Article

Safety Assessment of Galactomannans as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) reviewed the safety of 16 galactomannans as used in cosmetics. These ingredients 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 Panel concluded that these galactomannans are safe in the present practices of use and concentration described in this safety assessment.

Keywords

galactomannans, safety, cosmetics

Introduction

As given in the International Cosmetic Ingredient Dictionary and Handbook, these 16 galactomannans function mostly as hair/skin-conditioning agents and viscosity-increasing agents in cosmetic products.[1] The ingredients included in this report are as follows:

- *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.

Gum guar, oxidized 2-hydroxypropyl 3-hydroxy-3-(tri-methylammonio) propyl ether, chloride—also known as cationic guar, is not a cosmetic ingredient. Because of the similarity of this ingredient to guar hydroxypropyltrimonium chloride,

acute oral toxicity data on cationic guar were considered. 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 *T foenum-graecum* is part of the chemical structure of *T foenum-graecum* hydroxy-propyltrimonium chloride.

Chemistry

Definition and Structure

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

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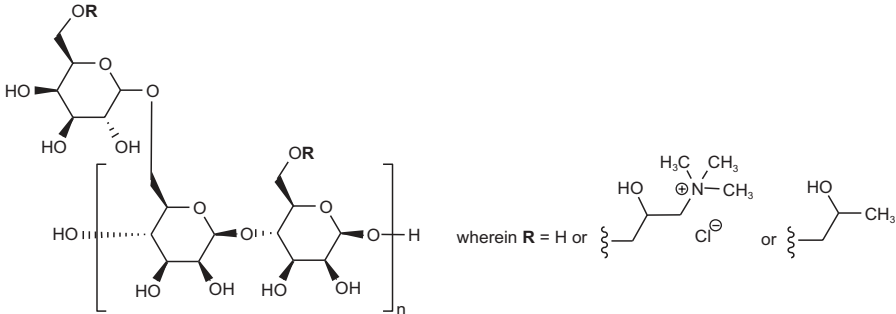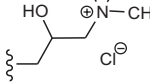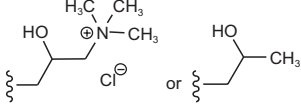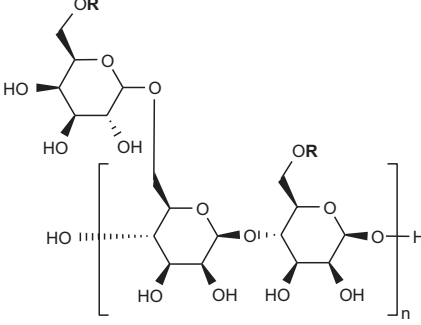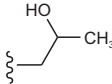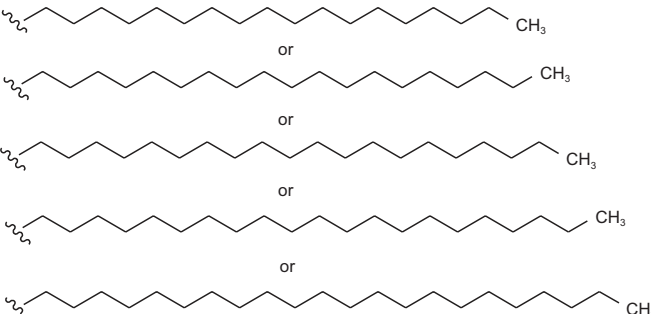Email: cirinfo@cir-safety.org

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

C tetragonoloba (guar) gum is a resinous material derived from the ground endosperm of *C 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 *C 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

wherein **R** = H or

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
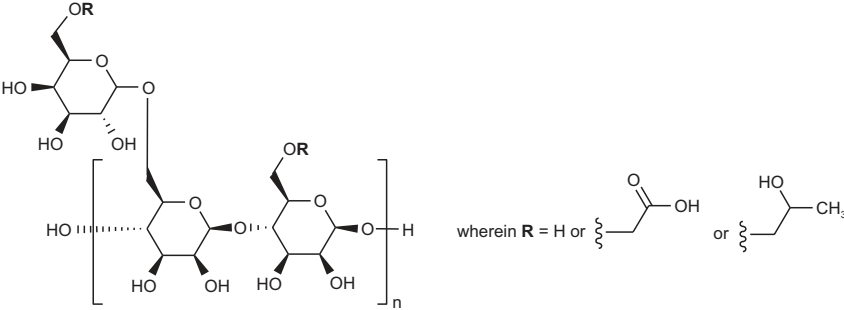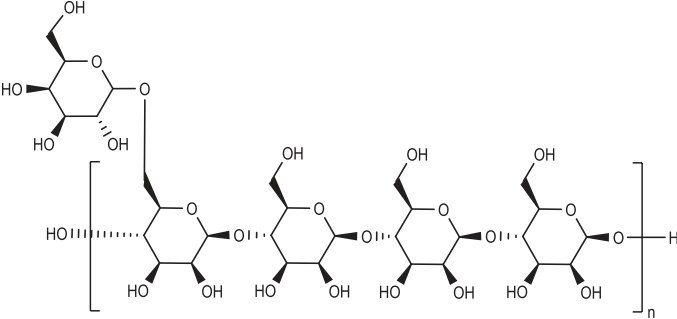
wherein **R** = H or

Table 1. (continued)

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	

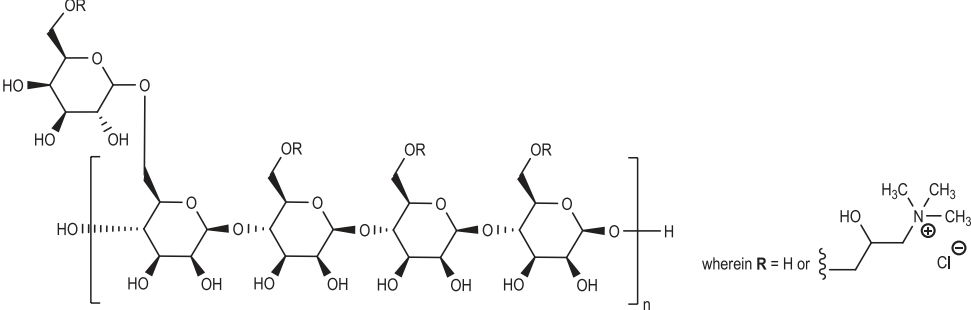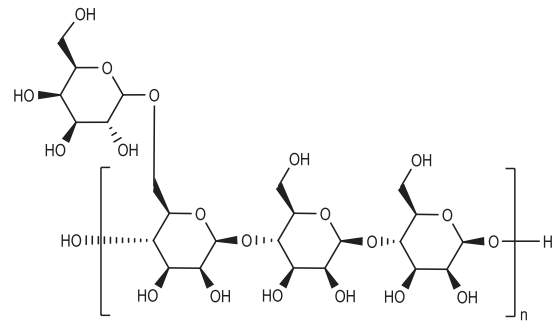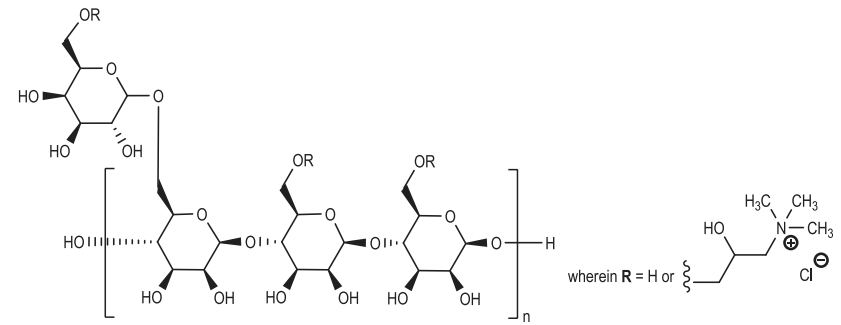| C18-22 Hydroxyalkyl hydroxypropyl guar | C18-22 hydroxyalkyl hydroxypropyl guar is the product formed by the reaction of hydroxypropyl guar with a C18-22 alkyl epoxide and propylene oxide. *It is a polysaccharide comprised of a polymannose backbone with mono-galactose pendent groups (whereby the mannose: 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 | |

Table 1. (continued)

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 | *C siliqua* (carob) gum is the material obtained from ground seed of *C 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 *C 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 | |
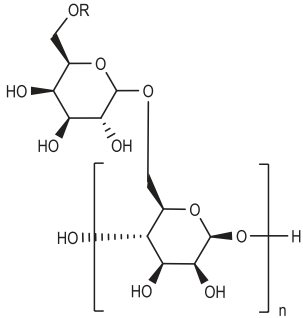
Table 1. (continued)

Ingredient CAS No.	Definition and Functions[1] (italicized text below has been added by CIR staff)	Formula/structure
Hydrolyzed *C siliqua* gum extract	Hydrolyzed *C siliqua* gum extract is the hydrolysate of an extract of *C siliqua* gum derived by acid, enzyme, or other method of hydrolysis. Functions: Hair-conditioning agents	Varied segments of locust bean gum

Tara gums: mannose–galactose 3:1

Caesalpinia spinosa gum 39300-88-4	*C spinosa gum is the material derived from the endosperm of C 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	

C spinosa Hydroxypropyltrimonium Chloride [742071-24-5]	*C 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 *C spinosa* gum	Hydrolyzed *C spinosa* gum is the hydrolysate of *C 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]	*T 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	

(continued)

Table 1. (continued)

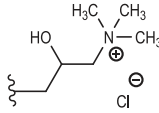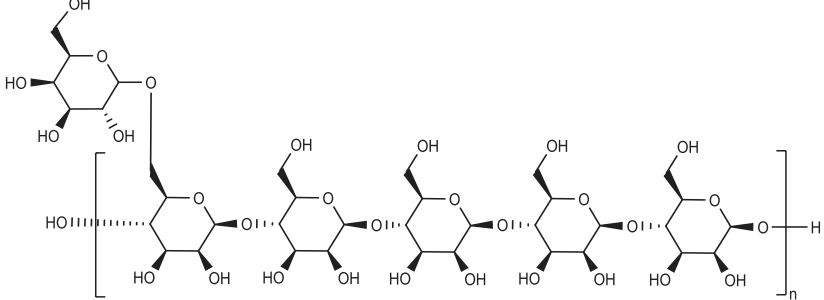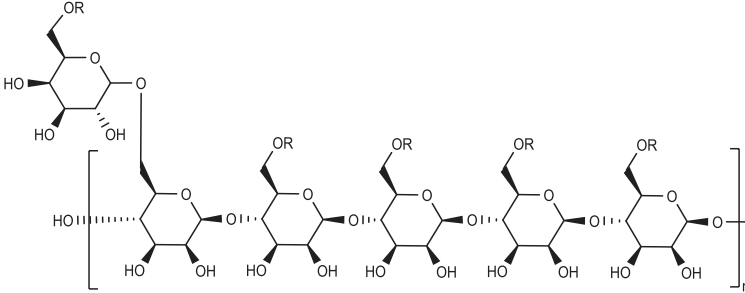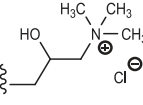| Ingredient CAS No.	Definition and Functions[1] (italicized text below has been added by CIR staff)	Formula/structure

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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 |

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 polymannose backbone with galactose pendent groups. They are commonly called galactomannans because of the mannose/galactose chemical makeup of these legume polysaccharides (see Figure 1). Unlike starch, which is stored in amyloplasts in the cytoplasm, nonstarch reserve polysaccharides, such as galactomannans, are deposited in the cell walls of the seeds.

The 5 primary galactomannan gums are guar gum from the seeds of *Cyamopsis tetragonoloba,* locust bean gum from the
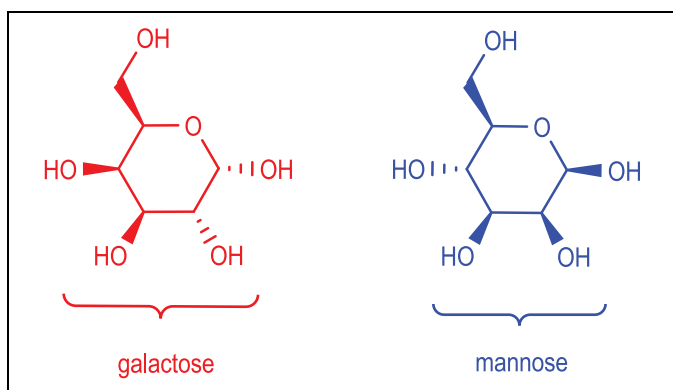
Figure 1. Galactose and mannose, the building blocks of the galactomannans.

seeds of *Ceratonia siliqua* (carob tree), tara gum from seeds of *Caesalpinia spinosa,* fenugreek gum from the seeds of *T foenum-graecum,* and cassia gum from seeds of *Cassia obtusifolia* or *tora*. Although 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 copolymer. In other words, within 1 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).

Although 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 g/mole and often exceed 2 000 000 g/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). The most likely point of derivatization is at the C6 positions of a galactose pendent groups and the polymannose backbone, although all of the free hydroxyl groups are potentially susceptible substrates for condensation. Reported degrees of substitution are related as saturated (ie, equal to 1.0) when there is 1 stoichiometric equivalent of substituent per 1 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 1 substituent (eg, hydroxypropyltrimonium chloride) per mannose or galactosylmannose. 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).

Those gums listed in this report as "hydrolyzed" are really *partially* hydrolyzed polysaccharides (eg, 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 *C tetragonoloba* (guar) gum and *C 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 precipitating with iso-propanol. 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 *C tetragonoloba* (guar) gum, hydroxypropyl guar, carboxymethyl hydroxypropyl guar, *C siliqua* gum, *Caesalpinia spinosa* gum, and cassia gum is included subsequently.

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 2.

Carboxymethyl hydroxypropyl guar. Carboxymethylation and hydroxypropylation of *C tetragonoloba* (guar) gum are carried out simultaneously using monochloroacetic acid and propylene oxide in the presence of a hydrophilic solvent (ie, 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 *C siliqua* Linné Taub. (Family: Leguminosae).[4]

Caesalpinia spinosa gum. Commercial production of *C spinosa* gum involves the incomplete separation of the endosperm from the germ and the husk. Thus, commercial products may contain small amounts of husk as well as varying amounts of protein and fat from unseparated germ. Consequently, commercially
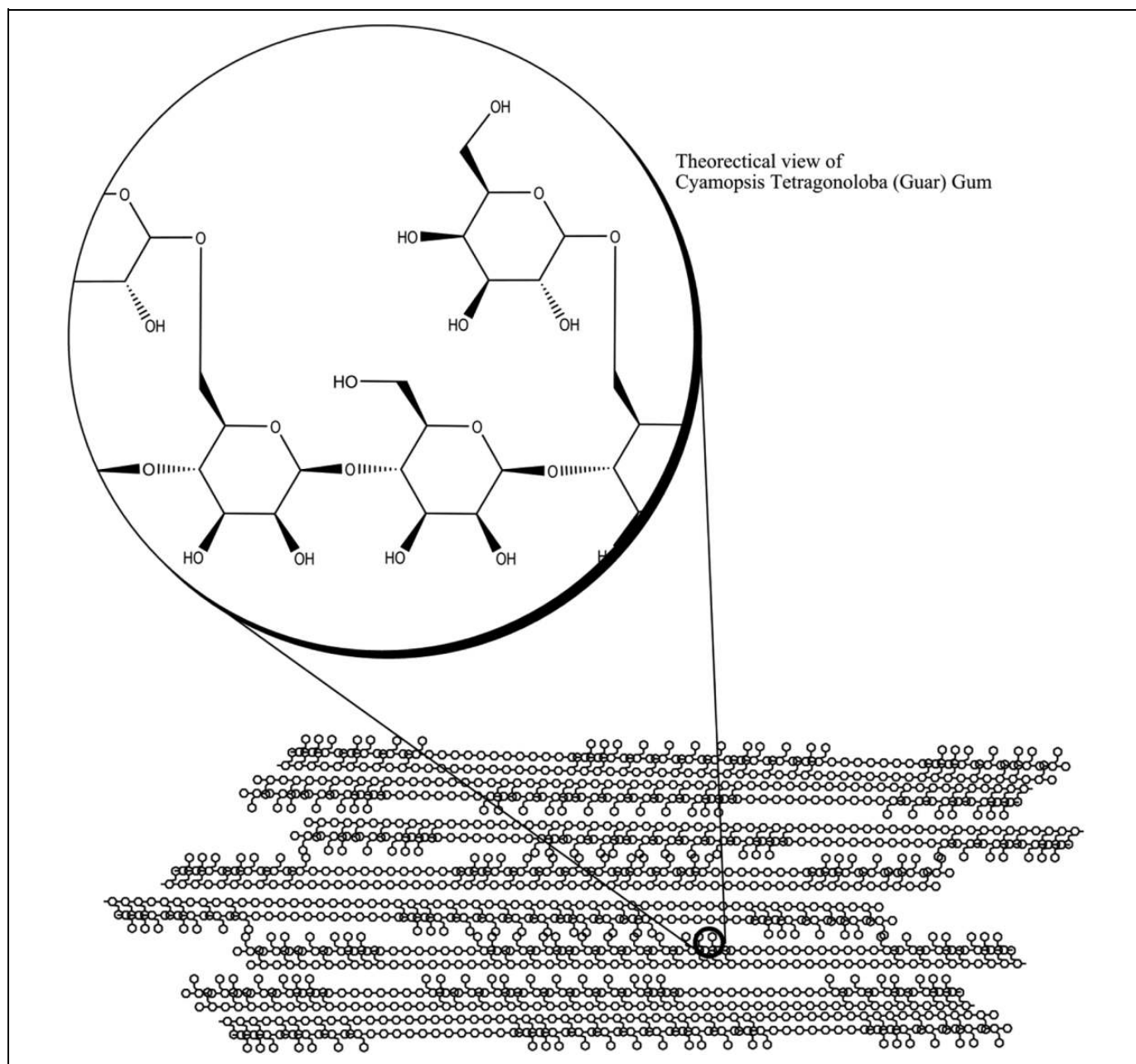
Figure 2. Packing and structure of *Cyamposis tetragonoloba* (guar) gum.

available *C 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 *C obtusifolia*.[1] The production method for cassia gum includes cleaning of the source material, dehusking, and degerming 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. Semirefined 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 3: *C tetragonoloba* (guar) gum, *C siliqua* gum, *C 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 relative proportions of the most abundant amino acids, glycine, glutamic acid, aspartic acid, serine,
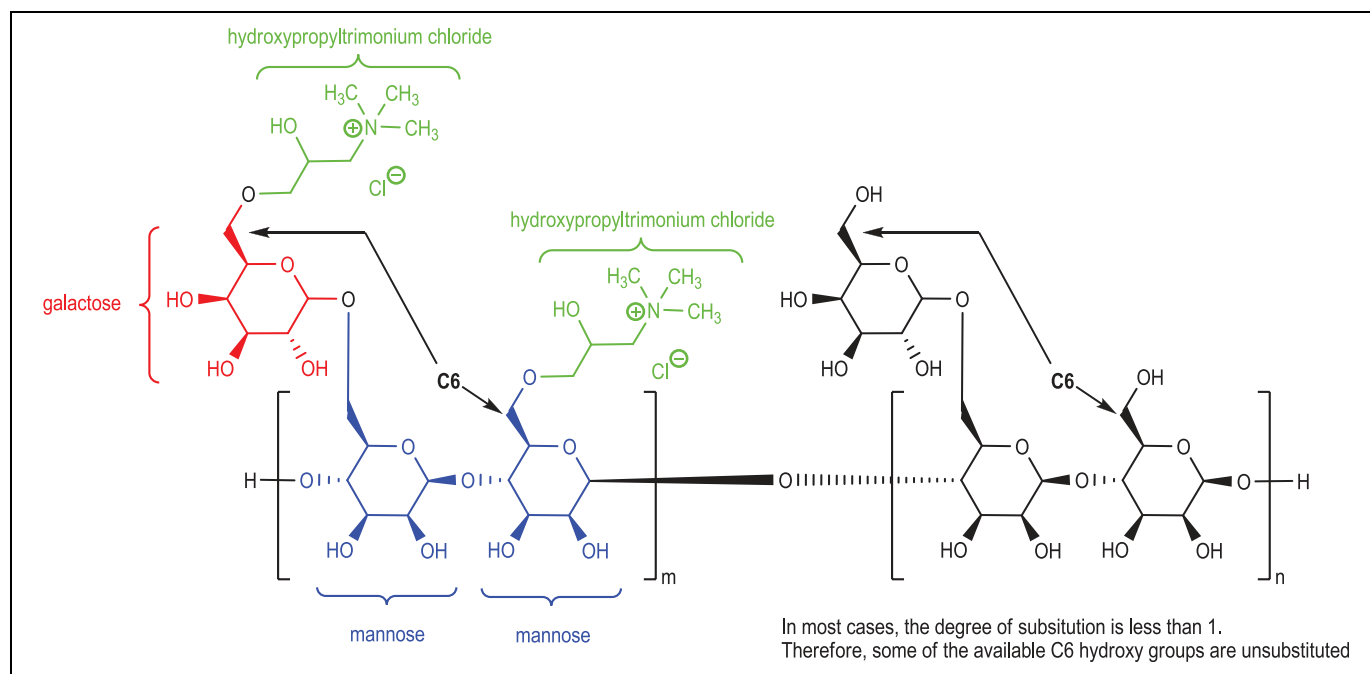
Figure 3. Idealized structure of guar hydroxypropyltrimonium chloride.[2]

Table 2. 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°C)[101]
Solubility	Very slightly soluble in water; practically insoluble in ethyl ether, chloroform, petrol ether, ethyl alcohol, and paraffin oil[6]
Active matter	Min 93%[6]; $\geq$ 90%[101]
Water	Max 7%[6]; $\leq$ 10%[101]
Ash	5.6%-8.7% (600°C)[6]
Chloride	Max 6%[6]

Abbreviations: max, maximum; min, minimum.

and alanine vary considerably. Proportions of histidine, isoleucine, phenylalanine, threonine, tyrosine, and valine remain remarkably constant.[11]

Commercial samples of *C tetragonoloba* (guar) gum, purified and unpurified, were analyzed in this study.[12] The 4 methods of purification included (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 constituents, 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, use of Fehling solution in methods 3 and 4 contaminated the gum with small amounts of Cu(II), 0.079% and 0.044%, respectively. Methods 2 and 4 resulted in purer (ie, small amount of protein) *C tetragonoloba* (guar) gum.

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

Using MS, very low fluoroacetate concentrations (0.07-1.42 μg/g, 10 samples) were detected in *C tetragonoloba* (guar) gum used as a raw material for a guar gum powder. A pharmaceutical formulation of guar gum contained 0.08 ppm fluoroacetate.[14]

The noncatalytic hydrolysis of *C tetragonoloba* (guar) gum under hydrothermal conditions (temperature range: 180°C-240°C) produced oligosaccharides with degrees of polymerization of up to ~20, monosaccharides containing mannose and galactose, and 5-hydroxymethyl-2-furaldehyde.[15]

In 2007, the Rapid Alert System for Food and Feed received a notification from Switzerland concerning a finding of serious contamination of *C tetragonoloba* (guar) gum, originating from India, with dioxins and pentachlorophenol (PCP).[16] The levels of these contaminants in certain batches of *C 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 *C tetragonoloba* (guar) gum or products containing *C tetragonoloba* (guar) gum at significant amounts originating in or consigned from India and imported into the

Table 3. Specifications and Purity of Gums for Use in Foods/Drugs.[3,4,8,16]

Constituents	Cassia gum	*Ceratonia siliqua* gum[a]	*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%[b]	≤20 mg/kg
Lead, mg/kg	<10	≤5	≤2	≤10
Copper, mg/kg	<10	NR	NR	NR
Arsenic, mg/kg	<2	≤3	3[b]	≤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	≤5000	NR	NR	NR
Coliforms (*Escherichia coli*)	Negative	NR	NR	NR
Yeasts, per g	≤100	NR	NR	NR
Moulds, per g	≤100	NR	NR	NR
Chrysophanic acid, ppm[c]	10 (maximum)	NR	NR	NR
Dioxins	NR	NR	NR	NR
Pentachlorophenol	NR	NR	NR	NR

Abbreviation: NR, not reported.
[a]Specifications for foods and drugs.
[b]Specifications for drugs.
[c]A measure for the naturally occurring anthraquinone derivatives in the product.

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. Because the 2008 decision resulted in no improvement in the control system and no significant reduction in the associated risks, in 2010 the European Commission added a requirement for official sampling, analysis, and certification by competent authorities of India of all consignments of *C 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 and additional data on the properties/composition of this trade name material are found in Table 2.

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

Cassia gum. Cassia gum (*C tora or C obtusifolia*) is composed of at least 75% high molecular mass (∼200 000-300 000) 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%-78.9%), galactose (15.7%-14.7%), and glucose 6.3%-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 *C occidentalis* is reduced to <0.05%. The concentration of anthraquinones in cassia gum is <0.5 mg/kg detection limit. Semirefined cassia gum contains ∼70 mg total anthraquinones/kg. Purified semirefined 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 the 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: *C tetragonoloba* (guar) gum, hydroxypropyl guar, guar hydroxypropyltrimonium chloride, hydroxypropyl guar hydroxypropyltrimonium chloride, hydrolyzed guar, *C siliqua* gum, *C spinosa* gum, hydrolyzed *C 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 of 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 (ie, 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 FDA: *C tetragonoloba* (guar) gum (21 CFR 133.124)[25]; *C siliqua* gum (12CFR 182.20)[26]; and *C tetragonoloba* (guar) gum and *C siliqua* gum (21 CFR 133.178; 133.179; 150.141; 150.161).[27,28,29,30] Additionally, *C tetragonoloba* (guar) gum and *C 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 *C siliqua* gum (aka carob bean gum) as a food, prepared for FDA, is available.[17]

Cyamopsis tetragonoloba (guar) gum. Noncosmetic uses of *C tetragonoloba* (guar) gum include[34] in paper sizing as a protective colloid, stabilizer, thickening and film-forming agent for cheese, salad dressings, ice cream, and soups; as a binding and disintegrating agent in tablet formulations; in pharmaceutical jelly formulations; in suspensions, emulsions, lotions, creams, and toothpastes; in the mining industry as a flocculant and 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 FDA because of the potential to 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 Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (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 the use of *C 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 (JECFA), and this committee assigned a not specified value for the ADI by man.[36] This means that the use of *C 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. *C 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 JECFA, and this committee assigned a not specified value for the ADI by man.[38] This means that the 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; and 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, the JECFA allocated an average daily intake "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.

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

Exposure type	Cyamopsis tetragonoloba (guar) gum # of uses	Conc (%)	Hydroxypropyl guar # of uses	Conc. (%)	Guar hydroxypropyl-trimonium chloride # of uses	Conc. (%)	Hydroxypropyl guar hydroxypropyltrimonium chloride # of uses	Conc. (%)
Eye area	1	NR	NR	NR	1	0.005-1	1	NR
Incidental ingestion	–	NR	NR	NR	NR	NR	NR	NR
Incidental inhalation-sprays	NR	NR	–	NR	4	0.05	NR	NR
Incidental inhalation-powders	NR	NR	–	NR	NR	NR	NR	NR
Dermal contact	32	0.02-1	73	0.05-0.8	203	0.02-1	80	0.2-0.6
Deodorant (underarm)	NR	–	NR	NR	NR	NR	NR	NR
Hair noncoloring	21	0.04-0.5	92	0.1-93	573	0.07-2	46	0.04-0.9
Hair coloring	14	2-5	2	0.1-2	38	0.1-0.3	–	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	12	0.1-1	21	NR	179	0.2-0.9	75	0.3-0.6
Baby products	1	0.09	–	NR	2	0.3	NR	NR
Duration of use								
Leave-on	31	0.02-1	111	0.05-2	107	0.005-2	8	0.04-0.9
Rinse off	36	0.09-5	56	0.1-93	709	0.02-2	113	0.2-0.8
Diluted for (bath) use	–	NR	NR	NR	2	0.2-0.9	6	0.3
Totals/conc range	68	0.02-5	167	0.05-93	818	0.005-2	127	0.04-0.9

Exposure type	Hydrolyzed guar # of uses	Conc. (%)	Ceratonia siliqua gum # of uses	Conc. (%)	Locust bean hydroxypropyltrimonium chloride # of uses	Conc. (%)	Caesalpinia spinosa gum # of uses	Conc. (%)
Eye area	NR	0.5	4	0.002-0.05	NR	NR	2	0.002
Incidental ingestion	NR	0.2	5	0.07	NR	NR	NR	0.02
Incidental inhalation-sprays	NR	NR	NR	0.002-0.003	NR	NR	NR	NR
Incidental inhalation-powders	NR	NR	1	NR	NR	NR	NR	NR
Dermal Contact	NR	0.1-0.5	41	0.0003-0.03	NR	NR	17	0.002-0.5
Deodorant (underarm)	NR	NR	NR	NR	NR	0.4	NR	NR
Hair noncoloring	–	0.03-3	1	NR	NR	NR	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	0.0003-0.07	NR	NR	1	0.02
Baby products	NR	NR	0	NR	NR	NR	NR	NR
Duration of use								
Leave-on	NR	0.03-3	41	0.0003-0.05	NR	NR	14	0.002-0.5
Rinse-off	NR	0.2-2	7	0.0003-0.07	NR	0.4	3	0.03
Diluted for (bath) use	NR	NR	0	NR	NR	NR	NR	NR
Totals/conc range	–	0.03-3	48	0.0003-0.07	NR	0.4	17	0.002-0.5

(continued)

Table 4. (continued)

Exposure type	Hydrolyzed *Caesalpinia spinosa* gum		Cassia hydroxypropyl-trimonium chloride	
	# of uses	Conc. (%)	# of uses	Conc. (%)
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	0.002-0.4	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair noncoloring	NR	NR	5	0.06-0.4
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	0.002-0.4	NR	NR
Rinse off	3	0.008	5	0.06-0.4
Diluted for (bath) use	NR	NR	NR	NR
Totals/conc range	11	0.0012-0.4	5	0.06-0.4

Abbreviations: Conc, concentration; NR, not reported; NS, not surveyed; totals = rinse-off + leave-on product uses.
[a]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.

Cyamopsis tetragonoloba (guar) gum. When a basal diet containing *C 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 (ie, 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 *C 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 *C 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 and 5 females per group; ages not stated) were fed 1% *C siliqua* gum in the diet for 18 hours.[42] Of the mannose fed as 1% *C siliqua* gum, 85% to 100% was excreted in the feces over a 30-hour period. It was noted that some decrease in galactomannan chain length may have occurred. This decrease was believed 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 JECFA noted that specific absorption, distribution, metabolism, and excretion data were not available on cassia gum at the time of evaluation of this food additive.[9] However, based on data on related galactomannans, the Committee concluded that cassia gum will be largely excreted unchanged, although 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 *C tetragonoloba* (guar) gum was evaluated using 10 F344 rats (5 males and 5 females; ages not stated) and 10 B6C3F1 mice (5 males and 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 *C tetragonoloba* (guar) gum (in cocoa butter) at a dietary concentration of 30% for 48 hours. 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 and 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 median lethal dose (LD50) was 12.5 g/kg (95% confidence limits of 10.22-14.78 g/kg).

The acute oral toxicity of a guar hydroxypropyltrimonium chloride trade name material (composition data in Table 2) was evaluated using Bor: WISW (SPF) Cpb rats (5 males and 5 females, ~10 weeks old).[46] A single oral dose of the test substance (in arachidis oil, 2000 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 postmortem examination. None of the animals died, and there were no macroscopic findings at necropsy. An LD50 of >2000 mg/kg was reported.

Gum guar, oxidized 2-hydroxypropyl 3-hydroxy-3-(trimethylammonio)propyl ether, chloride (aka 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 and 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, hypothermia, 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 13-17 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 9.2-14.8 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 and 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 13.1-22.5 g/kg).

Hydrolyzed guar. An acute oral toxicity study on partially hydrolyzed guar was performed using groups of 16 (8 males and 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 1 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 >6000 mg/kg in both the species.

Ceratonia siliqua gum. The acute oral toxicity of *C 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 LD50s were reported: 13 100 mg/kg body weight (mice), 9100 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 semirefined cassia gum was evaluated using 5 male Wistar-Han-Schering rats.[9,53] The animals received 2 oral doses of 5000 mg/kg body weight at a 2-hour interval. An oral LD50 value of >5000 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-hour 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 *C tetragonoloba* (guar) gum (in cocoa butter) at a dietary concentration of 30% for 48 hours.[55] There was no evidence of adverse effects.

Five male Sprague-Dawley rats received oral doses of *C 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% *C tetragonoloba* (guar) gum to rats for 7 days resulted in the death of 7 to 10 animals. The deaths were probably due to intestinal blockage.[55]

Groups of rats (strain not stated) were fed *C tetragonoloba* (guar) gum in the diet at concentrations of 0%, 1%, 2%, and 5%, respectively, for 90 days.[57] Dosing did not affect general behavior, appearance, or survival. Growth was described as relatively low in males fed the 2% and 5% *C tetragonoloba* (guar) gum diets. No effect was observed 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 levels of *C tetragonoloba* (guar) gum were fed to 6 groups of 130 male and female Osborne-Mendel rats (~4-week-old; 65 males and 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 observed for female rats of all dietary groups and in males of the 7.5% and 15% dietary groups. There were no deaths were reported. 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 *C tetragonoloba* (guar) gum. Although 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 results for several rats fed 15.0% *C tetragonoloba* (guar) gum were at the lower end of the normal range and suggested a subtle or borderline effect.

A long-term toxicity study on *C 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% *C 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 and strain 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% *C 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% *C tetragonoloba* (guar) gum. The serum immunoglobulin (Ig) G (IgG) level of rats fed 5% *C tetragonoloba* (guar) gum was significantly lower when compared to that of rats fed 5% cellulose. Also, the productivity of IgA, IgG, and IgM in mesenteric lymph node (MLN) lymphocytes was significantly higher in rats fed 5% *C tetragonoloba* (guar) gum than in rats fed 5% cellulose. The effect of 5% *C tetragonoloba* (guar) gum on productivity of IgA, IgG, and IgM 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 *C 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 and 5 females/group) were fed partially hydrolyzed *C 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 C siliqua gum. A precooked mixture of *C tetragonoloba* (guar) and *C siliqua* gum (proportions not stated) was fed to groups of 5 female Beagle dogs (5 males and 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% *C 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% *C 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 the test and the 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 *C 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 *C 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 *C siliqua* gum in the diet was also 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% *C 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% *C 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 *C 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 *C 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% *C spinosa* gum for 13 weeks.[65] The gum 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% *C 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 *C 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% *C 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 were also no gross or microscopic findings that were related to feeding with diets containing *C spinosa* gum.

Cassia gum. Groups of 5 male and 5 female crl: CD (SD)BR Sprague-Dawley rats (5-6 weeks old) were fed semirefined cassia gum daily at the following dietary concentrations in a 28-day study: 0, 2500, 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 = 1000 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 (1000 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 1 sex only. These values were within the normal range for this species, however, historical control data were not provided. The only changes outside the historical control range that could have been treatment related were increased mean concentrations of glucose and triglyceride in the 10 000 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 and 50 000 mg/kg (in diet) groups

and for the 1000 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 1000 mg/kg/d.[67]

Groups of Sprague-Dawley rats (10 males and 10 females per group) were fed cassia gum in the diet at doses of 0, 250, 500, and 1000 mg/kg body weight per day for 30 days.[54] There were no treatment-related effects on the following: mortality, body weight gain, food consumption, food utilization, hematological parameters, or various biochemical parameters (eg, albumin, cholesterol, and 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 were also no histopathologic changes in the stomach or intestines. An no-observable-adverse-effect-level (NOAEL) of 1000 mg/kg body weight was reported for cassia gum in rats.

Semirefined cassia gum (in dog food) was administered to 2 groups of 4 male and 4 female Beagle dogs at dietary doses of 1 and 3.5 g/kg/d, 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 semirefined 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, C siliqua gum, C 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-, 24-, 48-, and 72-hour postinstillation. *Cyamopsis tetragonoloba* (guar) gum induced minimal ocular irritation in rinsed and unrinsed eyes. Results for other gums (same procedure) were as follows: *C siliqua* gum (minimally irritating, rinsed, and unrinsed eyes) and cassia gum (nonirritating—rinsed eyes; minimally irritating—unrinsed eyes).

Skin Irritation and Sensitization

Cyamopsis tetragonoloba (guar) gum, C siliqua gum, C spinosa gum, and cassia gum. The skin irritation potential of *C tetragonoloba* (guar) gum was evaluated using New Zealand white rabbits (3 males and 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 semiocclusive wrap for 4 hours. Reactions were scored according to the Draize scale at 4.5, 24, 48, and 72 hours. *Cyamopsis tetragonoloba* (guar) gum was nonirritating to the skin of rabbits. Results for other gums (same procedure) were as follows: *C siliqua* gum (minimally irritating; PII = 0.04/8.0), *C spinosa* gum (nonirritating), and cassia gum (nonirritating).

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

Allergenicity

Cyamopsis tetragonoloba (guar) gum. The prevalence of occupational asthma and immunologic sensitization to *C tetragonoloba* (guar) gum was evaluated in 162 employees of a carpet-manufacturing plant, where this gum was used to adhere dye to the fiber.[72] Immunoglobulin E and IgG antibodies to *C tetragonoloba* (guar) gum were measured in 133 of the 162 participants who agreed to blood tests. Thirty-seven (23%) participants had a history of occupational asthma, and 59 (39%) had a history of occupational rhinitis. Skin prick tests with *C tetragonoloba* (guar) gum (1 mg/mL) were conducted. Immediate skin reactivity to *C tetragonoloba* (guar) gum was observed in 8 participants, and 11 participants had serum IgE antibodies to *C tetragonoloba* (guar) gum. In the second part of the study (161 participants), 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 participants had a concentration of methacholine causing a 20% decrease in forced expiratory volume of < 16 mg/mL (significant bronchial hyperresponsiveness) and positive skin reactions to *C tetragonoloba* (guar) gum. It was concluded that the prevalence of IgE sensitization to guar gum was between 5% (8 of 162 participants, as assessed by skin tests) and 8.3% (11 of 133 participants, 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 *C tetragonoloba* (guar) gum.[73] Two of the participants developed rhinitis after 2 years of exposure to fine *C tetragonoloba* (guar) gum (insulator in rubber cables) powder when opening cables in a power cable factory. The allergenicity of *C tetragonoloba* (guar) gum in these participants was confirmed using scratch chamber, nasal provocation, radioallergosorbent (RAST) tests, and observations of nasal eosinophilia. A third participant also developed allergic rhinitis after 2 years of exposure to another *C 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 participants (29, 30, and 32 years) after exposure to *C tetragonoloba* (guar) gum on the job.[74] An immediate skin reaction to *C tetragonoloba* (guar) gum was observed in skin prick tests, and all 3 had high levels of serum IgE antibodies to the gum. When the participants were exposed for short intervals (≤ 4 minutes) to *C tetragonoloba* (guar) gum powder, isolated immediate bronchospastic reactions were observed in 2 participants , and a dual reaction was observed in the remaining participant.

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 *C tetragonoloba* (guar) gum. A 10-mm wheal with pseudopods and surrounding flare was observed initially. After 4 hours, the reaction developed into an erythematous swelling (2 cm diameter) that remained for 24 hours.

A 52-year-old male participant experienced generalized urticaria and anaphylactic shock after consuming a meal substitute that contained *C tetragonoloba* (guar) gum.[76] Skin and radioallergosorbent (CAP system) tests on this gum as well as *C 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 C 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 *C tetragonoloba* (guar) gum. Severe contact urticaria and dyspnea were reported, and the

patient collapsed.[77] A 1-fold positive prick test reaction to *C 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 *C siliqua* gum were negative. Negative IgE assay results for *C tetragonoloba* (guar) gum and *C siliqua* gum were reported. A possible explanation for the discrepancy between prick test and IgE assay results for *C 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 *C tetragonoloba* (guar) gum.

A 48-year-old male complained of work-related rhinitis, irritated eyes, and asthma after exposure to *C siliqua* gum and *C tetragonoloba* (guar) gum on the job in a jam factory.[78] Skin prick tests on *C siliqua* gum and a blend of *C tetragonoloba* (guar) gum, *C 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 minutes) was performed, cough, rhinitis, and sneezing developed. Both *C tetragonoloba* (guar) gum and *C siliqua* gum were evaluated in the RAST, and the 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 *C siliqua* gum in saline (11 mm wheal), and the test concentration was not stated. Skin prick test results for *C siliqua* gum at concentrations of 5, 15, and 25 mg/mL induced 6, 8, and 9 wheals, respectively. Positive skin prick tests were also reported for raw *C siliqua* gum (14 mm wheal) and boiled *C siliqua* gum (9 mm wheal). Control skin prick test results were negative in 10 nonatopic participants. The positive test results and high titers of serum-specific IgE to *C siliqua* gum supported an IgE-mediated mechanism. Skin prick test results for *C 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 *C siliqua* gum and an 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 *C 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 *T 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 *T foenum-graecum* seed powder. These signs were followed by persistent coughing, wheezing, and fainting. Scratch testing with 10 μL of the legume extract (contained ∼ 22-25 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 *T 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 *C 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 pretreatment levels after a 3-week washout period. It was concluded that *C 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 *C 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 who received *C tetragonoloba* (guar) gum, when compared to patients who received a placebo (weighted mean difference −0.04 kg; 95% confidence interval [CI]: −2.2-2.1). 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 *C 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 *C tetragonoloba* (guar) gum in the diet for at least 16 weeks.[85] Each participant was able to consume 4 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 *C tetragonoloba* (guar) gum per day for prolonged periods is without serious consequences. Five participants ingested *C 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

C 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/d, respectively, during gestation. The animals were killed on gestation day 20. None of the females died during the study. The ingestion of *C 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% *C 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 *C tetragonoloba* (guar) gum in the diet had no effect on fetal development or sex distribution and was not teratogenic.

In another teratogenicity study on *C 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 *C 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/d), 26 mice (37 mg/kg/d), 25 mice (170 mg/kg/d), and 29 mice (800 mg/kg/d). A sham-treated control group was also included, and aspirin served as the positive control. Doses up to 170 mg/kg/d 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/d dose group, a significant number of maternal deaths (6 of 29) were 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 were noted. It was concluded that, under the conditions of this test, *C tetragonoloba* (guar) gum was not teratogenic in mice. The teratogenicity of *C 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 subsequently.

Four groups of 24 mated female rats (ages not stated) received *C tetragonoloba* (guar) gum (in corn oil) at daily oral doses of 9, 42, 200, and 900 mg/kg/d, respectively. Doses up to 900 mg/kg/d 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 *C tetragonoloba* (guar) gum (in corn oil): 22 hamsters (6 mg/kg/d),

22 hamsters (28 mg/kg/d), 25 hamsters (130 mg/kg/d), and 20 hamsters (600 mg/kg/d) on days 6 through 10 of gestation. Doses up to 600 mg/kg/d 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 and 10 females per group).[90] Two groups were fed chow diet containing 2% and 5% *C 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 premating body weight gain (F_0 females fed 2% *C siliqua* gum) and final body weight (F_0 females fed 5% *C siliqua* gum) were noted. Compared to controls, the following significant differences in organ weight ratios were reported for the F_{3b} group fed 5% *C 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 *C siliqua* gum did not cause significant treatment-related effects on reproductive indices or gross microscopic pathology.

The teratogenicity of *C 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 *C siliqua* gum (20 mice), 60 mg/kg (20 mice), 280 mg/kg (21 mice), 1300 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 cesarean 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 *C 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 *C 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 *C 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 cesarean 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 *C siliqua* gum was not teratogenic. In the experiment involving pregnant adult female, golden outbred hamsters, the following groups were used: 10 mg/kg *C 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 cesarean 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 *C siliqua* gum was not teratogenic in hamsters.[91]

The teratogenicity of *C siliqua* gum (in anhydrous corn oil) was evaluated using the following 6 groups of pregnant adult Dutch-belted female rabbits: 9 mg/kg *C 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 cesarean section on day 29. Except for the dosing period, doses administered, and day of cesarean 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 mucosa (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 *C siliqua* gum was not teratogenic in rabbits.[91]

Caesalpinia spinosa gum. A multigeneration reproduction study on *C 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 *C 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 *C spinosa* gum did not have an adverse effect on reproductive performance or development of progeny.

The teratogenicity and embryotoxicity of *C spinosa* gum were 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 cesarean section. None of the animals died, and there were no statistically significant differences in food consumption, body weight gain, general health, or behavior between dams that received control diet and those that received *C 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 *C spinosa* gum did not induce maternal toxicity, embryotoxicity, or teratogenicity. Based on the results from this study and the preceding study, the NOAEL was considered to be >50 000 ppm (5%) in the diet.[92]

Cassia gum. In a 2-generation reproductive toxicity study (OECD Test Guideline 416), semirefined cassia gum was administered to groups of 25 female Ico: OFA.SD Sprague-Dawley rats (6 weeks old) at dietary concentrations of 0, 5000, 20 000, or 50 000 mg/kg.[93] An additional group was fed a diet containing purified semirefined 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, nonsignificant 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 no-observed-effect level NOEL.

Groups of 12 pregnant female SD rats received oral doses of cassia gum (by gavage) at doses of 0, 250, 500, or 1000 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 1000 mg/kg body weight per day.

The developmental toxicity of semirefined 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 1000 mg/kg per day on gestation days 6 to 19 post-coitum, in accordance with OECD Test Guideline 414. Purified semirefined cassia gum (1000 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 postcoitum. There were no test substance-related effects on pregnancy incidence, implantations, postimplantation loss, or fetal defects at necropsy. In pregnant animals that received semirefined cassia gum or purified semirefined cassia gum at the 1000 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 toxico-logically relevant. A statistically significant increase in fetal weight after dosing with purified semirefined cassia gum was the only finding in offspring. There was no evidence of embry-otoxicity or teratogenicity in any of the treatment groups, and the NOAEL was 1000 mg/kg body weight per day.

In another developmental toxicity study, groups of 20 pregnant New Zealand white rabbits (14-17 weeks old) were dosed with semirefined cassia gum or purified semirefined cassia gum, following the procedure (same doses for each) in the preceding study.[95] The rabbits were dosed on days 6 to 27 postcoitum and were killed on day 28 postcoitum. The follow-ing animals died or were killed moribund during the study: 4 controls, 1 and 4 rabbits dosed with semirefined cassia gum (350 and 1000 mg/kg body weight, respectively), and 2 rabbits dosed with purified semirefined cassia gum (1000 mg/kg body weight). All deaths were attributed to improper gavaging and/or were incidental. A nonsignificant reduction in mean daily food consumption was observed in the group dosed with 1000 mg/kg semirefined cassia gum. A slight, nonsignificant reduction in mean fetal weight was also observed in this group and, possibly, was a secondary effect to the reduced feed con-sumption. These effects may be related to the viscous nature of cassia gum and were not considered to be of toxicological relevance. No treatment-related adverse effects were observed relative to pregnancy incidence, implantations, postimplanta-tion loss, or fetal defects upon necropsy. Cassia gum was neither teratogenic nor embryotoxic in rabbits, and an NOAEL of 1000 mg/kg body weight per day was reported.

In a 1-generation reproductive toxicity study (OECD Test Guideline 415), semirefined cassia gum was administered to 2 groups of cats (*Felis catus*) of the Ico: FecEur strain (10 males and 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 neo-natal deaths. In the absence of treatment-related hisotpatholo-gical alterations, the changes in ovarian weight were thought to have been of little biological relevance. Because of the unu-sually high mortality rate in the control group, the JECFA considered this study unsuitable for use in evaluating the repro-ductive toxicity of semirefined cassia gum.[9]

Dermal Study

Cyamopsis tetragonoloba (guar) gum. The teratogenicity of *C 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 nonocclusive dermal application (6 hours), to 3 groups at doses of 2, 10, and 50 mg/kg/d (dose volume = 2 mL/kg), respectively, on days 6 through 18 of gestation. Applications were made to dorsal skin (10×20 cm^2). Deionized water was administered to the control group according to the same procedure. Three mortal-ities were reported, and 3 rabbits either aborted or 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 postimplanta-tion loss, accompanied by a decrease in viable fetuses, was noted in the highest dose group (50 mg/kg/d). The increase in early resorptions observed in this group was found to be statis-tically significant ($P < 0.05$). A slight increase in mean post-implantation loss was noted in the 10-mg/kg/d dose group; however, uncertainty over the significance of this observation was expressed. Increased postimplantation loss was not observed in the 2-mg/kg/d dose group. No other abnormalities were observed in any of the cesarean section parameters. Anal-yses 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, C siliqua gum, and C spinosa gum. The carcinogenicity of *C tetragonoloba* (guar) gum, *C siliqua* gum, and *C 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 *C tetragonoloba* (guar) gum), male mice (50 000 ppm *C siliqua* gum), and male and female mice (50 000 ppm *C spinosa* gum). In all groups, mean daily feed consumption for dosed rats and mice was ≥79% of respective control values. A variety of nonneoplastic 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 *C tetragonoloba* (guar) gum (25 000 and 50 000 ppm). However, the combined incidence of female rats with pheochromocytoma or malignant pheochromocytoma of the adrenal gland was not significantly different from control values. Similarly, the incidence of pituitary adenomas in male rats fed *C tetragonoloba* (guar) gum and the incidence of alveolar/bronchiolar adenomas (in lung) in male mice fed *C 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 *C 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 *C siliqua* gum groups.

Additionally, the incidence of pituitary adenomas in female mice fed 25 000 ppm *C 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 *C 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 B6C3F₁ 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, *C tetragonoloba* (guar) gum, *C siliqua* gum, and *C spinosa* gum were not carcinogenic in F344 rats or B6C3F₁ mice.[98]

Cassia gum. Carcinogenicity data on cassia gum were not available for review by the JECFA 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 *C siliqua* gum and *C spinosa* gum, the Committee determined that a long-term toxicity and/or carcinogenicity study was not necessary for the safety evaluation of cassia gum.

Cocarcinogenicity

The effect of *C 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% *C 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 postinjection 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 *C tetragonoloba* (guar) gum + DMH had more tumors than those fed the basic diet; however, the difference was not statistically significant. It was concluded that *C tetragonoloba* (guar) gum did not significantly influence carcinogenesis in rats initiated with DMH.

Anticarcinogenicity

The effect of dietary supplementation with *C 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 subcutaneous injection of DMH for 8 weeks (initiation phase), and the animals were then subdivided into 2 groups. One group of

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 Salmonella typhimurium	Ames test	Negative [102]
	1% and 5% w/v	Strains TA 1530 and G 46 of S typhimurium	Host-mediated assay	Not genotoxic[56]
	2.5 mg/disk ± metabolic activation		Spore rec assay	Not genotoxic[103]
	Rats received up to 5000 mg/kg, and bone marrow cells obtained. WI-38 cells tested at concentrations up to 1000 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 5000 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 1000 μg/plate ± metabolic activation	Strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of S 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 1000 μg/plate ± metabolic activation	Strains TA 98, TA100, TA 1535, TA 1537, and TA 1538 of S typhimurium	Ames test	Not genotoxic[106]
Hydrolyzed guar	Up to 5000 μg/plate ± metabolic activation	Strains TA 100, TA 1535, TA 98, and TA 1537 of S 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 S typhimurium (plate test). Strain D4 of S cerevisiae (suspension test)	Ames test	Not genotoxic[107]
C 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 S typhimurium	Ames test	Not genotoxic[102]
	5% w/v	Strain TA 1530 of S typhimurium and strain D3 of S 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 5000 mg/kg, and bone marrow cells obtained. WI-38 cells tested at concentrations up to 1000 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]

Table 5. (continued)

Ingredient	Doses/concentrations	Strain/cell type	Assay	Results
	Rats received oral doses up to 5000 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 1000 μg/plate ± metabolic activation	Strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of *S 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 1000 μg/plate (semirefined gum) ± metabolic activation	Strains TA 98, TA 100, TA 1535, and TA 1537 of *S typhimurium*. Strain WP2uvrAm of *E 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]
Cassia gum	Up to 5000 μg/plate ± metabolic activation (semi-refined gum containing 8.6 mg total anthraquinones/kg)	Strains TA98, TA 100, TA 1535, and TA 1537 of *S typhimurium*. Strain WP2uvrA of *E coli*	Ames test	Not genotoxic[18]
	5 mg/plate ± metabolic activation (semirefined gum)	Strains TA 97, TA 98, TA 100, and TA 102 of *S typhimurium*	Ames test	Not genotoxic[54]
	Up to 10 000 μg/mL ± metabolic activation (semirefined 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 2500 mg/kg	Mouse bone marrow	Micronucleus test	Not genotoxic[54]
	KM mice received oral doses up to 2500 mg/kg (1 dose/day for 5 days)	KM mouse sperm	Sperm abnormality test	Not genotoxic[54]

30 rats was then maintained on a basal fiber-free diet supplemented with 10% *C 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% *C 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: *C tetragonoloba* (guar) gum, hydroxypropyl guar, C18-22 hydroxyalkyl hydroxypropyl guar, guar hydroxypropyltrimonium chloride, hydroxypropyl guar hydroxypropyltrimonium chloride, carboxymethyl hydroxypropyl guar, hydrolyzed guar, *C siliqua* gum, locust bean hydroxypropyltrimonium chloride, hydrolyzed *C siliqua* gum extract, *C spinosa* gum, *C spinosa* hydroxypropyltrimonium chloride, hydrolyzed *C spinosa* gum, *T foenum-graecum* hydroxypropyltrimonium chloride, cassia gum, and cassia

hydroxypropyltrimonium chloride. Because of the mannose/galactose chemical makeup of these legume polysaccharides, they are commonly called galactomannans.

Data reported to the FDA's VCRP in 2011 indicated the use of the following 9 ingredients in cosmetics: *C tetragonoloba* (guar) gum, hydroxypropyl guar, guar hydroxypropyltrimonium chloride, hydroxypropyl guar hydroxypropyltrimonium chloride, hydrolyzed guar, *C siliqua* gum, *C spinosa* gum, hydrolyzed *C 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 precipitating 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 *C tetragonoloba* (guar) gum include heavy metal impurities and fluoroacetate. In 2007, the impurities dioxin and PCP were detected in certain batches of *C tetragonoloba* (guar) gum originating from India. Anthraquinone impurities have been detected in cassia gum (where *C occidentalis* is a natural contaminant) and tannins, and trypsin inhibitors have been detected in *C 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 *C tetragonoloba* (guar) gum in a basal diet, the galactomannan was fermented quantitatively and approximately 1% of the mannose and 4% of the galactose were excreted in the feces. The feeding of rats with *C 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 *C 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 *C 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 *C siliqua* gum (LD50 = 5 g/kg). The LD50s for *C 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: *C tetragonoloba* (guar) gum (up to 27%), hydrolyzed guar (up to 5%), *C siliqua* gum (up to 30%), *C spinosa* gum (up to 5%), and cassia gum (up to 50 000 mg/kg dietary concentration). Significant reductions in liver weights (at 1%-15% in diet) and kidney weights (at 4%, 7.5%, and 15% in diet) in rats were noted after feeding with *C tetragonoloba* (guar) gum, and 7 of 10 rats died (possibly due to intestinal blockage) after feeding with *C 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 *C 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 1000 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, *C siliqua* gum, and cassia gum were minimally irritating when instilled (0.1 g) into the eyes of rabbits. In semiocclusive patch tests (0.5 g applied), *C siliqua* gum was minimally irritating and *C tetragonoloba* (guar) gum, *C spinosa* gum, and cassia gum were nonirritating 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 repeated insult patch test RIPT. The allergenicity of *C tetragonoloba* (guar) gum and *C siliqua* gum following inhalation exposure and ingestion has been demonstrated in various case reports. Also, no effects were apparent after ingestion of *C tetragonoloba* (guar) gum in another case report. The allergenicity of *T 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 *C 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/d), rats (doses up to 11 800 mg/kg/d), or hamsters (doses up to 600 mg/kg/d) 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 1300 mg/kg/d), mice (doses up to 1300 mg/kg/d), hamsters (doses up to 1000 mg/kg/d), and rabbits (doses up to 910 mg/kg/d). However, in one of the studies, significant maternal toxicity was induced by *C siliqua* gum (at 910 mg/kg/d) in rabbits of the highest dose group. *Caesalpinia spinosa* gum (up to 50 000 ppm/d) 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 6120 mg/kg/d), rabbits (doses up to 1000 mg/kg/d), or cats

(doses up to 2950 mg/kg/d) when dosed orally. However, a statistically significant reduction in maternal body weight gain in rats was observed in the highest dose group (1000 mg/kg/d) 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 1000 mg/kg/d), nonsignificant 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 JECFA, the usefulness of the study involving cats is questionable, given the high mortality rate in the control group.

In a dermal teratogenicity study on *C tetragonoloba* (guar) gum involving rabbits (doses up to 50 mg/kg/d), 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/d).

In bacterial and mammalian assays, *C tetragonoloba* (guar) gum, *C siliqua* gum, *C 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, *C siliqua* gum, and *C spinosa* gum (concentrations up to 50 000 ppm/d) were not carcinogenic in a dietary carcinogenicity study involving F344 rats and B6C3F1 mice.

Rats fed *C 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 *C tetragonoloba* (guar) gum has been demonstrated using rats.

Discussion

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, and 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 (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 *C 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 Panel expressed concern regarding pesticide residues and heavy metals that may be present. For example, dioxin and PCP impurities have been detected in certain batches of *C 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% to 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 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*; and
- 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.

Author Contribution

W. Johnson contributed to conception and design, acquisition, analysis, and interpretation and drafted the manuscript. B. Heldreth contributed to conception and design, acquisition, analysis, and interpretation, drafted the manuscript, and critically revised manuscript. L. Gill, W. Bergfeld, R. Hill, C. Klaassen, J. Marks, R. Shank, T. Slaga and P. Snyder contributed to conception and design, analysis, and interpretation and critically revised the manuscript. D. Belsito contributed to conception and design, analysis, and interpretation and critically revised the manuscript. D. Liebler contributed to conception and design, analysis, and interpretation and critically revised manuscript. Former CIR Director F. Alan Anderson contributed to conception and design, analysis, and interpretation and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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