Final Report

On the Safety Assessment of Galactomannans As Used in Cosmetics

March 6, 2012

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The 2012 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Manager/Lead Specialist and Bart Heldreth, Ph.D., Chemist.

1101 17th Street, NW, Suite 412 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢ cirinfo@cir-safety.org

ABSTRACT: The galactomannans are legume polysaccharides that function mostly as hair/skin conditioning agents and viscosity increasing agents in cosmetic products. Their substantial molecular sizes suggest that skin penetration of these ingredients would be unlikely. The CIR Expert Panel concluded that the galactomannans are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

Available data relevant to the safety of the following legume polysaccharides, commonly called galactomannans, as used in cosmetics are reviewed in this draft report:

- Cyamopsis Tetragonoloba (Guar) Gum
- Hydroxypropyl Guar
- C18-22 Hydroxyalkyl Hydroxypropyl Guar
- Guar Hydroxypropyltrimonium Chloride
- Hydroxypropyl Guar Hydroxypropyltrimonium Chloride
- Carboxymethyl Hydroxypropyl Guar
- Hydrolyzed Guar
- Ceratonia Siliqua Gum
- Locust Bean Hydroxypropyltrimonium Chloride
- Hydrolyzed Ceratonia Siliqua Gum Extract
- Caesalpinia Spinosa Gum
- Caesalpinia Spinosa Hydroxypropyltrimonium Chloride
- Hydrolyzed Caesalpinia Spinosa Gum
- Trigonella Foenum-Graecum Hydroxypropyltrimonium Chloride
- Cassia Gum
- Cassia Hydroxypropyltrimonium Chloride

These ingredients function mostly as hair/skin conditioning agents and viscosity increasing agents in cosmetic products.[1]

Gum guar (oxidized 2-hydroxypropyl 3-hydroxy-3-(trimethylammonio) propyl ether, chloride – also known as cationic guar), while not a cosmetic ingredient, is similar to guar hydroxypropyltrimonium chloride, and acute oral toxicity data on cationic guar are being considered along with the limited acute oral toxicity data on guar hydroxypropyltrimonium chloride. Similarly, acute oral toxicity data on carboxymethyl guar (not a cosmetic ingredient) are being considered in the absence of acute oral toxicity data on carboxymethyl hydroxypropyl guar. Data on trigonella foenum-graecum seed powder/paste are included because the gum derived from trigonella foenum-graecum is part of the chemical structure of trigonella foenum-graecum hydroxypropyltrimonium chloride.

CHEMISTRY

Definition and Structure

Definitions of the ingredients reviewed in this safety assessment along with their chemical structures are found in Table 1.[1]

Properties

Seed-bearing plants deposit energy-containing reserves to support the growth of the embryo within the seed. Seed reserves can be of protein, lipid or polysaccharide character. Although the most ubiquitous reserve polysaccharide is starch, the reserve polysaccharides, or gums, of the plant family Leguminoseae, consist of polysaccharides described as having a poly-mannose backbone with galactose pendent groups. Because of the mannose/galactose chemical make-up of these legume polysaccharides, they are commonly called galactomannans. Unlike starch, which is stored in amyloplasts in the cytoplasm, non-starch reserve polysaccharides, such as galactomannans, are deposited in the cell walls of the seeds.

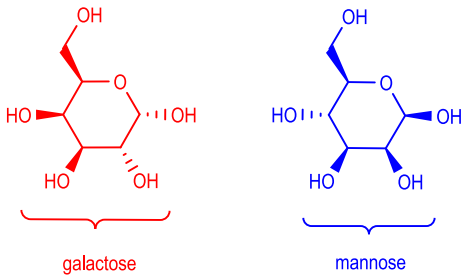


Figure 1. Galactose and Mannose, the building blocks of the Galactomannans

The five primary galactomannan gums are guar gum from the seeds of *Cyamopsis tetragonoloba,* locust bean gum from the seeds of *Ceratonia siliqua* (carob tree), tara gum from seeds of *Cesalpinia spinosa,* fenugreek gum from the seeds of *Trigonella foenum-graecum,* and cassia gum from seeds of *Cassia obtusifolia* or *tora*. While all seed galactomannans possess the same basic structure of a β(1→4)linked polymannose backbone with α(1→6)linked galactose pendent residues, the ratio of galactose to mannose is species specific, and is roughly a constant average within each species. In other words, guar gums average a mannose:galactose ratio of 2:1, locust bean gums are 4:1, tara gums are 3:1, fenugreek gums are 1:1 and cassia gums are 5:1, roughly. The distribution of galactose pendent groups along the polymannose backbone, in each group, is not uniform but more closely resembles a random block, co-polymer. In other words, within one polysaccharide chain there are sections that are highly substituted with galactose pendent groups and there are sections that are more sparsely substituted with galactose pendent groups. Yet, the overall average ratio is maintained within the gum of a species (Figure 2).

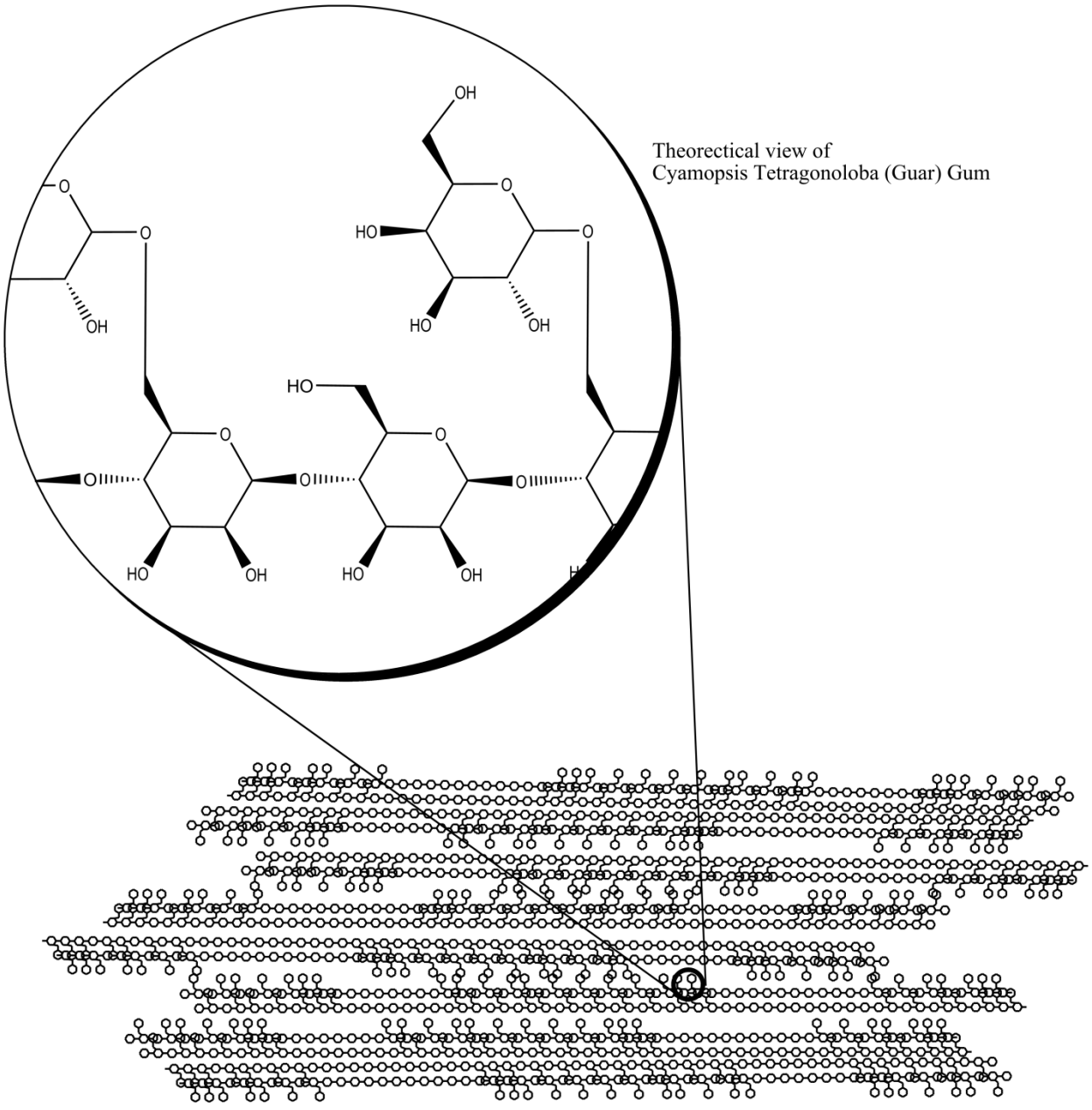


Figure 2. Packing and structure of Cyamposis Tetragonoloba (Guar) Gum

While the ratio of mannose to galactose is 2:1, in guar gums, and the above exploded theoretical structure depicts a galactose pendent group on every other mannose, the true structure is an assortment of pendent placements. These natural gums are typically of a molecular weight greater than 50,000 grams per mole, and often exceed 2,000,000 grams per mole.

In addition to these underivatized, natural gums, are those ingredients that have been etherified at the C6 position of galactose and/or mannose, with various substituents (Figure 3). While the most likely point of derivatization is at the C6 positions of a galactose pendant groups and the polymannose backbone, all of the free hydroxyl groups are potentially susceptible substrates for condensation. That being said, reported degrees of substitution are related as saturated (i.e. equal to 1.0) when there is one stoichiometric equivalent of substituent per one potentially free C6 hydroxyl group (Figure 3). The average degree of substitution, for these types of derivatized gums, is reportedly 0.7 or less. Accordingly, these ingredients have less than one substituent (e.g., hydroxypropyltrimonium chloride) per mannose or galactosyl-mannose. For example, a hydroxypropyl trimonium derivative of guar gum (Guar Hydroxypropyltrimonium Chloride) would be substituted at some available C6 hydroxyls, but might not be at all (Figure 3).

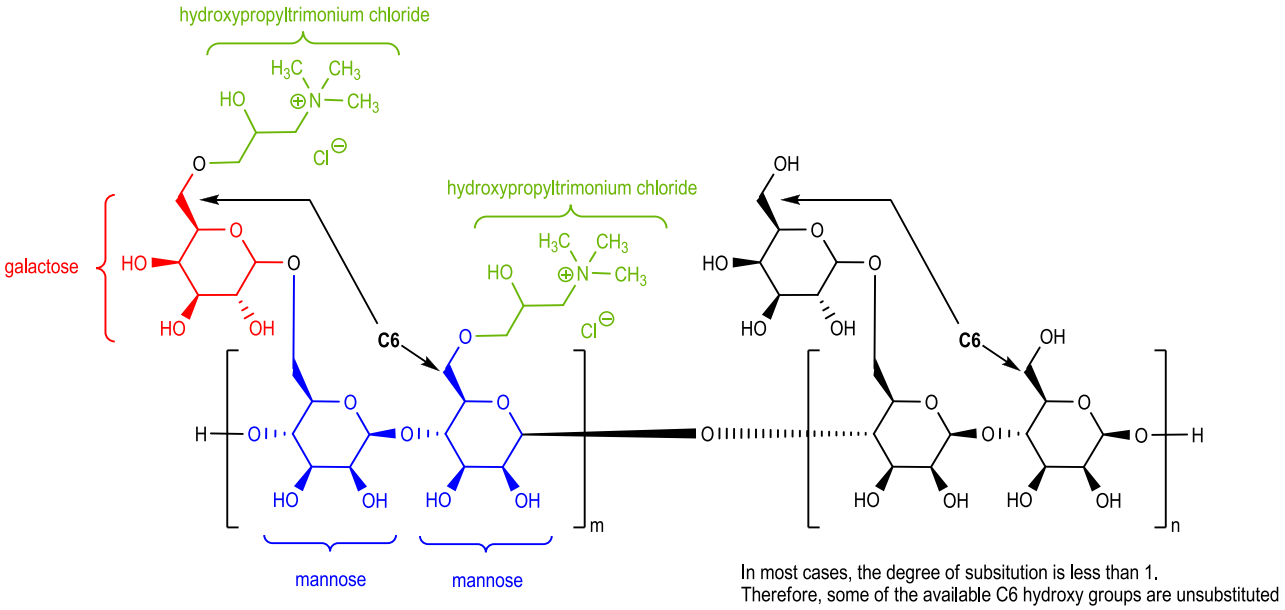


Figure 3. Idealized structure of Guar Hydroxypropyltrimonium Chloride.[2]

Those gums listed in this report as "hydrolyzed" are really ***partially*** hydrolyzed polysaccharides (e.g., hydrolyzed guar gum = guar oligomers). For example, Hydrolyzed Guar is a mixture of guar gum fragments that have been broken down at the 1→6 and 1→4 linkages (via acidic, enzymatic or other methods of hydrolysis) into shorter, lower molecular weight oligosaccharides.

According to the *Food Chemicals Codex*, both cyamopsis tetragonoloba (guar) gum and ceratonia siliqua gum occur as a white to yellow-white powder.[3] Each gum is dispersible in either hot or cold water, forming a sol (pH between 5.4 and 7.0) that may be converted to a gel by addition of small amounts of sodium borate.

Method of Manufacture

Production of natural gums consists of various techniques for the milling of seeds, followed by simple purification steps such as dissolving in hot water, filtering and precipitation with isopropanol. Typical production of the derivatized gums in this report involves the reaction of the natural gum with the appropriate epoxide. Additional information relating to the production of cyamopsis tetragonoloba (guar) gum, hydroxypropyl guar, carboxymethyl hydroxypropyl guar, ceratonia siliqua gum, caesalpinia spinosa gum, and cassia gum, and is included below.

Cyamopsis Tetragonoloba (Guar) Gum

Cyamopsis tetragonoloba (guar) gum is a gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (Linné) Taub.[4]

Hydroxypropyl Guar

Hydroxypropyl guar gum can be prepared by alkaline etherification of guar gum with propylene oxide.[5]

Guar Hydroxypropyltrimonium Chloride

One method of production of a Guar Hydroxypropyltrimonium Chloride trade name material involves the conversion of guar with 3-chloro-2 hydroxypropyl trimethyl ammonium chloride.[6] Data on the properties/composition of this trade name material are found in Table 3.

Carboxymethyl Hydroxypropyl Guar

Carboxymethylation and hydroxypropylation of cyamopsis tetragonoloba (guar) gum are carried out simultaneously using monochloroacetic acid and propylene oxide, in the presence of a hydrophilic solvent (i .e., 2-propanol) with an alkaline pH.[7] These simultaneous reactions result in the formation of carboxymethyl hydroxypropyl guar gum.

Ceratonia Siliqua Gum

Ceratonia siliqua gum is a gum obtained from the ground endosperms of *Ceratonia siliqua* Linné Taub. (Fam. Leguminosae).[4]

Caesalpinia Spinosa Gum

Commercial production of caesalpinia spinosa gum involves the incomplete separation of the endosperm from the germ and husk. Thus, commercial products may contain small amounts of husk as well as varying amounts of protein and fat from unseparated germ. Consequently, commercially available caesalpinia spinosa gum may contain larger percentages of ash and acid insoluble than are present in the hand-dissected endosperm.[8]

Cassia Gum

Cassia gum is derived from *Cassia tora* or *Cassia obtusifolia*.[1] The production method for cassia gum includes cleaning of the source material, de-husking, and de-germing by thermal and mechanical treatment.[9] These steps are followed by milling and screening of the endosperm, which is further purified by extraction with isopropanol. Semi-refined cassia gum is produced in a similar manner, with the exception of an additional isopropanol step to significantly reduce the level of anthraquinones in the latter.

Composition/Impurities

Specifications on the following gums relating to their use in foods/drugs in the United States are included in Table 2: cyamopsis tetragonoloba (guar) gum, ceratonia siliqua gum, caesalpinia spinosa gum, and cassia gum.

Cyamopsis Tetragonoloba (Guar) Gum

Cyamopsis tetragonoloba (guar) gum typically consists of the following: galactomannan (80%), water (12%), protein (5%), acid insoluble matter (2%), and fat (1%).[10] Available data on 11 bulk commercial samples of this gum indicate that glycine, glutamic acid, aspartic acid, serine, and alanine are the most abundant amino acids and that their relative proportions vary considerably. Proportions of the following amino acids remain remarkably constant: histidine, isoleucine, phenylalanine, threonine, tyrosine, and valine.[11]

Commercial samples of cyamopsis tetragonoloba (guar) gum, purified and unpurified, were analyzed in this study.[12] The gum was purified using the following 4 methods: (1) treatment with proteolytic enzyme (porcine pancreatin), (2) successive steps of dissolution, centrifugation and precipitation with acetone and ethanol, (3) Fehling solution used as precipitation agent, and (4) application of the second method, followed by the third one. In all samples (purified and unpurified), mannose and galactose were the major consituents, and glucose and arabinose (2 monosaccharide contaminants) were also present. Uronic acid content ranged from 3.28 to 4.17%. The unpurified sample had a protein content of 3.6%. All purification methods reduced the protein and mono/oligo/polysaccharide contaminants. Method 4 resulted in total elimination of protein. However, the 2 methods (methods 3 and 4) that used Fehling solution contaminated the gum with small amounts of Cu(II), 0.079% and 0.044%, respectively. Methods 2 and 4 resulted in purer (i.e., small amount of protein) cyamopsis tetragonoloba (guar) gum.

The following main components in the lipid fraction of cyamopsis tetragonoloba (guar) gum were identified using GLC-MS: palmitate (hexadecanoate), oleate (9-octadecenaoate), and linoleate (9,12-octadecadienoate).[13]

Using mass spectrometry, very low fluoroacetate concentrations (0.07 -1.42 µg/g, 10 samples) have been detected in cyamopsis tetragonoloba (guar) gum used as a raw material for a guar gum powder. A sample of a guar gum pharmaceutical formulation contained 0.08 ppm fluoroacetate.[14]

The noncatalytic hydrolysis of cyamopsis tetragonoloba (guar) gum under hydrothermal conditions (temperature range: 180 to 240ºC) resulted in the following major products: oligosaccharides with degrees of polymerization up to ~ 20, monosaccharides containing mannose and galactose, and 5-hydroxymethyl-2-furaldehyde.[15]

In 2007, the Rapid Alert System for Food and Feed (RASFF) received a notification from Switzerland concerning a finding of serious contamination of cyamopsis tetragonoloba (guar) gum, originating from India, with dioxins and pentachlorophenol (PCP).[16] The levels of these contaminants in certain batches of cyamopsis tetragonoloba (guar) gum were approximately 1000 times the level of what can be considered as normal background contamination. According to a European Commission decision in 2008, all consignments of cyamopsis tetragonoloba (guar) gum or products containing cyamopsis tetragonoloba (guar) gum at significant amounts originating in or consigned from India and imported into the Community intended for human or animal consumption shall be accompanied by an analytical report, endorsed by the competent authority from the country where the laboratory that has performed the analysis is located. With the 2008 decision in effect, it was determined that there had been no improvement in the control system and no significant reduction in the associated risks. Therefore, in accordance with a 2010 European Commission decision (to replace the 2008 decision), additional measures were taken, requiring official sampling, analysis, and certification by competent authorities of India of all consignments of cyamopsis tetragonoloba (guar) gum intended for export to the European Union.

Guar Hydroxypropyltrimonium Chloride

When a Guar Hydroxypropyltrimonium Chloride trade name material is heated to 600°C, 5.6 to 8.7% of the material remains as ash.[6] This information as well as additional data on the properties/composition of this trade name material are found in Table 3.

Ceratonia Siliqua Gum

Ceratonia siliqua gum has been known to contain tannins and trypsin inhibitors.[17]

Cassia Gum

Cassia gum (*Cassia tora or Cassia obtusifolia*) is composed of at least 75% high molecular mass (~ 200,000 to 300,000) polysaccharide, which consists primarily of a linear chain of 1,4-β-D-mannopyranose units with 1,6-linked α-D-galactopyranose units.[9] The saccharides have the following composition: mannose (77.2 to 78.9%), galactose (15.7 to 14.7%), and glucose 6.3 to 7.1%). The ratio of mannose to galactose is 5:1. *Cassia occidentalis* is a naturally occurring contaminant of cassia gum. In the process of cleaning the source material in the manufacture of this gum, the content of *Cassia occidentalis* is reduced to < 0.05%. The concentration of anthraquinones in cassia gum is < 0.5 mg/kg detection limit. Semi-refined cassia gum contains ~70 mg total anthraquinones/kg. Purified semi-refined cassia gum can contain 8.6 mg total anthraquinones/kg.[9,18]

USE

Cosmetic

The ingredients reviewed in this safety assessment function mostly as hair/skin conditioning agents and viscosity increasing agents in cosmetic products. These and additional functions are included in Table 1.

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2011, the following 9 ingredients were being used in cosmetic products: cyamopsis tetragonoloba (guar) gum, hydroxypropyl guar, guar hydroxypropyltrimonium chloride, hydroxypropyl guar hydroxypropyltrimonium chloride, hydrolyzed guar, ceratonia siliqua gum, caesalpinia spinosa gum, hydrolyzed caesalpinia spinosa gum, and cassia hydroxypropyltrimonium chloride.[19] These data are summarized in Table 4. Results from a survey of ingredient use concentrations conducted by the Personal Care Products Council (also included in Table 4) in 2011 indicate

that locust bean hydroxypropyltrimonium chloride was also being used in cosmetics.[20] Additionally, results from this survey indicate that galactomannans were being used at concentrations up to 93% (hydroxypropyl guar, in a hair straightener leave-on product) in cosmetic products. Additionally, guar hydroxypropyltrimonium chloride was being used in foot powders and sprays at a maximum concentration of 0.05%. Together, the VCRP data and Council survey results suggest that the remaining 6 ingredients included in this safety assessment are not being used in cosmetic products.

Cosmetic products containing the ingredients reported as being used 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.

Hydroxypropyl guar and guar hydroxypropyltrimonium chloride are used in hair sprays, and possibly could 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.[21,22] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions of the respiratory tract and would not be respirable (i.e., able to enter the lungs) to any appreciable amount.[23,24]

Noncosmetic

The following ingredients reviewed in this safety assessment are approved for use as direct food additives by the U.S. Food and Drug Administration (FDA): cyamopsis tetragonoloba (guar) gum (21 CFR 133.124)[25] ; ceratonia siliqua gum (12CFR 182.20)[26]; and cyamopsis tetragonoloba (guar) gum and ceratonia siliqua gum (21 CFR 133.178; 133.179; 150.141; 150.161)[27,28,29,30]. Additionally, cyamopsis tetragonoloba (guar) gum and ceratonia siliqua gum are direct food additives that are considered generally recognized as safe (21 CFR 184.1339; 184.1343)[31,32]. Hydroxypropyl guar is approved for use as an indirect food additive by FDA (21 CFR 176.170)[33]. An evaluation of the health aspects of ceratonia siliqua gum (aka carob bean gum) as a food, prepared for FDA, is available.[17]

Cyamopsis Tetragonoloba (Guar) Gum

Noncosmetic uses of cyamopsis tetragonoloba (guar) gum include:[34] in paper sizing; as a protective colloid, stabilizer, thickening and film forming agent for cheese, salad dressings, ice cream, soups; as a binding and disintegrating agent in tablet formulations; in pharmaceutical jelly formulations; in suspensions, emulsions, lotions, creams, toothpastes; in the mining industry as a flocculant, as a filtering agent; and in water treatment as a coagulant aid. It also functions as an emulsifier.[3]

The distribution of Cal-Ban 3000 diet tablets and capsules was halted by the Food and Drug Administration because it was determined that they may cause esophageal, gastric, and intestinal obstruction .[35] Cyamopsis tetragonoloba (guar) gum, was listed as the main ingredient of Cal-Ban 3000. This gum is a complex sugar that swells when it becomes wet and can create a sense of fullness when ingested.

Cyamopsis tetragonoloba (guar) gum has been approved for use as a food ingredient by the Joint FAO/WHO Expert Committee on Food Additives, and this committee assigned a “not specified” value for the acceptable daily intake (ADI) by man.[36] This means that use of cyamopsis tetragonoloba (guar) gum as a food substance does not represent a human health hazard, and, therefore, the establishment of an ADI in mg/kg body weight was not deemed necessary.

Hydroxypropyl Guar

Hydroxypropyl guar is used as a gelling polymer in an artificial tear solution. It is believed to mimic the mucin layer of the tear film.[37]

Ceratonia Siliqua Gum

Ceratonia siliqua gum has been approved for use as a food ingredient by the Joint FAO/WHO Expert Committee on Food Additives, and this committee assigned a “not specified” value for the acceptable daily intake (ADI) by man.[36] This means that use of ceratonia siliqua gum as a food substance does not represent a human health hazard, and, therefore, the establishment of an ADI in mg/kg body weight was not deemed necessary. Ceratonia siliqua gum functions as a stabilizer and thickener in food.[3]

Caesalpinia Spinosa Gum

Caesalpinia spinosa gum has also been approved for use as a food ingredient by the Joint FAO/WHO Expert Committee on Food Additives, and this committee assigned a "not specified" value for the acceptable daily intake (ADI) by man.[38] This means that use of cyamopsis tetragonoloba (guar) gum as a food substance does not represent a human health hazard, and, therefore, the establishment of an ADI in mg/kg body weight was not deemed necessary.

Cassia Gum

Noncosmetic uses of cassia gum include: thickener, emulsifier, foam stabilizer, moisture retention agent and/or texturizing agent in processed cheese, frozen dairy desserts and mixes, meat products, and poultry products. After considering data supporting the low oral toxicity and negative genotoxicity of cassia gum (included in current CIR report), the Joint FAO/WHO Expert Committee on Food Additives allocated an average daily intake (ADI) " not specified" for cassia gum, when used in the applications specified and in accordance with Good Manufacturing Practice. [9]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

The only available data for these ingredients that relate to absorption, distribution, metabolism, and excretion were found in dietary studies.

Cyamopsis Tetragonoloba (Guar) Gum

When a basal diet containing cyamopsis tetragonoloba (guar) gum (dose = 100 g/kg) was fed to 5 rats, the galactomannan of the gum was digested almost quantitatively. Thus, approximately 1% of the mannose and 4% of the galactose were excreted in the feces.[39] The minor components (i.e., arabinose, glucose, and uronic acids) were also fermented almost completely.

Caesalpinia Spinosa Gum

Two groups of 20 Wistar rats were fed a semisynthetic diet containing caesalpinia spinosa gum (73.9% galactomannan) at galactomannan dietary concentrations of 2% and 5%, respectively, for 11 days.[40] At the end of this feeding period, 12 rats from each dietary group were selected (based on body weight gain, etc.), for an experimental feeding period of 10 days. Digestibility was defined as the portion of ingested material that was not excreted in the stool. Digestibility of galactomannan was 97% and 98.1% for the 2% and 5% diets, respectively. In another study, rats were fed a normal diet containing caesalpinia spinosa gum.[41] The composition and dietary concentration of the gum as well as the feeding periods were not stated. Stools were analyzed for mannose obtained by hydrolysis. It was concluded that all of the mannose added to the feed in the form of galactomannan was excreted in the feces.

Ceratonia Siliqua Gum

Groups of Purdue rats (5 males, 5 females per group; ages not stated) were fed 1% ceratonia siliqua gum in the diet for 18 h.[42] Eighty-five to 100% of the mannose fed as 1% ceratonia siliqua gum was excreted in the feces over a 30-h period. It was noted that some decrease in galactomannan chain length may have occurred. This decrease was belived to have been due to the action of the microflora, because mammals are not known to have the mannosidase enzyme. The liberation of galactose units was not determined.

Cassia Gum

The Joint FAO/WHO Expert Committee on food Additives noted that specific absorption, distribution, metabolism, and excretion data were not available on cassia gum at the time of its evaluation of this food additive.[9] However, based on data on related galactomannans, the Committee concluded that cassia gum will be largely excreted unchanged, though fermentation by gut microflora may occur to some extent. It was noted that if hydrolysis of cassia gum occurs, the resulting oligosaccharides or monosaccharides would be expected to be absorbed and metabolized in normal biochemical pathways.

TOXICOLOGY

Acute Oral Toxicity

Cyamopsis Tetragonoloba (Guar) Gum

The acute oral toxicity of cyamopsis tetragonoloba (guar) gum was evaluated using 10 F344 rats (5 males, 5 females; ages not stated) and ten B6C3F1 mice (5 males, 5 females).[43] Each animal received a single dose (0.42 g/kg) of the gum (in water) by gavage. None of the animals died and no test substance-related effects were observed.

In another acute oral toxicity study, 18 rats (strain not stated) received cyamopsis tetragonoloba (guar) gum (in cocoa butter), at a dietary concentration of 30% for 48 h. No adverse effects were observed.[44]

Guar Hydroxypropyltrimonium Chloride

In an acute oral toxicity study on guar hydroxypropyltrimonium chloride (40% w/v in corn oil), 4 groups of 10 rats (5 males, 5 females) received doses of 7.1, 10.0, 14.2, and 20.0 g/kg, respectively, by oral intubation.[45] Dosing was followed by a 14-day observation period, and gross necropsy was performed on all animals that died spontaneously. Clinical signs observed included: ataxia; tremors; nasal and oral discharge; urinary and fecal staining; abdominal griping; soft stool; decreased motor activity; labored breathing; and piloerection. The acute oral LD50 was 12.5 g/kg (95% confidence limits of 10.22 to 14.78 g/kg).

The acute oral toxicity of a guar hydroxypropyltrimonium chloride trade name material (composition data in Table 3) was evaluated using Bor: WISW (SPF) Cpb rats (5 males, 5 females; ~ 10 weeks old).[46] A single oral dose of the test substance (in arachidis oil, 2,000 mg/kg) was administered to each animal by gavage. Dosing was followed by a 14-day observation period. Animals that survived were killed and subjected to post-mortem examination. None of the animals died and there were no macroscopic findings at necropsy. An LD50 of > 2,000 mg/kg was reported.

Gum guar, oxidized 2-hydroxypropyl 3-hydroxy-3-(trimethylammonio)propyl ether, chloride (a.ka. (Cationic Guar and Guar Hydroxypropyltrimonium Chloride)

The acute oral toxicity of guar hydroxypropyltrimonium chloride (40% w/v solution in corn oil) was evaluated using 3 groups of 10 Sprague-Dawley albino rats (5 males, 5 females/group) receiving doses of 10.0, 14.2, and 20.0 g/kg, respectively.[47] Dosing was followed by a 14-day observation period, and gross necropsy was performed on animals that died spontaneously. In-life observation included: ataxia; nasal, oral, and ocular discharge; urinary and fecal staining; abdominal griping; decreased motor activity; irritability; and piloerection. Convulsions, tremors, hyopothermia, and prostration were observed only at the highest dose (20.0 g/kg), which yielded 90% mortality. The acute oral LD50 was 15 g/kg (95% confidence limits of 13 to 17 g/kg).

Hydroxypropyl Guar Hydroxypropyltrimonium Chloride

In an acute oral toxicity study on hydroxypropyl guar hydroxypropyltrimonium chloride (40% w/v solution in corn oil), 4 groups of 10 Sprague-Dawley albino rats (5 males, 5 females/group) received doses of 7.1,10.0, 14.2, and 20.0 g/kg, respectively, by oral intubation.[48] Dosing was followed by a 14-day observation period, and gross necropsy was performed on all animals. Clinical signs observed included: ataxia; fine and coarse tremors; nasal, oral, and ocular discharge; decreased respiratory rate and motor activity; abdominal griping; piloerection; irritability; and generally poor condition. The acute oral LD50 was 12.0 g/kg (95% confidence limits of 9.2 to 14.8 g/kg).

Carboxymethyl Guar

The acute oral toxicity of carboxymethyl guar (40% w/v solution in corn oil) was evaluated using 5 groups of 10 Sprague-Dawley albino rats (5 males, 5 females/group) receiving doses of 5.0, 7.1, 10.0, 14.2, and 20.0 g/kg, respectively, by oral intubation.[49] Dosing was followed by a 14-day observation period, and gross necropsy was performed on all animals that died spontaneously. Clinical signs observed included: ataxia; tremors; nasal, oral, and ocular discharge; labored breathing; piloerection; increased/decreased activity; hypothermia; generally poor condition; urinary and fecal staining; and irritability. The acute oral LD50 was 17.8 g/kg (95% confidence limits of 13.1 to 22.5 g/kg).

Hydrolyzed Guar

An acute oral toxicity study on partially hydrolyzed guar was performed using groups of 16 (8 males, 8 females per group) 4-week-old Jcl:ICR mice and Jcl:SD rats.[50] Partially hydrolyzed guar was administered by gavage at a concentration of 30% in distilled water (dose = 6000 mg/kg body weight; dose volume = 20 ml/kg) to one group per species. The control group was dosed orally with distilled water. Dosing was followed by a 14-day observation period, after which all animals were killed and examined macroscopically. Soft feces were reported for male and female mice, but no abnormal signs were reported for rats. There were no test substance-related effects on body weight (rats and mice), food consumption (rats), or necropsy findings (mice and rats). None of the animals died, and the LD50 was > 6,000 mg/kg in both species.

Ceratonia Siliqua Gum

The acute oral toxicity of ceratonia siliqua gum (in corn oil; dose = 10 g/kg body weight) was evaluated using 5 male Sprague-Dawley rats.[51] None of the animals died, and transient depression was the only sign observed in animals tested. In other studies involving rats (number and strain not stated), acute oral LD50s of 5000 mg/kg body weight and 13,100 mg/kg body weight were reported. Details relating to the test protocol and study results were not included.[52]

In an acute oral toxicity studies involving mice, rabbits, and hamsters (number and strain not stated for each), the following LD50's were reported: 13,100 mg/kg body weight (mice), 9,100 mg/kg (rabbits), and 10,300 mg/kg (hamsters). In each of the 3 studies, details relating to the test protocol and study results were not included.[52]

Cassia Gum

The acute oral toxicity of semi-refined cassia gum was evaluated using 5 male Wistar-Han-Schering rats.[9,53] The animals received 2 oral doses of 5,000 mg/kg body weight at a 2-h interval. An oral median lethal dose (LD50 value) of > 5,000 mg/kg body weight was reported. In a similar test, 10 male and 10 female KM mice received 4 oral doses of cassia gum (gavage, 10,000 mg/kg body weight) over a 24-h period.[54] The acute oral LD50 was > 10,000 mg/kg body weight.

Repeated Dose Toxicity – Oral Studies

Cyamopsis Tetragonoloba (Guar) Gum

In a short-term oral toxicity study, 18 rats (strain not stated) received cyamopsis tetragonoloba (guar) gum (in cocoa butter), at a dietary concentration of 30% for 48 h.[55] There was no evidence of adverse effects.

Five male Sprague-Dawley rats received oral doses of cyamopsis tetragonoloba (guar) gum (in corn oil; dose = 5 g/kg) daily for 5 days.[56] No unusual or adverse effects were observed. The feeding of 27% cyamopsis tetragonoloba (guar) gum to rats for 7 days resulted in the death of 7 of 10 animals. The deaths were probably due to intestinal blockage.[55]

Groups of rats (strain not stated) were fed cyamopsis tetragonoloba (guar) gum in the diet at concentrations of 0, 1, 2, and 5%, respectively, for 90 days.[57] Dosing with this gum did not affect general behavior, appearance, or survival. Growth was described as relatively low in males fed the 2% and 5% cyamopsis tetragonoloba (guar) gum diets. Dietary feeding also had no effect on the following: hematology, urinalysis, serum enzyme activities, or blood glucose levels. However, blood urea nitrogen values were slightly increased in males of the 5% dietary group. The relative weight of the thyroid was increased only in males of the 2% and 5% dietary groups. The results of gross and histopathological examinations did not reveal any changes that were attributable to gum ingestion.

The following dietary levels of cyamopsis tetragonoloba (guar) gum were fed to 6 groups of 130 male and female Osborne-Mendel rats (~ 4 wk. old; 65 males, 65 females/group) for 91 days: 0, 1.0, 2.0, 4.0, 7.5, and 15.0% in diet.[58] A significant decrease in body weight was noted for female rats of all dietary groups and in males of the 7.5% and 15% dietary groups. There were no deaths related to dietary administration of the gum. Hematocrit values for males were less than control values in all dietary groups; however, this decrease was of borderline significance. Male hemoglobin levels and erythrocyte and leucocyte counts were all within control ranges. In females, hemoglobin levels and erythrocyte counts were significantly decreased only in the 4% dietary group. Compared to control males, liver weights in all dietary groups were significantly decreased. Kidney weights were significantly decreased in 7.5% and 15.0% dietary groups, and were also decreased (borderline significance) in the 4.0% dietary group. Except for the bone marrow of male rats in the 15.0% dietary group, no tissue examined had consistent histopathological alterations attributed to ingestion of cyamopsis tetragonoloba (guar) gum. Though there was a suggestion of regressive changes in the bone marrow (moderate bone marrow cellularity) at this dietary level, this finding was within normal limits. The fact that results for several rats fed 15.0% cyamopsis tetragonoloba (guar) gum were at the lower end of the normal range suggested a subtle or borderline effect.

A long-term toxicity study on cyamopsis tetragonoloba (guar) gum was performed using 2 groups of rats (15 males, 15 females/group; ages and strain not stated). One of the groups was fed 5% cyamopsis tetragonoloba (guar) gum in the diet, and the other group (control) was fed diet only. Seven males and 8 females in each group survived and were monitored for 24 months. Of these, 1 test animal died after 12, 18, 19, and 22 months, and the last survivor was killed after 24 months. Three control animals survived to 24 months. All animals appeared in good health and had similar body weights.

Cyamopsis tetragonoloba (guar) gum (1 g in diet) was fed daily to 2 monkeys (ages not stated).[44] After 16 months of feeding, one of the monkeys died. The other monkey was killed at 24 months. Well-being, growth, and hematology (red blood cells, white blood cells, hemoglobin, and urea) were considered normal. The results of gross and histopathological examinations did not indicate any abnormalities in any of the following organs/tissues: liver, kidney, spleen, gut, and bone marrow.

Cyamopsis Tetragonoloba (Guar) Gum and Hydrolyzed Guar

Diets containing 5% cyamopsis tetragonoloba (guar) gum and 5% hydrolyzed guar (partially hydrolyzed) were fed to 2 groups of 5 Sprague-Dawley rats (8 months old), respectively, for 3 weeks.[59] Another group of rats was fed a diet containing 5% cellulose. A significant decrease in food intake and weight gain as well as a significant increase in liver weight were reported after feeding with 5% cyamopsis tetragonoloba (guar) gum. The serum IgG level of rats fed 5% cyamopsis tetragonoloba (guar) gum was significantly lower when compared to that of rats fed 5% cellulose. Also, the IgA, IgG, and IgM productivity in mesenteric lymph node (MLN) lymphocytes was significantly higher in rats fed 5% cyamopsis tetragonoloba (guar) gum, compared to rats fed 5% cellulose. The effect of 5% cyamopsis tetragonoloba (guar) gum on IgA, IgG, and IgM productivity in spleen cells was not as marked. The epididymal adipose tissue weight in rats fed 5% hydrolyzed guar was significantly higher than that reported for rats fed 5% cellulose. The results of this study suggest that the enhancement of immune function by cyamopsis tetragonoloba (guar) gum is expressed mainly in the gut immune system.

Hydrolyzed Guar

In a 28-day oral feeding study, 2 groups of 10 rats (5 males, 5 females/group) were fed partially hydrolyzed cyamopsis tetragonolobus (guar) gum in the diet (500 and 2,500 mg/kg doses, respectively) daily.[60] Body weights and food consumption were measured, and gross and microscopic pathology were evaluated. No adverse effects were observed at either administered dose.

A repeated dose oral toxicity study was performed using 7-week-old male and female Jcl:SD rats. The 2 groups of 20 rats per sex were control (diet without partially hydrolyzed guar) and 5.0% partially hydrolyzed guar dietary groups, respectively.[50] The remaining 2 groups of 10 rats per sex received dietary concentrations of 0.2 and 1.0 %. All groups were fed daily for 13 weeks. Ten rats per sex per group were then randomly selected from control and 5.0% dietary groups and maintained on the control diet for an additional 4 weeks (recovery period). Recovery animals were used to investigate the reversibility of possible partially hydrolyzed guar toxicity. All surviving animals (recovery animals included) were killed and subjected to macroscopic and microscopic examination. There were no deaths during dosing or recovery periods, or test substance-related effects on body weight, or food/water consumption. Additionally, there were no test substance-related changes relative to the following: ophthalmoscopic examination, urinalysis, hematological examination, blood biochemical examination, necropsy, organ weights, or histopathological examination.

Cyamopsis Tetragonoloba (Guar) and Ceratonia Siliqua Gum

A pre-cooked mixture of cyamopsis tetragonoloba (guar) and ceratonia siliqua gum (proportions not stated) was fed to groups of 5 female Beagle dogs (5 males, 5 females per group) for 30 weeks.[61] The gum was fed at dietary concentrations of 0, 1, 5, and 10%. Hypermotility was observed at the highest dietary concentration. There was no evidence of adverse hematological, urinary, gross/histopathological, or ophthalmological findings.

Ceratonia Siliqua Gum

Three groups of 8 rats (ages and strain not stated) were fed a stock diet, a stock diet with 1% cholesterol, and a stock diet with 1% cholesterol and 10% ceratonia siliqua gum, respectively for 28 days.[62] There were no significant differences in weight gain between the 3 groups, and no adverse effects were reported. A soybean-corn meal diet containing 2% ceratonia siliqua gum was fed to groups of newly weaned Sprague-Dawley rats (10 rats per group, ages not stated) for 36 days.[63] There were no significant effects on growth.

Ceratonia siliqua gum was fed, in the diet, to groups of rats (strain not stated) at concentrations of 0, 1, 2, and 5%, respectively, daily for 90 days.[57] Except for increased blood glucose in the 5% dietary group, there were no treatment-related differences between test and control groups regarding the following parameters: general behavior, survival, growth, food intake, hematology, blood biochemistry, and urinalysis. Neither gross nor microscopic examination results indicated any pathological changes that were due to ingestion of the gum.

Five male Sprague-Dawley rats (ages not stated) received oral doses of ceratonia siliqua gum (in corn oil; dose = 5 g/kg) daily for 5 days.[51] No unusual or adverse effects were observed.

In a study investigating the effect of various gums on nitrogen balance and dry matter digestibility, a group of 12 weanling Sprague-Dawley rats was fed ceratonia siliqua gum at a concentration of 10% in a casein-saccharose-corn starch diet.[87] Following a 3-day adaptation period, feed remnants, urine, and feces were collected during an 8-day balance period. Trypsin inhibitory activity of ceratonia siliqua gum in the diet also was measured. Only slight enzyme inhibition was associated with this gum.

Caesalpinia Spinosa Gum

In a 90-day oral feeding study, 50 rats (strain and ages not stated) of each sex were fed diets containing 0, 1, 2, or 5% caesalpinia spinosa gum.[64] At the 5% dietary level, body weight gains were depressed in both sexes, and possibly, in males at the 2% dietary level. Compared to the other dietary groups, food intake in the 5% dietary group was decreased. There were no effects on hematology or urinalysis parameters in any of the groups tested. A statistically significant increase in blood urea nitrogen was noted in rats fed 5% caesalpinia spinosa gum in the diet; however, blood levels were within the normal range of values for rats. There were no treatment-related differences in other clinical chemistry parameters between the control group and any group fed caesalpinia spinosa gum in the diet. Increased male kidney-body weight ratios (5% group) and increased relative weights of the thyroids and testes (2% and 5% groups) were observed. Results of gross and microscopic examination of tissues, including those associated with increased relative organ weight, were not indicative of changes related to caesalpinia spinosa gum in the diet.

Groups of 10 F344 rats and 10 B6C3F1 mice of each sex (ages of animals not stated) were fed diets containing 0, 0.31, 0.63, 1.25, 2.50, or 5.0% caesalpinia spinosa gum for 13 weeks.[65] The gum supplied contained 86.2% galactomannan. The animals were killed at the end of the study and microscopic examination was performed on control animals and those fed 5% caesalpinia spinosa gum in the diet. None of the mice or rats in any of the groups died during the feeding period. Compared to controls, male rats experienced small decreases in body weight gain, while weight increases were reported for female rats. Opposite effects on body weight gain were reported for mice. Changes in body weight gain were not dose-related. The only changes related to feeding with caesalpinia spinosa gum included fewer mature spermatozoa in 4 of 10 male rats in the 5% dietary group.

Purebred Beagle dogs (3 per sex) were fed experimental diets containing 1% or 5% caesalpinia spinosa gum for 90 days and the control group was fed α-cellulose.[66] For male dogs fed the 5% diet, feed intake values were 14% below those reported for the control group. No behavioral changes were reported, and hematological, urinalysis, and clinical chemistry results were unremarkable. There also were no gross or microscopic findings that were related to feeding with diets containing caesalpinia spinosa gum.

Cassia Gum

Groups of 5 male and 5 female crl:CD (SD)BR Sprague-Dawley rats (5 to 6 weeks old) were fed semi-refined cassia gum daily at the following dietary concentrations in a 28-day study: 0; 2,500; 10,000; 25,000; or 50,000 mg/kg.[67,67] The control group was fed an untreated powdered diet. An additional group of rats received the test substance (in distilled water; dose = 1,000 mg/kg body weight) by gavage twice daily. Histopathologic examination was performed only on the major organs of animals from the following groups: control; 50,000 mg/kg (in feed) group, and the group dosed (1,000 mg/kg body weight) via gavage twice daily. There were no treatment-related deaths or clinical changes in any of the groups. Statistically significant reductions in body weight were noted in males (50,000 mg/kg group) and females (10,000 and 25,000 mg/kg groups); however, these changes were considered related to the viscous nature of cassia gum and toxicologically irrelevant.

The statistically significant hematological and clinical chemistry findings were not dose-related or occurred in one sex only. These values were within the normal range for this species, however, historical control data were not provided. The only changes outside of the historical control range that could have been treatment-related were increased mean concentrations of glucose and triglyceride in the 10,000 mg/kg and 25,000 mg/kg, but not the 50,000 mg/kg groups. Statistically significant reductions in group mean absolute kidney weights were reported for the 10,000 mg/kg and 50,000

mg/kg (in diet) groups and in the 1,000 mg/kg dose (gavage) group. Additionally, a statistically significant increase in relative kidney weights was reported for the 50,000 mg/kg group. The minimal changes in absolute and relative organ weights were considered effects due to decreased body weights at termination. At necropsy or during microscopic examination of major organs (kidneys included), no treatment-related effects were observed. It was concluded that cassia gum did not elicit any apparent toxic changes that were attributable to dosing at dietary levels up to 50,000 mg/kg or at a dose (intragastric) of 1,000 mg/kg/day.[67]

In a 30-day study, groups of Sprague-Dawley rats (10 males,10 females per group) were fed cassia gum in the diet at doses of 0; 250; 500; and 1,000 mg/kg body weight per day.[54] There were no treatment-related effects on the following: mortality, body weight gain, food consumption, food utilization, hematological parameters, or various biochemical parameters (e.g., albumin, cholesterol, aspartate aminotransferase). Gross examination results were negative and there were no treatment-related histopathologic changes or effects on weight in the following organs: liver, kidney, spleen, ovaries, and testes. There also were no histopathologic changes in the stomach or intestines. An NOAEL of 1,000 mg/kg body weight was reported for cassia gum in rats.

Semi-refined cassia gum (in dog food) was administered to 2 groups of 4 male and 4 female Beagle dogs at dietary doses of 1 g/kg/day and 3.5 g/kg/day, respectively, for 90 days.[68] The control group received dog food without cassia gum; however, cassia gum was replaced by a substance with similar technological characteristics. A dose-related increase in water consumption was the only treatment-related effect noted, but was not considered toxicologically significant. Hematological effects and effects on biochemical parameters and organ weight were not considered treatment-related, and there were no treatment-related necropsy or histopathologic findings. It was concluded that cassia gum in the diet did not induce any remarkable effects.

Two groups of 5 male and 5 female cats (species: *Felix catus*) of the European (mongrel]) strain (9 months old) were fed semi-refined cassia gum in the diet (pet feed) at concentrations of 0.5% and 2.5%, respectively, for 13 weeks.[69] The control group received a standard (pet feed) diet without the gum. Neither adverse effects nor treatment-related effects on the following were reported: mortality, behavior, clinical signs, body weight gain, food and water consumption, hematology, clinical biochemistry, organ weights, macroscopy, or microscopy. No lesion was found at necropsy that was indicative of either a local effect on the digestive tract or a general effect on other organs. At microscopic examination, the incidence of changes was similar in all groups, and no lesions indicative of a toxic effect of cassia gum were found.

Ocular Irritation

Cyamopsis Tetragonoloba (Guar) Gum, Ceratonia Siliqua Gum, Caesalpinia Spinosa Gum, and Cassia Gum

Cyamopsis tetragonoloba (guar) gum (0.1 g) was instilled into the right eyes of New Zealand white rabbits.[70] The eyes of 3 rabbits were rinsed after instillation, and the eyes of 6 were not rinsed. Ocular irritation was scored according to the Draize scale at 1 h, 24 h, 48 h, and 72 h post-instillation. Cyamopsis tetragonoloba (guar) gum induced minimal ocular irritation in rinsed and unrinsed eyes. Results for other gums (same procedure) were as follows: ceratonia siliqua gum (minimally irritating, rinsed and unrinsed eyes), and cassia gum (non-irritating - rinsed eyes; minimally irritating – unrinsed eyes).

Skin Irritation and Sensitization

Cyamopsis Tetragonoloba (Guar) Gum Ceratonia Siliqua Gum, Caesalpinia Spinosa Gum, and Cassia Gum

The skin irritation potential of cyamopsis tetragonoloba (guar) gum was evaluated using New Zealand white rabbits (3 males, 3 females).[70] The gum (0.5 g/test site) was moistened with saline and applied to shaved, intact skin. Test sites were covered with a semi-occlusive wrap for 4 h. Reactions were scored according to the Draize scale at 4.5 h, 24 h, 48 h, and 72 h. Cyamopsis tetragonoloba (guar) gum was non-irritating to the skin of rabbits. Results for other gums (same procedure) were as follows: ceratonia siliqua gum (minimally irritating; PII = 0.04/8.0), caesalpinia spinosa gum (non-irritating), and cassia gum (non-irritating).

Hydroxypropyl Guar

A leave-on hair styling product containing 2% hydroxypropyl guar was evaluated in a Draize repeated insult patch test involving 111 human subjects (ages not stated).[71] During induction, the undiluted test substance (0.02 to 0.05 ml) was applied to the back under occlusive conditions (8 mm aluminum Finn chamber supported on occlusive tape or an equivalent) for 24 h. Applications were made 3 times per week for 3 consecutive weeks. After a 2-week non-treatment period, challenge patches were applied to adjacent new sites on the back for 24 h. Reactions were scored at 48 h and 96 h post-application. There was no evidence of skin reactivity in any of the subjects during the study.

Allergenicity

Cyamopsis Tetragonoloba (Guar) Gum

The prevalence of occupational asthma and immunologic sensitization to cyamopsis tetragonoloba (guar) gum was evaluated in 162 empolyees of a carpet-manufacturing plant where this gum was used to adhere dye to the fiber.[72] IgE and IgG antibodies to cyamopsis tetragonoloba (guar) gum were measured in 133 of the 162 subjects who agreed to blood tests. Thirty-seven subjects (23%) had a history of occupational asthma and 59 (39%) had a history of occupational rhinitis. Skin prick tests with cyamopsis tetragonoloba (guar) gum (1 mg/ml) were conducted. Immediate skin reactivity to cyamopsis tetragonoloba (guar) gum was observed in 8 subjects and 11 subjects had serum IgE antibodies to cyamopsis tetragonoloba (guar) gum. In the second part of the study (161 subjects), spirometry and assessment of bronchial responsiveness to methacholine were performed during a regular working day at the time of the workshift or in the following 3 to 4 hours. Five subjects had a concentration of methacholine causing a 20% decrease in forced expiratory volume (FEV_1) of < 16 mg/ml (significant bronchial hyperresponsiveness) and positive skin reactions to cyamopsis tetragonoloba (guar) gum. It was concluded that the prevalence of IgE sensitization to guar gum was between 5% (8 of 162 subjects, as assessed by skin tests) and 8.3% (11 of 133 subjects, as assessed by measurement of serum IgE antibodies).

Case Reports

Cyamopsis Tetragonoloba (Guar) Gum

Three male patients (27, 42, and 49 years) developed allergic rhinitis after exposure to cyamopsis tetragonoloba (guar) gum.[73] Two of the subjects developed rhinitis after 2 years of exposure to fine cyamopsis tetragonoloba (guar) gum (insulator in rubber cables) powder when opening cables in a power cable factory. The allergenicity of cyamopsis tetragonoloba (guar) gum in these subjects was confirmed using scratch-chamber, nasal provocation, and radioallergosorbent (RAST) tests, and observations of nasal eosinophilia. A third subject also developed allergic rhinitis after 2 years of exposure to another cyamopsis tetragonoloba (guar) gum product in a paper factory. A positive skin test and nasal provocation test confirmed the gum-induced allergenicity.

Symptoms of rhinitis and asthma were reported for 3 male atopic subjects (29, 30, and 32 years) after exposure to cyamopsis tetragonoloba (guar) gum on the job.[74] An immediate skin reaction to cyamopsis tetragonoloba (guar) gum was observed in skin prick tests, and all 3 had high levels of serum IgE antibodies to the gum. When the subjects were exposed for short intervals ($\leq$ 4 minutes) to cyamopsis tetragonoloba (guar) gum powder, isolated immediate bronchospastic reactions were observed in 2 subjects, and a dual reaction was observed in the remaining subject.

An allergy prick test was performed on a 38-year-old male employee of a pet food processing company, where he frequently inhaled guar powder.[75] Within 20 minutes of the test, the patient reacted positively to cyamopsis tetragonoloba (guar) gum. A 10 mm wheal with pseudopods and surroundiong flare was observed initially. At 4 h later, the reaction developed into an erythematous swelling (2 cm diameter) that remained for 24 h.

A 52-year-old male subject experienced generalized urticaria and anaphylactic shock after consuming a meal substitute that contained cyamopsis tetragonoloba (guar) gum.[76] Skin and radioallergosorbent (CAP system) tests on this gum as well as ceratonia siliqua gum were performed. Details relating to test procedures were not provided. Results were positive for both gums, with evidence of an IgE-mediated mechanism.

Cyamopsis Tetragonoloba (Guar) Gum and Ceratonia Siliqua Gum

A 63-year-old male experienced a life-threatening immediate-type hypersensitivity reaction after mucosal application of a local anesthetic gel that contained cyamopsis tetragonoloba (guar) gum. Severe contact urticaria and dyspnea

were reported, and the patient collapsed. [77] A 1-fold positive prick test reaction to cyamopsis tetragonoloba (guar) gum and a 2-fold positive prick test reaction to native guar beans were reported. Prick test results for a highly purified molecular grade ceratonia siliqua gum were negative. Negative IgE assay results for cyamopsis tetragonoloba (guar) gum and ceratonia siliqua gum were reported. A possible explanation for the discrepancy between prick test and IgE assay results for cyamopsis tetragonoloba (guar) gum could be the varying degree of allergen contamination in different guar products, remaining from the germ or hull of the Cyamopsis bean, that are not detected by commercial IgE assays that were probably established with highly purified cyamopsis tetragonoloba (guar) gum.

A 48-year old male complained of work-related rhinitis, irritated eyes, and asthma after exposure to ceratonia siliqua gum and cyamopsis tetragonoloba (guar) gum on the job in a jam factory.[78] Skin prick tests on ceratonina siliqua gum and a blend of cyamopsis tetragonoloba (guar) gum, ceratonia siliqua gum, and carrageenan were negative. Asthma attacks did not occur after the patient stopped handling the gums. When a single-blind provocation test (manipulation of carob bean flour for 15 min) was performed, a cough, rhinitis, and sneezing developed. Both cyamopsis tetragonoloba (guar) gum and ceratonia siliqua gum were evaluated in the RAST, and results were positive.

A 59-year-old female developed lip edema a few minutes after ingesting a dessert.[79] She also complained of nasal hydrorrhea and sneezing while handling powder to prepare the dessert. Results of skin prick tests indicated a positive reaction to ceratonia siliqua gum in saline (11 mm wheal); the test concentration was not stated. Skin prick test results for ceratonia siliqua gum at concentrations of 5, 15, and 25 mg/ml induced 6 mm, 8 mm, and 9 mm wheals, respectively. Positive skin prick tests were also reported for raw ceratonia siliqua gum (14 mm wheal) and boiled ceratonia siliqua gum (9 mm wheal). Control skin prick test results were negative in 10 nonatopic subjects. The positive test results and high titers of serum specific IgE to ceratonia siliqua gum supported an IgE-mediated mechanism. Skin prick test results for cyamopsis tetragonoloba (guar) gum were negative.

Ceratonia Siliqua Gum

A 30-year old male with allergic rhinitis developed asthma regularly after handling carob bean flour.[80] A prick test for ceratonia siliqua gum and a radioallergosorbent test (RAST) were both positive (U RAST = 8.86, class 2).

Urticaria and vomiting were reported after feeding of an 8-month-old infant with a milk-based antiregurgitation formula containing ceratonia siliqua gum as a thickening agent.[81] Feeding with a milk-based antiregurgitation formula thickened with waxy rice starch was readily accepted.

Trigonella Foenum-Graecum Seed Powder

Cases of immediate allergy following exposure to trigonella foenum-graecum seed powder have been reported.[82] A 36-year-old female with a history of allergy to chickpeas and mild asthma experienced sneezing, rhinorrhea, and excessive tearing after smelling trigonella foenum-graecum seed powder. These signs were followed by persistent coughing, wheezing, and fainting. Scratch testing with 10 µl of the legume extract (contained ~ 22 to 25 µg protein) revealed a severe (4+) reaction. According to another report, a 45-year-old female with a history of allergic rhinitis and asthma developed congestion and hoarseness shortly after applying trigonella foenum-graecum seed paste to the scalp. These signs were followed by facial angioedema, wheezing, and numbness of the head. Scratch testing revealed a 3+ reaction to the legume extract.

Clinical Testing

Cyamopsis Tetragonoloba (Guar) Gum

An experimental trial to evaluate the effect of cyamopsis tetragonoloba (guar) gum on arterial blood pressure was performed using 40 moderately overweight men with mild hypertension.[83] Each participant received 7 g of the gum 3 times daily for 2 weeks. There were no changes in body weight or body composition; however, total cholesterol decreased during the feeding period. Blood pressure was found to decrease by 9.8% (systolic) and 9% (diastolic) after 2 weeks of feeding. Blood pressure readings returned to pre-treatment levels after a 3-week wash-out period. It was concluded that cyamopsis tetragonoloba (guar) gum exerts a lowering effect on high blood pressure in moderately obese men, even in the absence of any change in body weight.

A study was conducted to determine the efficacy of dietary fiber cyamopsis tetragonoloba (guar) gum as a therapeutic option for reducing body weight, by performing a meta-analysis of randomized controlled trials.[84] Of the 34

experimental trials identified, only 11 provided data that were suitable for statistical pooling. Results of the meta-analysis indicated a nonsignificant difference in patients that received cyamopsis tetragonoloba (guar) gum, when compared to patients that received a placebo (weighted mean difference -0.04 kg; 95% confidence interval (CI): -2.2 to 2.1). Furthermore, these findings were corroborated by an analysis of 6 trials with similar methodologic features (weighted mean difference -0.3 kg; 95% CI: -4.0 to 3.5). The more frequently reported adverse events included abdominal pain, flatulence, diarrhea, and cramps. The meta-analysis suggested that cyamopsis tetragonoloba (guar) gum is not efficacious for decreasing body weight.

Eight patients (5 men, 3 women; 49.6 ± 3.05 years) with noninsulin-dependent diabetes mellitus consumed at least 30 g of cyamopsis tetragonoloba (guar) gum in the diet for at least 16 weeks.[85] Each subject was able to consume four granola-type bars (6.6 g guar gum/bar) per day. There were no changes in hematologic, hepatic, or renal function. Serologic screening results indicated no changes in lipid, protein, or mineral metabolism, and no changes in electrolyte balance. It was concluded that consumption of 30 g cyamopsis tetragonoloba (guar) gum per day for prolonged periods is without serious consequences.

Five subjects ingested cyamopsis tetragonoloba (guar) gum (1 g in capsule) daily for 10 days.[86] No effects were apparent.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral Studies

Cyamopsis Tetragonoloba (Guar) Gum

Groups of male and female Osborne-Mendel rats (4 weeks old; 34 to 40/group) were fed cyamopsis tetragonoloba (guar) gum in the diet at concentrations of 0, 1, 3, 4, 7.5, or 15% 13 weeks prior to mating, during mating, and throughout gestation.[88] Groups of female rats consumed 0, 0.7, 1.4, 2.7, 5.2, or 11.8 g/kg body weight/day, respectively, during gestation. The animals were killed on gestation day 20. None of the females died during the study. The ingestion of cyamopsis tetragonoloba (guar) gum prior to mating had no effect on fertility. No effects on the number of corpora lutea or implantations were observed in the 1% to 7.5% cyamopsis tetragonoloba (guar) gum dietary groups. When compared to the control group, slightly fewer corpora lutea and implantations were observed in the 15% dietary group; however, there was no effect on implantation efficiency. A slight reduction (not statistically significant) in the number of viable fetuses per litter was also noted in the 15% dietary group. Because the number of resorptions was not affected in this group, this reduction appeared to have been an effect of the decreased number of corpora lutea. It was concluded that cyamopsis tetragonoloba (guar) gum in the diet had no effect on fetal development or sex distribution and was not teratogenic.

In another teratogenicity study on cyamopsis tetragonoloba (guar) gum, groups of virgin adult female albino CD-1 outbred mice (ages not stated) were mated with young adult males, and observation of the vaginal sperm plug was considered day 0 of gestation.[89] The following groups of mated female mice received daily oral doses of cyamopsis tetragonoloba (guar) gum (in corn oil; dose volume = 1 ml/kg body weight) on days 6 through 15 of gestation: 22 mice (8 mg/kg/day), 26 mice (37 mg/kg/day), 25 mice (170 mg/kg/day), and 29 mice (800 mg/kg/day). A sham-treated control group was also included and aspirin served as the positive control. Doses up to 170 mg/kg/day had no clearly discernible effect on nidation or on maternal or fetal survival. Additionally, the number of abnormalities observed in either skeletal or soft tissues of test groups did not differ from the number that occurred spontaneously in sham-treated controls. In the 800 mg/kg/day dose group, a significant number of maternal deaths (6 of 29) was reported. Surviving dams appeared completely normal and the same was true of fetuses. No effects on the rate of nidation or survival of live pups in utero was noted. It was concluded that, under the conditions of this test, cyamopsis tetragonoloba (guar) gum was not teratogenic in mice. The teratogenicity of cyamopsis tetragonoloba (guar) gum in rats and hamsters was also evaluated in this study. Except for the administration of different doses and a shorter dosing period for hamsters, the test procedure was the same. Results are summarized below.

Four groups of 24 mated female rats (ages not stated) received cyamopsis tetragonoloba (guar) gum (in corn oil) at daily oral doses of 9, 42, 200, and 900 mg/kg/day, respectively. Doses up to 900 mg/kg/day had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities observed in either skeletal or soft tissues of test groups did not differ from the number that occurred spontaneously in sham-treated controls. The following groups of mated female hamsters (ages not stated) received daily oral doses of cyamopsis tetragonoloba (guar) gum (in corn oil): 22 hamsters (6 mg/kg/day), 22 hamsters (28 mg/kg/day), 25 hamsters (130 mg/kg/day), and 20 hamsters (600 mg/kg/day) on days 6 through 10 of gestation. Doses up to 600 mg/kg/day had no clearly discernible effect on nidation or on maternal or fetal

survival. Furthermore, the number of abnormalities observed in either skeletal or soft tissues of test groups did not differ from the number that occurred spontaneously in sham-treated controls.[89]

Ceratonia Siliqua Gum

A 3-generation reproduction study was performed using groups of Charles River albino rats of the CD strain (10 males, 10 females per group).[90] Two groups were fed chow diet containing 2% and 5% ceratonia siliqua gum, respectively. The control group was fed chow diet containing 5% cellulose. Parental animals in each generation were fed the test diet for 11 weeks prior to mating and through mating, gestation, and weaning. Two or 3 litters were raised per generation, and the second litter was used to produce the F_{3b} generation. Histopathological examination of major organs and tissues was performed on 10 males and 10 females from each treatment group of the F_{3b} generation. All of the other animals were subjected to gross necropsy only. Statistically significant decreases in pre-mating body weight gain (F_0 females fed 2% ceratonia siliqua gum) and final body weight (F_0 females fed 5% ceratonia siliqua gum) were noted. Compared to controls, the following significant differences in organ weight ratios were reported for the F_{3b} group fed 5% ceratonia siliqua gum: smaller spleen-to-body weight and liver-to-body weight ratios, smaller absolute liver weights, and larger brain-to-body weight ratio. These differences were due to the highly variable values for these parameters in young rats and because all of the animals may not have been at the same age when killed. These age differences may have also had an effect on organ weight ratios in young animals. It was concluded that ceratonia siliqua gum did not cause significant treatment-related effects on reproductive indices or gross microscopic pathology.

The teratogenicity of ceratonia siliqua gum (in anhydrous corn oil) was evaluated using the following 6 groups of pregnant adult female albino, CD-1 outbred mice: 13 mg/kg ceratonia siliqua gum (20 mice), 60 mg/kg (20 mice), 280 mg/kg (21 mice), 1,300 mg/kg (21 mice), 0 mg/kg (20 mice, sham treated), and aspirin, 150 mg/kg (21 mice).[91] Doses were administered orally (intubation) on gestation days 6 through 15 (10 days). On day 17, fetuses were removed by Caesarean section and each was examined grossly for the presence of external congenital abnormalities. Detailed visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects. There were no clearly discernible effects on nidation or on maternal or fetal survival at doses up to 280 mg/kg. The number of soft or skeletal tissue abnormalities in test groups did not differ from the number that occurred spontaneously in sham-treated controls. A significant number of maternal deaths (5 of 21 females) occurred in the 1300 mg/kg dose group. However, the surviving dams in this group appeared completely normal and delivered normal fetuses, and there were no effects on the rate of nidation or survival of live pups in utero. It was concluded that ceratonia siliqua gum was not teratogenic in mice at the doses administered in this study. The positive control was teratogenic.

In other experiments in the preceding study, the teratogenicity of ceratonia siliqua gum was evaluated in rats, hamsters, and rabbits according to a similar test procedure. The following 6 groups of adult female Wistar albino rats were used: 13 mg/kg ceratonia siliqua gum (23 rats), 60 mg/kg (21 rats), 280 mg/kg (24 rats), 1300 mg/kg (23 rats), 0 mg/kg (23 rats, sham treated), and aspirin (250 mg/kg, 21 rats). On day 20, the fetuses were delivered by Caesarean section. There were no clearly discernible effects on nidation or on maternal or fetal survival at doses up to1300 mg/kg. The number of soft or skeletal tissue abnormalities in test groups did not differ from the number that occurred spontaneously in sham-treated controls. It was concluded that ceratonia siliqua gum was not teratogenic. In the experiment involving pregnant adult female, golden outbred hamsters, the following groups were used: 10 mg/kg ceratonia siliqua gum (21 hamsters), 45 mg/kg (20 hamsters), 220 mg/kg (24 hamsters), 1000 mg/kg (20 hamsters), 0 mg/kg (20 hamsters, sham treated), and aspirin, 250 mg/kg (20 hamsters). Doses were administered orally on gestation days 6 through 10 (5 days). Except for the dosing period, doses administered, and day of Caesarean section (day 14), the protocol was identical to the one used for mice and rats. There were no clearly discernible effects on nidation or on maternal or fetal survival at doses up to1300 mg/kg. The number of soft or skeletal tissue abnormalities in test groups did not differ from the number that occurred spontaneously in sham-treated controls. It was concluded that ceratonia siliqua gum was not teratogenic in hamsters.[91]

The teratogenicity of ceratonia siliqua gum (in anhydrous corn oil) was evaluated using the following 6 groups of pregnant adult Dutch-belted female rabbits: 9 mg/kg ceratonia siliqua gum (11 rabbits), 42 mg/kg (12 rabbits), 196 mg/kg (13 rabbits), 910 mg/kg (12 rabbits), 0 mg/kg (14 rabbits, sham treated), and 6-amino nicotinamide, 2.6 mg/kg (13 rabbits, on day 9). Doses were administered orally (intubation) on gestation days 6 through 18 (13 days) of gestation, and the fetuses were delivered by Caesarean section on day 29. Except for the dosing period, doses administered, and day of Caesarean section, the protocol was identical to the one used for mice and rats. Significant maternal toxicity was observed at doses of 910 mg/kg, and, other than hemorrhage of the intestinal mucoasa (small intestine), there were no gross pathological findings at necropsy. The fetuses of the highest dose group were normal. All fetuses were examined grossly for the presence of external congenital abnormalities, and subjected to examination for visceral abnormalities and skeletal defects. There were no discernible effects on nidation or on maternal or fetal survival at doses up to 910 mg/kg. The number of soft or skeletal

tissue abnormalities in test groups did not differ from the number that occurred spontaneously in sham-treated controls. It was concluded that ceratonia siliqua gum was not teratogenic in rabbits.[91]

Caesalpinia Spinosa Gum

A multigeneration reproduction study on caesalpinia spinosa gum was performed using groups of Charles River CD albino rats (22 days old).[92] The gum was administered to male and female rats at a dietary level of 5% (50,000 ppm) through 3 successive generations. All matings involved 10 males and 20 females per group, and fertility was described as high. Litters were maintained until the end of lactation, at which time they were at least 21 days old. There were no consistent, statistically significant test substance-related adverse effects on any of the parameters evaluated, including mortality, food consumption, body weight gains, general health, and behavior. Similarly, regarding mating and reproductive performance indices, there were no consistent, statistically significant differences between control and gum-treated groups. These data suggest that caesalpinia spinosa gum had no adverse effect on reproductive performance and in utero development. Data from those progeny selected as parental animals for subsequent generations (F_1 and F_2 parents) indicated that these animals had normal growth patterns and reproductive performance. Gross examination of the parental animals and offspring and microscopic examination of tissues from selected F_{3b} progeny did not identify any abnormalities that were related to administration of the gum. It was concluded that caesalpinia spinosa gum did not have an adverse effect on reproductive performance or development of progeny.

The teratogenicity and embryotoxicity of caesalpinia spinosa gum was evaluated using groups of Wistar/HAN rats. Groups of 25 rats were fed pellet-sized diets containing 0; 1.25% (12,500 ppm); 2.5% (25,000 ppm); or 5% (50,000 ppm) of the gum from days 6 to 16 of gestation. All females were killed on day 21 postcoitum, and fetuses removed by caesarean section. None of the animals died and there were no statistically statistically significant differences in food consumption, body weight gain, general health, or behavior between dams that received control diet and those that received caesalpinia spinosa gum in the diet. Necropsy results did not reveal any abnormalities that were related to gum administration. There was no evidence of test substance-related abnormalities after external, visceral, and skeletal examinations of fetuses were performed. Additionally, there were no differences in the sex ratios of fetuses or statistically significant differences in fetal body weights. It was concluded that caesalpinia spinosa gum did not induce maternal toxicity, embryotoxicity, or teratogenicity. Based on results from this study and the preceding study, the no-observable-adverse-effect-level (NOAEL) was considered to be > 50,000 ppm (5%) in the diet.[92]

Cassia Gum

In a two-generation reproductive toxicity study (OECD Test Guideline 416), semi-refined cassia gum was administered to groups of 25 female Ico:OFA.SD Sprague-Dawley rats (6 weeks old) at dietary concentrations of 0; 5,000; 20,000, or 50,000 mg/kg.[93] An additional group was fed a diet containing purified semi-refined cassia gum (which resulted from an additional isopropano extraction step) at a dose of 50,000 mg/kg. Parental animals were dosed for approximately 10 weeks prior to mating and during mating, gestation, and lactation. The only effects observed included a slightly reduced pregnancy rate (not observed in a subsequent second mating resulting in an F_{1b} generation), and a slight, non-significant decrease in pup weights in the F_{1a} and F_2 generations. These effects were observed at the highest dose level (both groups), and, therefore, 50,000 mg/kg feed (equal to 5280 mg/kg body weight per day) was considered the NOEL.

Groups of 12 pregnant female SD rats received oral doses of cassia gum (by gavage) at doses of 0; 250; 500; or 1,000 mg/kg body weight per day on days 7 through 16 of gestation.[54] There were no treatment-related effects on maternal body weight, the number of resorptions or dead embryos, or the weight and length of fetuses. Also, abnormalities were not observed at skeletal or visceral examination of the fetuses. Therefore, no adverse effects were observed in dams or offspring at doses up to and including 1,000 mg/kg body weight per day.

The developmental toxicity of semi-refined cassia gum (in distilled water) was evaluated using groups of 28 pregnant Crl:CD (SD)BR Sprague-Dawley rats (8 to 12 weeks old).[94] The test substance was administered orally (by gavage) at doses of 0; 350; or 1,000 mg/kg per day on gestation days 6 to 19 post-coitum, in accordance with OECD Test Guideline 414. Purified semi-refined cassia gum (1,000 mg/kg body weight) was administered to a fourth group of 29 pregnant rats according to the same procedure. The animals were killed and examined on day 20 post-coitum. There were no test substance-related effects on pregnancy incidence, implantations, post-implantation loss, or fetal defects at necropsy. In pregnant animals that received semi-refined cassia gum or purified semi-refined cassia gum at the 1,000 mg/kg dose level, a statistically significant reduction in mean daily food consumption and mean body weight gain was noted. These effects were thought to have been related to the viscous nature of the gum and were not considered toxicologically relevant. A statistically significant increase in fetal weight after dosing with purified semi-refined cassia gum was the only finding in

offspring. There was no evidence of embryotoxicity or teratogenicity in any of the treatment groups, and the NOAEL was 1,000 mg/kg body weight per day.

In another developmental toxicity study, groups of 20 pregnant New Zealand White rabbits (14 to 17 weeks old) were dosed with semi-refined cassia gum or purified semi-refined cassia gum, following the procedure (same doses for each) in the preceding study.[95] The rabbits were dosed on days 6 to 27 post-coitum and were killed on day 28 post-coitum. The following animals died or were killed moribund during the study: 4 controls, 1 and 4 rabbits dosed with semi-refined cassia gum (350 and 1,000 mg/kg body weight, respectively), and 2 rabbits dosed with purified semi-refined cassia gum (1,000 mg/kg body weight). All deaths were attributed to improper gavaging and/or were incidental. A non-significant reduction in mean daily food consumption was observed in the group dosed with 1,000 mg/kg semi-refined cassia gum. A slight, non-significant reduction in mean fetal weight was also observed in this group, and, possibly, was a secondary effect to the reduced feed consumptin. These effects were probably related to the viscous nature of cassia gum and were not considered to be of toxicological relevance. There were no treatment-related adverse effects relative to the following: pregnancy incidence, implantations, post-implantation loss, or fetal defects upon necropsy. Cassia gum was neither teratogenic nor embryotoxic in rabbits, and an NOAEL of 1,000 mg/kg body weight per day was reported.

In a one-generation reproductive toxicity study (OECD Test Guideline 415), semi-refined cassia gum was administered to 2 groups of cats (*Felis catus*) of the Ico:FecEur strain (10 males, 20 females per group) at dietary concentrations of 0.75% w/w and 2.5% w/w, respectively for 83 to 85 weeks.[96] The control group was fed a standard diet without cassia gum. High mortality in the control group resulted in a high litter loss, which impaired appropriate comparison between treatment and control groups. Generally, no obvious effects on short-term toxicity parameters were observed in the parental generation and offspring. Reproductive performance was not affected, and the same was true for growth and development of the offspring. The following effects, possibly related to dosing, were observed only at the highest administered dose: slight decrease in food consumption during late gestation, and a slight increase in absolute and relative ovarian weights in parental females + a significantly higher combined incidence of stillborns and neonatal deaths. In the absence of treatment-related hisotpathological alterations, the changes in ovarian weight were thought to have been of little biological relevance. Because of the unusually high mortality rate in the control group, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered this study unsuitable for use in evaluating the reproductive toxicity of semi-refined cassia gum.[9]

Dermal Study

Cyamopsis Tetragonoloba (Guar) Gum

The teratogenicity of cyamopsis tetragonoloba (guar) gum (in deionized water) was evaluated using groups of 20 New Zealand White SPF rabbits (4 months old when received).[97] After a 2-month acclimation period, the test substance was administered, via non-occlusive dermal application (6 h), to 3 groups at doses of 2, 10, and 50 mg/kg/day (dose volume = 2 ml/kg), respectively, on days 6 through 18 of gestation. Applications were made to dorsal skin (10 x 20 cm^2). Deionized water was administered to the control group according to the same procedure. Three mortalities were reported, and 3 rabbits produced litters prematurely. A dose-related increase in dermal irritation was noted in 10 and 50 mg/kg dose groups, with frequent observations of erythema, edema, and desquamation. Analyses of behavior observations, body weights, and food consumption were not indicative of test substance-related responses in any of the 3 dose groups. A moderate increase in mean post-implantation loss, accompanied by a decrease in viable fetuses, was noted in the highest dose group (50 mg/kg/day). The increase in early resorptions observed in this group was found to be statistically significant ($p < 0.05$). A slight increase in mean post-implantation loss was noted in the 10 mg/kg/day dose group; however, uncertainty over the significance of this observation was expressed. Increased post-implantation loss was not observed in the 2 mg/kg/day dose group. No other abnormalities were observed in any of the Cesarean section parameters. Analyses of fetal morphological observations were not indicative of test substance-related responses in any of the 3 dose groups.

GENOTOXICITY

Genotoxicity data on galactomannans are summarized in Table 5. Most of the results for bacterial and mammalian assays are negative.

CARCINOGENICITY

Cyamopsis Tetragonoloba (Guar) Gum,

Ceratonia Siliqua Gum, and Caesalpinia Spinosa Gum

The carcinogenicity of cyamopsis tetragonoloba (guar) gum, ceratonia siliqua gum, and caesalpinia spinosa gum was evaluated in a National Toxicology Program study using groups of F344 rats (50 males, 50 females/group; 4 weeks old) and groups of B6C3F1 mice (50 males, 50 females/group; 4 to 5 weeks old).[98] The respective groups received either gum in feed at concentrations of 25,000 and 50,000 ppm, respectively, daily for 103 consecutive weeks. Untreated control groups were also used. Animals that were moribund as well as those that survived to the end of the study were killed and necropsied. There were no significant differences in survival between any dose group (rats or mice) and respective control groups. A 10% reduction in body weight gain, compared to controls, was noted in the following dose groups: female mice (50,000 ppm cyamopsis tetragonoloba (guar) gum), male mice (50,000 ppm ceratonia siliqua gum), and male and female mice (50,000 ppm caesalpinia spinosa gum). In all groups, mean daily feed consumption for dosed rats and mice was ≥ 79% of respective control values. A variety of non-neoplastic degenerative and inflammatory lesions was observed in rats and mice of all dose groups. However, these lesions were not related to feeding with any of the gums. A number of significant changes in the incidences of primary tumors ($P < 0.05$, in both positive and negative directions) was reported for rats and mice. In all cases, differences in the tumor incidence observed in one sex were not observed in statistically significant proportions in the other sex of the same species.

A statistically significant increase in the incidence of pheochromocytomas of the adrenal gland was noted in female rats fed both dietary concentrations of cyamopsis tetragonoloba (guar) gum (25,000 and 50,000 ppm). However, the combined incidence of female rats with phaeochromocytoma or malignant phaeochromocytoma of the adrenal gland was not significantly different from control values. Similarly, the incidence of pituitary adenomas in male rats fed cyamopsis tetragonoloba (guar) gum and the incidence of alveolar/bronchiolar adenomas (in lung) in male mice fed ceratonia siliqua gum were not significantly different from control values, when combined with incidences of the corresponding carcinomas at those sites. Alveolar /bronchiolar adenomas of the lung in male mice fed 25,000 ppm ceratonia siliqua gum and pituitary adenomas in female mice fed the same dietary concentration were considered unrelated to feeding, in that the incidences of these tumors were not significantly increased in the respective 50,000 ppm ceratonia siliqua gum groups.

Additionally, the incidence of pituitary adenomas in female mice fed 25,000 ppm ceratonia siliqua gum was not significantly different from the historical control rate of this tumor in control male and female mice. The increased incidence of interstitial cell tumors of the testis of male rats was not related to dietary administration of caesalpinia spinosa gum because of the high spontaneous rate of this tumor. Therefore, in each case in which a significant incidence ($P < 0.05$) of primary tumors was observed in F344 rats or $B6C3F_1$ mice, a definite association between increased tumor incidence and gum administration could not be made. Decreased incidences of certain other tumor types were also reported for rats and mice fed these gums in the diet. However, when compared to historical control rates, the differences reported were not statistically significant. No histopathologic effects were associated with administration of either of the gums. It was concluded that, under the conditions of these bioassays, cyamopsis tetragonoloba (guar) gum, ceratonia siliqua gum, and caesalpinia spinosa gum were not carcinogenic in F344 rats or $B6C3F_1$ mice.[98]

Cassia Gum

Carcinogenicity data on cassia gum were not available for review by the Joint FAO/WHO Expert Committee on Food Additives during its evaluation of the safety of cassia gum as a food additive in 2009.[9] However, given the negative results for cassia gum in genotoxicity assays and negative results reported in carcinogenicity assays on ceratonia siliqua gum and caesalpinia spinosa gum, the Committee determined that a long-term toxicity and/or carcinogenicity study was not necessary for the safety evaluation of cassia gum.

Co-Carcinogenicity

The effect of cyamopsis tetragonoloba (guar) gum in the diet on 1,2-dimethylhydrazine (DMH) initiation of colon tumors was studied using groups of 30 male Sprague-Dawley rats (3 weeks old).[99] One group of rats was fed 5% cyamopsis tetragonoloba (guar) gum in the diet during the entire initiation period: 4 weeks of acclimatization, 12-week period of DMH injections, and a 2-week post-injection period. During the last 10 weeks (promotion period), the rats were given standard rat pellets. The control group was fed the basic diet. All animals were killed randomly during the 13th week after the last DMH injection and necropsies performed. None of the animals died spontaneously during the study. Rats fed the cyamopsis tetragonoloba (guar) gum + DMH had more tumors than those fed the basic diet; however, the difference was not statistically significant. It was concluded that cyamopsis tetragonoloba (guar) gum did not significantly influence carcinogenesis in rats initiated with DMH.

Anticarcinogenicity

The effect of dietary supplementation with cyamopsis tetragonoloba (guar) gum on 1,2-dimethylhydrazine (DMH)-induced carcinogenesis was studied using groups of 30 male Sprague-Dawley rats (5 weeks old).[100] Each of 60 rats received a basal, fiber free diet (supplemented with 5% cellulose) and a weekly s.c. injection of DMH for 8 weeks (initiation phase), and the animals were then subdivided into 2 groups. One group of 30 rats was then maintained on a basal fiber-free diet supplemented with 10% cyamopsis tetragonoloba (guar) gum for 24 weeks (promotional stage). The other group of 30 (control) was maintained on a basal diet (fiber-free) for 24 weeks. The animals were killed 32 weeks after initiation of the study, and the tumor incidence, location, and frequency in the colon were determined. Compared to the control group, dietary fiber supplementation with 10% cyamopsis tetragonoloba (guar) gum resulted in a 27% ($P = 0.01$) decreased incidence of the total colon adenocarcinomas and a 43% ($P < 0.0005$) decreased incidence of adenocarcinomas in the descending colon.

SUMMARY

The safety of the following ingredients in cosmetics is reviewed in this safety assessment: cyamopsis tetragonoloba (guar) gum, hydroxypropyl guar, C18-22 hydroxyalkyl hydroxypropyl guar, guar hydroxypropyltrimonium chloride, hydroxypropyl guar hydroxypropyltrimonium chloride, carboxymethyl hydroxypropyl guar, hydrolyzed guar, ceratonia siliqua gum, locust bean hydroxypropyltrimonium chloride, hydrolyzed ceratonia siliqua gum extract, caesalpinia spinosa gum, caesalpinia spinosa hydroxypropyltrimonium chloride, hydrolyzed caesalpinia spinosa gum, trigonella foenum-graecum hydroxypropyltrimonium chloride, cassia gum, and cassia hydroxypropyltrimonium chloride. Because of the mannose/galactose chemical make-up of these legume polysaccharides, they are commonly called galactomannans.

Data reported to the Food and Drug Administration's Voluntary Cosmetic Registration Program in 2011 indicated use of the following 9 ingredients in cosmetics: cyamopsis tetragonoloba (guar) gum, hydroxypropyl guar, guar hydroxypropyltrimonium chloride, hydroxypropyl guar hydroxypropyltrimonium chloride, hydrolyzed guar, ceratonia siliqua gum, caesalpinia spinosa gum, hydrolyzed caesalpinia spinosa gum, and cassia hydroxypropyltrimonium chloride. Results from a survey of ingredient use concentrations conducted by the Personal Care Products Council in 2011 indicate that locust bean hydroxypropyltrimonium chloride was also being used in cosmetics. Additionally, results from this survey indicate that galactomannans were being used at concentrations up to 93% (hydroxypropyl guar in a leave-on hair straightener) in cosmetic products.

Production of natural gums consists of various techniques for the milling of seeds, followed by simple purification steps such as dissolving in hot water, filtering and precipitation with isopropanol. Typical production of the derivatized gums in this report involves the reaction of the natural gum with the appropriate epoxide.

Impurities that have been detected in cyamopsis tetragonoloba (guar) gum include heavy metal impurities and fluoroacetate. In 2007, the impurities dioxin and pentachlorophenol (PCP) were detected in certain batches of cyamopsis tetragonoloba (guar) gum originating from India. Anthraquinone impurities have been detected in cassia gum (where *Cassia occidentalis* is a natural contaminant) and tannins and trypsin inhibitors have been detected in ceratonia siliqua gum. A guar hydroxypropyltrimonium chloride trade name material, when heated up to 600°C, contains ash (signifying the presence of inorganic salts) as an impurity at concentrations up to 8.7% .

In rats fed cyamopsis tetragonoloba (guar) gum in a basal diet, the galactomannan was fermented quantitatively and approximately 1% of the mannose and 4% of the galactose was excreted in the feces. The feeding of rats with ceratonia siliqua gum in the diet resulted in 98% digestibility of galactomannan; all of the mannose added to the feed in the form of galactomannan was excreted in the feces. Similarly, 85 to 100% of the mannose fed to rats as ceratonia siliqua gum in the diet was excreted in the feces. Based on these study results, it is expected that cassia gum would be largely excreted unchanged and that fermentation by gut microflora may occur to some extent.

In acute oral toxicity studies, the feeding of rats with cyamopsis tetragonoloba (guar) gum did not cause death or test-substance related adverse effects. The following acute oral LD50 values (rats) have been reported for related ingredients: guar hydroxypropyltrimonium chloride (LD50 = 12.5 g/kg), hydroxypropyl guar hydroxypropyltrimonium chloride (LD50 = 12.0 g/kg), carboxymethyl guar (LD50 = 17.8 g/kg), hydrolyzed guar (LD50 > 6 g/kg), cassia gum (LD50 > 5 g/kg), and ceratonia siliqua gum (LD50 = 5 g/kg). LD50s for ceratonia siliqua gum in other species include: 13.1 g/kg (mice), 9.1 g/kg (rabbits), and 10.3 g/kg (hamsters).

Most of the repeated dose oral toxicity studies (rats, mostly dietary feeding) involving the following ingredients indicated no test-substance related adverse effects: cyamopsis tetragonoloba (guar) gum (up to 27%), hydrolyzed guar (up to 5%), ceratonia siliqua gum (up to 30%), caesalpinia spinosa gum (up to 5%), and cassia gum (up to 50,000 mg/kg dietary concentration). Significant reductions in liver weights (at 1% to 15% in diet) and kidney weights (at 4%, 7.5%, and 15% in diet) in rats were noted after feeding with cyamopsis tetragonoloba (guar) gum, and 7 of 10 rats died (possibly due to intestinal blockage) after feeding with ceratonia siliqua gum. Increased male kidney-body weight ratios (at 5% in diet) and increased relative weights of the thyroid and testes (at 2% and 5% in diet) in rats were observed after feeding with caesalpinia spinosa gum; however, the results of gross and microscopic examination of these organs were not indicative of test substance-related changes. Furthermore, feeding with caesalpinia gum (at 5% in diet) resulted in fewer mature spermatozoa in 4 of 10 male rats. Statistically significant reductions in group mean absolute kidney weights in rats fed cassia gum at dietary concentrations of 10,000 mg/kg and 50,000 mg/kg and at a dose (intragastric) of 1,000 mg/kg body weight were not considered treatment-related, in that results of gross and microscopic examinations of the kidneys were negative. The same was true for the statistically significant increase in relative kidney weights associated with the 50,000 mg/kg dietary concentration.

Cyamopsis tetragonoloba (guar) gum, ceratonia siliqua gum, and cassia gum were minimally irritating when instilled (0.1 g) into the eyes of rabbits. In semi-occlusive patch tests (0.5 g applied), ceratonia siliqua gum was minimally irritating and cyamopsis tetragonoloba (guar) gum, caesalpinia spinosa gum, and cassia gum were non-irritating to the skin of rabbits. Results for a hair styling product containing 2% hydroxylpropyl guar were negative for skin irritation and sensitization in a human RIPT. The allergenicity of cyamopsis tetragonoloba (guar) gum and ceratonia siliqua gum following inhalation exposure and ingestion has been demonstrated in various case reports. Also, no effects were apparent after ingestion of cyamopsis tetragonoloba (guar) gum in another case report. The allergenicity of trigonella foenum-graecum seed powder following inhalation exposure has also been demonstrated in a case study. It was concluded that the prevalence of IgE sensitization to cyamopsis tetragonoloba (guar) gum was between 5% and 8.3% in an occupational study.

Cyamopsis tetragonoloba (guar) gum was not teratogenic in mice (doses up to 800 mg/kg/day), rats (doses up to 11,800 mg/kg/day), or hamsters (doses up to 600 mg/kg/day) when administered orally, and there was no evidence of maternal toxicity. Ceratonia siliqua gum also was not teratogenic when administered orally to rats (doses up to 1,300 mg/kg/day), mice (doses up to 1,300 mg/kg/day), hamsters (doses up to 1,000 mg/kg/day), and rabbits (doses up to 910 mg/kg/day). However, in one of the studies, significant maternal toxicity was induced by ceratonia siliqua gum (at 910 mg/kg/day) in rabbits of the highest dose group. Caesalpinia spinosa gum (up to 50,000 ppm/day) was not a reproductive toxicant or teratogen when administered orally to rats, and also did not induce maternal toxicity.

Cassia gum was not teratogenic in rats (doses up to 6,120 mg/kg/day), rabbits (doses up to 1,000 mg/kg/day), or cats (doses up to 2,950 mg/kg/day) when dosed orally. However, a statistically significant reduction in maternal body weight gain in rats was observed in the highest dose group (1,000 mg/kg/day) in one study. This finding was thought to have been related to the viscous nature of the gum and was not considered toxicologically relevant. In another study on cassia gum (doses of 1,000 mg/kg/day), non-significant reductions in feed consumption and fetal weight in rabbits were also thought to have been due to the viscous nature of the gum, and were not considered toxicologically relevant. According to the Joint FAO/WHO Expert Committee on Food Additives, the usefulness of the study involving cats is questionable, given the high mortality rate in the control group.

In a dermal teratogenicity study on cyamopsis tetragonoloba (guar) gum involving rabbits (doses up to 50 mg/kg/day), a statistically significant increase in early resorptions was observed in the highest dose group. However, analyses of fetal morphological observations were not indicative of test substance-related responses at any dose level. A dose-related increase in dermal irritation was noted in the 2 higher dose groups (10 and 50 mg/kg/day).

In bacterial and mammalian assays, cyamopsis tetragonoloba (guar) gum, ceratonia siliqua gum, caesalpinia spinosa gum, and cassia gum were not found to be genotoxic. In the Ames test, hydroxypropyl guar was mutagenic in 1 of 5 bacterial strains without metabolic activation and in 4 of 5 strains with metabolic activation. Ames test results were negative for hydrolyzed guar and guar hydroxypropyltrimonium chloride (trade name material) with and without metabolic activation. Cyamopsis tetragonoloba (guar) gum, ceratonia siliqua gum, and caesalpinia spinosa gum (concentrations up to 50,000 ppm/day) were not carcinogenic in a dietary carcinogenicity study involving F344 rats and B6C3F1 mice.

Rats fed cyamopsis tetragonoloba (guar) gum and 1,2-dimethylhydrazine had more tumors than those fed the basic diet, however, the difference was not statistically significant. The anticarcinogenic activity of cyamopsis tetragonoloba (guar) gum has been demonstrated using rats.

DISCUSSION

While data on toxicokinetics, short-term and repeated dose toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, and dermal irritation and sensitization are not available for all of the ingredients included in this safety assessment, these data are available for several of the ingredients. Because these ingredients are legume polysaccharides, or derivatives thereof, used for similar purposes in cosmetics, the CIR Expert Panel determined that the available data could be used to support the safety of the entire group. In the absence of dermal penetration data, the Panel noted that the galactomannans are large molecules and probably would not be absorbed systemically to any significant level.

The Panel is aware of the prevalence of IgE sensitization to cyamopsis tetragonoloba (guar) gum reported in an occupational study, but determined that the findings were not relevant to cosmetic use. The Panel concluded that this finding was likely due to: (1) protein contamination of the gum, considering that allergenicity is generally not associated with carbohydrate moieties, and (2) the high breathing zone exposures that are possible in an occupational setting, but not relevant to the use of these ingredients in cosmetics.

Given the botanical sources of the galactomannans reviewed in this safety assessment, the Expert Panel expressed concern regarding pesticide residues and heavy metals that may be present. For example, dioxin and pentachlorophenol (PCP) impurities have been detected in certain batches of cyamopsis tetragonoloba (guar) gum. The absence of significant findings in repeated dose toxicity, teratogenicity, or carcinogenicity studies on this gum, however, suggested that the levels of impurities present were not toxic. There was also no evidence that any of the other galactomannans reviewed induced significant toxicity in these types of studies or in skin irritation/sensitization studies. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit pesticide residues and heavy metals in the ingredient before blending into cosmetic formulations.

Because hydroxypropyl guar and guar hydroxypropyltrimonium chloride can be used in cosmetics that may be sprayed, the Panel discussed the issue of incidental inhalation exposure. Guar hydroxypropyltrimonium chloride has been used in foot powders and sprays at a maximum concentration of 0.05%. In the absence of inhalation data, the Panel considered data characterizing the potential for galactomannans to cause systemic toxicity, reproductive and developmental toxicity, carcinogenicity, and dermal irritation or sensitization. The Panel noted that 95 – 99% of the droplets/particles produced in cosmetic aerosols would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

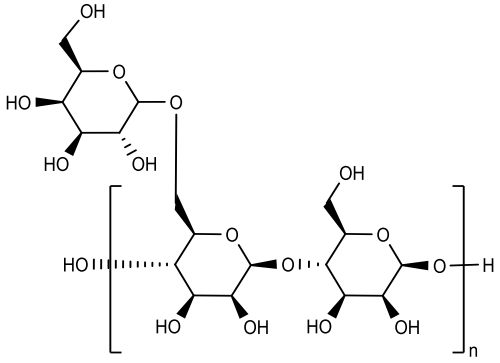
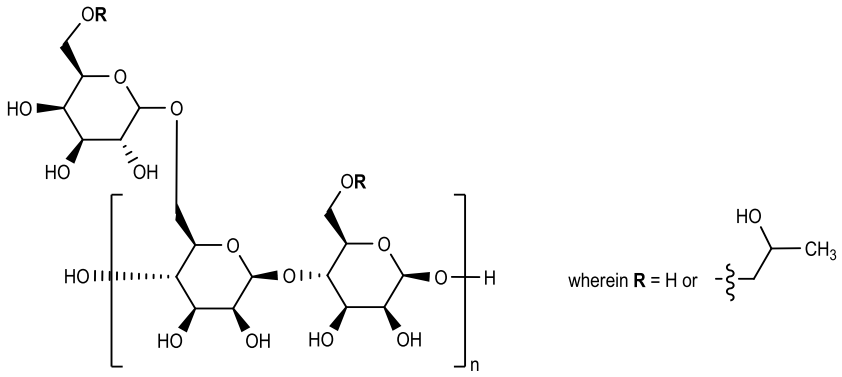
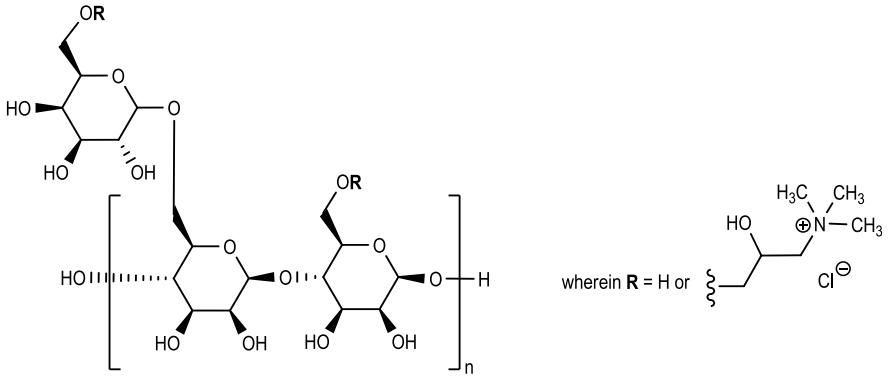
CONCLUSION

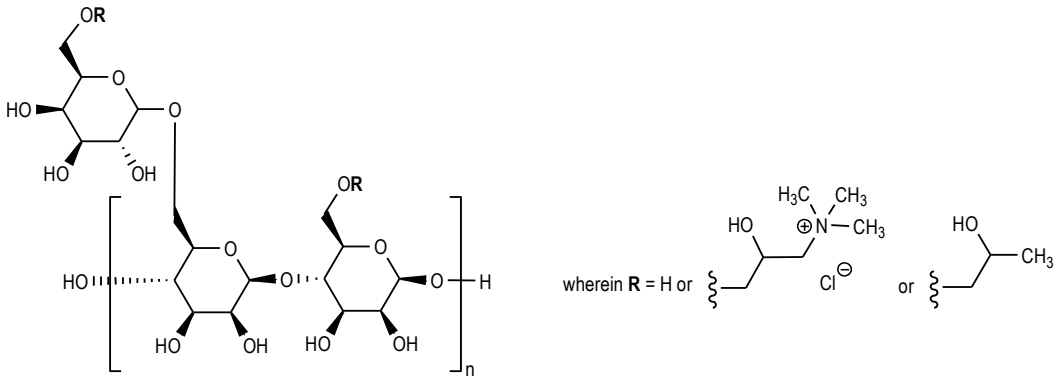
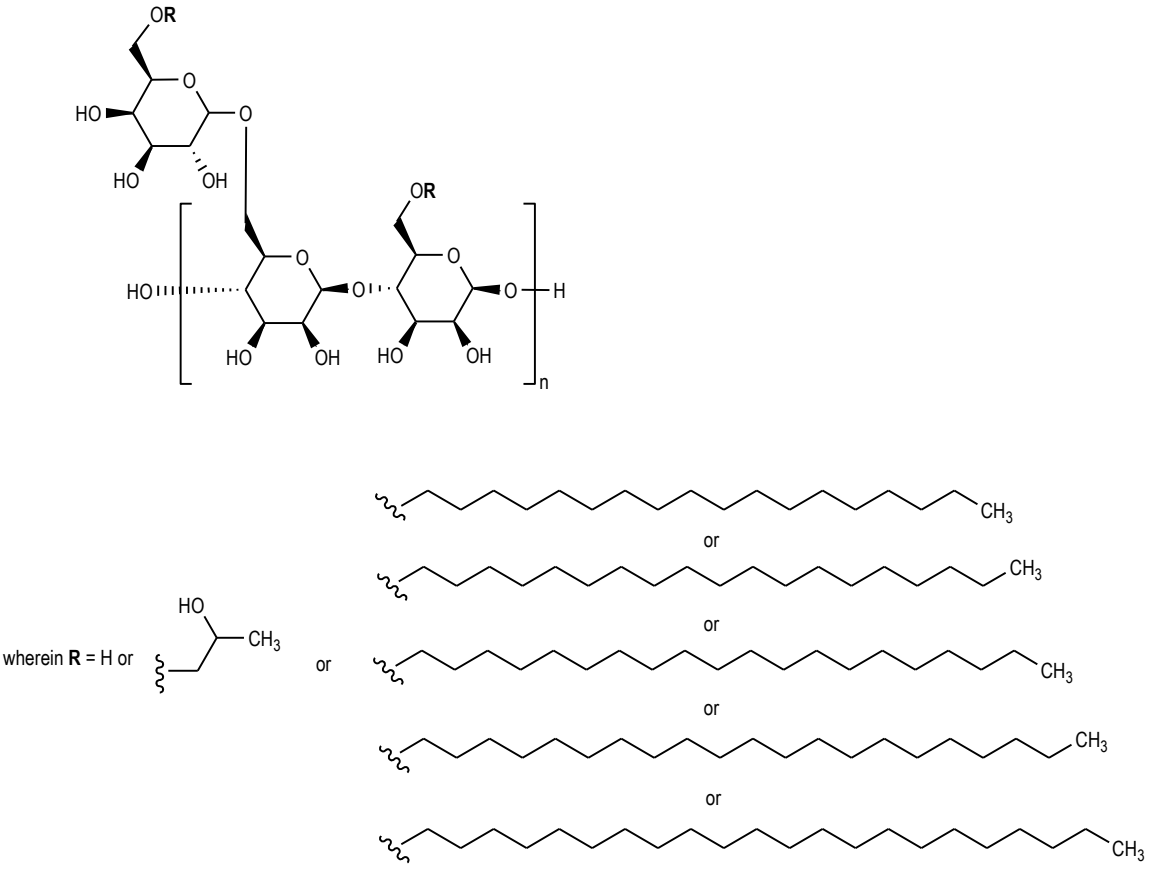
The CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment:

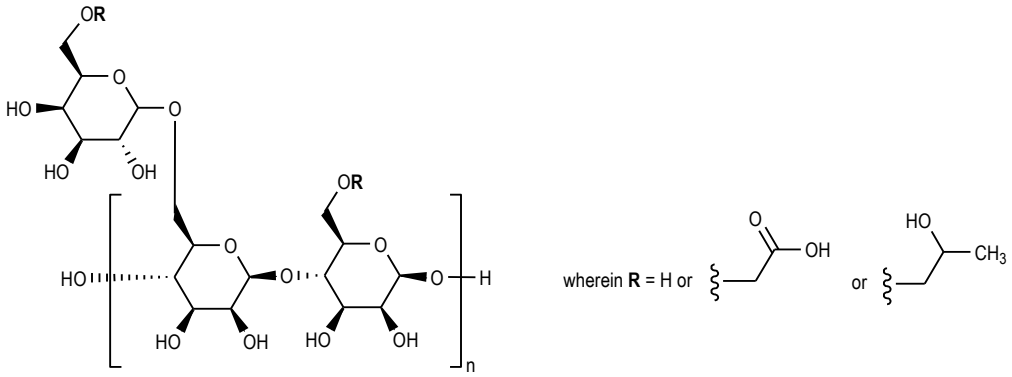
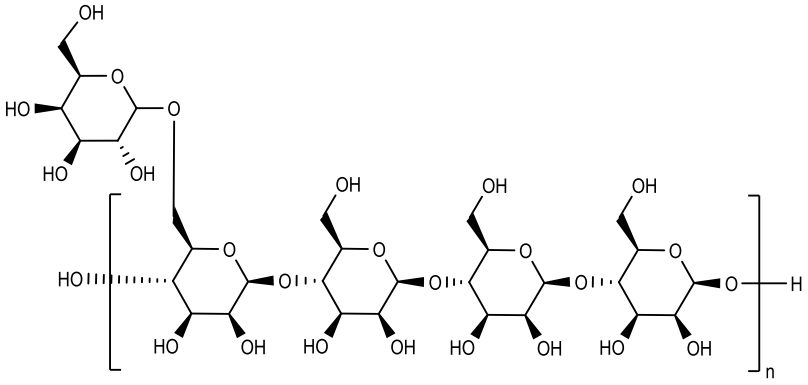
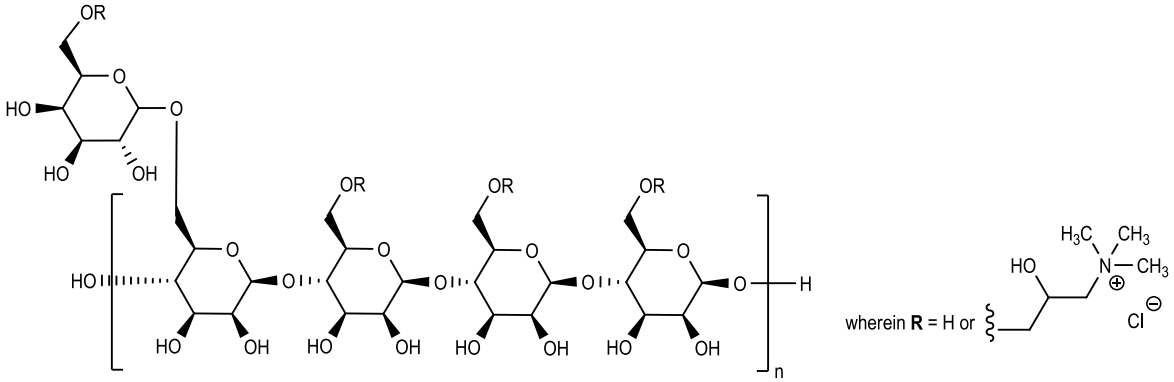
- Cyamopsis Tetragonoloba (Guar) Gum
- Hydroxypropyl Guar
- C18-22 Hydroxyalkyl Hydroxypropyl Guar*
- Guar Hydroxypropyltrimonium Chloride
- Hydroxypropyl Guar Hydroxypropyltrimonium Chloride
- Carboxymethyl Hydroxypropyl Guar*
- Hydrolyzed Guar
- Ceratonia Siliqua Gum
- Locust Bean Hydroxypropyltrimonium Chloride
- Hydrolyzed Ceratonia Siliqua Gum Extract*
- Caesalpinia Spinosa Gum
- Caesalpinia Spinosa Hydroxypropyltrimonium* Chloride
- Hydrolyzed Caesalpinia Spinosa Gum
- Trigonella Foenum-Graecum Hydroxypropyltrimonium Chloride*
- Cassia Gum*
- Cassia Hydroxypropyltrimonium Chloride

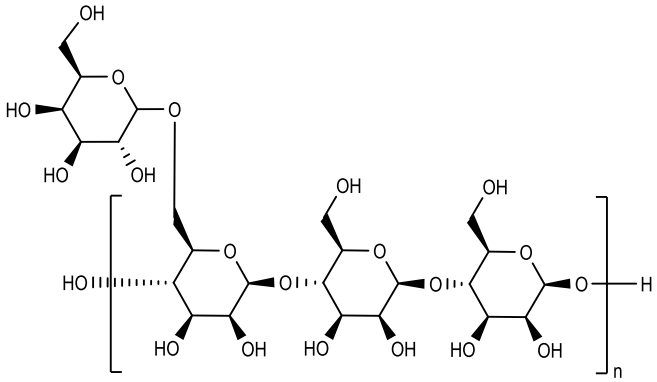
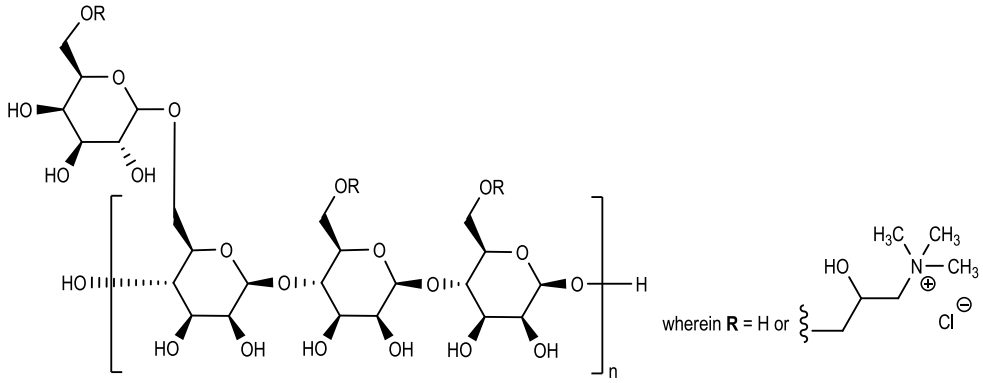
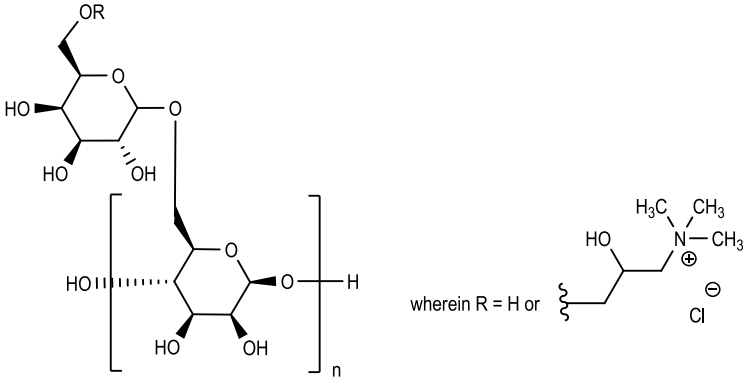
Were ingredients in this group not in current use to be used in the future (indicated by *), the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Galactomannan Ingredients

Ingredient CAS No.	Definition and Functions[1] (italicized text below has been added by CIR staff)	Formula/structure
Guar gums - mannose:galactose 2:1		
Cyamopsis Tetragonoloba (Guar) Gum 9000-30-0	Cyamopsis Tetragonoloba (Guar) Gum is a resinous material derived from the ground endosperm of *Cyanopsis tetragonoloba*. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 2:1).* Functions: binders; emulsion stabilizers; fragrance ingredients; and viscosity increasing agents - aqueous	
Hydroxypropyl Guar 39421-75-5	Hydroxypropyl Guar is a propylene glycol ether of Cyamopsis Tetragonoloba (Guar) Gum. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 2:1), derivatized via ether linkages with propylene glycol, at some of the free hydroxyl groups of the polysaccharide backbone.* Functions: binders; emulsion stabilizers; film formers; and viscosity increasing agents - aqueous	
Guar Hydroxypropyltrimonium Chloride 65497-29-2	Guar Hydroxypropyltrimonium Chloride is a quaternary ammonium derivative of Hydroxypropyl Guar. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 2:1), derivatized via ether linkages with trimethylammonium propylene glycol ether, at some of the free hydroxyl groups of the polysaccharide backbone.* Functions: antistatic agents; hair conditioning agents; skin-conditioning agents - miscellaneous; and viscosity increasing agents - aqueous	

Ingredient CAS No.	Definition and Functions[1] (italicized text below has been added by CIR staff)	Formula/structure
Hydroxypropyl Guar Hydroxypropyltrimonium Chloride 71329-50-5	Hydroxypropyl Guar Hydroxypropyltrimonium Chloride is the hydroxypropyl derivative of Guar Hydroxypropyltrimonium Chloride. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 2:1), derivatized via ether linkages with a mixture of propylene glycol and trimethylammonium propylene glycol ether, at some of the free hydroxyl groups of the polysaccharide backbone.* Functions: antistatic agents and hair conditioning agents	
C18-22 Hydroxyalkyl Hydroxypropyl Guar	C18-22 Hydroxyalkyl Hydroxypropyl Guar is the product formed by the reaction of Hydroxypropyl Guar with a C18-22 alkyl epoxide and propylene oxide. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 2:1), derivatized via ether linkages with a mixture of propylene glycol and an alkylene glycol that is 18-22 carbons in length, at some of the free hydroxyl groups of the polysaccharide backbone.* Functions: hair conditioning agents and skin-conditioning agents - miscellaneous	

Ingredient CAS No.	Definition and Functions[1] (italicized text below has been added by CIR staff)	Formula/structure
Carboxymethyl Hydroxypropyl Guar 68130-15-4	Carboxymethyl Hydroxypropyl Guar is the sodium salt of a propylene glycol ether of carboxymethyl guar. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 2:1), derivatized via ether linkages with propylene glycol and carboxymethyl groups, at some of the free hydroxyl groups of the polysaccharide backbone*. Functions: binders; emulsion stabilizers; and viscosity increasing agents - aqueous	
Hydrolyzed Guar [70892-12-5]	Hydrolyzed Guar is the hydrolysate of Tetragonoloba (Guar) Gum derived by acid, enzyme or other method of hydrolysis. Function not reported.	Varied segments of Guar Gum
Locust bean gums (Carob gums) - mannose:galactose 4:1		
Ceratonia Siliqua Gum 9000-40-2	Ceratonia Siliqua (Carob) Gum is the material obtained from ground seed of *Ceratonia siliqua. It is a polysaccharide, extracted from locust beans, comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 4:1).* Functions: adhesives; binders; emulsion stabilizers; fragrance ingredients; and viscosity increasing agents - aqueous	
Locust Bean Hydroxypropyltrimonium Chloride	Locust Bean Hydroxypropyltrimonium Chloride is the quaternary ammonium chloride formed by the reaction of hydroxypropyl trimethylamine and Ceratonia siliqua (locust bean) gum. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 4:1), derivatized, via ether linkages with trimethylammonium propylene glycol ether, at some of the free hydroxyl groups of the polysaccharide backbone.* Functions: antistatic agents; hair conditioning agents; and skin-conditioning agents - miscellaneous	
Hydrolyzed Ceratonia Siliqua Gum Extract	Hydrolyzed Ceratonia Siliqua Gum Extract is the hydrolysate of an extract of Ceratonia Siliqua Gum derived by acid, enzyme or other method of hydrolysis. Functions: Hair conditioning agents	Varied segments of Locust Bean Gum

Ingredient CAS No.	Definition and Functions[1] (italicized text below has been added by CIR staff)	Formula/structure
Tara gums - mannose:galactose 3:1		
Caesalpinia Spinosa Gum 39300-88-4	Caesalpinia Spinosa Gum is the material derived from the endosperm of *Caesalpinia spinosa. It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 3:1).* Functions: adhesives; skin-conditioning agents - miscellaneous; and viscosity increasing agents - aqueous	
Caesalpinia Spinosa Hydroxypropyltrimonium Chloride [742071-24-5]	*Caesalpinia Spinosa Hydroxypropyltrimonium Chloride (quaternary ammonium salt) is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 3:1), derivatized, via ether linkages with trimethylammonium propylene glycol ether, at some of the free hydroxyl groups of the polysaccharide backbone.* Functions: antistatic agents; hair conditioning agents; and skin-conditioning agents - miscellaneous	
Hydrolyzed Caesalpinia Spinosa Gum	Hydrolyzed Caesalpinia Spinosa Gum is the hydrolysate of Caesalpinia Spinosa Gum derived by acid, enzyme or other method of hydrolysis. Functions: absorbents; hair conditioning agents; skin-conditioning agents - emollient	Varied segments of Tara gum.
Fenugreek gums - mannose:galactose 1:1		
Trigonella Foenum-Graecum Hydroxypropyltrimonium Chloride [742071-25-6]	*Trigonella Foenum-Graecum Hydroxypropyltrimonium Chloride (quaternium ammonium salt) is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 1:1), derivatized, via ether linkages with trimethylammonium propylene glycol ether, at some of the free hydroxyl groups of the polysaccharide backbone.* Functions: antistatic agents; hair conditioning agents; and skin-conditioning agents - miscellaneous	

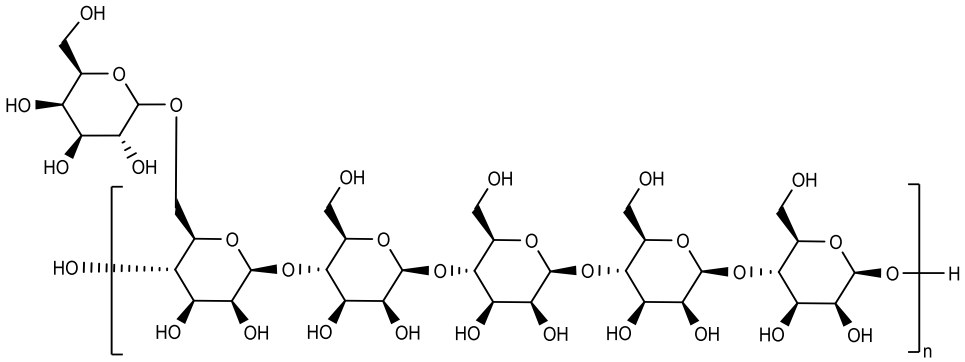
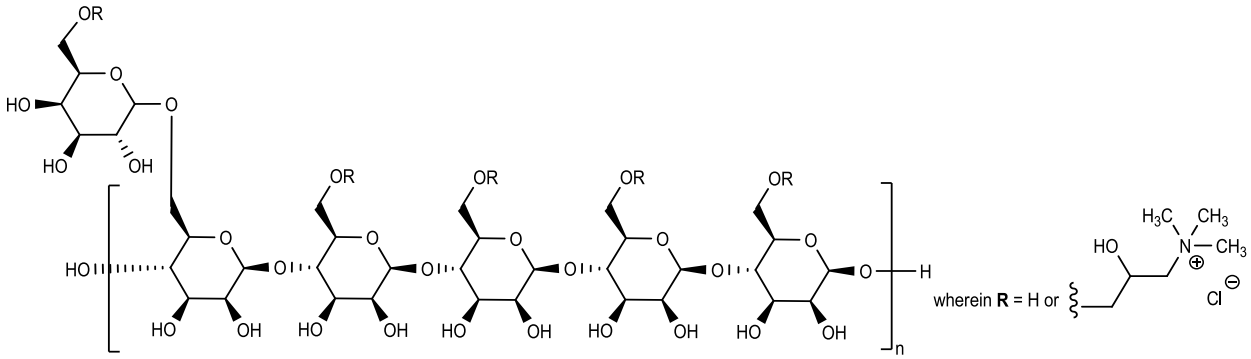
Ingredient CAS No.	Definition and Functions[1] (italicized text below has been added by CIR staff)	Formula/structure
Cassia Gums - mannose:galactose 5:1		
Cassia Gum	Cassia Gum is the material obtained from the endosperm of Cassia tora or Cassia obtusifolia seeds. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendant groups (whereby the mannose:galactose ratio is 5:1)*. Functions: binders; skin-conditioning agents - miscellaneous; and viscosity increasing agents - aqueous	
Cassia Hydroxypropyltrimonium Chloride	*Cassia Hydroxypropyltrimonium Chloride is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose:galactose ratio is 5:1), derivatized, via ether linkages with trimethylammonium propylene glycol ether, at some of the free hydroxyl groups of the polysaccharide backbone.* Functions: antistatic agents and hair conditioning agents	

Table 2. Specifications and Purity of Gums for Use in Foods/Drugs[3,4,8]

Constituents	Cassia Gum	Ceratonia Siliqua Gum*	Cyamopsis Tetragonoloba (Guar) Gum	Caesalpinia Spinosa Gum
Galactomannan (%)	≥ 75	≥ 75	≥ 70	≥ 82%
Acid-insoluble residue (%)	≤ 2	≤ 4	≤ 7	≤ 2.2
Moisture (%)	≤ 12	NR	NR	NR
Ash (%)	≤ 2	≤ 1.2	≤ 1.5	≤ 1.5
Protein (%)	≤ 7	≤ 7	≤ 10	≤ 3
Fat (%)	≤ 2	NR	NR	≤ 1
Loss on drying	-	-	Not more than 15%	-
Heavy Metals				
Heavy metals	NR	NR	0.002%**	≤ 20 mg/kg
Lead (mg/kg)	< 10	≤ 5	≤ 2	≤ 10
Copper (mg/kg)	< 10	NR	NR	NR
Arsenic (mg/kg)	< 2	≤ 3	3**	≤ 3
Zinc (mg/kg)	< 10	NR	NR	NR
Mercury (mg/kg)	< 1	NR	NR	NR
Impurities				
Mycotoxins (mg/kg)	< 0.001	NR	NR	NR
Pesticides	< 0.001	NR	NR	NR
Total germ count (g)	≤ 5,000	NR	NR	NR
Coliforms (*E. coli*)	Negative	NR	NR	NR
Yeasts (per g)	≤ 100	NR	NR	NR
Moulds (per g)	≤ 100	NR	NR	NR
Chrysophanic acid (ppm)§	10 (maximum)	NR	NR	NR

§A measure for the naturally occurring anthraquinone derivatives in the product
*Specifications for foods and drugs; **Specifications for drugs; NR = Not Reported

Table 3. Properties of Guar Hydroxypropyltrimonium Chloride Trade Name Materials

Properties/Components	Values
Form	White to yellow fine powder[6]
Odor	Characteristic[6]
pH	6.0 to 7.5 (1% solution);[6] 9.0 to 10.5 (1% aqueous, 25℃)[101]
Solubility	Very slightly soluble in water; practically insoluble in ethyl ether, chloroform, petrol ether, ethyl aocohol, and paraffin oil[6]
Active matter	Min. 93%;[6] ≥ 90%[101]
Water	Max. 7%;[6] ≤ 10%[101]
Ash	5.6 to 8.7% (600°C)[6]
Chloride	Max. 6%[6]

Table 4. Current Frequency of Use According to Duration and Type of Exposure[19,20]

	Cyamopsis Tetragonoloba (Guar) Gum		**Hydroxypropyl Guar**		**Guar Hydroxypropyl-trimonium Chloride**		**Hydroxypropyl Guar Hydroxypropyltrimonium - Chloride**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type								
Eye Area	1	NR	NR	NR	1	0.005 to 1	1	NR
Incidental Ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	NR	1	NR	4	0.05	NR	NR
Incidental Inhalation-powders	NR	NR	1	NR	NR	NR	NR	NR
Dermal Contact	32	0.02 to 1	73	0.05 to 0.8	203	0.02 to 1	80	0.2 to 0.6
Deodorant (underarm)	NR	1	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	21	0.04 to 0.5	92	0.1 to 93	573	0.07 to 2	46	0.04 to 0.9
Hair-Coloring	14	2 to 5	2	0.1 to 2	38	0.1 to 0.3	1	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	12	0.1 to 1	21	NR	179	0.2 to 0.9	75	0.3 to 0.6
Baby Products	1	0.09	1	NR	2	0.3	NR	NR
Duration of Use								
Leave-On	31	0.02 to 1	111	0.05 to 2	107	0.005 to 2	8	0.04 to 0.9
Rinse off	36	0.09 to 5	56	0.1 to 93	709	0.02 to 2	113	0.2 to 0.8
Diluted for (bath) use	1	NR	NR	NR	2	0.2 to 0.9	6	0.3
Totals/Conc. Range	68	0.02 to 5	167	0.05 to 93	818	0.005 to 2	127	0.04 to 0.9

	Hydrolyzed Guar		**Ceratonia Siliqua Gum**		**Locust Bean Hydroxypropyltrimonium Chloride**		**Caesalpinia Spinosa Gum**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type								
Eye Area	NR	0.5	4	0.002 to 0.05	NR	NR	2	0.002
Incidental Ingestion	NR	0.2	5	0.07	NR	NR	NR	0.02
Incidental Inhalation-sprays	NR	NR	NR	0.002 to 0.003	NR	NR	NR	NR
Incidental Inhalation-powders	NR	NR	1	NR	NR	NR	NR	NR
Dermal Contact	NR	0.1 to 0.5	41	0.0003 to 0.03	NR	NR	17	0.002 to 0.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	0.03 to 3	1	NR	NR	0.4	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.2	5	0.0003 to 0.07	NR	NR	1	0.02
Baby Products	NR	NR	0	NR	NR	NR	NR	NR
Duration of Use								
Leave-On	1	0.03 to 3	41	0.0003 to 0.05	NR	NR	14	0.002 to 0.5
Rinse-Off	NR	0.2 to 2	7	0.0003 to 0.07	NR	0.4	3	0.03
Diluted for (bath) use	NR	NR	0	NR	NR	NR	NR	NR
Totals/Conc. Range	1	0.03 to 3	48	0.0003 to 0.07	NR	0.4	17	0.002 to 0.5

Table 4. Current Frequency of Use According to Duration and Type of Exposure[19,20]

	Hydrolyzed Caesalpinia Spinosa Gum		**Cassia Hydroxypropyl-trimonium Chloride**			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Exposure Type						
Eye Area	1	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation-sprays	NR	NR	NR	NR		
Incidental Inhalation-powders	NR	NR	NR	NR		
Dermal Contact	11	0.002 to 0.4	NR	NR		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	5	0.06 to 0.4		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	1	NR	NR	NR		
Baby Products	NR	NR	NR	NR		
Duration of Use						
Leave-On	8	0.002 to 0.4	NR	NR		
Rinse off	3	0.008	5	0.06 to 0.4		
Diluted for (bath) use	NR	NR	NR	NR		
Totals/Conc. Range	11	0.0012 to 0.4	5	0.06 to 0.4		

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 5. Genotoxicity of Galactomannans

Ingredient	Doses/Concentrations	Strain/cell type	Assay	Results
Cyamopsis tetragonoloba (Guar) Gum	up to 10,000 µg/plate ± metabolic activation	Strains TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535, TA 1537, and TA 1538 of S*almonella typhimurium*	Ames test	Negative [102]
	1% and 5% w/v	Strains TA 1530 and G 46 of *Salmonella typhimurium*	Host mediated assay	Not genotoxic[56]
	2.5 mg/disk ± metabolic activation		Spore rec- assay	Not genotoxic[103]
	Rats received up to 5,000 mg/kg, and bone marrow cells obtained. WI-38 cells tested at concentrations up to 1,000 µg/ml *in vitro*	Human embryonic lung cells (WI-38) and rat bone marrow cells	Cytogenetic assay	Not genotoxic in bone marrow metaphase chromosomes; increase in aberrant WI-38 anaphase cells[56]
	Rats received single and multiple oral doses up to 5,000 mg/kg		Dominant lethal gene test	Not genotoxic; statistically significant findings relating to implants and corpora lutea considered random occurrences[56]
	Doses not stated	*Drosophila melanogaster*	Sex-linked recessive lethals test	Not genotoxic[104]
Hydroxypropyl guar	up to 1,000 µg/plate ± metabolic activation	Strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium*. Strain D4 of *Saccharomyces cerevisiae*	Ames test	Negative without metabolic activation. Genotoxic (dose-related) to the following strains with metabolic activation: TA 1537, TA 1538, TA 98, and TA 100[105]
Guar hydroxypropyltrimonium chloride	up to 1,000 µg/plate ± metabolic activation	Strains TA 98, TA100, TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium*	Ames test	Not genotoxic[106]
Hydrolyzed guar	up to 5,000 µg/plate ± metabolic activation	Strains TA 100, TA 1535, TA 98, and TA 1537 of *Salmonella typhimurium*. Strain WP2 uvrA of *Escherichia coli*	Ames test	Not genotoxic[50]
Ceratonia siliqua gum	up to 1.8% (plate test) and up to 3% (suspension test); ± metabolic activation in both assays	Strains TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium* (plate test). Strain D4 of *Saccharomyces cerevisiae* (suspension test)	Ames test	Not genotoxic[107]

Table 5. Genotoxicity of Galactomannans

Ingredient	Doses/Concentrations	Strain/cell type	Assay	Results
Ceratonia siliqua gum	up to 10,000 µg/plate ± metabolic activation	Strains TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium*	Ames test	Not genotoxic[102]
	5% w/v	Strain TA 1530 of *Salmonella typhimurium* and strain D3 of *Saccharomyces cerevisiae*	Host mediated assay	Not genotoxic[51]
	2.5 mg/disk ± metabolic activation	*Bacillus subtilis*	Spore rec- assay	Not genotoxic[103]
	Rats received up to 5,000 mg/kg, and bone marrow cells obtained. WI-38 cells tested at concentrations up to 1,000 µg/ml *in vitro*	Human embryonic lung cells (WI-38) and rat bone marrow cells	Cytogenetic assay	Not genotoxic in bone marrow metaphase or WI-38 anaphase cells[51]
	Rats received oral doses up to 5,000 mg/kg		Dominant lethal gene test	Not genotoxic; statistically significant findings relating to implants and corpora lutea considered random occurrences[51]
Caesalpinia spinosa gum	up to 1,000 µg/plate ± metabolic activation	Strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of Salmonella typhimurium.	Ames test	No significant increase in revertant number[108]
	Swiss Crl mice received oral dose of 350 mg/kg		Micronucleus test	Number of micronuclei in polychromatic bone marrow cells not significantly different when compared to negative control values[109]
Cassia gum	up to 1,000 µg/plate (semi-refined gum) ± metabolic activation	Strains TA 98, TA 100, TA 1535, and TA 1537 of *Salmonella typhimurium.* Strain WP2uvrAm of *Escherichia coli*	Ames test	Dose-related increases in number of revertants in 3 strains -activation, in strain 1537 + activation, and in strain TA 100 ± activation. All increases within historical control range (TA 98, TA 1535, and TA 1537). In other experiment, negative results for these 3 strains ± activation. Results negative for *E. coli* strain[110]

Table 5. Genotoxicity of Galactomannans

Ingredient	Doses/Concentrations	Strain/cell type	Assay	Results
Cassia gum	up to 5,000 µg/plate ± metabolic activation (semi-refined gum containing 8.6 mg total anthraquinones/kg)	Strains TA98, TA 100, TA 1535, and TA 1537 of *Salmonella typhimurium*. Strain WP2uvrA of *Escherichia coli*	Ames test	Not genotoxic[18]
	5 mg/plate ± metabolic activation (semi-refined gum)	Strains TA 97, TA 98, TA 100, and TA 102 of *Salmonella typhimurium*	Ames test	Not genotoxic[54]
	up to 10,000 µg/ml ± metabolic activation (semi-refined gum)	Mouse lymphoma L5178Y TK+/- cells	Gene mutation assay	Not genotoxic[111]
	up to 10 µg/ml ± metabolic activation (semi-refined gum)	Human lymphocytes	Chromosome aberrations assay	Not genotoxic[112]
	KM mice received oral dose up to 2,500 mg/kg	Mouse bone marrow	Micronucleus test	Not genotoxic[54]
	KM mice received oral doses up to 2,500 mg/kg (1 dose/day for 5 days)	KM mouse sperm	Sperm abnormality test	Not genotoxic[54]

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