Safety Assessment of Plant Polysaccharide Gums as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this ssafety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian J. Gill.

The 2014 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.; 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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INTRODUCTION

The safety of plant polysaccharide gums as used in cosmetics is reviewed in this safety assessment. Based on chemical similarities, relevant data on the following are also included for use in evaluating the safety of ingredients included in this review: fructooligosaccharides (FOS) (inulin-type fructans) - for safety assessment of inulin, a fructan; wheat bran extract (contains ~ 80% arabinoxylan oligopeptides) - for safety assessment of arabinoxylan; croscarmellose sodium - for safety assessment of croscarmellose; pectin-derived acidic oligosaccharides (mixture of linear oligomers and small polymers of galacturonic acid) - for safety assessment of pectin, which consists chiefly of partially methoxylated polygalacturonic acids; and carboxymethyl inulin - for safety assessment of sodium carboxymethyl inulin. Many of the plant polysaccharide gums reviewed in this safety assessment function as viscosity increasing agents in cosmetic products.[1]

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

CHEMISTRY

Definition and Structure

Definitions and structures of the plant polysaccharide gums reviewed in this safety assessment are presented in Table 1.[1] Ingredient functions and use frequency and concentration data are presented in Table 2.[1,12,13] Data on acacia senegal gum, acacia catechu gum, acacia farnesiana gum, astragalus gummifer gum, and glyceryl alginate, all previously reviewed by CIR, are included in in Tables 1 and 2 for comparative purposes (definitions, use concentrations, etc.), but the safety of these ingredients is not being re-evaluated in this safety assessment. Polysaccharide nomenclature follows the general principles of established organic (1) and carbohydrate (2) nomenclature. Polysaccharide (glycan) is the name given to a macromolecule consisting of a large number of monosaccharide (glycose) residues joined to each other by glycosidic linkages. The term poly(glycose) is not a synonym for polysaccharide (glycan), because it refers to macromolecules composed of glycose residues joined to each other by non-glycosidc linkages. Polysaccharides may be linear, branched, or cyclic. Definitions from additional sources are included below.

Algin

Algin is a linear polymer of anhydro-β-D-mannuronic acid. The main structural feature of this molecule is a chain of 1,4-linked –β-D-mannuronic acid residues.[14]

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

Alginate, a term that refers to salts and derivatives of alginic acid, is a gelling polysaccharide and a structural component extracted from marine brown algae (*Phaeophyceae*), where it occurs in the cell wall as water insoluble salts.[15] Alginates are polymers composed of β-1,4-D-mannuronic acid (M) and α-1,4-L-guluronic acid (G). Alginates have been determined to be true block copolymers, organized in homopolymeric blocks consisting of either mannuronate or guluronate, or mixed as heteropolymeric MG-block structures.

According to another source, alginate, the monovalent salt form of alginic acid, is a non-repeating copolymer that contains two urocanic acids, 1,4 linked beta-D-mannuronic and alfa-L-guluronic acid.[16] These residues exist in linear polysaccharide chains that can dimerize to form hydrogels at room temperature in the presence of divalent ions such as calcium.

Amylopectin

Starch is composed of two polysaccharides, amylose and amylopectin.[17] Both are complex α-glucans. Amylopectin is a highly branched polysaccharide composed of segments of linear α(1→4)-linked glucopyranose units joined at branching points via α(1→6) glycosidic linkages to give a structure that resembles a dendrimer.

According to another source, amylopectin consists of numerous short chains of α(1→4)-linked D-glucopyranosyl residues with a chain length of approximately 6 to 35 units.[18] 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.

Amylose

Amylose is an essentially linear polymer made up of α(1-4)-linked glucopyranose units.[17]

Arabinoxylan

Arabinoxylan is a non-starch polysaccharide, and is also described as a pentosan.[19] It is further categorized as water-extractable arabinoxylan and water-unextractable arabinoxylan. Arabinoxylans consist of D-xylopyranosyl residues, connected together by *β*-(1/4) glycosidic bonds.[20,21] Moreover, acetic acid, hydroxycinnamic acids, ferulic acid, and p-coumaric acid are also linked with xylose residues.[22,23] They are partly or wholly lost when arabinoxylan is extracted from cereal or their subfractions using alkaline extraction.[19,24,25,]

Carrageenan

Carrageenan is a high-molecular-weight sulfated polygalactan derived from several species of red seaweeds of the class *Rhodophyceae*.[26]

The most common forms of carrageenan are designated as kappa-, iota-, and lambda carrageenan.[27] 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 second carbon. Between kappa and iota carrageenan, there is a continuum of intermediate compositions that differ only in the degree of sulfation at the second carbon. 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).

Cassia Angustifolia Seed Polysaccharide

Cassia angustofolia seed polysaccharide has been defined as a water-soluble galactomannan, consisting of D-galactose and D-mannose in the molar ratio of 3:2, and has been isolated from the seeds of *Cassia angustifolia*.[28]

Croscarmellose

Croscarmellose is a cellulose-based, ether-linked polymer with a typical carboxymethyl substitution of ~ 0.7.[29] An ester linkage between carboxy and hydroxyl groups on neighboring units is the cross-link that renders the molecule insoluble. Thirty percent of the carboxymethyl groups participate in the cross-linking, leaving the majority of the remaining substitutions as a sodium salt.

Cyclodextrin

Cyclodextrins are cyclic amylose-derived oligomers composed of a varying number of a-1-4-linked glucose units.[30] Cyclodextrins contain 6, 7, and 8 glucose units, respectively.

Ghatti Gum

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

Inulin

Inulin has been identified as a fructan, a general term that is used for naturally occurring plant oligo- and polysaccharides.[33] The term refers to any carbohydrate (linear or branched) in which one of more fructosyl-fructose links constitute the majority of glycosidic bonds. Within the inulin-type fructans are two general groups of materials, inulin and its subsets, oligofructose and fructooligosaccharides (FOS). 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, with one terminal glucose (G), and can vary from 2 to 70. The terms oligofructose and fructooligosaccharides (FOS) refer to inulin-type fructans with a maximum average degree of polymerization (DP) of less than 10.

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

Karaya gum, the dried exudate from *Sterculia wens* Roxb. and other *Sterculia* spp. (fam. *Sterculiaceae),* is a complex, partially acetylated polysaccharide with a very high molecular weight.[34]

Xyloglucan

The xyloglucan derived from tamarind seeds is composed of a (1-4)-β-glucan backbone chain, which has (1-6)-α-D-xylose branches that are partially substituted by (1-2)-β-D-galactoxylose.[35]

Physical and Chemical Properties

Arabinoxylan

The molecular weight of water-extractable wheat arabinoxylan, obtained by sedimentation, ranged from 65 to 66 KDa.[36] In comparison, estimation of molecular weight through gel filtration yielded results in the range of 800–5000 KDa[37] and 70-l000 KDa.[38] High molecular weight arabinoxylan forms rigid cross-linked hydrogels, owing to their greater water-holding capacities.[39]

Carrageenan

Food-grade carrageenan has an average molecular weight greater than 100,000 Da, with a low percentage of smaller fragments.[26]

Cassia Angustifolia Seed Polysaccharide

The average molecular weight of the purified seed galactomannan is 9.66×10^4, and the intrinsic viscosity is 209 mL/g.[40]

Cyclodextrin

β-Cyclodextrin, a carbohydrate consisting of seven glucose units, is soluble in water.[41]

Ghatti Gum

Ghatti gum has a molecular weight of approximately 8.94×10^7 Da.[42]

Method of Manufacture

Amylodextrin

The linear dextrin amylodextrin has been prepared from waxy maize by enzymatic hydrolysis with pullulanase.[43]

Carboxymethyl Inulin

Carboxymethyl inulin has been synthesized by incorporation of carboxymethyl groups into the inulin framework; by reacting inulin with the sodium salt of monochloro acetic acid in the presence of sodium hydroxide.[44]

Glyceryl Dimaltodextrin

The production of maltodextrins involves the obtention of products consisting of D-glucose units that are linked primarily by α(1→4) bonds and having dextrose equivalents less than 20.[45]

Maltodextrin

Maltodextrin is prepared as a white powder or concentrated solution by partial hydrolysis of corn starch, potato starch, or rice starch with suitable acids and enzymes.[46]

Composition/Impurities

Acacia Seyal Gum

The gum polysaccharide exuded from *Acacia seyal* trees contains D-galactose (38%), L-arabinose (45%), L-rhamnose (4%), D-glucuronic acid (7%), and 4-O-methyl-D-glucuronic acid (6%).[47]

Algin

After exhaustive methylation of alginic acid, reduction to the corresponding mannoside derivative, and hydrolysis, chromatographic separation indicated that the hydrolyzate contained 88% 2,3-dimethylmannose, 4.5% monomethylmannose, 1% 2,3,4-trimethylmannose, and 6% dimethylglucose.[14]

Arabinoxylan

Arabinoxylans are complex, as the side branches of arabinose and xylose contain small amounts of xylopyranose, galactopyranose, and *α*-D-glucuronic acid or 4-O-methyl-*α*-D-glucuronic acid.[48]

Carrageenan

Carrageenan is a high-molecular weight sulfated polygalactan.[26] The low-molecular-weight forms are <5% of the total composition of the commercial product.

Concerning the use of carrageenans in the food and pharmaceutical industries, the major problem identified has been the presence of degraded carrageenan (known as poligeenan), which can cause lesions in laboratory animals.[49] Twenty-nine samples of food-grade refined carrageenan were analyzed using high performance liquid gel permeation chromatography directly connected to vacuum-ultraviolet, inductively coupled plasma-atomic emission spectrometry. Each sample had no obvious peak of poligeenan (detection limit ≈ 5%).

Cassia Angustifolia Seed Polysaccharide

The purified seed galactomannan contains mannose:galactose in a ratio of 2.90.[40]

Croscarmellose

The availability of the following 5 croscarmellose sodium brands has been reported: Primellose, Ac-Di-Sol, Solutab, Vivasol, and Nymcel ZSX.[50] Collectively, these brands of croscarmellose sodium also contain a low percentage of sodium glycolate (0.01% to 0.08%) and sodium chloride (0.05% to 0.17%).

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

Commercial karaya gum contains 19%-21% of rhamnose with similar proportions of galactose and galacturonic acid.[51] Nitrogen content (probably non-protein in nature) of 0.07% has also been reported.[52]

USE

Cosmetic

Many of the ingredients reviewed in this safety assessment function as viscosity increasing agents in cosmetic products.[1] According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), the following 46 plant polysaccharide gums are being used in cosmetic products:[13] maltodextrin, agar, agarose, algin, alginic acid, amylodextrin, avena sativa (oat) starch, calcium alginate, carrageenan, cassia angustifolia seed polysaccharide, cichorium intybus (chicory) root oligosaccharides, corn starch modified, cyclodextrin, cyclodextrin laurate, dextrin, dextrin palmitate, galactoarabinan, glyceryl starch, hydrogenated starch hydrolysate, hydrolyzed corn starch octenylsuccinate, hydrolyzed pectin, hydrolyzed wheat starch, hydroxypropyltrimonium hydrolyzed corn starch, hydroxypropyltrimonium hydrolyzed wheat starch, hydroxypropyl starch, inulin, laurdimonium hydroxypropyl hydrolyzed wheat starch, mannan, methyl cyclodextrin, natto gum, pectin, polianthes tuberosa polysaccharide, potassium alginate, potato starch modified, propylene glycol alginate, sodium carboxymethyl starch, sodium carrageenan, sodium hydrolyzed potato starch dodecenylsuccinate, sodium oxidized starch acetate/succinate, sodium starch octenylsuccinate, solanum tuberosum (potato) starch, starch acetate, starch diethylaminoethyl ether, starch hydroxypropyltrimonium chloride, stearoyl inulin, tapioca starch, and triticum vulgare (wheat) starch.

FDA's VCRP database indicates that the following 11 plant polysaccharide gums are not being used in cosmetics:[13] croscarmellose, dextrin myristate, dextrin palmitate/stearate, glycerol alginate, hydrolyzed starch, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, hydroxypropyltrimonium maltodextrin crosspolymer, pueraria lobata starch, sterculia urens gum, and tamarindus indica seed gum. However, results from a survey of ingredient use concentrations conducted by the Personal Care Products Council (Council) in 2013 indicate that these 11 ingredients are being used in cosmetics, in addition to the 46 included in FDA's VCRP database.[12] Therefore, collectively (VCRP + Council survey data), 57 plant polysaccharide gums are being used in cosmetics. The Council survey data also indicate that plant 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).

Cosmetic products containing plant 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.

Plant polysaccharide gums are being used at maximum use concentrations up to 0.25% (hydroxypropyl starch) in pump hair sprays, up to 1% (hydroxypyl cyclodextrin) in aerosol (propellant) hair sprays, up to 15% (corn starch modified) in face powders, and up to 33% (tapioca starch) in dusting and talcum powders. Because plant 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.[53,54,55,56] 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.[53,54]

Non-cosmetic

Maltodextrin

According to FDA, maltodextrin is an approved direct food additive affirmed as generally recognized as safe.[46] It should be noted that, of the ingredients reviewed in this safety assessment, maltodextrin has the highest reported cosmetic ingredient use frequency.

Algin

The viscosity of blood substitutes is among the important determinants in restoring microcirculation.[57] Sodium alginate (algin) is frequently mentioned as a viscosity modifier in creating blood substitutes.

Alginates

Alginate dressings are among the types of absorbent dressings that are used to treat exuding wounds.[58] Alginate is composed of two uronic acid monomers, mannuronic acid and guluronic acid.

Arabinoxylan

Arabinoxylans are mainly found in the following cereal grains: wheat, rye, barley, oat, rice, and sorghum.

Carrageenan

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

Cyclodextrin

α-, β- and γ-Cyclodextrins have been used to suspend drugs in aqueous vehicles.[30]

Ghatti Gum

Ghatti gum (thickening agent) is used to stabilize table syrup emulsions, as a glaze in candy products, and as a component of chewing gum, cough drops, and candy lozenges.[31]

Inulin

The food industry can use three plant species for large-scale production of inulin: agave (*Agave azul tequilana*), Jerusalem artichoke (*Helianthus tuberosus*), and chicory (*Cichorium intybus*).[33] Inulin is a prebiotic, meaning a non-digestible food ingredient that is believed to improve health by selectively stimulating the growth and/or activity of one or several bacterial species in the colon.[59]

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

World Health Organization (WHO) reports affirming the safety of karaya gum as a food additive are available.[60,61]

TOXICOKINETICS

Animal

Carrageenan

Carrageenan is not degraded or absorbed in the gastrointestinal tracts of rodents, dogs, and non-human primates.[26]

Cyclodextrin

The absorption of orally administered (per os) ^{14}C-β-cyclodextrin, in methylcellulose solution, was studied using 4 Wistar R x Long Evans F_1 male rats.[62] 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.

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 radioactivity. 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.[62]

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

In a study involving rats, 95% of ingested karaya gum was excreted in the feces.[51]

Human

Starch Acetate

The pharmacokinetics of starch acetate (acetyl starch) and hydroxyethyl starch was studied in 32 surgical patients undergoing major elective general surgical procedures.[63] When compared to hydroxyethyl starch, rapid and nearly complete enzymatic degradation 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.[34] Total um 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 rhamonose 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.[64] Blood was collected after a 12-h fast. Tapioca starch (30 g) containing 0.1 g of aspartame was dissolved in 150 l of water, and the solution or dispersion was held 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.

Other

Inulin

Total hydrolysis of inulin yields fructose and glucose.[33]

TOXICOLOGY

Cyclodextrin

A toxicity profile of β-cyclodextrin is available from the World Health Organization.[65] The toxicity profile of cyclodextrins can differ depending on the route of administration. For example, β-cyclodextrin administered orally induces limited toxicity.[66,67] In both rats and dogs, β-cyclodextrin is considered non-toxic at a daily dose of less than 600 mg/kg body weight or 3% and less in the diet.[68] However, if β-cyclodextrin is administered at higher doses in animals via a subcutaneous 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.[68,69] In another study (rats), subcutaneous administration of β-cyclodextrin (≥ 450 mg/kg) induced similar changes in kidney proximal tubules.[70]

Acute Toxicity

Oral

Fructooligosaccharides (FOS)

Data on FOS are included for use in the safety assessment of inulin. An acute oral toxicity study on FOS (average DP = 3.5) was performed using mice and rats.[33] Four-week-old male and female JcL-IcR mice (SPF) and 6-week-old male and 10-week-old female Sprague–Dawley rats were used in four groups of 6 (total of 24 male and 24 female mice; 24 male and 24 female rats). The groups were administered 0, 3, 6, and 9 g/kg FOS by gavage. The concentrations were adjusted so that the total volume of solution given per animal was 0.5 ml for mice and 2 ml for rats. Following a single oral dose, the animals were observed for signs of toxicity until the seventh day exposure. No abnormalities were seen in the general state of health of the test animals. There were no deaths, and the increases in body weight on day 7 was indistinguishable from controls. The LD_{50} for FOS was determined to be greater than 9 g/kg.

Intravenous

Iota (ι)-Carrageenan and Potassium Carrageenan

Groups of 5 female MF1 mice were injected i.v. (lateral tail vein) with ι-carrageenan or potassium carrageenan (2 mg in phosphate-buffered saline [PBS]).[71] Controls were injected with PBS (0.3 ml). The animals were killed 1 h and 24 h post-injection, and tissues were prepared for microscopic examination. Within 24 h of i.v. injection, damage to liver Küpffer cells and changes in the microcirculation characteristic of disseminated intravascular coagulation (DIC) in the liver and kidney were observed. Carrageenan persisted for at least 6 months in the livers and kidneys. This contact with tissues did not appear to cause adverse effects in hepatocytes, but resulted in chronic renal damage. The authors noted that ι-carrageenan was less toxic to mouse liver and kidney compared to the potassium carrageenan, which was less pure than the ι-carrageenan.

Groups of 9 to 15 female CAF_1 mice (Balb/c x A/He) were injected i.v. with potassium or iota (ι)-carrageenan and studied for 7 or 14 days, respectively, thereafter.[72] Treatment with either compound induced anemia, granulocytosis, and early profound thrombocytopenia. Treatment with ι-carrageenan resulted in an early lymphocytosis, and both compounds induced lymphopenia by 18 h post-treatment. Additionally, treatment with either compound was associated with an early moderate reduction in the number of nucleated cells and granulocyte/macrophage colony-forming cells per femur. Potassium carrageenan and ι-carrageenan induced splenomegaly, and ι-carrageenan-treated mice developed hypoplasia of the thymus by 18 h post-injection. There was also a sustained increase in the numbers of colony-forming cells in the spleen after treatment with each compound. The authors noted that ι-carrageenan had a profound effect on hematopoiesis.

Parenteral

λ-Carrageenan

Groups of 6 adult female Balb/c mice (6 to 7 weeks old) received single intrapleural injections of λ-carrageenan.[73] Animals of one group each received a single intrapleural injection of 0.1 ml sterile saline (0.9% NaCl) and λ-carrageenan (1%; solvent not stated), which induced pleurisy. The lungs were not examined microscopically. Animals of another group each received a single intrapleural injection of 1% λ-carrageenan (0.1 ml) only. The animals were killed, and lung tissue samples obtained for microscopic examination at 4 h and 24 h post-injection. Dense inflammation with lobar lung pneumonia and thickened alveolar septum (with occasionally obliterated alveoli) were observed in these animals.

In another study involving groups of 10 mice, the injection of 2% λ-carrageenan in saline (200 mg/kg) into the pleural cavity induced pleurisy.[74] This acute reaction is characterized by marked accumulation of fluid and the migration of leukocytes to the site of inflammation in the lung.

Repeated Dose Toxicity

Oral

Animal

Algin and Starch Acetate

A chronic feeding study was carried out in mice with sodium alginate (also known as algin) and starch acetate (a chemically modified potato starch).[75] Two groups of mice (75 males and 75 females per test substance) were fed sodium

alginate and starch acetate in the diet, respectively, for 89 weeks. At week 87, half of the surviving male and female mice in each test group were placed on control diet (contained 55% pregelatinized potato starch). The dietary levels of the test substances were gradually increased until the diets contained (by weight) 55% starch acetate or 25% sodium alginate. All survivors were killed during weeks 89 to 92. Sodium alginate and starch acetate caused increased water consumption, distinct caecal and colonic enlargement, and a slightly increased incidence of intratubular nephrosis. Sodium alginate caused slightly lower body weights. An increased incidence of gastric trichobezoars was observed in mice fed starch acetate. The occurrence of concrements in the renal pelvis with slight urinary changes, such as increased amounts of amorphous material in the urine and increased urinary calcium content, in the mice fed starch acetate was regarded as an effect of little, if any, toxicological significance.

Sodium alginate at 25% (w/w) of the diet was nephrotoxic to mice, as manifested by extremely high water consumption, high urine production, urinary incontinence, high pH and low specific gravity of the urine, increased level of blood urea nitrogen, increased kidney weights, distension of the renal calyx and high incidence of dilated distal tubules. Caecal and colonic enlargement and changes in urinalysis results were found to be reversible, completely or largely disappearing within 2-5 weeks of the cessation of the treatment (in week 87). The incidence of intratubular calcinosis or concrements in the pelvic space was not reduced during the recovery period. Study results are also included in the section on Carcinogenicity.[75]

Arabinoxylan and Inulin

The repeated dose oral toxicity of wheat bran extract (~ 80% arabinoxylan oligopeptides) was evaluated using groups of 20 Wistar rats of the Crl:(WI)BR strain (10 males/group, 10 females/group).[76] The 3 test groups were fed 0.3%, 1.5%, and 7.5% wheat bran extract in the diet, respectively. These concentrations corresponded to average intakes of 0.2 g/kg, 0.9 g/kg, and 4.4 g/kg wheat bran extract per day. A basal diet control group and a 7.5% inulin control group were included in the study. The exposure duration was 13 weeks. There was no evidence of adverse macroscopic or microscopic findings considered to be test-substance related. However, on histopathologic examination, minimal bilateral hypertrophy of the renal cortical tubules was observed in males and females, particularly in the highest-dose group. These findings were not accompanied by degenerative changes or changes in kidney weight, and were, therefore, considered to be suggestive of an adaptive response rather than a toxic effect. There were no remarkable findings in the control animals. The no-observed-adverse effect level for wheat bran extract was 4.4 g/kg/day, the highest dose administered.

Carboxymethyl Inulin

Repeated dose oral toxicity was investigated in groups of rats that received carboxymethyl inulin (31.1% aqueous), by gavage, at doses of 0, 50, 150 and 1000 mg/kg/day for 4 weeks.[77] Groups of five male and five female Wistar Crl rats of approximately 6 weeks of age were included in each test group. No treatment-related effects were observed with respect to body weight, food consumption, mortality, hematology, clinical blood chemistry, organ weights or gross or microscopic pathology up to the highest dose (1000 mg/kg/day) tested. Motor activity, as observed in a functional observation battery, was elevated in high-dose females, but was not considered to be toxicologically significant.

Croscarmellose

In a repeated dose oral toxicity study on croscarmellose sodium, groups of Sprague-Dawley rats (20/sex/group) received 0 (control), 10,000 ppm, or 50,000 ppm Ac-Di-Sol (croscarmellose sodium) in the diet for 90 consecutive days (equivalent to 757 and 893 mg/kg/day for males and females fed 10,000 ppm, respectively, and to 3922 and 4721 mg/kg/day for males and females fed 50,000 ppm, respectively).[78] No mortality, clinical signs of toxicity, or adverse toxicological effects on hematology or serum chemistry parameters, feed consumption, or ophthalmologic examinations were noted in any treatment group. Body weight gain was depressed in high-dose males during the final 3 weeks. The only treatment-related histological lesion noted was moderate renal mineralization at the corticomedullary junction in one high-dose female. This lesion was not considered a specific effect of croscarmellose sodium but, rather, a secondary effect from increases in urinary pH and renal excretion of sodium (attributable to the high intake of sodium associated with sodium croscarmellose). Thus, under the conditions of this study, daily administration of up to 50,000 ppm croscarmellose sodium in the diet for 90 days resulted in no adverse effects in rats.

Cyclodextrin

A 52-wk oral toxicity (dietary administration) study on β-cyclodextrin, a starch derivative, was performed using CrI:CD (SD) BR Sprague-Dawley rats and pure-bred beagle dogs.[67] Doses of 0 (control), 12, 500, 25,000 and 50,000 ppm were selected for the rat study, and 0 (control), 6200, 12,500 and 50,000 ppm were selected for the dog study. The liver and

kidney were identified at histopathological examination as target organs for toxicity in the rat at doses of 50,000 ppm and 25,000 ppm, with the hepatic changes associated with increased plasma liver enzyme and reduced plasma triglyceride concentrations. In the dog study, there was no pathological evidence of systemic toxicity, although there were minor changes in urinalysis and biochemical parameters and a slightly higher incidence of liquid feces. These changes were considered to be of no toxicological importance. The results in these studies, therefore, indicate that the "non-toxic dietary inclusion level" of β-cyclodextrin was 12,500 ppm in the rat (equivalent to 654 or 864 mg/kg/day for males or females, respectively) and 50,000 ppm in the dog (equivalent to 1,831 or 1,967 mg/kg/day for males or females, respectively).

The oral toxicity of γ-cyclodextrin was examined in a 13-week feeding study in which four groups of four male and four female Beagle dogs received γ-cyclodextrin in the diet at concentrations of 0 (control), 5%, 10%, or 20%.[79] No treatment-related changes were noted in behavior or appearance of the dogs and no mortalities occurred. There were no treatment-related differences with respect to ophthalmoscopic examinations, hematological parameters, clinochemical analyses of the plasma, and semiquantitative urine analyses. Relative ovary weights were significantly increased in the 10% and 20% dose groups, but the authors noted that this observation was probably a result of an unusually low ovarian weight in the controls. An increase in relative liver weights in males of the 10% and 20% dose groups was also considered to lack toxicological relevance, because this observation was not associated with changes in plasma enzyme levels or with histopathological changes. No abnormalities were seen at necropsy that could have been attributed to treatment. At microscpopic examination, no treatment-related effects were observed in any of the various organs and tissues. It was concluded that daily consumption of up to 20% γ-cyclodextrin in the diet (≈ 7.7 g/kg body weight in males and 8.3 g/kg body weight in females) was tolerated with no toxic effects observed.

Fructooligosaccharides (FOS)

Data on FOS are included for use in the safety assessment of inulin. Groups of 18 male Wistar rats (SPF strain), 6 to 7 weeks old, were tested in a repeated dose oral toxicity study. FOS (average DP = 3.5) were used as test substances, while sucrose and glucose were the control substances.[33] Test and control substances were given daily by gavage at doses of 1.5, 3, and 4.5 g/kg/day for 6 weeks. On the second, fourth, and sixth weeks, blood samples were obtained from 6 animals in each group. After the animals were killed, the liver, pancreas, adrenal glands, kidneys, brain, cerebellum, heart, lungs, spleen, pituitary gland, and testes were removed and fixed in formalin, and slides were prepared. Results revealed that there were no abnormalities or deaths during the study. A slight increase in body weight was observed in the 3 and 4.5 g/kg/day groups compared to controls. The other group showed the same trend as the controls.

No consistent, treatment-related changes in serum chemistries were observed over the range of administered doses, although significant fluctuations were observed occasionally. These did not correlate with either dose or time of administration and were, therefore, considered chance occurrences. On dissection, swelling of the appendix was noted in the rats dosed with FOS, while this abnormality was not observed in the other groups. It was concluded that there was no treatment-related toxicity in any of the FOS-treated groups, up to a dose of 4.5 g/kg/day administered orally for 6 weeks.[33]

No consistent, treatment-related changes in serum chemistries were observed over the range of administered doses, although significant fluctuations were observed occasionally. These did not correlate with either dose or time of administration and were, therefore, considered chance occurrences. On dissection, swelling of the appendix was noted in the rats dosed with FOS, while this abnormality was not observed in the other groups. It was concluded that there was no treatment-related toxicity in any of the FOS-treated groups, up to a dose of 4.5 g/kg/day administered orally for 6 weeks.[33]

Another repeated dose toxicity study involved groups of 18 male Wistar rats (SDP strain, 6 to 7 weeks old).[33] Feed containing 5% or 10% FOS (average DP = 3.5) was evaluated in this study, and sucrose, glucose, and sorbitol served as controls (conentrations not stated). The feed was provided *ad libitum* for 6 weeks. On the second, fourth, and sixth weeks, blood samples were obtained from 6 rats of each group. At the same time, at necropsy, the liver, pancreas, and adrenal glands were removed for further histopathologic examination. On the sixth week, kidneys, brain, cerebellum, heart, lungs, spleen, pituitary gland, and testes were removed at necropsy. The specimens were fixed in formalin and slides were prepared.

The results of this study revealed no treatment-related abnormalities or deaths. Diarrhea was observed on the 3rd day in the sorbitol group, and on the 10th day for animals fed FOS. Sorbitol and FOS groups showed a lower body weight in the 1st to 5th week, but the growth trends near the end of the study were the same as those of the control groups. The only blood chemistry finding that appeared to be treatment-related was the reduction in cholesterol for the FOS groups. In the 2nd- and 6th-week necropsies, swollen appendices were identified in test and control groups. A few hepatic specimens, from all groups, including controls, exhibited slight necrosis and infiltration of round cells. Renal changes and cases of degeneration of the proximal tubular epithelial cells were seen in all sucrose-, glucose-, sorbitol-, and FOS-treated groups. The changes were greatest in the test animals exposed to sorbitol and sucrose. Animals in the FOS and glucose groups also demonstrated

dilatation of the proximal renal tubules. Calcium deposits were found in some animals in the FOS, sorbitol, and control groups.[33]

Feeding diets with FOS added caused a decrease in body weight, a reduction in cholesterol, and swelling of the appendix, as well as a few instances of pathological changes in the kidneys and liver. The latter changes were similar to those noted in some animals of the control groups. The changes seen in the proximal renal tubules were less severe in the FOS group than in the sucrose group, while the calcium deposits observed in the kidney cortex were also identified in the control groups. It was concluded that FOS showed no toxicity, compared to sugars commonly used in the food supply. The study also demonstrated that blood glucose is not raised significantly by a single oral dose of FOS. The authors suggested that the reduction in body weight was attributable to the low caloric content of FOS.[33]

Ghatti Gum

Groups of Sprague-Dawley rats (10 males/group, 10 females/group) were given ghatti gum at concentrations of 0, 0.5, 1.5 and 5% in the diet (AIN-93M diet) for at least 90 days.[80] Ghatti gum intake at the 5% dietary level ranged from 3044 to 3825 mg/kg body weight/day. Feed consumption among treated and control groups was similar for each sex. Incidentally, 2 of 10 females of the 5% ghatti gum group had a single colon ulcer, with associated acute inflammation. The ulcers were considered to be sporadic occurrences, possibly attributable to the basal diet. The authors noted that this explanation for the occurrence of ulcers is speculative, and that it was not proven that ulcer formation was related to the AIN-93M diet. The 5% dietary administration was the NOAEL. NOAELs for males and females in the first study were estimated to be 3044 and 3309 mg/kg/day, respectively.

In a second study, groups of 20 female Sprague-Dawley rats were given ghatti gum in the diet (AIN-93M or NIH-07 diet) at concentrations of 0 and 5% for at least 90 days. A single colon ulcer, with associated acute inflammation, occurred in 1 of 20 control females given the AIN-93M basal diet. Again, the colon ulcer was considered to be sporadic, possibly attributable to the basal diet. A few statistically significant alterations in clinical chemistry were observed and considered sporadic and unrelated to treatment. Feed consumption among treated and control groups was similar for each sex. Specifically, feed consumption was measured weekly and showed that the amount of test substance consumed in this second study (females only) was equivalent to the amount consumed in the 5% dose group (males and females) in the preceding study. The 5% dietary administration was the NOAEL. NOAELs for females were estimated to be 3670 and 3825 mg/kg/day for the AIN-93M and NIH-07 diets, respectively.[80]

Pectin

A repeated dose oral toxicity study involved F_1 rats (from outbred strain of Wistar rats (Crl:WI(WU)) administered a test diet containing pectin-derived acidic oligosaccharides (pAOS) (±7 g/kg body weight/day) and control diets for 13 weeks.[81] F_1 rats were produced in a reproductive toxicity study summarized in the section on Reproductive and Developmental toxicity. There were two control groups. One control group received the standard rodent diet supplemented with 10% potato starch, and the other control group received 10% short-chain FOS (scFOS) in the diet. Two experimental groups received the standard diet supplemented with 5% or 10% pAOS. To keep the total level of added test substance equal in each diet, the low-dose diet (5% pAOS) was adjusted with 5% potato starch. No treatment- related clinical signs were observed, and none of the rats died during the study. Ophthalmoscopic examination did not reveal any treatment-related ocular changes. Neurobehavioral examination and motor activity assessment did not indicate any neurotoxic potential. There were no relevant differences in body weight, growth rate and feed intake.

No increase in the mean number of micronuclei in erythrocytes was observed in male or female rats fed pAOS, compared to the negative control group. The ratio between normochromatic and polychromatic erythrocytes was not changed by treatment with pAOS, indicating that pAOS was not cytotoxic in this study. The positive controls exhibited the expected increased numbers of micronucleated polychromatic erythrocytes.[81]

Macroscopic examination of the F_1 rats at necropsy did not reveal any adverse effects. Microscopic examination revealed treatment-related histopathological changes in the urinary bladder of animals of the 10% pAOS group. These changes were characterized by thickening of the transitional epithelial layer of the urinary bladder (diffuse simple urothelial hyperplasia). The changes were slightly more prominent in males than in females. One male and one female of the 5% pAOS group and one male of the control group showed diffuse hyperplasia (very slight). In addition, two males and two females of the 5% pAOS group showed simple hyperplasia in a part of the urinary bladder lining (‘focal hyperplasia’). No treatment-related hyperplasia of the transitional epithelium was observed in the kidney. Slight diffuse hyperplasia of the epithelial layer of the urinary bladder was suggested to be attributable to the concurrently elevated urinary sodium that, in turn, can be explained by the high sodium content of the pAOS and elevated urinary pH. In contrast, in rats fed pAOS in

combination with NH_4Cl, an acidifying agent, the reduced urinary pH was associated with the absence of urothelial hyperplasia. The authors noted that hyperplasia induced by this mechanism in rats is considered not relevant to humans. It was concluded that administration of pAOS at dietary levels up to 10% (equivalent to 7.1 g/kg body weight/day) did not reveal any relevant effects to could be attributed to the ingestion of acidic oligosaccharides.[81]

Human

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 over a 7-day period.[82] Actually, a weight of propylene glycol alginate equal to 175 mg/kg body weight was consumed 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. The ingestion of propylene glycol alginate had no significant effect on the following: hematological indices, plasma biochemistry parameters, urinalysis parameters, blood glucose levels, plasma insulin concentrations, and breath hydrogen concentrations. Therefore, the results of this study indicated that the ingestion of propylene glycol alginate at a high level for 23 days caused no adverse dietary or physiological effects. Particularly, the enzymatic and other sensitive indicators of toxicological effects remained unchanged.

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

The ingestion of karaya gum (10.5 g in diet) by 5 male volunteers (30 to 56 years old) daily for 21 days did not cause toxicity.[83] No significant effects on plasma biochemistry, hematological indices, or urinalysis parameters were noted.

Dermal

Carboxymethyl Inulin

The sensitization potential of A 31.1% aqueous carboxymethyl inulin was evaluated in a maximization test using 10 adult Dunkin–Hartley albino guinea pigs (4 weeks old).[77] Five female guinea pigs served as vehicle controls. No mortality occurred and no symptoms of systemic toxicity were observed. Body weights and weight gains were considered similar between treated and control groups.

Mucous Membrane Irritation

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.[84] 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 quite similar to those of the control (physiological saline; 0.9% NaCl). Using confocal laser scanning microscopy, no changes in nasal epithelial cell morphology were observed after a single intranasal administration of 2% randomly methylated β-cyclodextrin, whereas 1 % sodium taurodihydrofusidate resulted in swelling of the cells and substantial mucus extrusion.

Skin Irritation and Skin Sensitization

Animal

Carboxymethyl Inulin

The skin irritation potential of carboxymethyl inulin (1% to 100%) was studied using groups of 2 adult Dunkin–Hartley albino guinea pigs (4 weeks old).[77] The test substance was injected into the clipped scapular region, and reactions were scored at 24 h and 48 h. Additionally, a series of test article concentrations was topically applied to the clipped external flank of two guinea pigs using Metalline patches secured with tape and an elastic bandage. Two different concentrations were applied (0.5 ml each) per animal. Test material was removed after 24 h and signs of irritation recorded at 24 h and 48 h after treatment. Undiluted carboxymethyl inulin produced necrosis after intradermal injection, both after 24 h and 48 h; concentrations of 20% to 50% did not cause necrosis, but grade 2 erythema was observed at either 24 h or 48 h. Signs of irritation were not observed at 24 h or 48 h at concentrations up to 100% in the patch tests.

The sensitization potential of 31.1% aqueous carboxymethyl inulin was evaluated in the maximization test using 10 adult Dunkin–Hartley albino guinea pigs (4 weeks old).[77] Five female guinea pigs served as vehicle controls. No evidence of dermal sensitization was observed.

Clinical Trials

Calcium Alginate

Fourteen patients (7 males) with spina bifida were treated for pressure sores. Each patient had a calcium alginate dressing applied for 4 to 6 weeks.[85] 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

Calcium Alginate

A 50-year-old woman was referred after the discovery of adenoid cystic carcinoma in an excised left submandibular gland.[86] 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 of time, the pack was reported to have stimulated a foreign body reaction which, on a computed tomogram, mimicked a recurrence of the tumor.

Alginate

Novabel® is an aesthetic injectable resorbable filler consisting of a purified polysaccharide, alginate, which is extracted from crusted brown algae.[87] A 52-year-old general practitioner injected 0.1 ml of an alginate solution (Novabel®) into the deep dermis of her left arm. 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 histopathologic 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 Novabel®, into tear troughs and⁄or dorsa of the hands, developed severe granulomatous reactions within months after injections.[88] The 40% incidence of this disfiguring effect was considered high.

Croscarmellose

An 87-year-old woman developed an allergic reaction to croscarmellose, used as an excipient in a generic drug, during treatment for chronic heart failure.[89]

Allergenicity/Immune System Effects

Animal

Polyanthes 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.[90] Pretreatment 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).[91] 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.

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 of gum) 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 sensititivity did not develop in guinea pigs dosed orally (singe or repeated doses) or i.p. Injection of albumen resulted in marked allergic sensitization.

Human

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.[82] 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

Potassium Alginate

The acute tissue reactions to potassium alginate, locally applied to a microvascular bed, were studied with the use using the vital microscopic hamster cheek-pouch model and correlative histology.[92] 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.

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

An animal model was used to investigate the immunogenicity of karaya gum (*Sterculia* spp.).[93] Groups of animals were intradermally immunized with the gum in complete Freund's adjuvant. Serum antibody levels were measured using an 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.

Cytotoxicity

Calcium Alginate

In a cytotoxicity assay, calcium alginate fibers were introduced into human embryonic kidney cells and human fibroblasts.[94] These cells were in their exponential growth phase, and were incubated for 48 h. Calcium alginate fibers were not cytotoxic.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Carrageenan, Calcium Carrageenan,

And Sodium Carrageenan

Long-term multigeneration effects of the dietary intake of calcium carrageenan were measured in a three-generation reproduction and teratology study using Osborne-Mendel rats.[95] Dietary levels of 0.5%, 1.0%, 2.5% or 5.0% were ingested throughout the study. Carrageenan ingestion caused dose-related and significant decreases in the weights of offspring at weaning, but no effects on the following parameters were detected: average litter size, average number of liveborn animals, viability or survival of offspring.

The teratogenicity/fetotoxicity of calcium κ,λ-carrageenan, sodium κ,λ-carrageenan, and ι-carrageenan was studied using Syrian hamsters (*Mesocricetus auratus*).[96] Doses of 10, 40, 100 or 200 mg/kg/day were given by oral intubation on days 6 through 10 of gestation. No dose-related teratogenic or fetotoxic effects occurred after dosing with either of the 3 test substances.

Croscarmellose

In a developmental toxicity study on croscarmellose sodium, groups of pregnant Sprague-Dawley rats (25/group) were fed 0 ppm (control), 10,000 ppm, or 50,000 ppm Ac-Di-Sol (croscarmellose sodium) in the diet on gestation days 6 to 15.[78] No evidence of maternal, fetal, or embryotoxicity was noted. External malformations were not observed in this study, and there were no statistically significant findings that were considered treatment-related. The no-observed-adverse-effect level (NOAEL) for croscarmellose in both studies exceeded 50,000 ppm in the diet, which represents doses of 3922 and 4712 mg/kg/day for males and females, respectively.

Cyclodextrin

The embryotoxicity/teratogenicity of γ-cyclodextrin was examined using Wistar Crl:(WI)WU BR rats.[97] γ-Cyclodextrin was fed at dietary concentrations of 0, 1.5, 5, 10, and 20% to groups of 25 pregnant female rats from day 0 to 21 of gestation. A comparison group received a diet containing 20% lactose. The rats were killed on day 21 and examined for standard parameters of reproductive performance. The fetuses were examined for signs of toxic and teratogenic effects. Generally, γ-cyclodextrin was well-tolerated and no deaths occurred in any group. Weight gain and food consumption were similar in all groups during gestation, except for a slightly reduced food intake in the 20% γ-cyclodextrin group from day 0 to 16. Reproductive performance was not affected by treatment with γ-cyclodextrin. Examination of the fetuses for external, visceral, and skeletal alterations did not reveal any fetotoxic, embryotoxic, or teratogenic effects of γ-cyclodextrin. It was concluded that no adverse effects were observed at γ-cyclodextrin concentrations up to approximately 20% in the diet (approximately 11 g/kg body weight/day).

In a similar study, the embryotoxicity/teratogenicity of α-cyclodextrin was examined in Wistar Crl:(WI)WU BR rats. α-Cyclodextrin was fed at dietary concentrations of 0, 1.5, 5, 10, or 20% to groups of 25 pregnant female rats from day 0 to 21 of gestation.[98] An additional group received a diet containing 20% lactose. The rats were killed on day 21 and examined for standard parameters of maternal reproductive performance. The fetuses were examined for skeletal and visceral abnormalities, body weight and crown rump length. Generally, α-cyclodextrin was well-tolerated and no deaths occurred in any group. Weight gain and food consumption were similar in all groups during gestation, except for a slightly, yet significantly, increased food intake in the 20% α-cyclodextrin group on days 6 to 16 ($p < 0.05$) and 16 to 21 ($p < 0.001$). Maternal reproductive performance was not affected by α-cyclodextrin treatment. Examination of the fetuses for external, visceral, and skeletal changes did not reveal any fetotoxic, embryotoxic, or teratogenic effects of α-cyclodextrin. It was concluded that no adverse effects were observed at α-cyclodextrin concentrations up to 20% in the diet, the highest concentration tested, which corresponded to approximately 13 g/kg body weight/day.

In a standard embryotoxicity/teratogenicity study, γ-cyclodextrin was administered to groups of 16 artificially inseminated New Zealand White rabbits at dietary concentrations of 0, 5, 10, or 20%.[99] A comparison group received a diet containing 20% lactose. Treatment started on day 0 of gestation and ended on day 29, when the animals were killed. Except for the occurrence of transient diarrhea in 2 and 3 rabbits of the 10% and 20% γ-cyclodextrin groups, respectively, in the first few days, the treatment was well-tolerated. Reduced food intake in the 20% γ-cyclodextrin group during the first week of treatment resulted in reduced weight gain during this period. However, after week 1, there were no differences in weight gain among the groups and, at termination of the study, body weights were similar in all groups. Even at the highest dose, which corresponded to an intake of 5–7 g/kg body weight/day, no signs of maternal toxicity were observed. Reproductive performance was not affected by the treatment. Uterine weight, placental weight, fetal weight, number of fetuses, sex ratio, number of implantation sites, resorptions, and corpora lutea did not differ among the groups. Visceral and skeletal examinations of the fetuses did not reveal any malformations, anomalies, or variations that could be attributed to treatment.

It was concluded that dietary γ-cyclodextrin was well-tolerated by pregnant rabbits, had no adverse effect on reproductive performance, and was not embryotoxic, fetotoxic, or teratogenic at dietary concentrations up to 20%.

α-Cyclodextrin was also administered to groups of 16 artificially inseminated New Zealand White rabbits at dietary concentrations of 0, 5, 10, or 20%.[100] An additional group received a diet containing 20% lactose. Treatment started on day 0 of gestation and ended on day 29, when the animals were killed. Except for the occurrence of transient diarrhea in one rabbit of the 20% α-cyclodextrin group for a few days, the treatment was well-tolerated. Reduced food intake in the 20% α-cyclodextrin group during the first week of treatment resulted in reduced weight gain from day 0 to 12 of the study. However, when compared to controls, the difference was not significant. At study termination, body weights were similar in all groups. Even at the highest dose level, which corresponded to an intake of 5.9–7.5 g/kg body weight/day, no signs of maternal toxicity were observed. Maternal reproductive performance was not affected by treatment. Uterine weight, placental weight, fetal weight, number of fetuses, sex ratio, number of implantation sites, resorptions, and corpora lutea did not differ among the groups. Visceral and skeletal examinations of the fetuses did not reveal any malformations, anomalies, or variations that could be attributed to treatment. It was concluded that dietary α-cyclodextrin was generally well-tolerated by pregnant rabbits, had no adverse effect on maternal reproductive performance, and was not embryotoxic, fetotoxic, or teratogenic at dietary concentrations of up to 20%, the highest dose level tested.

Fructooligosaccharides (FOS)

Data on FOS are included for use in the safety assessment of inulin. Twelve female Wistar rats with a copulation plug were fed a diet containing 20% FOS from day 1 to 21 of gestation.[33] A separate group of 17 female Wistar rats with a copulation plug was fed a control diet for the same period of time. In the first 6 h after birth, the litters were numbered, sexed, and weighed. Thirty-six hours after delivery, the newborns were equally distributed (9/mother) between the lactating mothers, which were continued on their gestational diet. No effect on the number of pregnancies was seen in the FOS group; however, a reduction in body weight gain of the pregnant rats was identified. The authors noted that this could have been due to a lower caloric value for FOS, decreased intake of food for this group, and/or diarrhea observed in the first week and softer stools in the second and third weeks of exposure. Despite the reduction in body weight gain of the pregnant rats in the FOS-exposed group, the fetuses and newborn weights were not affected. However, during the nursing period, a growth delay was observed in the pups (specifically males) of the FOS-exposted group. This may be indicative of the restricted nutritional status of the lactating mothers. The study concluded that a diet containing 20% FOS had no significant effects on the course of pregnancy in rats and on the development of their fetuses and newborns.

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Possible maternal and developmental toxicity in the rat (strain Crl CD (SD) BR) following administration of FOS during gestation was evaluated.[33] Four groups of 24 to 27 pregnant females were pretreated with FOS at a dietary level of 4.75% from day 0 to 6 post coitum. A fifth group received a FOS-free diet throughout the entire study. On postcoital day 6, the FOS pretreatment diet was replaced, with each of the four treatment groups receiving one of the following diets: FOS-free diet, and 5, 10, and 20% FOS. This regimen was continued until day 15, when all pregnant females were placed on an FOS-free diet. On day 20, the rats were killed and litters were examined. Approximately half of the fetuses were dissected and examined fresh prior to skeletal staining, while the rest were fixed in Bouin's solution. Results of the experiment revealed no treatment-related effects during pretreatment (days 0 to 6 post coitum) and treatment (days 6 to 15 post coitum) with FOS at dietary levels up to 20%. No diarrhea was observed in any of the test animals and no deaths were recorded. FOS administered during the pretreatment period did not affect body weight and body weight change in any of the groups. However, 2 days after the start of the treatment (postcoital day 8), body weight was reduced in all FOS groups relative to controls. Additionally, body weight change in the treatment groups decreased in a dose-related manner. The 5% group exhibited a lower weight gain relative to that of controls, whereas, the 10% and 20% groups lost weight. From day 11 to the

end of the study, body weights were similar among groups, with the exception of the 20% FOS group, the body weights of which remained below those of the controls.

At necropsy, the findings in dams were unremarkable. The number of pups/litter, the sex ratio, and viability of both the embryo and the fetus were not affected by dietary supplementation with FOS. Litter and fetal weights were not reduced, while the fetal weight of the 20% group was statistically greater than that of the controls. Structural development of the fetuses was unremarkable. It was concluded that dietary supplementation with FOS, at concentrations up to 20%, did not cause adverse effects or negatively affect pregnancy outcome or *in utero* development of the rat. The only treatment-related effect was the alteration in body weight of the dams, with a moderate reduction seen in the 20% FOS group.[33]

Pectin

Parental (F_0) rats (Wistar (Crl:WI(WU), outbred) were fed the various test diets containing pectin-derived acidic oligosaccharides (pAOS) and control diets. Feeding was initiated at 4 weeks prior to mating and continued throughout mating, gestation, and lactation periods, until weaning of the offspring (F_1).[81] To form the F_0 groups, rats were allocated to four groups (16 females and 8 males per group) by computer randomization. At the start of the premating period, the parental (F_0) rats were approximately 11 weeks (males) or 10 weeks (females) old. There were two control groups, one that received the standard rodent diet supplemented with 10% potato starch, and one that received 10% short-chain (sc) FOS in the diet. Two experimental groups received the standard diet supplemented with 5% or 10% pAOS. To keep the total level of added substance (test substance, reference substance and/or starch) equal in each diet, the low-dose diet (5% pAOS) was adjusted with 5% potato starch. All macro- and micronutrients in the RM3breeding diet were well in excess of the minimal requirement of the laboratory rat to allow 10% dilution of the diet, except for vitamin B12. Therefore, all experimental diets (including the control diets) were supplemented with vitamin B_{12} to meet the requirement (50 µg/kg diet) in the finished diet.

No clinical signs attributable to pAOS were observed in the F_0 females during premating and the gestation period. There were no relevant effects on body weights, growth rate or feed intake of the F_0 rats during the premating, gestation, and lactation periods. Daily examination of vaginal smears of F_1 females during the last three weeks of the study did not reveal any effect of pAOS on estrus cycle length and normality. Sperm analysis at the end of the study did not reveal relevant changes in epididymal sperm motility and sperm count, testicular sperm count (including daily sperm production), and sperm morphologic changes. Macroscopic examination of the F_0 males and females of the test groups (5% and 10% pAOS) at necropsy did not reveal any relevant changes. In addition, no treatment-related effects on reproductive indices were observed. The general condition and macroscopy of pups were not affected by treatment, nor were litter size, pup viability or sex ratio different from controls. It was concluded that dietary pAOS did not affect parental health or pup characteristics.[81]

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

The oral administration of karaya gum (suspension in anhydrous corn oil) had no effects on nidation or fetal survival of implanted embryos in groups of 87 to 90 pregnant female Dutch-belted rabbits at doses up to 635 mg/kg/day for 13 consecutive days.[101] The number and type of abnormalities observed in either soft or skeletal tissues of pups at term from treated dams did not differ significantly from those observed in sham-treated control dams. It was concluded that karaya gum was not teratogenic in rabbits in this study.

In another study, karaya gum (suspension in anhydrous corn oil) was administered to groups of 87 to 90 pregnant female albino CD-1 outbred mice for 10 consecutive days.[101] The gum was administered at doses up to 170 mg/kg body weight. Dosing had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities observed in either soft or skeletal tissues of treated animals did not differ from the number occurring spontaneously in the sham-treated controls. In a concurrent group of mice dosed with 800 mg/kg body weight, a significant number of maternal deaths (9 out of 28) occurred. The surviving dams appeared completely normal and delivered normal fetuses, with no effect on the rate of nidation or survival of live pups in utero. It was concluded that karaya gum was not teratogenic in mice in this study. When groups of 87 to 89 pregnant female Wistar-derived albino rats were dosed orally with karaya gum (doses up to 900 mg/kg body weight) according to the same procedure, the results were identical to those stated for mice.[101]

GENOTOXICITY

Genotoxicity data (bacterial and mammalian) on plant polysaccharide gums are summarized in Table 3. Most of the results were negative, with and without metabolic activation. The results for pectin-derived acidic oligosaccharides were

equivocal in the mouse lymphoma assay and positive (clastogenic) in the chromosome aberrations assay, but only at highly cytotoxic concentrations.

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

Reportedly**,** results were negative for karaya gum in a genotoxicity assay.[34,102] This study was ordered from the National Technical Information Service.

CARCINOGENICITY/HYPERPLASIA

Algin and Starch Acetate

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

Carrageenan

Groups of 16 Fischer 344 rats were fed a basal diet supplemented with 5% ι-carrageenan for up to 91 days in a study evaluating the proliferative response of the colonic epithelium to ι-carrageenan.[103] 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, and 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.[103]

In another study, groups of 5 male and 5 female mice of two strains were administered at concentrations of 0, 0.1, 5, 15, and 25% carrageenan in the diet for their lifespan, without evidence of adverse effects or carcinogenicity.[104] 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% dose.

A long-term carcinogenicity study on *kappa* carrageenan was performed using rats and hamsters.[105] 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, but 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

an 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.

Cyclodextrin

The carcinogenicity of β-cyclodextrin, a cyclic, water-soluble carbohydrate composed of seven glucose units, was examined using Fischer 344 (F344) rats. Groups of 50 males and 50 females were given the compound in their diet at concentrations of 0 (control), 2.5%, or 5% for 104 weeks.[41] 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.[106] 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 the 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.

Fructooligosaccharides (FOS)

Data on FOS are included for use in the safety assessment of inulin. A 104-week carcinogenicity study was performed using 50 male and 50 female Fischer 344 rats.[107] The animals received FOS (average DP = 3.5) in the diet at concentrations of 0, 8000 ppm, 20,000 ppm, and 50,000 ppm. FOS intake by the 8000 ppm, 20,000- ppm and 50,000 ppm groups was equivalent to 341, 854, and 2170 mg/kg/day, respectively, for male rats and 419, 1045, and 2664 mg/kg/day, respectively, for female rats. Results indicated that survival of both sexes, in all test groups, was unrelated to treatment. A decreased rate of survival in male rats (20,000-ppm dose group) was observed, however, this was not considered treatment-related because a dose–response relationship was not evident. Body weight gain, food intake, and organ weights for both sexes were unaffected by FOS supplementation. Overall, food efficiencies by FOS-treated male and female groups were comparable to their control groups.

Hematology parameters were not influenced by FOS supplementation. Blood chemistry results demonstrated a slight, but significant elevation of Na^+ and Cl^- in male rats. Male rats in the 20,000 ppm FOS group had slightly elevated levels of blood glucose and creatinine. The males in the 50,000 ppm group had decreased creatinine levels. All other parameters for treated males were similar to controls. In females, all blood chemistry parameters were similar to those of controls, except for slight elevation of uric acid in the 8000 ppm and 20,000 ppm groups. No treatment-related macro- or microscopic changes were found in either males or females. The only non-neoplastic lesions observed were said to have been common in aging rats of this strain, as demonstrated by their incidence in historical controls.[107]

Pectin

The effects of pectin on the morphological parameters of the small intestine were investigated.[108] 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.

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.[109] The 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 nuclear, cytosolic, and membrane pools. The levels of β-catenin, cyclin D1 and E-cadherin were determined by Western blotting at both time points (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 h-catenin, and increased amount 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.

Co-carcinogenicity

Pectin

The effect of low-methoxylated pectin and high-methoxylated pectin on 1,3-dimethylhydrazine initiation of colon cancer was investigated using groups of 30 Sprague-Dawley rats.[110] 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.

Antitumor Activity

Arabinoxylan

The antitumor activity of wheat bran arabinoxylan was investigated using groups of 10 ICR male mice.[111] The mice were injected i.p. with mouse sarcoma S180 cells, human chronic myelogenous K562 cells, or human leukemia HL-60 cells, and dosed orally with arabinoxylan. All three doses of arabinoxylan (100, 200, and 400 mg/kg body weight) conferred significant inhibitory activity against solid tumor formation in S180 tumor-bearing mice, with inhibitory ratios of 14.34%, 31.37%, and 56.73%, respectively. Treatment with the positive control, cyclophosphamide, conferred the highest inhibitory rate (78.4%) on S180 sarcomas transplanted in mice ($p < 0.01$). Dosing with arabinoxylan also remarkably promoted thymus and spleen indexes, splenocyte proliferation, natural killer cell and macrophage phagocytosis activity, interleukin 2 production, and delayed-type hypersensitivity reaction. Additionally, it increased peripheral leukocyte count and bone-marrow cellularity in tumor-bearing mice. Arabinoxylan did not have any effect on the growth of K562 and HL-60 cells *in vitro*. The authors stated that arabinoxylan can be considered to be an antitumor agent with immunomodulatory activity.

Anticarcinogenicity

Arabinoxylan

Two types of preneoplastic lesions [aberrant crypt foci (ACF) and mucin depleted foci (MDF)] were detected in the colon of rats treated with the colon carcinogen 1,2-dimethylhydrazine (DMH) and fed either a control diet or a diet containing Arabinoxylan-oligosaccharides (4.8% w/w) (15 rats in each group).[112] 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.

Inulin

Thirty Sprague-Dawley rats (4 months old) were experimentally treated with the procarcinogen, dimethylhydrazine to induce colon cancer.[113] The rats were randomly assigned to the following 3 groups: control group, group treated with dimethylhydrazine (DMH), and a group given DMH and inulin. 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 group. Dosing with inulin increased the concentration of inulin that had been reduced by DMH. 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.[114] 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 regular 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.

OTHER EFFECTS

Acetylcholinesterase Inhibition

Cichorium Intybus (Chicory) Root

The dichloromethane extract of chicory roots (*Cichorium intybus* L.) caused a pronounced inhibitory effect (70% inhibition) on acetylcholinesterase at a concentration of 1 mg extract/ml in a microplate enzyme test assay using Ellman's spectrophotometry.[115] This effect on acetylcholinesterase was considered significant. Furthermore, two sesquiterpene lactones isolated from the chicory root, 8-deoxylactyucin and lactucopicrin, induced both statistically significant and dose-dependent inhibitory activity on acetylcholinesterase (IC_{50} values of 308.1 µM and 15.3 µM, respectively).

Antifungal Activity

Calcium Alginate

The antifungal properties of calcium alginate fiber were studied after contact with *Candida albicans*.[94] 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.

Inflammation

Carrageenan

Local muscle inflammation was induced by injecting an algal-derived polysaccharide, carrageenan (10 mg/kg), into the right tibialis anterior muscle in 22 healthy ARC mice (6 weeks old).[116] 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. Conclusions: These results indicate that carrageenan directly affects contractile function and causes skeletal muscle weakness.

Anti-inflammatory/Antioxidant Activity

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.[117] Alginic acid treatment (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

Many of the plant polysaccharide gums reviewed in this safety assessment function as viscosity increasing agents in cosmetic products. 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 with safe and suitable acids and enzymes. It is an approved direct food additive affirmed as generally recognized as safe by the Food and Drug Administration.

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) and results from a Personal Care Products Council (C0uncil) survey of ingredient use concentrations combined, the following 57 plant polysaccharide gums are being used in cosmetic products: maltodextrin, agar, agarose, algin, alginic acid, amylodextrin, avena sativa (oat) starch, calcium alginate, carrageenan, cassia angustifolia seed polysaccharide, cichorium intybus (chicory) root oligosaccharides, corn starch modified, croscarmellose, cyclodextrin, cyclodextrin laurate, dextrin, dextrin myristate, dextrin palmitate, dextrin palmitate/stearate, galactoarabinan, glycerol alginate, glyceryl starch, hydrogenated starch hydrolysate, hydrolyzed corn starch octenylsuccinate, hydrolyzed pectin, hydrolyzed starch, hydrolyzed wheat starch, hydroxypropyltrimonium hydrolyzed corn starch, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, hydroxypropyltrimonium hydrolyzed wheat starch, hydroxypropyltrimonium maltodextrin crosspolymer, hydroxypropyl starch, inulin, laurdimonium hydroxypropyl hydrolyzed wheat starch, mannan, methyl cyclodextrin, natto gum, pectin, polianthes tuberosa polysaccharide, potassium alginate, potato starch modified, propylene glycol alginate, pueraria lobata starch, sodium carboxymethyl starch, sodium carrageenan, sodium hydrolyzed potato starch dodecenylsuccinate, sodium oxidized starch acetate/succinate, sodium starch octenylsuccinate, solanum tuberosum (potato) starch, starch acetate, starch diethylaminoethyl ether, starch hydroxypropyltrimonium chloride, stearoyl inulin, sterculia urens gum, tamarindus indica seed gum, tapioca starch, and triticum vulgare (wheat) starch.

The Council survey data also indicate that plant 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).

In studies involving rats, there was no specific accumulation of orally administered clyclodextrin 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. In human studies, 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.

In an acute oral toxicity study on fructooligosaccharides, an LD_{50} of > 9 g/kg (rats) was reported. Repeated dose oral toxicity studies on the following were performed: algin and starch acetate (mice), arabinoxylan (in wheat bran extract) and inulin (rats), carboxymethyl inulin (rats), croscarmellose (rats), cyclodextrin (rats and dogs), fructooligosaccharides (rats), ghatti gum (rats), and pectin (rats). Sodium alginate was nephrotoxic to mice, but results for starch acetate were of little, if any, toxicological significance. The no-observed-adverse effect level 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 croscarmellose, fructooligosaccharides, and 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.

Repeated oral feeding of humans with propylene glycol alginate or sterculia urens gum did not cause toxicity.

Systemic toxicity was not observed in guinea pigs that received repeated dermal applications of carboxymethyl inulin.

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

Skin irritation was not observed in albino guinea pigs patch tested with 100% carboxymethyl inulin. In the guinea pig maximization test, carboxymethyl inulin did not induce sensitization. Allergenicity was not associated with the oral dosing of human subjects with propylene glycol alginate. Dermal application of a calcium alginate dressing to patients did not cause any side effects that were classified as severe.

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.

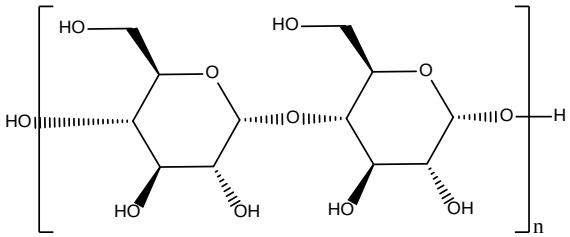
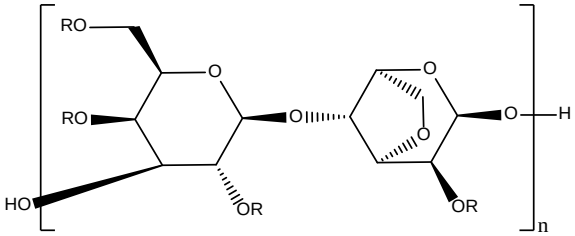
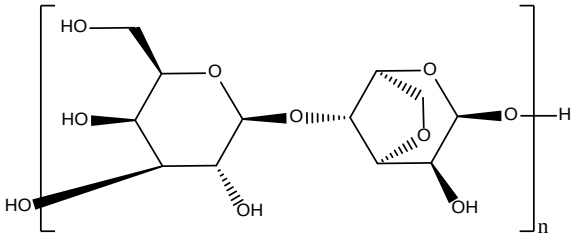
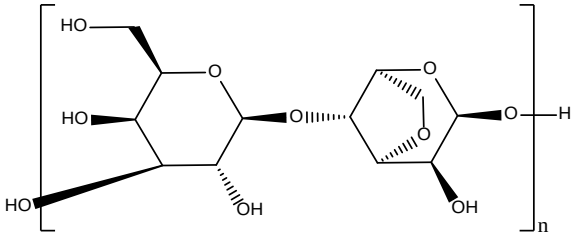
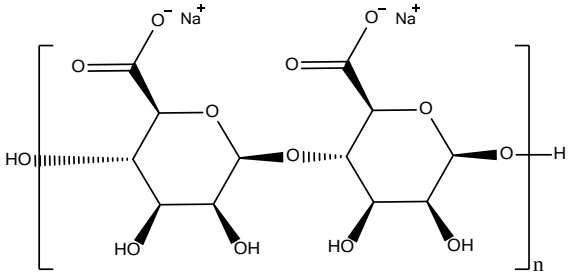
Neither reproductive nor developmental toxicity was observed in rat dietary feeding studies involving carrageenan, calcium carrageenan, sodium carrageenan, croscarmellose, cyclodextrin, fructooligosaccharides, or pectin. Sterculia urens gum was not teratogenic when administered in a corn oil suspension to rabbits.

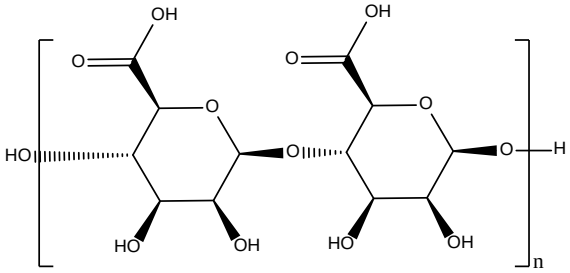
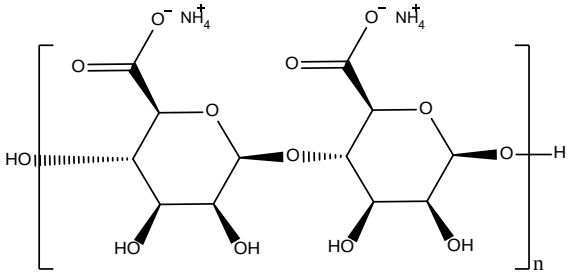
In bacterial assays, the following were not genotoxic either with or without metabolic activation: arabinoxylan, carboxymethyl inulin, fructooligosaccharides, ghatti gum, and pectin-derived acidic oligosaccharides. In mammalian assays with and without metabolic activation, wheat bran extract, carboxymethyl inulin, fructooligosaccharides, and ghatti were not genotoxic. However, results for pectin-derived acidic oligosaccharides were either equivocal or it was classified as clastogenic.

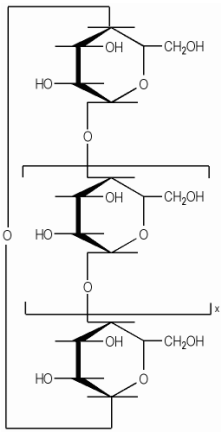
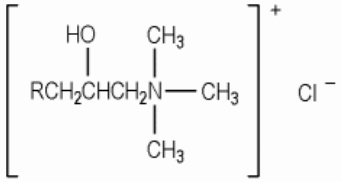
Neither algin nor starch acetate was found to be carcinogenic in an oral feeding study involving mice. When fed in the diet to rats, carrageenan, cyclodextrin, fructooligosaccharides also were not carcinogenic. The feeding of rats with an inulin-enriched diet resulted in the promotion of adenoma growth. Mucosal hyperplasia in the small intestine was observed in rats fed pectin in the diet. In another feeding study, methoxylated pectin in the diet increased the multiplicity of colon tumors in rats injected with 1,3-dimethylhydrazine.

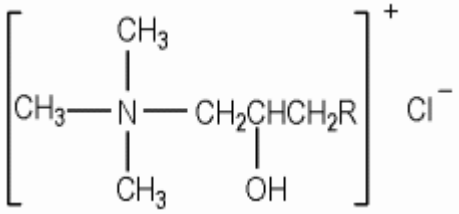
Anticarcinogenic effects have been associated with arabinoxylan and inulin in studies involving rats. The antitumor activity of wheat bran arabinoxylan in mice has also been reported.

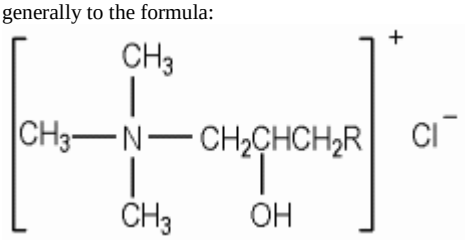
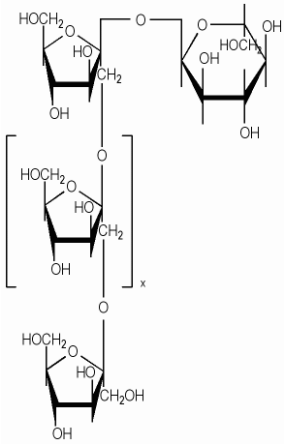
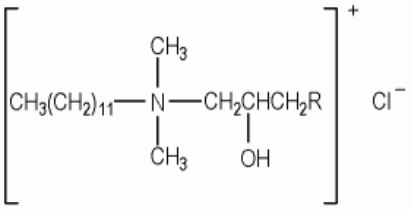
Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Plant Polysaccharide Gums.[1]
[*Italicized text* and all structures below have been added by CIR staff.]

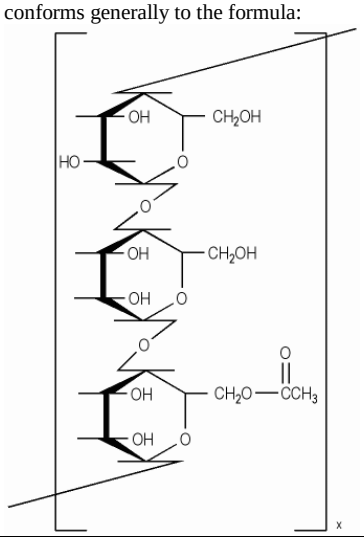
Ingredient CAS No.	Definition	Formula/structure
Maltodextrin 9050-36-6	Maltodextrin is the saccharide material obtained by hydrolysis of starch. *Maltodextrin is a linear-chain oligosaccharide of glucose, usually obtained from starch by partial, enzymatic treatment.*[118] *The term "maltodextrin" can be applied to any starch hydrolysis product that contains fewer than 20 dextrose (glucose) units linked together.*	
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.*[119]	 and  wherein R is hydrogen, sulfate, or pyruvate
Agarose 9012-36-6	Agarose is the polysaccharide extracted from the red seaweed Gracilaria.	
Algae Exopolysaccharides	Algae Exopolysaccharides are exopolysaccharides produced and secreted by various species of microalgae of the divisions, Rhodophyta and Chlorophyta.	
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.*	

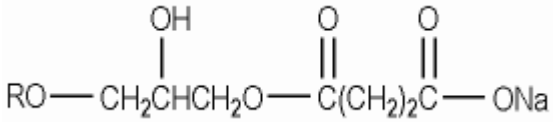
Ingredient CAS No.	Definition	Formula/structure
Alginic Acid 9005-32-7	Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae. *Alginic acid is a polysaccharide comprised of 1,4-linked-b-D-mannuronic and a-L-guluronic acids.*[120]	
Ammonium 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.*	
Amylodextrin 9005-84-9	Amylodextrin is the product obtained by treating potato or corn starch with dilute hydrochloric acid.	
Amylopectin 9037-22-3	Amylopectin is the branched chain polysaccharide portion of starch.	
Amylose 9005-82-7	Amylose is the carbohydrate stored by plants that consists of a linear (1→4)-(structure)-D-glucan polymer.	
Aphanothece Sacrum Polysaccharide	Aphanothece Sacrum Polysaccharide is the polysaccharide fraction isolated from the alga, Aphanothece sacrum.	
Arabinoxylan 9040-27-1	Arabinoxylan is a polysaccharide composed of a xylose backbone with arabinose side chains.	
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)	
Avena Sativa (Oat) Starch 9005-25-8 (generic)	Avena Sativa (Oat) Starch is a starch obtained from oats, Avena sativa.	
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 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.	
Cassia Angustifolia Seed Polysaccharide	Cassia Angustifolia Seed Polysaccharide is the polysaccharide fraction derived from the seed of Cassia angustifolia.	
Cichorium Intybus (Chicory) Root Oligosaccharides	Cichorium Intybus (Chicory) Root Oligosaccharides is the carbohydrate fraction isolated from the roots of Chicorium intybus.	

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.	
Croscarmellose 9000-11-7	Croscarmellose is a cross-linked polymer of Cellulose Gum.	
Cyclodextrin 12619-70-4 7585-39-9	Cyclodextrin is a cyclic polysaccharide comprised of six to eight glucopyranose units. It conforms to the formula:  where x may have values from 4 to 6.	
Cyclodextrin Hydroxypropyltrimonium Chloride	Cyclodextrin Hydroxypropyltrimonium Chloride is the organic compound that conforms to the formula:  where R represents the Cyclodextrin polymer.	
Cyclodextrin Laurate	Cyclodextrin Laurate is the product obtained by the reaction of Cyclodextrin and lauric acid chloride.	
Cyclotetraglucose 159640-28-5	Cyclotetraglucose is a cyclic polysaccharide comprised of four Glucose units.	
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.	
Dextrin Isostearate	Dextrin Isostearate is the ester of Dextrin and Isostearic Acid.	
Dextrin Laurate 79748-56-4	Dextrin Laurate is the ester of Dextrin and Lauric Acid.	
Dextrin Myristate 93792-77-9	Dextrin Myristate is the ester of Dextrin and Myristic Acid.	
Dextrin Palmitate 83271-10-7	Dextrin Palmitate is the palmitic acid ester of Dextrin.	
Dextrin Palmitate/Ethylhexanoate 183387-52-2	Dextrin Palmitate/Ethylhexanoate is the mixed ester of Dextrin with palmitic and ethylhexanoic acids.	
Dextrin Stearate 37307-33-8	Dextrin Stearate is the ester of Dextrin and Stearic Acid.	

Ingredient CAS No.	Definition	Formula/structure
Echinacin 8001-18-1	Echinacin is a polysaccharide fraction derived from the dried rhizome and roots of *Echinacea pallida.*	
Galactoarabinan 9036-66-2	Galactoarabinan is the polysaccharide obtained from the extraction of one or more species of the larch tree, *Larix.*	
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.	
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 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.*	
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.*	
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.	
Hydroxyethyl Cyclodextrin	Hydroxyethyl Cyclodextrin is the hydroxyethyl ether of Cyclodextrin.	
Hydroxypropyl Cyclodextrin 128446-33-3 128446-35-5	Hydroxypropyl Cyclodextrin is a propylene glycol ether of Cyclodextrin.	
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.	

Ingredient CAS No.	Definition	Formula/structure
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.	
Inulin 9005-80-5	Inulin is the polysaccharide that conforms to the formula: 	
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.	
Magnesium Alginate 37251-44-8	Magnesium Alginate is the magnesium salt of Alginic Acid.	

Ingredient CAS No.	Definition	Formula/structure
Mannan 9036-88-8 51395-96-1	Mannan is a natural polysaccharide consisting of glucose, mannose, and acetyl mannose monomers. It conforms generally to the formula: 	
Methyl Cyclodextrin 128446-36-6	Methyl Cyclodextrin is the product obtained by the methylation of Cyclodextrin.	
Palmitoyl Inulin	Palmitoyl Inulin is the condensation product of palmitic acid chloride and the carbohydrate, Inulin.	
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.	
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.*	
Polianthes Tuberosa Polysaccharide	Polianthes Tuberosa Polysaccharide is the polysaccharide fraction produced by the cultured cells of *Polianthes tuberosa*.	
Potassium Alginate 9005-36-1	Potassium Alginate is the potassium salt of Alginic Acid.	
Potassium 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.	
Pueraria Lobata Starch 9005-25-8 (generic)	Pueraria Lobata Starch is the starch obtained from the roots of *Pueraria lobota.*	
Sodium Algin Sulfate 9010-06-4	Sodium Algin Sulfate is the sulfate ester of Algin.	
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.	

Ingredient CAS No.	Definition	Formula/structure
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 Hydroxypropyl Oxidized Starch Succinate	Sodium Hydroxypropyl Oxidized Starch Succinate is the organic compound that conforms to the formula:  where R represents the oxidized starch moiety.	
Sodium Oxidized Starch Acetate/Succinate	Sodium Oxidized Starch Acetate/Succinate is the sodium salt of product of the esterification of oxidized starch with acetic acid and succinic acid anhydrides.	
Sodium Starch Octenylsuccinate 52906-93-1 66829-29-6 70714-61-3	Sodium Starch Octenylsuccinate is the sodium salt of the reaction product of octenylsuccinic anhydride with Zea Mays (Corn) Starch.	
Sodium/TEA-Undecylenoyl Alginate	Sodium/TEA-Undecylenoyl Alginate is the mixed sodium and triethanolamine salt of the condensation product of undecylenic acid chloride and Alginic Acid.	
Solanum Tuberosum (Potato) Starch 9005-25-8 (generic)	Solanum Tuberosum (Potato) Starch is a polysaccharide obtained from the potato, *Solanum tuberosum.*	
Starch Acetate 9045-28-7	Starch Acetate is the product obtained by the reaction of acetic acid with starch.	
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.	
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.	
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.	
Starch Laurate	Starch Laurate is the product obtained by the reaction of lauric acid with starch.	
Starch Tallowate	Starch Tallowate is the ester of starch with the fatty acids derived from Tallow.	
Stearoyl Inulin	Stearoyl Inulin is the condensation product of stearic acid chloride with the carbohydrate, Inulin.	
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.	
Tapioca Starch Crosspolymer	Tapioca Starch Crosspolymer is Tapioca Starch crosslinked with epichlorohydrin.	
TEA-Alginate	TEA-Alginate is the triethanolamine salt of Alginic Acid.	
TEA-Dextrin Octenylsuccinate	TEA-Dextrin Octenylsuccinate is the triethanolamine salt of the reaction product of octenylsuccinic anhydride with Dextrin.	
Triticum Vulgare (Wheat) Starch 9005-25-8 (generic)	Triticum Vulgare (Wheat) Starch is a starch obtained from wheat, *Triticum vulgare.*	

Ingredient CAS No.	Definition	Formula/structure
Undecylenoyl Inulin	Undecylenoyl Inulin is the condensation product of undecylenic acid chloride with the carbohydrate, Inulin.	
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.	
Not necessarily just polysaccharides (e.g., may be protienaceous)		
Acacia Catechu Gum 8001-76-1	Acacia Catechu Gum is the dried, crushed core of Acacia catechu. *Extractives and their physically modified derivatives. It is a resinous product which may contain resin acids and their esters, terpenes, and oxidation or polymerization products of these terpenes. (Acacia catechu), Leguminosae).*(CAS file)	
Acacia Farnesiana Gum	Acacia Farnesiana Gum is the dried, gummy exudate obtained from Acacia farnesiana.	
Acacia Senegal Gum 9000-01-5	Acacia Senegal Gum is the dried, gummy exudate obtained from Acacia senegal. *A.k.a. gum arabic*	
Acacia Seyal Gum	Acacia Seyal Gum is the dried, gummy exudate obtained from Acacia seyal.	
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*.	
Ghatti Gum 9000-28-6	Ghatti Gum is the dried, gummy exudate obtained from the stems and bark of *Anogeissus latifolia*.	
Hydrolyzed Carrageenan 53973-98-1	Hydrolyzed Carrageenan is the hydrolysate of Carrageenan derived by acid, enzyme or other method of hydrolysis.	
Natto Gum 9079-02-1	Natto Gum is a fermentation product of soy protein by *Bacillus natto* or *Bacillus subtilis.*	
Potassium Carrageenan 64366-24-1	Potassium Carrageenan is the potassium salt of Carrageenan.	
Potassium Undecylenoyl Carrageenan	Potassium Undecylenoyl Carrageenan is the potassium salt of the condensation product of undecylenic acid chloride and Carrageenan.	
Prunus Persica (Peach) Gum	Prunus Persica (Peach) Gum is the dried, gummy exudate obtained from *Prunus persica*.	
Sodium Carrageenan 60616-95-7 9061-82-9	Sodium Carrageenan is the sodium salt of Carrageenan.	
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.	
Sterculia Urens Gum 9000-36-6 [VCRP name: Karaya Gum]	Sterculia Urens Gum is a dried exudate from the tree, *Sterculia urens.*	
Tamarindus Indica Seed Gum	Tamarindus Indica Seed Gum is the gum obtained from the seeds of *Tamarindus indica.*	
Tapioca Starch	Tapioca Starch is the starch obtained from the roots of *Manihot esculenta.* It consists primarily of amylose and amylopectin.	
Tapioca Starch Crosspolymer	Tapioca Starch Crosspolymer is tapioca starch crosslinked with epichlorohydrin.	
TEA-Alginate	TEA-Alginate is the triethanolamine salt of alginic acid.	
TEA-Dextrin Octenylsuccinate	TEA-Dextrin Octenylsuccinate is the triethanolamine salt of the reaction product of octenylsuccinic anhydride with dextrin.	
Triticum Vulgare (Wheat) Starch	Triticum Vulgare (Wheat) Starch is a starch obtained from wheat, *Triticum vulgare.*	
Undecylenoyl Inulin	Undecylenoyl Inulin is the condensation product of undecylenic acid chloride with the carbohydrate, inulin.	
Xyloglucan	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.	

Table 2. Ingredient Functions, Use Frequencies, and Maximum Use Concentrations.[12,13]

Ingredient Name and Functions	Frequency of Use	Maximum Use Concentrations (%)
Maltodextrin - Absorbents; Binders; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Film Formers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous	520	0.00001-4
Acacia Catechu Gum - Adhesives; Fragrance Ingredients	NR	NR
Acacia Farnesiana Gum - Adhesives	NR	NR
Acacia Senegal Gum - Adhesives; Fragrance Ingredients	430	0.0001-11
Acacia Seyal Gum - Skin-Conditioning Agents - Humectant	NR	NR
Agar - Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous	81	0.002-1
Agarose - Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous	10	0.2-0.7
Algae Exopolysaccharides - Film Formers; Skin Protectants; Skin-Conditioning Agents - Humectant; Slip Modifiers	NR	NR
Algin - Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous	434	0.001-50
Alginic Acid - Binders; Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Aqueous	13	NR
Ammonium Alginate - Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous	0	NR
Amylodextrin - Absorbents; Bulking Agents	2	0.00004
Amylopectin - Binders; Viscosity Increasing Agents - Aqueous	NR	NR
Amylose - Skin-Conditioning Agents - Humectant	NR	NR
Aphanothece Sacrum Polysaccharide - Absorbents; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous	NR	NR
Arabinoxylan - Film Formers	NR	NR
Astragalus Gummifer Gum - Adhesives; Binders; Emulsion Stabilizers; Film Formers; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous	11	NR
Avena Sativa (Oat) Starch - Absorbents	5	0.1-9.5
Calcium Starch Isododecenylsuccinate - Absorbents; Skin-Conditioning Agents - Emollient	NR	NR
Calcium Starch Octenylsuccinate (a "modified food starch") - Absorbents; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous	NR	NR
Calcium Alginate - Fragrance Ingredients; Viscosity Increasing Agents - Aqueous	8	0.01-3
Calcium Carrageenan - Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous	NR	NR
Carrageenan - Binders; Fragrance Ingredients; Hair Conditioning Agents; Viscosity Increasing Agents - Aqueous	243	0.003-15.7
Cassia Angustifolia Seed Polysaccharide - Skin-Conditioning Agents - Emollient	35	0.0025-0.075
Cichorium Intybus (Chicory) Root Oligosaccharides - Skin-Conditioning Agents - Miscellaneous	1	NR
Corn Starch Modified - Absorbents; Film Formers; Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Nonaqueous	81	0.0062-45.7
Croscarmellose - Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous	NR	3.2
Cyclodextrin - Film Formers; Skin Protectants; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous	135	0.000025-4
Cyclodextrin Hydroxypropyltrimonium Chloride - Film Formers; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous	NR	NR
Cyclodextrin Laurate - Film Formers; Skin Protectants; Skin-Conditioning Agents - Humectant	4	0.0035
Cyclotetraglucose - Binders; Bulking Agents; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous	NR	NR

Table 2. Ingredient Functions, Use Frequencies, and Maximum Use Concentrations.[12,13]

Ingredient Name and Functions	Frequency of Use	Maximum Use Concentrations (%)
Dextrin - Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous	176	0.000008-43
Dextrin Behenate - Anticaking Agents; Surfactants - Emulsifying Agents	NR	NR
Dextrin Isostearate - Skin-Conditioning Agents - Miscellaneous	NR	NR
Dextrin Laurate - Anticaking Agents; Surfactants - Emulsifying Agents	NR	NR
Dextrin Myristate - Anticaking Agents; Surfactants - Emulsifying Agents	NR	0.05-19
Dextrin Palmitate - Anticaking Agents; Surfactants - Emulsifying Agents	94	0.0001-16.8
Dextrin Palmitate/Ethylhexanoate - Anticaking Agents; Surfactants - Emulsifying Agents	NR	NR
Dextrin Palmitate/Stearate - Emulsion Stabilizers; Viscosity Controlling Agents	NR	0.1-18
Dextrin Stearate - Anticaking Agents; Surfactants - Emulsifying Agents	NR	NR
Echinacin - Function not reported	NR	NR
Galactoarabinan - Film Formers; Fragrance Ingredients	92	0.005-3
Ghatti Gum - Binders; Emulsion Stabilizers; Surfactants - Emulsifying Agents; Viscosity Increasing Agents - Aqueous	NR	NR
Glyceryl Alginate - Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Aqueous	NR	0.5
Glyceryl Dimaltodextrin - Humectants; Skin-Conditioning Agents - Humectant	NR	NR
Glyceryl Starch - Absorbents; Binders	1	4
Hydrogenated Potato Starch - Viscosity Increasing Agents - Aqueous	NR	NR
Hydrogenated Starch Hydrolysate - Film Formers; Humectants; Oral Care Agents; Skin-Conditioning Agents - Humectant	56	0.00007-3.8
Hydrolyzed Carrageenan - Skin-Conditioning Agents - Miscellaneous	NR	NR
Hydrolyzed Corn Starch Hydroxyethyl Ether - Emulsion Stabilizers; Humectants; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous	NR	NR
Hydrolyzed Corn Starch Octenylsuccinate - Absorbents; Binders; Film Formers	13	0.06-0.67
Hydrolyzed Furcellaran - Skin Protectants	NR	NR
Hydrolyzed Pectin - Skin-Conditioning Agents - Miscellaneous	14	NR
Hydrolyzed Soy Starch - Skin-Conditioning Agents - Miscellaneous	NR	NR
Hydrolyzed Starch - Humectants; Skin Protectants; Skin-Conditioning Agents - Humectant	NR	0.000013-0.00046
Hydrolyzed Triticum Spelta Starch - Skin-Conditioning Agents - Miscellaneous	NR	NR
Hydrolyzed Wheat Starch - Skin-Conditioning Agents - Humectant	259	0.000003-0.06
Hydroxyethyl Cyclodextrin - Skin-Conditioning Agents - Miscellaneous	NR	1.2
Hydroxypropyl Cyclodextrin - Chelating Agents; Emulsion Stabilizers	NR	0.00001-2
Hydroxypropyltrimonium Hydrolyzed Corn Starch - Antistatic Agents; Film Formers; Hair Conditioning Agents; Hair Fixatives; Hair-Waving/Straightening Agents	7	0.19-0.65
Hydroxypropyltrimonium Hydrolyzed Wheat Starch - Antistatic Agents; Hair Conditioning Agents	6	NR
Hydroxypropyl Oxidized Starch - Film Formers	NR	NR
Hydroxypropyl Starch - Dispersing Agents - Nonsurfactant; Viscosity Increasing Agents - Aqueous	7	0.25-8.2
Hydroxypropyltrimonium Maltodextrin Crosspolymer - Dispersing Agents - Nonsurfactant	NR	0.00045

Table 2. Ingredient Functions, Use Frequencies, and Maximum Use Concentrations.[12,13]

Ingredient Name and Functions	Frequency of Use	Maximum Use Concentrations (%)
Inulin - Skin-Conditioning Agents - Humectant	41	0.0005-3
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch - Antistatic Agents; Hair Conditioning Agents	6	0.017
Magnesium Alginate - Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous	NR	NR
Mannan - Film Formers; Viscosity Increasing Agents - Aqueous	19	0.01-0.25
Methyl Cyclodextrin - Chelating Agents	25	4 to 5
Natto Gum - Viscosity Increasing Agents - Aqueous	35	NR
Palmitoyl Inulin - Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents	NR	NR
Pectin - Binders; Emulsion Stabilizers; Oral Health Care Drugs; Viscosity Increasing Agents - Aqueous	138	0.0001-9
Phaseolus Angularis Seed Starch - Absorbents	NR	NR
Phaseolus Radiatus Seed Starch - Abrasives; Bulking Agents	NR	NR
Pisum Sativum (Pea) Starch - Absorbents; Opacifying Agents; Slip Modifiers	NR	NR
Polianthes Tuberosa Polysaccharide - Skin-Conditioning Agents - Miscellaneous	1	0.001-0.1
Potassium Alginate - Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous	102	1
Potassium Carrageenan - Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous	NR	NR
Potassium Dextrin Octenylsuccinate - Emulsion Stabilizers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents	NR	NR
Potassium Undecylenoyl Alginate - Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous	NR	NR
Potassium Undecylenoyl Carrageenan - Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous	NR	NR
Potato Starch Modified - Viscosity Increasing Agents - Aqueous	62	0.3-1.3
Propylene Glycol Alginate - Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous	16	0.00001-0.15
Prunus Persica (Peach) Gum - Viscosity Increasing Agents - Aqueous	NR	NR
Pueraria Lobata Starch - Absorbents; Opacifying Agents; Slip Modifiers	NR	3.6
Sodium Algin Sulfate - Skin-Conditioning Agents - Humectant	NR	NR
Sodium Carboxymethyl Inulin - Chelating Agents; Viscosity Increasing Agents - Aqueous	NR	NR
Sodium Carboxymethyl Starch - Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous	11	0.05-4.7
Sodium Carrageenan - Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous	4	NR
Sodium Dextrin Octenylsuccinate - Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous	NR	NR
Sodium Hydroxypropyl Oxidized Starch Succinate - Film Formers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Miscellaneous	NR	NR
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate - Surfactants - Foam Boosters	2	NR
Sodium Oxidized Starch Acetate/Succinate - Film Formers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Miscellaneous	7	0.05
Sodium Starch Octenylsuccinate - Absorbents; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous	37	0.0001-0.26
Sodium/TEA-Undecylenoyl Alginate - Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous	NR	NR

Table 2. Ingredient Functions, Use Frequencies, and Maximum Use Concentrations.[12,13]

Ingredient Name and Functions	Frequency of Use	Maximum Use Concentrations (%)
Sodium/TEA-Undecylenoyl Carrageenan - Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous	NR	NR
Solanum Tuberosum (Potato) Starch - Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous	4	3.4-3.6
Starch Acetate - Hair Conditioning Agents; Skin-Conditioning Agents - Emollient	11	2
Starch Acetate/Adipate - Viscosity Increasing Agents - Aqueous	NR	NR
Starch Diethylaminoethyl Ether - Film Formers; Skin-Conditioning Agents - Miscellaneous	1	NR
Starch Hydroxypropyltrimonium Chloride - Antistatic Agents; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Hair Conditioning Agents; Viscosity Increasing Agents - Aqueous	19	0.002-1.2
Starch Laurate - Abrasives	NR	NR
Starch Tallowate - Skin-Conditioning Agents - Emollient	NR	NR
Stearoyl Inulin - Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents	6	0.44-4.8
Sterculia Urens Gum - Adhesives; Binders; Emulsion Stabilizers; Fragrance Ingredients; Hair Fixatives; Viscosity Increasing Agents - Aqueous	NR	0.2-0.7
Tamarindus Indica Seed Gum - Adhesives; Emulsion Stabilizers; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous	NR	0.01-0.3
Tapioca Starch - Viscosity Increasing Agents - Aqueous	142	0.45-33
Tapioca Starch Crosspolymer - Absorbents; Binders	NR	NR
TEA-Alginate - Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous	NR	NR
TEA-Dextrin Octenylsuccinate - Emulsion Stabilizers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents	NR	NR
Triticum Vulgare (Wheat) Starch - Abrasives; Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous	38	0.01-6
Undecylenoyl Inulin - Emulsion Stabilizers; Skin-Conditioning Agents - Emollient	NR	NR
Xyloglucan - Humectants	NR	NR

NR = Not Reported

Table 3. Genotoxicity of Plant 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[76]
Carboxymethyl inulin	Same as above	Ames test	Same as above	Not genotoxic[77]
Fructooligosaccharides (FOS) (for genotoxicity evaluation of Inulin)	Same as above + *Salmonella typhimurium* strain TA1538	Ames test	Same as above	Not genotoxic[107]
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[121]
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[81]
		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[76]
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[77]
FOS (for genotoxicity evaluation of Inulin)	L5178Y mouse lymphoma cells	Mouse lymphoma assay	up to 5,000 µg/ml, with and without metabolic activation	Not genotoxic[107]
FOS (for genotoxicity evaluation of Inulin)	HeLa S3 epithelioid cells	Unscheduled DNA synthesis assay	up to 51,200 µg/ml, with and without metabolic activation	Not genotoxic[107]
Ghatti gum	Chinese hamster ovary (CHO-WBL) cells	Chromosome aberrations assay	up to 6,000 µg/ml, with and without metabolic activation	Not genotoxic[121]
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[121]

Table 3. Genotoxicity of Plant Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
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[81]
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[81]

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