myristate (> 95%); moisture, based on loss of drying (< 1%); myristic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detectioin limit).[169]

Dextrin Palmitate

Dextrin palmitate contains: dextrin palmitate (> 95%); moisture, based on loss on drying (< 1%); palmitic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm; < 1,000 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detection limit).[170,171]

Dextrin Palmitate/Ethylhexanoate

Dextrin Palmitate/Ethylhexanoate contains: dextrin palmitate/ethylhexanoate (> 95%); moisture, based on loss on drying (< 3%); palmitic acid and 2-ethylhexanoic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm).[172]

Table 4. Composition/Impurities Data on Polysaccharide Gums

Dextrin Isostearate

Dextrin isostearate contains: dextrin isostearate (> 95%); isostearic acid (< 5%); 3-methylpyridine (beta-picoline) (< 300 ppm); heptane (< 200 ppm); and methanol (< 5 ppm, detection limit).[173]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

Impurities: antimony (7.53 mg/kg), arsenic (< 2 mg/kg), barium (0.271 mg/kg), cadmium (< 0.2 mg/kg), chromium (< 0.25 mg/kg), cobalt (< 1.5 mg/kg), copper (<0.25 mg/kg), lead (< 1.5 mg/kg), nickel (< 1 mg/kg), selenium (< 4.86 mg/kg), zinc (1.49 mg/kg), and mercury (< 0.1 mg/kg).[174]

Starch Hydroxypropyltrimonium Chloride

Starch hydroxypropyltrimonium chloride consists of approximately 30% solids, and is preserved with food grade sodium benzoate.[135]

Impurities/residuals data: diol levels (< 2%), enol levels (< 1.5%), and quaternizing agent (< 0.1%).[159]

Stearoyl Inulin

Stearoyl inulin contains: stearoyl inulin (> 95%); moisture, based on loss on drying (< 1%); stearic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detection limit).[175]

Unknown Structural Configuration

Cassia Angustifolia Seed Polysaccharide
The purified seed galactomannan contains mannose:galactose in a ratio of 2.90:1.[162]

Unknown Structural Configuration – Modified

Hydrolyzed Starch

Composition/Properties data on two hydrolyzed starch products are available **(See Table 6)**.[163,164]

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18,19]

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

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

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

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

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

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

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

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Hydrolyzed Starch		**Hydrolyzed Wheat Starch**		**Hydroxyethyl Cyclodextrin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	NR	0.000013-0.00046	274	0.000003-0.31	NR	1.2
Duration of Use						
Leave-On	NR	0.00046	114	0.00005-0.31	NR	1.2
Rinse off	NR	0.000013	156	0.000003-0.25	NR	NR
Diluted for (bath) Use	NR	NR	4	0.000003	NR	NR
Exposure Type						
Eye Area	NR	NR	6	0.03-0.038	NR	1.2
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	0.00046*	66	0.00005-0.02	NR	NR
Incidental Inhalation- Powders	NR	NR	6	0.0002**-0.06**	NR	NR
Dermal Contact	NR	NR	58	0.000003-0.06	NR	1.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.00046	186	0.000003-0.31	NR	NR
Hair-Coloring	NR	0.000013	26	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	47	0.000003-0.003	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Hydroxypropyl Cyclodextrin		**Hydroxypropyltrimonium Hydrolyzed Corn Starch**		**Hydroxypropyltrimonium Hydrolyzed Wheat Starch**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%
Totals/Conc. Range	53	0.00001-2	11	0.19-0.65	8	NR
Duration of Use						
Leave-On	52	0.00001-2	3	0.24-0.65	NR	NR
Rinse off	1	0.02-0.1	8	0.19-0.43	8	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	13	0.02-1.3	NR	0.65	NR	NR
Incidental Ingestion	NR	0.75	NR	NR	NR	NR
Incidental Inhalation- Sprays	33	0.34-1	3	0.24*	NR	NR
Incidental Inhalation- Powders	29	0.1-2	NR	NR	NR	NR
Dermal Contact	50	0.00001-2	NR	0.65	8	NR
Deodorant (underarm)	1	0.34-2	NR	NR	NR	NR
Hair - Non-Coloring	2	1	11	0.19-0.43	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.02	NR	NR	NR	NR
Mucous Membrane	NR	0.75	NR	NR	8	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Hydroxypropyl Starch		**Hydroxypropyltrimonium Maltodextrin Crosspolymer**		**Inulin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	9	0.25-8.2	NR	0.00045	41	0.0005-3
Duration of Use						
Leave-On	8	0.25-8.2	NR	0.00045	14	0.0005-3
Rinse off	1	0.5-6	NR	NR	27	0.25
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	NR	NR	NR	1	0.0005
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	6	0.25-0.88	NR	NR	8	NR
Incidental Inhalation- Powders	NR	8.2**	NR	NR	9	0.0008**-2.5**
Dermal Contact	3	0.5-8.2	NR	0.00045	22	0.0005-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	6	0.25-1.4	NR	NR	18	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.5	NR	NR	4	0.25
Baby Products	NR	NR	NR	NR	1	NR

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

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

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

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

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

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

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for (Bath)Use Product Uses.
*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
**It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
***Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 6. Composition/Properties Data on Two Hydrolyzed Starch (unknown structural configuration – modified) Products.[163,164]

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

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

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

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

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

Table 7. Acute Toxicity Studies on Polysaccharide Gums

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 LC50 of > 0.0015 mg/l was reported.[176]

Oral

Branched - Natural/Unmodified

Glucomannan: Male and female mice (number and strain not stated). LD_{50} > 2,800 mg/kg body weight. No abnormalities with respect to the following: appearance, behavior, body weight changes, occult blood in the urine and feces, or macroscopic findings.[177]

Glucomannan: Male and female rats (number and strain not stated. LD_{50} > 5,000 mg/kg body weight.[176]

Sterculia Urens Gum: Vehicle: corn oil. 5 fasted male Sprague-Dawley rats. LD_{50} > 10,000 mg/kg body weight. Transient depression, but no other toxic effects.[178]

Branched - Modified

Corn Starch Modified: Vehicle: distilled water. 5 male and 5 female Wistar albino rats. Organisation for Economic Co-operation and Development (OECD) 401 protocol. 14-day observation period. Alopecia in one animal. LD_{50} > 2,000 mg/kg body weight.[90]

Dextrin Myristate: Rats (number and strain not stated). LD_{50} > 2,000 mg/kg body weight.[91]

Dextrin Palmitate: Rats (number and strain not stated). LD_{50} > 2,000 mg/kg body weight.[92,93]

Potato Starch Modified: 30% aqueous solution. Albino rats (5 males, 5 females). OECD 401 protocol. 14-day observation period. Soft stool (1 female); and no other signs. Body weight changes at necropsy normal. LD_{50} > 5,000 mg/kg body weight.[94,179]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate: Material structurally similar to this gum tested. 5 male and 5 female Wistar albino rats. OECD Guideline 401 test protocol. Dosing followed by 14-day observation period. No abnormal systemic signs. LD_{50} > 5,000 mg/kg body weight.[95,96,180]

Stearoyl Inulin: Rats (number and strain not stated). Protocol not stated. LD_{50} > 2,000 mg/kg body weight.[98,99]

Dermal

Branched - Natural/Unmodified

Glucomannan: Male and female rabbits (number and strain not stated). Protocol not stated. LD_{50} > 2,000 mg/kg body weight.[176]

Branched - Modified

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs (4 weeks old). Maximization test. No mortality occurred and no clinical signs of systemic toxicity. Body weights and weight gains similar in treated and control groups.[181]

Corn Starch Modified: Corn starch modified (Amaze® [28-1890]) in distilled water (30% solids). 5 male and 5 female New Zealand White rabbits. OECD 402 protocol. 14-day observation period. Nine of 10 rabbits survived. LD_{50} > 2,000 mg/kg body weight.[90]

Dextrin Myristate: Rats (number and strain not stated). Occlusive dressing technique (details not included). LD_{50} > 2,000 mg/kg body weight.[91]

Dextrin Palmitate: Rats (number and strain not stated). Occlusive dressing technique (details not included). LD_{50} > 2,000 mg/kg body weight.[92,93]

Potato Starch Modified: 10 rats (strain not specified). OECD 402 test guideline. LD_{50} > 2,000 mg/kg body weight.[179]

Potato Starch Modified: 18.5% solids aqueous solution. 10 New Zealand White rabbits (5 males and 5 females). Semi-occlusive patch application. Dose per cm^2 was not stated. Very slight to slight erythema/edema at application sites (all animals); reactions had cleared by 72 h. Signs of local irritation may have been due to mechanical trauma. LD_{50} > 2,000 mg/kg body weight.[94]

Intravenous

Linear Polysaccharides and Salts Thereof

Carrageenan and Potassium Carrageenan: ι-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units) or potassium carrageenan (2 mg in phosphate-buffered saline [PBS]). Groups of 5 female MF1 mice. i.v. injection (lateral tail vein). Controls injected with PBS (0.3 ml). Animals killed at 1 h and 24 h post-injection, and tissues prepared for microscopic examination. Carrageenan persisted for at least 6 months in livers and kidneys. Within 24 h of i.v. injection, damage to liver Küpffer cells and changes in the microcirculation characteristic of disseminated intravascular coagulation (DIC) in the liver and kidney observed. No adverse effects in hepatocytes, but chronic renal damage observed. ι-carrageenan less toxic to liver and kidney, compared to the potassium carrageenan (less pure, compared to ι-carrageenan).[182]

Carrageenan and Potassium Carrageenan: ι-carrageenan or potassium carrageenan in saline (0.5 ml or 1 ml i.v. injection). Groups of 9 to 15 female CAF_1 mice (Balb/c x A/He). 7- or 14-day observation period. Treatment with either compound induced anemia, granulocytosis, and early profound thrombocytopenia. Treatment with ι-carrageenan caused an early lymphocytosis, and both compounds induced lymphopenia by 18 h post-treatment. Treatment with either compound was associated with an early moderate reduction in the number of nucleated cells and granulocyte/macrophage colony-forming cells per femur. Each compound induced splenomegaly, and ι-carrageenan-treated mice developed hypoplasia of the thymus by 18 h post-injection. Sustained increase in numbers of colony-forming cells in spleen after treatment with each compound.[183]

Table 7. Acute Toxicity Studies on Polysaccharide Gums

Intrapleural
Linear Polysaccharides and Salts Thereof
Carrageenan: Groups of 6 adult female Balb/c mice (6 to 7 weeks old). One group received single intrapleural injection of 0.1 ml sterile saline (0.9% NaCl) and λ-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units; 1% in solvent [not stated]), which induced pleurisy. Another group each received single intrapleural injection of 1% λ-carrageenan (0.1 ml) only. Animals were killed, and lung tissue samples obtained for microscopic examination at 4 h and 24 h post-injection. Dense inflammation with lobar lung pneumonia and thickened alveolar septum (with occasionally obliterated alveoli) were observed.[184]
Carrageenan: Injection of 2% λ-carrageenan in saline (200 mg/kg) into pleural cavity. Groups of 10 mice. Dosing caused pleurisy, characterized by marked accumulation of fluid and the migration of leukocytes to the site of inflammation in lung.[185]
Transbronchial
Linear Polysaccharides and Salts Thereof
Carrageenan: Transbronchial injection of 0.75% carrageenan in physiological saline. 27 male albino rabbits. Surviving animals were killed according to the following schedule: 2 at 24 h; 3 each at 3 days, 1 and 2 weeks, and 1 month; 5 at 2 months; and 8 at 4 months. Pneumonia, followed by emphysema in the insulted lung, observed. Of the 8 animals injected with carrageenan and killed at 4 months, 3 were deemed inappropriate for morphometry because of developing fibrosis, abscesses and/or emphysematous bullae in the lungs. Thus, the lungs (mild to severe erythema observed) of the remaining 5 animals injected with carrageenan and of the 5 control rabbits killed at 4 months were prepared for morphometric analysis. Scattered infiltration of polymorphonuclear leukocytes throughout the affected lobe, subsequently replaced by accumulation of carrageenan-laden macrophages; changes lasted for 1 to 2 months. Enlargement of alveoli and alveolar ducts observed at 2 weeks to 2 months post-injection, and pulmonary emphysema observed at 4 months. The lobes not injected with carrageenan had normal appearance throughout study.[186]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Oral - Non-Human

Linear Polysaccharides and Salts Thereof

Algin: 25% Sodium alginate (also known as algin) in diet. Two groups of mice (75 males and 75 females per test substance). Feeding with sodium alginate in the diet for 89 weeks. At week 87, half of the surviving male and female mice in each test group placed on control diet (containing 55% pregelatinized potato starch). During feeding period, dietary levels of test substances gradually increased until diets contained (by weight) 25% sodium alginate. All survivors killed during weeks 89 to 92. Sodium alginate caused increased water consumption, distinct caecal and colonic enlargement, and a slightly increased incidence of intratubular nephrosis. Sodium alginate was nephrotoxic, causing increased kidney weights, distension of the renal calyx and high incidence of dilated distal tubules. Increased incidence of gastric trichobezoars observed in mice fed starch acetate. The incidence of intratubular calcinosis or concretions in the pelvic space was not reduced during the recovery period. Caecal and colonic enlargement and changes in urinalysis results were found to be reversible.[57]

Carrageenan: 25,000 ppm or 50,000 ppm kappa carrageenan. Groups of Fischer 344 rats (20/sex/group). Feeding in diet for 90 days. Clinical signs limited to soft feces in high dose rats, and to a lesser extent, in low dose rats. No treatment-related effects on body weights, urinalysis, hematology or clinical chemistry parameters, or on organ weights or ophthalmic, macroscopic or microscopic findings. Gastrointestinal tract appeared normal in detailed histopathological evaluation. NOAEL = 50,000 ppm (mean calculated test material consumption of 3394 ± 706 mg/kg/day in males and 3867 ± 647 mg/kg/day in females).[138]

Carrageenan: kappa/lambda-carrageenan (from *C. crispus* or *G. mamillosa)* at concentrations of 0, 0.1, 5, 15, or 25%. Five male and five female mice of 2 unidentified strains. Lifetime dietary feeding had no adverse effect. Ref 71 Same test material and dietary concentrations. Five male and 5 female rats of 2 unidentified strains. Lifetime dietary feeding. Evidence of hepatic cirrhosis, only at the 25% concentration, with no effect on mortality.[89]

Carrageenan: Extracts of kappa-carrageenan (from *Hypnea musciformis* or *Irideae crispata)* at concentration of 1% or 5%. Groups of 15 male and female Sprague-Dawley rats. Feeding in diet for 1 year. Weight loss ($p = 0.05$) in all treatment groups, compared to control (alphacel) group. Livers of rats fed 1% concentration normal at gross and microscopic examination. Livers from rats given 5% kappa-carrageenan from *H. musciformis* normal at gross and microscopic examination, except for nodules in 2 of 12 livers. Gross examination of livers from rats fed 5% kappa-carrageenan (from *I. crispata*) showed decreased size, rough surface, and vascularization in 10/13 rats, probably treatment-related. Microscopically, these livers were normal, except for focal necrosis in 1 of 10 livers. No evidence of storage of carrageenan-like material (metachromatic) in liver cells of any of the treated rats, and no fibrillar material observed using electron microscopy. No changes observed in stools of rats receiving 1% of either carrageenan. Loose stools in female rats given 5% kappa-carrageenan from *I. crispata* and in males given either carrageenan at 5% concentrations. Blood found sporadically in stools, but frequency was not significant.[89]

Carrageenan: kappa/lambda-carrageenan. Groups of 19 male and 21 female rhesus monkeys. Feeding (gavage) with 0, 50, 200, or 500 mg/kg body weight (6 days/week for five years, and dietary feeding for an additional 2.5 years. Random distribution of loose stools, chronic intestinal disorders, poor appetite, and emaciation. Stool consistency decreased in dose-related trend over entire 7.5 years of the study; findings of fecal occult blood increased in similar fashion. Mean survival time similar in all groups; no gross or microscopic changes in tissues examined. Sporadic differences in body weight observed randomly. Females had significant body-weight depression (not dose-related) in last 2.5 years of study. No consistent, statistically significant changes in hamatological or clinical chemical values, absolute organ weights, or organ-to-body weight ratios after 7.5 years of feeding. Cytochemical and ultrastructural observations revealed no storage of carrageenan-like material in livers, obtained at biopsy or in other organs obtained at necropsy; no dose-related gross or microscopic changes in other tissues.[89]

Inulin: 7.5% inulin. 20 Wistar rats of the Crl:(WI)BR strain (10 males, 10 females). Daily dietary feeding for 13 weeks. No remarkable microscopic or macroscopic findings.[187]

Branched - Natural/Unmodified

Arabinoxylan: Wheat bran extract (~ 80% arabinoxylan oligopeptides) at concentrations of 0.3%, 1.5%, and 7.5%. 3 groups of 20 Wistar rats of the Crl:(WI)BR strain (10 males/group, 10 females/group). Feeding resulted in average daily intakes of 0.2 g/kg (0.3% concentration), 0.9 g/kg (1.5%), and 4.4 g/kg (7.5%) for 13 weeks. No evidence of test substance-related adverse macroscopic or microscopic findings. At histopathological examination, minimal bilateral hypertrophy of renal cortical tubules in males and females, particularly in highest-dose group. Findings were not accompanied by degenerative changes or changes in kidney weight, and were considered non-toxic and suggestive of an adaptive response. No remarkable findings in control rats fed basal diet. NOAEL = 4.4 g/kg/day.[187]

Ghatti Gum: Ghatti gum concentrations of 0, 0.5, 1.5 and 5%. Groups of Sprague-Dawley rats (10 males/group, 10 females/group). Dietary feeding (in basal diet) for at least 90 days. Ghatti gum intake at 5% dietary level ranged from 3044 to 3825 mg/kg body weight/day. Feed consumption among treated and control groups was similar for males and females. 2 of 10 females in 5% ghatti gum group had a single colon ulcer, with associated acute inflammation. Ulcers were considered sporadic occurrences, possibly attributable to basal diet. NOAEL = 5% in diet; NOAELs for males and females estimated at 3044 and 3309 mg/kg/day, respectively.[188]

Ghatti Gum: 5% Ghatti gum. Groups of 20 female Sprague-Dawley rats. Dietary feeding for at least 90 days. Single colon ulcer, with associated acute inflammation, in 1 of 20 control females given basal diet. Colon ulcer considered sporadic, possibly attributable to basal diet. Statistically significant alterations in clinical chemistry were considered sporadic and unrelated to treatment. Feed consumption among treated and control groups similar for each sex. NOAEL = 5% in diet; NOAELs at 3670 and 3825 mg/kg/day for different control diets.[188]

Glucomannan: 10% konjac (plant consisting mostly of glucomannan). Groups of four male Sprague-Dawley rats were fed either 5% cellulose (control), 10% pectin, or 10% konjac for 28 days. After dosing period, rats were fasted for 24 h, fed 5 g/kg body weight brown rice, and killed 5 h later. No indication of toxicity.[189,190]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Branched - Natural/Unmodified

Glucomannan: 2.5%, 5%, or 10% refined konjac meal. Groups of 12 five-week-old Sprague-Dawley rats of each sex . Feeding with either a normal basal diet, a hypercholesterolaemic diet (control diet containing 1% cholesterol), or one of three test diets. Because refined konjac meal contains ~ 80% glucomannan, the highest concentration of glucomannan tested was ~ 8%. Four animals of each sex from each group killed after 4, 8, and 12 weeks of feeding. Histological and gross examination of livers from rats fed 1% cholesterol showed spreading fatty degeneration with focal necrosis and a nonspecific inflammation reaction. Similar changes observed in group receiving refined konjac meal at the end of 4 weeks, but the changes disappeared gradually with longer feeding times, and the morphology of the liver was similar to that in the normal control group at the end of 12 weeks. Changes were also observed at gross examination of the liver.[191]

Glucomannan: Basal diet in which 1% of the cornstarch replaced with refined glucomannan (i.e., 1% konjac meal). Groups of 15 Sprague-Dawley rats of each sex. Dietary feeding for 18 months. At the end of feeding period, the animals were killed and the brain, liver, aorta, kidney, spleen, and heart removed. At microscopic examination, the livers of treated rats contained smaller, more lightly stained nuclei and reduced bile-duct proliferation in the portal area. Endothelial cells in the aorta of treated animals were smaller and there was less thickening of the aortic wall. These changes were related to less senescence in the treated group than in the control group. No evidence of treatment-related pathological changes. NOAEL = 1% konjac meal, equivalent to an intake of 500 mg/kg body weight per day.[189]

Pectin and Solanum Tuberosum (Potato) Starch: Test diets containing 5% or 10% pectin-derived acidic oligosaccharides (pAOS). Two groups of F_1 rats (from outbred strain of Wistar rats (Crl:WI(WU); number not stated). Dietary feeding with test (±7 g/kg body weight/day) and control diets for 13 weeks. To keep the total level of added test substance equal in each diet, the low-dose diet (5% pAOS) was adjusted with 5% potato starch. One control group received the standard rodent diet supplemented with 10% potato starch, and the other control group received 10% short-chain FOS (scFOS) in the diet. No treatment- related clinical signs observed, and none of the rats died . Ophthalmoscopic examination did not reveal any treatment-related ocular changes. Neurobehavioral examination and motor activity assessment did not indicate any neurotoxic potential. No relevant differences in body weight, growth rate and feed intake. Macroscopic examination at necropsy did not reveal any adverse effects. Microscopic examination revealed treatment-related histopathological changes in the urinary bladder of animals of the 10% pAOS group. One male and one female of the 5% pAOS group and one male of the control group showed diffuse hyperplasia (very slight). In addition, two males and two females of the 5% pAOS group showed simple hyperplasia in a part of the urinary bladder lining ('focal hyperplasia'). No treatment-related hyperplasia of the transitional epithelium was observed in the kidney. Administration of pAOS at dietary levels up to 10% (equivalent to 7.1 g/kg body weight/day) did not reveal any relevant effects that could be attributed to the ingestion of acidic oligosaccharides.[192]

Starch Acetate: 55% Starch acetate (a chemically modified potato starch) in diet. Two groups of mice (75 males and 75 females per test substance). Feeding with sodium starch acetate in the diet, respectively, for 89 weeks. At week 87, half of the surviving male and female mice in each test group placed on control diet (containing 55% pregelatinized potato starch). During feeding period, dietary level of test substance gradually increased until diet contained (by weight) 55% starch acetate. All survivors killed during weeks 89 to 92. Starch acetate caused increased water consumption, distinct caecal and colonic enlargement, and a slightly increased incidence of intratubular nephrosis. Increased incidence of gastric trichobezoars. Concretions in renal pelvis with slight urinary changes, such as increased amounts of amorphous material in the urine and increased urinary calcium content, in the mice fed starch acetate not toxicologically significant. The incidence of intratubular calcinosis or concretions in the pelvic space was not reduced during the recovery period. Caecal and colonic enlargement and changes in urinalysis results were found to be reversible.[57]

Sterculia Urens Gum: 5 non-fasted male Sprague-Dawley rats. Animals intubated with 5 g/kg/day, daily for 5 days. No adverse effects.[178]

Sterculia Urens Gum: 7% (w/w) sterculia urens gum. Albino Wistar rats (rats housed 3 per cage; number tested not stated) Transmission electron microscopy used to study ultrastructure of jejunum, ileum, and cecum after dietary supplementation for 45 days [15 micrographs analyzed] for 45 days. No abnormalities in any of the organelles.[193]

Branched - Modified

Carboxymethyl Inulin: Carboxymethyl inulin (31.1% aqueous). Groups of five male and five female Wistar Crl rats. Doses of 0, 50, 150 and 1000 mg/kg/day (by gavage) for 4 weeks. In all dose groups, no treatment-related effects with respect to: body weight, feed consumption, mortality, hematology, clinical blood chemistry, organ weights or gross or microscopic pathology.[181]

Cyclic

Cyclodextrin: β-cyclodextrin (12,500, 25,000 and 50,000 ppm). Groups of 40 (20 males, 20 females/group) CrI:CD (SD) BR Sprague-Dawley rats. Feeding in the diet for 52 weeks. Control group fed basal diet. The liver and kidney were identified at histopathological examination as target organs for toxicity at concentrations of 50,000 ppm and 25,000 ppm, with the hepatic changes associated with increased plasma liver enzyme and decreased plasma triglyceride concentrations. The only finding for kidneys was a statistically significant ($p < 0.01$) increased incidence of minimal/trace amounts of pigment in the epithelium of the cortical tubules in female rats that received 25,000 ppm or 50,000 ppm β-cyclodextrin in the diet. The "non-toxic dietary inclusion level" of β-cyclodextrin was 12,500 ppm (equivalent to 654 or 864 mg/kg/day for males or females, respectively).[45]

Cyclodextrin: β-cyclodextrin (6200, 12,500 and 50,000 ppm). Groups of 40 (20 males, 20 females/group) pure-bred Beagle dogs. Preceding test protocol in rat study used. No pathological evidence of systemic toxicity, although there were minor changes in urinalysis and biochemical parameters and a slightly higher incidence of liquid feces. These changes were considered to be of no toxicological importance. The "non-toxic dietary inclusion level" of β-cyclodextrin was 50,000 ppm (equivalent to 1,831 or 1,967 mg/kg/day for males or females, respectively).[45]

Cyclic

Cycodextrin: γ-cyclodextrin (5%, 10%, or 20%). Groups of 8 (4 males, 4 females) Beagle dogs. Feeding in the diet for 13 weeks. Control group fed basal diet. No treatment-related changes in behavior or appearance and no mortalities. No treatment-related differences with respect to ophthalmoscopic examinations, hematological parameters, clinochemical analyses of the plasma, and semiquantitative urine analyses. Relative ovary weights ignificantly increased in the 10% and 20% concentration groups, but this observation was probably a result of an unusually low ovarian weight in the controls. An increase in relative liver weights in males of the 10% and 20% concentration groups was also considered to lack toxicological relevance, because this observation was not associated with changes in plasma enzyme levels or with histopathological changes. No treatment-related abnormalitiesobserved at necropsy. At microscopic examination, no treatment-related effects in any of the various organs and tissues. Daily consumption of up to 20% γ-cyclodextrin in the diet (≈ 7.7 g/kg body weight in males and 8.3 g/kg body weight in females) did not cause toxicity.[194]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Oral - Human

Branched Natural/Unmodified

Sterculia Urens Gum: 5 male volunteers (30 to 56 years old). Ingestion of sterculia urens gum (10.5 g in diet) daily for 21 days. No toxicity or significant effects on plasma biochemistry, hematological indices, or urinalysis parameters were noted.[195]

Branched – Modified

Propylene Glycol Alginate: 5 male volunteers. Following a 7-day control period, the men consumed an amount of propylene glycol alginate equal to 175 mg/kg body weight during the first 7 days of the test period. The amount consumed was increased to 200 mg/kg body weight for the remainder (i.e., 16 days) of the 23 days of dietary supplementation. No significant effect (statistical analysis not performed) on the following: hematological indices, plasma biochemistry parameters, urinalysis parameters, blood glucose levels, plasma insulin concentrations, and expired hydrogen concentrations. Ingestion of propylene glycol alginate caused no adverse dietary or physiological effects. The enzymatic indicators of toxicological effects remained unchanged.[54]

Dermal - Non-Human

Branched - Modified

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs. Maximization test. 5 female guinea pigs (vehicle controls). No mortalities or clinical signs of systemic toxicity were observed. Body weights and weight gains were considered similar when treated and control groups were compared.[181]

Potato Starch Modified: Rats (10 males, 10 females). Applied to skin under occlusive dressing for 28 days (2 g/kg body weight/day) according to OECD 410 test guideline. Sporadic gains and losses of body weight. Compared to the vehicle control group, statistically significant (p value not stated) decrease in body weight gain in treated females during weeks 1 and 4. Clinical biochemical test results indicated statistically significant (p value not stated) decrease in serum triglycerides and slight increase in serum calcium, sodium, and phosphorus in treated males, but not in females. However, none of the other test parameters supported these findings. Decreased organ weights and differences in hematologic test parameters, but these findings were within historical control ranges for this species of rat. Signs of systemic toxicity not observed at gross examination of treated animals. NOAEL $\geq$ 2,000 mg/kg body weight/day.[179]

Potato Starch Modified: 10% solids aqueous solution. New Zealand albino rabbits (10 males and 10 females) tested; 20 rabbits (controls). Applied to skin under a non-occlusive patch (dose = 2 g/kg bodyweight). Area of application and concentration/dose per cm^2 were not stated. Distilled water, under a non-occlusive patch, applied to controls. Daily evaluations for signs of systemic toxicity, mortality, or morbidity occurred daily; necropsy on day 28. The following considered within normal parameters: body weights, food consumption, gross pathology, and histopathology. Minor differences in organ weight and clinical chemistry changes observed, but considered irrelevant. No significant toxic effects in rabbits.[94]

Table 9. 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.[89]
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.[89]
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.[89]
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.[89]
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.[89]
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.[89]
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.[89]
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.[89]
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.[89]
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).[196]
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).[197]
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.[198]

Table 9. Reproductive and Develpmental Toxicity Studies on Polysaccharide Gums

Ingredient	Animals	Procedure	Results
α-Cyclodextrin	Groups of 16 pregnant female New Zealand White rabbits	Concentrations of 5%, 10%, or 20% in the diet on gestation days 0 to 29.	No effect on reproductive performance, and not fetotoxic, embryotoxic, or teratogenic.[199]
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.[132]
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.[192]
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.[200]
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.[200]
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.[200]
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.[200]
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.[201]
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.[201]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
		Bacterial Assays		
Arabinoxylan	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *Escherichia coli* (*E. coli*) strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[187]
Carboxymethyl inulin	Same as above	Ames test	Same as above	Not genotoxic.[181]
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.[202]
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.[89]
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.[202]
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.[90]
Dextrin myristate (Rheopearl MKL2)	*Salmonella typhimurium* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[91]
Dextrin palmitate (Rheopearl KL2 and Rheopearl TL2)	*Salmonella typhimurium* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[92,93]
Dextrin isostearate (Unifilma HVY)	*Salmonella typhimurium* and *E. coli* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[152]
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.[203]
Glucomannan	*Salmonella typhimurium* (5 strains, not stated)	Ames test	With and without metabolic activation (doses not stated)	Not genotoxic.[176]

Table 10. 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.[100]
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.[192]
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.[95]
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.[204]
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.[98,99]
		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.[187]
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.[181]
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.[202]
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.[202]
Ghatti gum	Chinese hamster ovary (CHO-WBL) cells	Chromosome aberrations assay	up to 6,000 µg/ml, with and without metabolic activation	Not genotoxic.[203]

Table 10. 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.[203]
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.[189]
Glucomannan	CD-1 (ICR) mouse bone marrow cells	Micronucleus test	Mice dosed orally with 5,000 mg/kg body weight	Not genotoxic.[189]
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.[192]
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.[192]
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.[192]
Potato starch modified	Mice (strain not stated)	Mouse lymphoma assay. OECD 476 test guideline.	Not stated	Not genotoxic.[179]
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.[178]
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.[178]
Sterculia urens gum	WI-38 human embryonic lung cells	Cytogenetic assay	up to 1,000 µg/ml	No effect on anaphase chromosomes.[178]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
Sterculia urens gum	Sprague-Dawley rats	Dominant lethal gene test	Groups of rats intubated with 5,000 mg/kg, 2500 mg/kg, and 30 mg/kg, respectively	No consistent responses suggestive of genotoxicity.[178]

Table11. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Skin Irritation and Sensitization - Non-Human

Linear Polysaccharides and Salts Thereof

Algin: 2% algin. Rabbits (number not stated). 3 primary skin irritation experiments. Occlusive patches applied to the skin. Mean skin irritation score of < 0.5 = non-irritating; 0.5 to 2.0 = slightly irritating. Primary irritation index (PII) values calculated. PII of < 0.5 deemed satisfactory, but PII no greater than also acceptable. PII values of 0, 0, and 0.08 were reported in the 3 experiments, respectively.[88]

Algin: 2% algin. Rabbits (3 per experiment). Test substance (2 ml) applied to flanks 5 days per week for 6 weeks. Mean maximum irritation index (MMII) values calculated. Macroscopic and histological examinations of test sites performed. MMII values of 0.67, 0, and 0.67 were reported in 3 experiments, respectively. Daily application of test substance did not induce a severe reaction at either macroscopic or histological examination.[88]

Carrageenan: Food grade iota-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units). Guinea pigs (number not stated). Study details not included. No skin sensitization.[89]

Branched - Natural/Unmodified

Glucomannan: Konjac flour (mechanically ground). Guinea pigs (number not stated). Application to skin according to the Buehler closed patch method. No sensitization.[176]

Branched - Modified

Corn Starch Modified: Corn starch modified in distilled water (30% solids). 10 Zealand White rabbits (5 males and 5 females). Application to skin (2,000 mg/kg); dose per cm^2 not stated. Dermal reactions either absent or classified as barely perceptible at 24-h and 48-h readings, and absent at the 74-h reading. Mild skin irritant (primary irritation index = 0.25).[90]

Corn Starch Modified: Corn Starch Modified (up to 30%). 20 guinea pigs (strain not stated; 10 males, 10 females). Maximization test (OECD protocol 406.) During induction,10% solution injected and 30% solution applied topically. Concentration per cm^2 was not stated. During challenge, application of 20% solution for 24 h. Reactions scored at 48 h and 72 h post-application. Control group (5 males, 5 females) tested with distilled water during induction and challenged with test substance. Reactions ranging from no erythema to moderate erythema observed after induction with the control or test substance. Erythema observed after challenge with test substance. However, rechallenge with same test substance concentration did not cause erythema. Not a sensitizer.[90]

Corn Starch Modified: 50% corn starch modified paste. 25 female Hartley guinea pigs. RIPT according to Buehler method (OECD protocol 4067). 10 guinea pigs treated with distilled water (control). Positive control (isoeugenol) tested in study performed within 6 months of current study. During induction, test material applied topically to shoulder area (~ 0.4 g on occlusive patch; area of application site not stated) . Topical challenge with 50% corn starch modified paste for 6 h. Challenge reactions scored at 24 h and 48 h post-application. No erythema or edema during induction or challenge. Non-sensitizer. Positive control induced sensitization.[95]

Carboxymethyl Inulin: Carboxymethyl inulin (1% to 100%). Groups of 2 adult Dunkin–Hartley albino guinea pigs. Test substance injected into clipped scapular region; reactions scored at 24 h and 48 h. Also, series of test article concentrations (0.5 ml) applied topically for 24 h to clipped external flank using Metalline patches secured with tape and an elastic bandage. Test material was removed after 24 h and signs of irritation recorded at 24 h and 48 h after treatment. Undiluted carboxymethyl inulin produced necrosis after intradermal injection, observed both after 24 h and 48 h; 20% to 50% did not cause necrosis, but grade 2 erythema was observed at either 24 h or 48 h. Signs of irritation were not observed at 24 h or 48 h at concentrations up to 100% in the patch tests.[181]

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs. Maximization test. Five female guinea pigs served as vehicle controls. No evidence of sensitization.[181]

Potato Starch Modified: 10 rats received single dose of potato starch modified (dose = 2 g/kg) dermally. Very slight to well-defined erythema and edema observed in all animals after 24 h. At 48 h, very slight erythema and very slight edema in 5 and 3 rats, respectively. All reactions had cleared by 72 h.[179]

Potato Starch Modified: Rats (10 males, 10 females). Dose of 2 g/kg body weight/day applied to the skin, under occlusive dressing, for 28 days . Neither erythema nor edema observed. However, small scabs observed on 5 males and 6 females, attributed to adhesion of test material to skin.[179]

Potato Starch Modified: Potato starch modified (18.5% aqueous suspension). 20 animals (species not stated). Buehler test (OECD 406 test guideline). Faint erythema (non-confluent) observed in 6 of 20 animals after second or third induction application. No evidence of sensitization.[179]

Potato Starch Modified: Potato Starch Modified (10% solids aqueous solution). 10 male and 10 female New Zealand albino rabbits (test animals)). Using non-occlusive patch, test substance (2 g/kg body weight) applied to the skin. The area of application and dose per cm^2 not stated. 20 control animals tested with distilled water under non-occlusive patch. Neither erythema nor edema observed in treated or control animals. No adverse morphologic effects on the skin.[94]

Potato Starch Modified: Potato starch modified (18.5% solids). 20 guinea pigs (10 males, 10 females). RIPT according to Buehler method (OECD 406 protocol). Concentration per cm^2 not stated. 10 control animals (5 males, 5 females) treated with distilled water. During induction, very faint erythema in 6 of 20 animals; reactions not observed in controls. Very faint erythema observed in 2 of 20 treated animals and in 2 of 10 controls during challenge phase. Non-sensitizer.[94]

Dextrin Myristate: 6 New Zealand white rabbits. Skin irritation study (test protocol not stated). Non-irritant.[91]

Dextrin Myristate: Guinea pigs (number and strain not stated). Magnusson-Kligman maximization test. No evidence of skin sensitization.[91]

Dextrin Palmitate: 3 New Zealand white rabbits. Skin irritation study (test protocol not stated). Non-irritant.[92,93]

Table11. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Branched - Modified

Dextrin Palmitate: Guinea pigs (number and strain not stated). Magnusson-Kligman maximization test. No evidence of skin sensitization.[92,93]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate: Test Material: Material (corn starch modified) described as structurally similar to sodium hydrolyzed starch dodecenylsuccinate and as the calcium salt of the ester formed from the reaction of 3-(dodecenyl)dihydro-2,5-furandione and corn starch, in which the degree of substitution per glucose unit is less than 0.1. 6 New Zealand White rabbits. OECD 404 test protocol. 50% slurry of test material (1 ml) applied topically (on occlusive patch, area of application site not stated) for 24 h to intact and abraded skin sites on the back of each animal. Reactions scored for up to 72 h after patch application. Erythema observed at intact and abraded sites on one animal, and reactions had cleared by 48 h. Mildly irritating to the skin (primary irritation index = 0.09).[95,205]

Stearoyl Inulin: 6 Japanese white rabbits. Skin irritation potential evaluated (concentrations and test protocol not stated). Non-irritant.[98,99]

Stearoyl Inulin: Guinea pigs (number and strain not stated). Skin sensitization potential evaluated (concentrations not stated) according to adjuvant and patch method. Skin irritation classified as weak. Very low skin sensitization potential.[98,99]

Skin Irritation and Sensitization - Human

Linear Polysaccharides and Salts Thereof

Algin: 20% aqueous sodium alginate. 12 male subjects with no history of allergy. Patch-testing (Finn chambers) with 20% aqueous sodium alginate according to International Contact Dermatitis Research Group (ICDRG) recommendations. Area (cm^2) of application and dose per cm^2 not stated. Reactions scored at 2 and 3 days post-application. ± reaction observed in one subject on days 2 and 3. Results negative for skin irritation and allergic contact dermatitis.[206]

Linear - Modified

Hydrolyzed Furcellaran: Mixture containing 1.35% furcellaran powder and 1% phenoxyethanol. 10 adults. Mixture applied (under occlusive patch) for 48 h to back. Area (cm^2) of application and dose per cm^2 not stated. Non-irritant.[100]

Hydrolyzed Furcellaran: Mixture containing 1.35% furcellaran powder, 0.1% potassium sorbate, and 0.05% citric acid. 10 adults. Mixture applied (under occlusive patch) for 48 h to back. Area (cm^2) of application and dose per cm^2 not stated. Non-irritant and non-sensitizer.[100]

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

Maltodextrin: Eye gel containing 2.45% maltodextrin. 103 subjects. HRIPT. Patch type, area (cm^2) of application, and dose per cm^2 not stated. Challenge patches applied to original and alternate sites, and challenge reactions scored at approximately 48 h and 96 h post-application. Five instances of erythema (grade 1) during induction. At 48-h challenge reading, a grade of 1 reported for alternate challenge site of one subject. Gel did not induce allergic contact dermatitis.[207]

Branched - Modified

Corn Starch Modified: 7.5% solution in distilled water. 26 female subjects. 21-day cumulative irritation study. Test material (0.2 ml per 24-h patch) applied topically. Area (cm^2) of application and dose per cm^2 not stated. Reactions ranged from no erythema to minimal erythema. Non-irritant. Distilled water (vehicle control) did not cause erythema. Sodium lauryl sulfate (positive control) induced marked erythema and papules.[90]

Corn Starch Modified: 7.5% solution in distilled water. 113 subjects (86 females, 27 males). HRIPT. Patch type, area (cm^2) of application, and dose per cm^2 not stated. Challenge eactions scored at 48 h and 96 h post-application. Test substance and distilled water caused slight erythema in 3 subjects. Test substance and distilled water classified as non-sensitizers.[90]

Dextrin: Rinse-off facial product containing 42.6919 % dextrin (1% aqueous; effective concentration ≈ 0.4%). 54 subjects (46 females, 8 males). HRIPT. During induction, product (0.1-0.15 g on occlusive patch) applied for 24 h to the back.. Dose/concentration per cm^2 not stated. Challenge patch applied to new test site and reactions scored at 24 h and 72 h post-application. Transient, barely perceptible erythema, in 1 subject, during induction. No reactions observed during challenge phase. No clinically significant skin irritation or evidence of allergic contact dermatitiss.[208]

Dextrin Myristate: Leave-on facial product containing 0.3% dextrin myristate. 51 subjects (40 females, 11 males). HRIPT. During induction, product (0.1-0.15 g on occlusive patch) applied for 24 h to the back.. Dose/concentration per cm^2 not stated. Challenge patch applied to new test site and reactions scored at 24 h and 72 h post-application. Skin reactivity was not observed during the induction or challenge phase. Product did not cause skin irritation or allergic contact dermatitis.[209]

Hydroxypropyltrimonium Hydrolyzed Corn Starch: 15% hydroxypropyltrimonium hydrolyzed corn starch. 47 male and female subjects. HRIPT. During induction, semi-occlusive patch (1" x 1") containing approximately 0.2 ml of test material applied for 24 h to upper back. 24-h challenge patch applied to new test site, adjacent to induction patch site. No reactions during study. No skin irritation or allergic contact sensitization potential.[210]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate: Test material (powder) described as structurally similar to sodium hydrolyzed starch dodecenylsuccinate and corn starch modified. 50% w/v slurry of test material in baby oil also tested. 23 subjects. Powder applied topically (0.2 g, moistened with distilled water; area of application site not stated) under occlusive conditions for 21 days. 50% w/v slurry applied acccording to same procedure. Powder caused dermal effects that ranged from no irritation to erythema and papules cumulative irritation score = 177). Superficial layer effects ranged from none to glazing with peeling and cracking. 50% w/v slurry caused milder reactions (cumulative irritation score = 50.6). Both test materials classified as probable mild irritants under normal use conditions.[95,96,211]

Branched - Modified

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate: Cleanser containing 10 wt% sodium hydrolyzed potato starch dodecenylsuccinate. 227 subjects (18 to 69 years old; 165 females, 62 males). HRIPT. During induction, occlusive patch containing ~ 0.2 g of the test material was applied to the back (area of application site not stated) for 24 h. week non-treatment period. Occlusive challenge patch containing the test material (~ 0.2 g) applied for 24 h to new site on back. Reactions were scored for up to 96 h post-application. Four subjects had low-level (±) reactions during induction, and 2 subjects had ± reactions duringchallenge phase. Non-sensitizer.[212]

Table11. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Unknown Structural Configuration

Algae Exopolysaccharides: 1% solution of algae exopolysaccharides. 50 subjects. HRIPT. During induction, occlusive patch containing test substance (0.2 ml or 0.2 g) applied for 24 h to infrascapular region of back. Dose per cm^2 not stated. Challenge dose (equivalent to induction application) of test substance applied once to new test site. Reactions scored at 24 h to 48 h post-application. No evidence of adverse reactions. Not a primary skin irritant or sensitizer.[213]

In Vitro

Branched - Modified

Hydroxypropyltrimonium Hydrolyzed Corn Starch: MatTek Corporation EpiDerm™ skin model *in vitro* toxicity testing system. Skin model consists of normal, human-derived epidermal keratinocytes (NHEK) that have been cultured to form a multilayered, highly differentiated model of the human epidermis. Test procedure utilizes a water-soluble, yellow tetrazolium salt MTT. In the mitochondria of viable cells, MTT is reduced by succinate dehydrogenase to an insoluble formazan derivative (purple color). Substances that damage this enzyme inhibit reduction of the tetrazolium salt. Undiluted test substance (100 µl) added to millicells containing EpiDerm™ samples; time at which % viability would be 50% (ET_{50}) estimated. Mild irritant (ET_{50} = 18.1h).[214]

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2015 FDA VCRP Data

Maltodextrin

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

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

Acacia Catechu Gum **NR**

Acacia Farnesiana Gum **NR**

Acacia Senegal Gum

Acacia Seyal Gum **NR**

Agar

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

Agarose

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

Algae Exopolysaccharides **NR**

Algin

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

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

Alginic Acid

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

Ammonium Alginate **NR**

Amylodextrin

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

Amylopectin **NR**

Amylose **NR**

Aphanothece Sacrum Polysaccharide **NR**

Arabinoxylan **NR**

Astragalus Gummifer Gum

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

Avena Sativa (Oat) Starch

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

Calcium Starch Isododecenylsuccinate **NR**

Calcium Starch Octenylsuccinate **NR**

Calcium Alginate

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

Calcium Carrageenan **NR**

Carrageenan

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

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

Cassia Augustifolia Seed Polysaccharide

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

Cichorium Intybus (Chicory) Root Oligosaccharides

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

Corn Starch Modified

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

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

Croscarmellose	**NR**

Cyclodextrin

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

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

Cyclodextrin Hydroxypropyltrimonium Chloride **NR**

Cyclodextrin Laurate

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

Cyclotetraglucose **NR**

Dextrin

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

Dextrin Behenate **NR**

Dextrin Isostearate **NR**

Dextrin Laurate **NR**

Dextrin Myristate **NR**

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

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

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

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

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

Ghatti Gum **NR**

Glyceryl Alginate **NR**

Glyceryl Dimaltodextrin **NR**

Glyceryl Starch

12A - Cleansing	1
Total	**1**

Hydrogenated Potato Starch **NR**

Hydrogenated Starch Hydrolysate

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

Hydrolyzed Carrageenan **NR**

Hydrolyzed Corn Starch Hydroxyethyl Ether **NR**

Hydrolyzed Corn Starch Octenylsuccinate

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

12G - Night	3
Total	**13**

Hydrolyzed Furcellaran	**NR**

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

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

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

Hydroxyethyl Cyclodextrin	**NR**

Hydroxypropyl Cyclodextrin

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

Hydroxypropyltrimonium Hydrolyzed Corn Starch

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

Hydroxypropyltrimonium Hydrolyzed Wheat Starch

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

Hydroxypropyl Oxidized Starch **NR**

Hydroxypropyl Starch

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

Hydroxypropyltrimonium Maltodextrin Crosspolymer **NR**

Inulin

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

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

Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch

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

Magnesium Alginate **NR**

Mannan

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

Methyl Cyclodextrin

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

Natto Gum

Palmitoyl Inulin **NR**

Pectin

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

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

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

Polianthes Tuberosa Polysaccharide

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

Potassium Alginate

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

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

Potato Starch Modified

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

Total	**61**

Propylene Glycol Alginate	
03D - Eye Lotion	1
03G - Other Eye Makeup Preparations	1
05I - Other Hair Preparations	1
07F - Makeup Bases	3
12C - Face and Neck (exc shave)	2
12F - Moisturizing	5
12G - Night	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	1
Total	**16**

Prunus Persica (Peach) Gum	**NR**
Pueraria Lobata Starch	**NR**
Sodium Algin Sulfate	**NR**
Sodium Carboxymethyl Inulin	**NR**

Sodium Carboxymethyl Starch	
03C - Eye Shadow	1
05I - Other Hair Preparations	1
06G - Hair Bleaches	8
12J - Other Skin Care Preps	1
Total	**11**

Sodium Carrageenan	
09A - Dentifrices	2
12C - Face and Neck (exc shave)	1
Total	**3**

Sodium Dextrin Octenylsuccinate	**NR**
Sodium Hydroxypropyl Oxidized Starch Succinate	**NR**

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate	
05F - Shampoos (non-coloring)	2
Total	**2**

Sodium Oxidized Starch Acetate/Succinate	
02B - Bubble Baths	1
05A - Hair Conditioner	2
05F - Shampoos (non-coloring)	2
10A - Bath Soaps and Detergents	1
12F - Moisturizing	1
Total	**7**

Sodium Starch Octenylsuccinate

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

Sodium/TEA-Undecylenoyl Alginate **NR**

Sodium/TEA-Undecylenoyl Carrageenan **NR**

Solanum Tuberosum (Potato) Starch

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

Starch Acetate

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

Starch Acetate/Adipate **NR**

Starch Diethylaminoethyl Ether

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

Starch Hydroxypropyltrimonium Chloride

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

Starch Laurate **NR**

Starch Tallowate **NR**

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

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

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

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

Triticum Vulgare (Wheat) Starch	
02A - Bath Oils, Tablets, and Salts	1
03C - Eye Shadow	5

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

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

Mannan

Glucomannan

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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

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: April 8, 2015

SUBJECT: Concentration of Use by FDA Product Category: Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate was included in a concentration of use survey. No uses of this ingredient were reported.

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: March 4, 2015

SUBJECT: Comments on the Draft Report on Polysaccharides (report removed from review at the March 2015 CIR Expert Panel meeting)

Key Issues

Please clarify with the CIR Expert Panel the classifications of these ingredients. Does linear, branched and cyclic refer to the polysaccharide before modification, or to the final compound? If these terms refer to the polysaccharide compound before modification, the modified algin ingredients should be moved from branched modified to linear modified and the hydrogenated and hydrolyzed starch ingredients should be moved from unknown structural configuration to branched modified.

Triticum Vulgare (Wheat) Starch needs to be moved to branched unmodified. A review (Maningat CC, Seib PA. 2010. Understanding the physicochemical and functional properties of wheat starch in various foods. Cereal Chemistry 87(4): 304-314.) of the function of wheat starch in food says: "At the macromolecular level, starch from common wheat contains a mixture of amylose-to-amylopectin at a weight ration of ~1:3." Amylopectin is branched. Therefore, starch containing amylopectin should also be classified as branched.

Cassia Angustifolia Seed Polysaccharide needs to be moved from unknown structural configuration to branched. The abstract of the paper by Alam and Gupta (attached) (reference 40 of the CIR report - so CIR staff should have the complete reference) states: "Thus, the main chain of the galactomannan was found to consist of (1-4)-linked mannoypyranosyl units having beta-glycosidic bonds while (1-6)-linked alpha-glycosidically bonded galactopyranosyl units form the branching points." (underlining added).

Further research on Echinacin indicates that it is actually a flavone compound (it has one glucose), and it should be deleted from this CIR report. The identity of this compound has been shared with Joanne Nikitakis and the definition and chemical class of the

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monograph will be updated and the structure will be added to the monograph. The structure was found on the internet in the book (in the chapter on flavones):

Felix D'Mello JP. 1997. Handbook of Plant and Fungal Toxicants. CRC Press.

In addition, the FDA UNI Code database gives the following additional name for this compound (there are several other additional names in the FDA database which can be searched using the UNI Code in the Dictionary): 4H-1-BENZOPYRAN-4-ONE, 5-HYDROXY-2-(4-HYDROXYPHENYL)-7-((6-O-((2E)-3-(4-HYDROXYPHENYL)-1-OXO-2-PROPEN-1-YL)-.BETA.-D-GLUCOPYRANOSYL)OXY)-

Throughout the report, including the Summary (specific examples presented under additional comments), please distinguish between konjac flour and Galactomannan. Although konjac flour is predominantly Galactomannan, we still do not know the purity of Galactomannan that may be used in cosmetics. Additional research suggests that the respiratory sensitizer in konjac flour is actually a protein rather than Galactomannan. Regarding konjac allergy, a review (Dobash K. 2012. Occupational asthma in Japan. Asia Pacific Association of Allergy, Asthma and Clinical Immunology 2:173-180.) states: "Antigen: The purified antigen named AG40D-2 is an acidic protein of about 24,000 daltons. Its ratio of basic to acidic amino acids is 1:3.7 and it induces a strong P-K reactions. The amino acid composition of this antigen has also been determined."

Draft Discussion - The Draft Discussion implies that it is appropriate to read across from one polysaccharide to another polysaccharide compound. Does the CIR Expert Panel agree with this approach?

Additional Comments

Throughout the report, please remove "Natural" from the heading Branched Natural/Unmodified

Introduction - The introduction states that the "safety data will be reorganized". This should be changed to describe how the report is organized.

The Introduction should also mention the CIR report on mono- and disaccharides.

Definition and Structure - Please change: "Definitions from additional sources..." to "Descriptions from additional sources..."

p.33, Glucomannan - Reference 33 is about konjac flour. The composition information appears to be for konjac flour rather than Glucomannan. It should be changed to "Konjac flour consists of the following:..."

Cosmetic Use - In the text, please state the number of uses of Maltodextrin reported to the FDA.

p.14 - Please correct "concentratiions"

p.17, 18, Table 6 - Reference 119 suggests that konjac flour not glucomannan was studied in the inhalation, acute oral and dermal studies, as well as the genotoxicity assays.

p.22-23, Table 6 - Please check references 136-142 and be sure the material tested is described correctly. The titles of a number of these studies indicate konjac flour or meal not Glucomannan was studied.

p.23 - Please correct: "a test diets containing..."

p.25 - Please correct "species of rat" to "strain of rat"

p.29, Potato Starch Modified - It is not necessary to state "species not stated" when it says that a Buehler test (OECD 406 test guideline) was completed. OECD 406 is a guideline for guinea pig sensitization tests - guinea pigs were used in this study. This is likely the same study as described in the last paragraph of this section.

p.30 - Please correct "starch nmodified"

p.32, Hydroxypropyltrimonium Hydrolyzed Corn Starch - Please revise: "Reactions were to have been scored at 24 h and 72 hr post-application. However, reactions...." to "Application sites were scored at 24 h and 72 h post-application. Reactions...."

p.32, Sodium Hydrolyzed Potato Starch Dodecenylsuccinate and Corn Starch Modified - In the description of the RIPT, please delete "(area of application site not stated)" - the summary states that the "test material was applied to the back".

Respiratory Irritation and Sensitization - This section should note that a protein in konjac flour, rather than Glucomannan may be the antigen that causes respiratory sensitization (see attached reference).

The units of mg for Glucomannan in konjac flour do not make sense. It is likely that the units should be g.

p.36 - Please add references to the Reproductive and Developmental Toxicity and Genotoxicity sections.

p. 41-42 - What was material studied in reference 202 and 203? The description of these studies appear to use konjac mannan, glucomannan and konjac flour interchangeably. The purity of Glucomannan compared to konjac flour is not known so these terms should not be used interchangeably.

p.45, Summary - The paragraph summarizing the repeat oral dose studies summarizes the doses then the results. This format is not helpful. Please include the doses when describing the results of the study.

What was the dose used in the intranasal study of Methyl Cyclodextrin?

p.45, 46 - Please correct "dodecdenylsuccinate" (occurs twice)

Table 1 - Please delete the incorrect CAS number (~~57606-04-9~~) associated with Algin (it has been deleted from the Dictionary database).

Please delete the extra space between Sodium Carrageenan and TEA-Alginate.

Pectin, Hydrolyzed Pectin - The Dictionary definition has been updated to indicate that Pectin may be derived from other fruits and vegetables in addition to citrus fruits and apples. See: Srivastava P, Malviya R. 2011. Sources of pectin, extraction and its application in pharmaceutica industry - An overview. Indian Journal of Natural Products and Resources 2(1): 10-18.

Table 6 - Please add "(*in vitro* and *in vivo*)" to the Mammalian Assays subheading. As genotoxicity was actually determined in bacteria, the host-mediated assays should be moved to the Bacterial Assays section.

Reference 139 - Please correct "konhjac"

PubMed

Abstract

Full text links

Full text THIEME CONNECT

Planta Med. 1986 Aug;(4):308-10.

Structure of a water-soluble polysaccharide from the seeds of Cassia angustifolia.

Alam N[1], Gupta PC.

Author information

Abstract

A water-soluble galactomannan consisting of D-galactose and D-mannose in the molar ratio 3:2 has been isolated from the seeds of Cassia angustifolia. Hydrolytic fission of the methylated polysaccharide resulted in three methylated sugars: (a) 2, 3-di- O-methyl- D-mannose, (b) 2, 3, 4-tri- O-methyl- D-galactose, and (c) 2, 3, 4, 6-tetra- O-methyl- D-galactose in the molar ratio 2:1:2. Partial acid hydrolysis of the polysaceharide afforded five oligosaccharides: (a) epimelibiose, (b) galactobiosylmannose, (c) mannobiose, (d) mannotriose, and (e) galactobiose. Periodate oxidation of the polysaceharide indicated 59.7% end group while methylation gave 60%. Sodium borohydride reduction of the periodate oxidised polysaceharide and subsequent hydrolysis revealed the presence of (1-->4) and (1-->6)-glycosidic bonds. Thus, the main chain of the galactomannan was found to consist of (1-->4)-linked mannoypyranosyl units having beta-glycosidic bonds while (1-->6)-linked alpha-glycosidically bonded galactopyranosyl units form the branching points.

PMID: 17345316 [PubMed]

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