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Final Report on the Safety Assessment of Tragacanth Gum

Tragacanth Gum is a complex polysaccharide composed of D-galacturonic acid, D-galactose, D-xylose, and L-arabinose. It is used in cosmetics at concentrations up to 10%. In acute toxicity studies, Tragacanth Gum was practically nontoxic when administered orally to mice, rats, hamsters, and rabbits. In subchronic studies, a diet containing 2% Tragacanth Gum produced a significant reduction in growth in chickens. However, no significant reductions in average body weights were noted in quail, rats, or insect larvae. In a chronic study, six baboons receiving Tragacanth Gum had no significant adverse effects. Cosmetic products containing up to 1.5% Tragacanth Gum were slightly to mildly irritating when applied topically to rabbits and nonirritating to mildly irritating to rabbit eyes. No significant toxic or teratogenic effects were produced by oral administration of Tragacanth Gum to pregnant mice. Tragacanth Gum was essentially nonmutagenic in a variety of mutagenic assays. Tragacanth Gum has been used as the solvent control in a carcinogenicity study. The number and type of tumors were not different from those seen in the untreated control mice. Cosmetic products containing up to 1.5% Tragacanth Gum were essentially nonirritating and nonsensitizing when evaluated in humans. Tragacanth Gum at a concentration of 10% did not induce a contact dermal phototoxic response when tested in humans. It is concluded that Tragacanth Gum is safe as a cosmetic ingredient in the present practices of use and concentration.

INTRODUCTION

This report reviews the most recently published scientific literature on Tragacanth Gum. The literature dating from 1920 to 1972 has been previously reviewed in a GRAS report and evaluation and is only briefly summarized here.[1,2] Pertinent articles not covered in the GRAS report as well as unpublished data from the cosmetic industry are included.

BACKGROUND AND PRODUCTION

Tragacanth Gum is the dried exudate from several *Astragalus* species, principally *Astragalus gummifer* (family Leguminosae). The plants are small, thorny

scrubs growing wild in the semidesert, mountainous regions of Iran, Syria, Turkey, and other areas of Asia Minor. Iran is the largest producer of the gum.[3,4]

The gum is collected after a series of incisions have been made in the tap root and the bark of the branches. The plants are perennials, with a lifespan of about 5 years, and each plant can be tapped in its first year and then in alternate years but will not produce good gum in 2 successive years. The best gum is obtained from the tap roots of the smaller bushes, generally 3–12 inches in height, whereas the branches of the larger bushes, 3–6 feet in height, yield inferior grades of gum.[3,4]

Tragacanth Gum formation is believed to be a process of cell degeneration or gummosis, in which the cell walls of the pith and medullary rays are slowly transformed into gum. An incision in the branch of a living tragacanth plant has been noted to result in the immediate exudation of soft, solid tragacanth. The gum is assumed to be preformed in the plant, and by the absorption of water in the cells, considerable internal pressure is produced after an injury, resulting in rapid exudation. In contrast, the other water-soluble gums exude much more slowly.[3]

The exuded gum dries in the form of ribbons or flakes, which become horny, translucent to opaque, and white to yellow-brown in color. The ribbons dry in a day or two, whereas the flakes sometimes require 2–3 weeks. A single plant can yield about 3 g of ribbons and up to 20 g of flakes. Ribbons are long, flat, flexible, and curled, usually 2–4 inches in length, and are considered superior in quality to the flakes. The name "tragacanth" is derived from the Greek words *tragos* (goat) and *akantha* (horn) and is believed to refer to the ribbon form of the gum. The flakes are usually oval, thick, brittle, and 0.5–2 inches in diameter. Ribbons can be collected from May to October; flakes are gathered from July to October. Climatic conditions greatly influence the yield of gum during any one season.[3–7]

Collections of the gum are first brought to local trading centers, after which they are transported to wholesale markets, usually in Teheran, Hamadan, and Isfahan. At these locations, the gum is sorted, graded, packed, and shipped. The final processor of the gum further grades, cleans, mills, and blends the gum, selling it in the form of ribbons, flakes, granules, or powder.[3,4]

CHEMICAL AND PHYSICAL PROPERTIES

Tragacanth Gum is a complex polysaccharide composed of D-galacturonic acid, D-galactose, D-xylose, and L-arabinose, with associated calcium, magnesium, and potassium cations. The molecular weight has been variously reported as 310,000 and 840,000. Tragacanth Gum is considered to have two primary constituents: bassorin and tragacanthin. Bassorin comprises 60–70% of the gum and is insoluble in water but swells to form a gel. Tragacanthin comprises 30–40% of the gum and is soluble in water. Bassorin is considered a complex structure of polymethoxylated acids yielding tragacanthin on demethoxylation. Tragacanthin is composed of a ring containing three molecules of glucuronic acid and one molecule of arabinose, with a side chain of two molecules of arabinose. Small amounts of cellulose, protein, and starch are also present in Tragacanth Gum.[3,4,8–10]

Tragacanth Gum is odorless and has a dull, mucilaginous taste. It is white to yellow-brown and has a horny texture. The powdered form of the gum is white to yellow-white. The gum is soluble in alkaline solutions and aqueous hydrogen peroxide solutions, although insoluble in alcohol and other organic solvents.[4,6,9-12]

Aqueous solutions of Tragacanth Gum are extremely viscous and are regarded as the most highly viscous solutions of all the plant gums. Viscosity is used as a measure of the gum's quality and uniformity. A 1% solution of a high-grade Tragacanth Gum has a viscosity of approximately 3400 cps and a pH of 5.1–5.9. Maximum viscosity is attained after 24 h at room temperature or after heating for 8 h at 40°C or 2 h at 50°C. Maximum viscosity has been reported to occur at pH 8 and pH 5, with maximum stability at pH 5. Tragacanth Gum solutions are not thixotropic, are heat stable, and are quite acid resistant, being reasonably stable to pH 2. Thick, gel-like pastes are formed at high concentrations of Tragacanth Gum (2–4%).[4,5,9,10,12-14] Table 1 presents the physicochemical properties of Tragacanth Gum.

Various factors affect the viscosity of the Tragacanth Gum solutions. The addition of acid, alkali, and sodium chloride reduced viscosity,[3] whereas the addition of polyhydroxy compounds, such as glycerol, sorbitol, and polyethylene glycol (PEG), in different concentrations increased viscosity.[15] The latter effect was attributed to associations or agglomerates between polymer molecules and not to chemical interaction. The addition of propylene glycol and PEG-200 and PEG-400 to the tragacanth solutions also caused the normally pseudoplastic gum to become thixotropic. Nonionic surfactants added in concentrations ranging from 5 to 20% increased the static and dynamic viscosities of 2–3% tragacanth solutions. Dobos[16] found that the addition of ethanol decreased the viscosity of a 2.5% Tragacanth Gum solution, the extent of the decrease being determined by the concentration of ethanol and temperature. He also reported that the viscosity-decreasing effect of ethanol could be counteracted by the addition of 1.5% colloidal silica.

Solutions or gels of Tragacanth Gum are very susceptible to microbial degradation. The source and collection process of Tragacanth Gum also naturally lead to contamination. In a study on fungal contaminants in pharmaceutical raw materials, such plant materials as Tragacanth Gum had the highest colony counts (mostly species of *Aspergillus: A. fumigatus, A. niger, A. versicolor, A. terreus,* and *A. flavus*).[17]

Tragacanth Gum solutions at a pH below 4 may be preserved with benzoic acid, sorbic acid, or sodium benzoate at concentrations of 0.1–0.15%.[9] However, Schwartz et al.[14] reported that the low pH of solutions preserved with benzoic acid results in rapid degeneration of the gum. Methylparaben and propylparaben in 0.2 and 0.05% concentrations, respectively, have been effective preservatives at pH 4 and above. Glycerol and propylene glycol may also be used.[5,9]

Jacobs and Simes[18] studied the effects of gamma-irradiation on the microbial contamination and rheology of Tragacanth Gum solutions. Radiation doses of 0.1–5.0 mrad rendered all gum samples free of contamination. However, a marked initial decrease in viscosity was noted with increasing radiation dosage. The minimal radiation dose of 0.1 mrad produced about a 7% decrease in viscosity.[18]

TABLE 1. Physicochemical Properties of Tragacanth Gum

Property	*Value*	*Reference*
Physical appearance		
Ribbons	Long, flat, flexible and curled, horny, translucent to opaque, white to yellowish-brown, 2–4 inches in length	4 3
Flakes	Oval, thick, brittle, horny, translucent to opaque, white to yellowish-brown, 0.5–2 inches in diameter	4 3
Powdered	Odorless, white to yellowish powder, with dull, mucilaginous taste	6, 11 13
Molecular weight	840,000	8, 10
	310,000	4
pH		
4% solution	5.1–5.9	1
1% solution	5.1–5.9	5, 9
0.4% gel	5.3–5.6	25
0.0004% solution	5.3–5.4	25
Solubility		
Water	Soluble and insoluble fractions; swells to a gel	5, 11 4, 6
Alcohol and other organic solvents	Insoluble	9, 12
Alkaline solutions	Soluble	10
Aqueous hydrogen peroxide solutions	Soluble	10
Viscosity		
1% solution of high-grade Tragacanth Gum	3400 cps; >250 cps; 200–500 cps	1, 5, 9, 10
Superior quality Tragacanth Gum (flow time)	>1000 seconds	20
Inferior quality Tragacanth Gum (flow time)	<1 second	20
Mean particle size	5.4 to 6.2 μm	25
Moisture	10–12%	7, 9, 10, 25
Arsenic	0.0003%	11
Lead	0.001%	11
Heavy metals	0.004%	11
Acid-insoluble ash	<0.5%	9
Ash	3%	7, 10
Cellulose	4%	7
Starch	3%	7

Tragacanth Gum is compatible with a wide range of formulations. It is compatible with other polysaccharides, proteins, carbohydrates, some waxes, emulsifiers, detergents, and electrolytes. Tragacanth Gum is incompatible with bismuth salts, although the resulting gel formation reportedly can be avoided by incorporating sodium acid phosphate.[5,9,11,12] Tragacanth Gum is stable under the normal conditions of cosmetic use.[10]

Various analytical methods may be used to identify Tragacanth Gum qualitatively. Powdered tragacanth appears as angular fragments when examined microscopically.[3,6] Tragacanth Gum solutions can be identified by numerous pre-

cipitation reactions (Table 2). Infrared (IR) spectroscopy, thin-layer chromatography (TLC), and gas chromatography have also been used for identification purposes.[19-22] A quantitative method of analysis has been described using methanolysis and capillary column gas chromatography.[23] Pechanek et al.[24] developed an electrophoretic method for qualitative and quantitative analysis based on migration behavior, staining ability, and characteristic shape of the electrophoretic zone. Stahl and Tugrul[20] have additionally described a method for the determination of inorganic constituents in Tragacanth Gum.

USE

Cosmetic Use

Tragacanth Gum is used in cosmetics as a fixative, suspending and thickening agent, emulsifier, film former, and viscosity builder.[10,26-28] Data submitted to the Food and Drug Administration (FDA) by firms participating in the voluntary cosmetic registration program indicated that, as of 1981, Tragacanth Gum was used in 29 of the registered formulations. These included eye and facial makeups, coloring and noncoloring hair preparations, oral hygiene products, shaving and skin care preparations. The concentrations of use were within the reported concentration ranges up to 10%. However, Tragacanth Gum was most frequently used (52% of the uses) at concentrations ranging from >0.1 to 1%[29] (Table 3). FDA recently confirmed that as of June 1984, Tragacanth Gum was incorporated in 28 formulations.[30]

The FDA cosmetic product formulation data are compiled through voluntary filing of such data in accordance with Title 21 part 720.4 (d)(1) of the Code of the

TABLE 2. Precipitation Reactions for the Identification of Tragacanth Gum Solutions

Reagent	*Precipitate*	*Reference*
Acetone	Stringy, gelatinous precipitate	3
Alcohol	Coagulated precipitant, long, stringy, adherent	1, 3
Aqueous ferric chloride (10% solution)	Deep yellow, stringy precipitant on heating	1, 13
Basic lead acetate (AOAC)	Voluminous precipitant, gels	1, 3
Borax (4% solution)	Negative	3
Cetalkonium chloride	Precipitate	20
Copper (II) acetate	Precipitate	20
Iodine solution	Blue	3, 7, 32
Millon's reagent	Voluminous, flocculent, translucent precipitate	1, 3
Neutral ferric chloride (5% solution)	Gelatinizes	3
Neutral lead acetate (20%)	Voluminous flocculent precipitate, gels	1, 3
Potassium hydroxide (10% solution)	Bright yellow, stringy precipitate	1, 3
Schiff's reagent	Negative	3
Schweitzer's reagent	Stringy precipitate on heating	1, 3, 13
Sulfuric acid (concentrated)	Stringy precipitate on heating	1, 3
Tannic acid (10% solution)	Negative	3

Federal Regulations (1979) (Table 3). Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

The formulation data presented in Table 3 indicate that cosmetic products containing Tragacanth Gum may contact all external body surfaces and hair, as well as ocular and oral mucosae. These products may be used daily or occasionally over a period of up to several years. The frequency and length of application could result in continuous exposure.

Tragacanth Gum is approved for use in cosmetics in Japan and must be listed on the product label.[31]

TABLE 3. Product Formulation Data for Tragacanth Gum[29]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*			
			>5–10	*>1–5*	*>0.1–1*	*≤0.1*
Eye shadow	2582	3	–	–	–	3
Tonics, dressings, and other hair grooming aids	290	1	–	–	1	–
Hair bleaches	111	2	–	2	–	–
Blushers (all types)	819	2	–	–	2	–
Face powders	555	6	–	–	2	4
Makeup foundations	740	1	–	–	1	–
Rouges	211	1	–	–	1	–
Dentifrices (aerosol, liquid, pastes, and powders)	42	2	–	1	1	–
Aftershave lotions	282	1	–	–	1	–
Preshave lotions (all types)	29	1	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	1	–	–	1	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	2	–	–	2	–
Moisturizing skin care preparations	747	1	–	–	1	–
Paste masks (mud packs)	171	5	2	2	1	–
1981 TOTALS		29	2	5	15	7

Noncosmetic

Tragacanth Gum is one of the oldest pharmaceutical ingredients known, being described by Theophrastus several centuries before the Christian era. It is used extensively as an emulsifier, suspending agent, adhesive, lubricant, demulcent, and tablet binder.[3,5,7,12,13,33,34] Tragacanth Gum is classified as an inactive ingredient in marketed prescription products[35] and as an inactive ingredient or pharmaceutical necessity in OTC (Over-The-Counter) vaginal drug products.[36] Tragacanth mucilage was considered ineffective in OTC preparations for use on the foot.[37]

Tragacanth Gum is a GRAS (Generally Recognized As Safe) direct food substance.[38] Its major uses are as a stabilizer in low pH salad dressings and ice cream and as a thickener and binder in confectionaries and bakery products.[4,5,7] The maximum usage concentrations of Tragacanth Gum permitted in foods are as follows[38]:

Baked goods and baking mixes, meat products, processed fruits, and fruit juices	0.2%
Condiments and relishes	0.7%
Gravies and sauces	0.8%
Fats and oils	1.3%
All others	0.1%

Tragacanth Gum is additionally used as an emulsifier, suspending agent, and adhesive in the textile and cigar industries. The gum has been incorporated in insecticide formulations, furniture, floor, leather, and auto polishes.[3,7,13,33] Tragacanth Gum has also been used in poultices, denture adhesives, and in a quantitative fluorescent antibody assay of polioviruses.[39-41]

GENERAL BIOLOGY

Biochemical Effects

Bachman et al.[42] studied the effects of repeated oral administration of Tragacanth Gum on a rat hepatic and myocardial cell mitochondria and mixed function oxidases of hepatic cell endoplasmic reticulum, as measured by 2- and 4-biphenyl hydroxylation. Tragacanth Gum was administered in distilled water twice daily to female rats at doses of 10, 20, and 40 mg/kg, 5 days per week for 4 weeks. Tragacanth Gum caused severe damage to myocardial mitochondria in the first week of the study, resulting in 20–40% uncoupling of oxidative phosphorylation at the lowest concentration of administration and 100% uncoupling at the two higher concentrations. However, heart mitochondrial function returned to normal about day 19 despite continued administration of Tragacanth Gum. Tragacanth Gum had a cumulative effect after 30 doses on the hepatic cell mitochrondria, resulting in a 30–40% reduction in oxidative phosphorylation; this effect did not have a clear dose-dependency. Tragacanth Gum did not have any adverse effects on the hepatic cell mixed function oxidases at the two lower

doses, although a partial (20%) inhibition was noted after 30 doses of the high concentration.

In response to the preceding study, Anderson et al.[43] examined the ultrastructure of rat hearts and livers with transmission electron microscopy after supplementation of the diet with 0, 0.5, 1.5, 2.5, and 3.5% (w/w) Tragacanth Gum for 91 days or 0 and 1% Tragacanth Gum for 5 days. No abnormalities were detected in the organelles of the hearts and livers from any of the test animals. No pathological changes were observed; all tissues appeared normal. Tragacanth Gum did not induce the cytochrome P-450 hepatic mixed function oxidases.

Tragacanth Gum has variously altered the bactericidal activities of preservatives and antibiotics. Tragacanth Gum significantly enhanced the antibacterial action of benzyl alcohol, whereas it reduced that of methylparaben, phenylmercuric nitrate, phenylmercuric acetate, phenol, merthiolate, benzalkonium chloride, aminosidin sulfate, neomycin, penicillin, streptomycin sulfate, and tetracycline hydrochloride. One percent Tragacanth Gum did not alter the activities of chlorbutanol and methyl-p-hydroxybenzoate, whereas 3% Tragacanth Gum had a strong neutralizing effect on these preservatives. One percent Tragacanth Gum did not alter the activities of chlorhexidine diacetate.[44-48]

Cellular Effects

Tragacanth Gum was suspended in dimethyl sulfoxide by agitation and added to test tubes containing WI-38 human embryonic lung cells in the logarithmic phase of growth. Cells were then observed for cytopathic effects and the presence of mitoses. Cytopathic effects were observed at Tragacanth Gum concentrations of 750 and 1000 μg/ml, although none were observed at concentrations of 500 μg/ml or less. Mitoses were unaffected.[49]

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

The accute oral LD_{50}s of Tragacanth Gum were determined in mice, rats, hamsters, and rabbits. In each test, Tragacanth Gum was administered by gavage as a 25% suspension in corn oil to five groups of 10 animals each (5 males and 5 females). Animals were observed for 14 days. LD_{50}s were 10.33, 10.20, 8.80, and 7.18 g/kg body weight in the mouse, rat, hamster, and rabbit, respectively. Acute signs of toxicity in each species were similar and included ataxia, increased urination, soft stools, anorexia, muscle spasms, prostration, and death[50-53] (Table 4).

TABLE 4. Acute Oral Toxicity

Ingredient	*Animal*	*LD_{50} value*	*Comments*	*Reference*
Tragacanth Gum—25% suspension in corn oil	Mice (25 males and 25 females)	10.33 g/kg	Practically nontoxic	50
	Rats (25 males and 25 females)	10.20 g/kg	Practically nontoxic	51
	Hamsters (25 males and 25 females)	8.80 g/kg	Practically nontoxic	52
	Rabbits (25 males and 25 females)	7.18 g/kg	Practically nontoxic	53

Subchronic Toxicity

Oral

Vohra et al.[54] studied the oral toxicity of Tragacanth Gum in chickens, Japanese quail, rats, and insect larvae. One of two diets, each containing 2% Tragacanth Gum, was fed to seven chickens for 24 days, 10 quail for 35 days, 10 quail for 37 days, 10 rats for 36 days, and 30 larvae for 14 days. The average body weight of the chickens fed the diet containing 2% Tragacanth Gum was significantly reduced compared to the control group fed only a basal diet. No significant reductions were noted in the average body weights of the quail, rats, or larvae.

Chronic Toxicity

Oral

Tragacanth Gum has been used as the vehicle for an oral suspension of 2-benzoyl-5-(2′-carboxyethyl)thiophene administered over a period of 26 weeks to baboons. Tragacanth Gum was administered orally (dose not stated) to three male and three female baboons as the control group. Observations were recorded daily, dry food intake twice weekly, body weight weekly, and water intake monthly. Prior to dosing and at 4, 8, 16, and 24 weeks, the eyes of the animals were examined by indirect opthalmoscopy, and blood samples were taken for the determination of hematological values. Urinalysis was conducted at monthly intervals, and examination for fecal occult blood was made on 3 consecutive days each week. The animals were killed at 26 weeks and subjected to necropsy, organ weight analysis, and microscopic evaluation of selected tissues. One male baboon had a cataract, a depression in the mucosa of the body of the stomach (seen in all dose groups), and was positive for fecal blood during weeks 2 and 3. No other adverse effects were noted.[55]

Irritation

Dermal

Two hair gels, each containing 1.5% Tragacanth Gum, were evaluated for dermal irritation in New Zealand white rabbits. A 0.5 ml dose of each gel was evenly spread over the clipped back of each animal. This procedure was repeated once daily for 4 days. Reactions were scored daily, and body weights were recorded at the initiation and termination of the study (at day 7). Primary Irritation Indices (PIIs) of 0.2 and 1.7 (max = 8) were determined from the 24 and 72 h readings. The gels were considered slightly and mildly irritating, respectively, by the Draize method of classification[56,57] (Table 5).

Two hair tonics, each containing 0.61% Tragacanth Gum, were evaluated for primary skin irritation. A 0.5 ml sample of each tonic was applied by occlusive patch to six female rabbits. Patches remained in place for 24 h; responses were scored for erythema and edema 24 and 72 h later in the first test and 2 and 24 h later in the second test. The hair tonics had PIIs of 1.66 and 1.75 (max = 8) and were considered mildly irritating by the Draize standard of classification.[58,59]

Ocular

Two hair gels, each containing 1.5% Tragacanth Gum, were evaluated for ocular irritation in New Zealand white rabbits. A 0.1 ml dose of each gel was instilled into one eye of each rabbit; the other eye served as the untreated control. Eye examination results were scored at 1, 24, 48, and 72 h and 7 days. One gel produced slight corneal dullness and iritis in one rabbit, which cleared by 24 h. Very slight conjunctivitis occurred by 1 h in all rabbits and cleared by day 7.[56] The other gel produced very slight conjunctivitis, which cleared by 48 h. No cor-

TABLE 5. Dermal Irritation

Ingredient	*Test method*	*Animal*	*Results*	*Reference*
Tragacanth Gum				
1.5% in a hair gel	Daily application of 0.5 ml for 4 days	New Zealand white rabbits (number not given)	PII[a] = 0.2; slightly irritating	56
1.5% in a hair gel	Daily application of 0.5 ml for 4 days	New Zealand white rabbits (number not given)	PII = 1.7; mildly irritating	57
0.61% in a hair tonic	Single occlusive patch containing 0.5 ml	Rabbits–6	PII = 1.66; mildly irritating	58
0.61% in a hair tonic	Single occlusive patch containing 0.5 ml	Rabbits–6	PII = 1.75; mildly irritating	59

[a]PII, Primary Irritation Index (max = 8).

neal or iridal irritation was evident.[57] (Ocular irritation test results are reported in Table 6.)

A styling gel containing 1.25% Tragacanth Gum was tested for ocular irritation in three New Zealand white rabbits. A 0.1 ml sample of the gel was instilled into the left eye of each rabbit; the right eye served as an untreated control. Eye examination results were scored according to Draize at 1 h and daily for up to 7 days. Two rabbits had a score of 4 (max = 110) at 1 h and 0 by day 1. The third rabbit had a score of 4 at 1 h and day 1, with no irritation detectable by day 2. The styling gel was considered minimally irritating by the Draize classification of eye irritation.[60]

Four hair tonics, each containing 0.6% Tragacanth Gum, were evaluated for ocular irritation in groups of three rabbits. A 0.1 ml sample of tonic was instilled into the left eye of each rabbit; the right eye served as an untreated control. Eye examination results were scored according to Draize (max = 110) at 1, 2, 3, 4, and 7 days. For two tonics, the scores were 0, and the preparations were classified as nonirritating.[61,62] With the third tonic, the score was 1 on day 1 and 0 on day 2; it was classified as practically nonirritating.[63] Animals treated with the fourth tonic had scores of 2, 2, 1, 1, and 0 on days 1, 2, 3, 4, and 7, respectively; the tonic was classified as mildly irritating.[64]

Teratogenicity

A series of studies was conducted to determine the teratogenic effects of Tragacanth Gum in mice, rats, hamsters, and rabbits.[65] Tragacanth Gum, suspended in anhydrous corn oil, was administered by oral intubation to pregnant animals of each species. Positive controls were treated with aspirin or 6-amino nicotinamide. Sham-treated controls also were used in each study. Dosage groups varied from 22 to 30 mice, 22 to 27 rats, 21 to 22 hamsters, and 15 rabbits. Daily doses of Tragacanth Gum were administered as follows:

Mice	12, 56, 210, or 1200 mg/kg; days 6–15 of gestation
Rats	12, 56, 210, or 1200 mg/kg; days 6–15 of gestation
Hamsters	9, 42, 185, or 900 mg/kg; days 6–10 of gestation
Rabbits	7, 33, 150, or 700 mg/kg; days 6–18 of gestation

No adverse effects were noted in mice and hamsters on nidation, maternal survival, fetal survival, or fetal soft and skeletal tissues. Similarly, rats and rabbits administered the lower doses of Tragacanth Gum had no adverse effects. However, significant maternal toxicity was noted in the rats and rabbits receiving the highest doses of Tragacanth Gum. Mortality was 5/20 rats dosed with 1200 mg/kg Tragacanth Gum and 6/15 and 9/15 rabbits dosed at 150 and 700 mg/kg Tragacanth Gum, respectively. Death was preceded by severe diarrhea, increased urination, and anorexia for 48–72 h. No gross lesions were noted at necropsy except for marked hemorrhages in the mucosa of the small intestine. The pregnant rats and rabbits surviving the high doses carried their young to full term; all dams and offspring appeared normal.[65]

Biagi[66] tested various suspension media to assess their possible influences on the teratogenic effect of thalidomide suspensions on chick embryos. Traga-

TABLE 6. Ocular Irritation

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
Tragacanth Gum				
1.5% in hair gel	Single instillation of 0.1 ml, unrinsed	3	Slight corneal dullness and iritis in one rabbit, cleared by 24 h; very slight conjunctivitis in all rabbits, cleared by day 7	56
1.5% in hair gel	Single instillation of 0.1 ml, unrinsed	6	Very slight conjunctivitis, cleared by 48 h; no corneal or iridal irritation	57
1.25% in a styling gel	Draize: instillation of 0.1 ml, unrinsed	3	Minimally irritating	60
0.61% in a hair tonic	Draize: instillation of 0.1 ml, unrinsed	3	Nonirritating	61
0.61% in a hair tonic	Draize: instillation of 0.1 ml, unrinsed	3	Nonirritating	62
0.61% in a hair tonic	Draize: instillation of 0.1 ml, unrinsed	3	Practically nonirritating	63
0.61% in a hair tonic	Draize: instillation of 0.1 ml, unrinsed	3	Mildly irritating	64

canth Gum, introduced into the chick embryos, was highly embryotoxic; however, no teratogenic effects were noted.

IMMUNOGENICITY

Strobel et al.[67] investigated the immunogenicity of natural gum exudates using an in vivo technique to assess delayed hypersensitivity reactions in mice. Tragacanth Gum was dissolved in 0.15 M sodium chloride at a concentration of 4 mg/ml, sterilized, and then emulsified in an equal volume of complete Freund's adjuvant. A group of six to eight female CBA mice were immunized by injection of 0.1 mg Tragacanth Gum (0.05 ml) into the left hind footpad. A control group received injections of complete Freund's adjuvant in saline. Delayed-type hypersensitivity was measured by a skin test 21 days after the primary immunization. The mice received similar intradermal injections of Tragacanth Gum (under ether anesthesia) into the plantar side of the right footpad. Footpad thickness was measured in triplicate with a microcaliper just before and 24 h after the injections. As controls, a group of unimmunized animals received an antigen injection and a group of immunized animals received a saline injection. One week later, the mice were killed and bled, and the serum was analyzed by several conventional immunochemical techniques.

Significant positive results were obtained with Tragacanth Gum and the

other gums tested. The footpad swelling indicated an antigen-specific hypersensitivity reaction. However, no antibodies were detected in the sera of mice immunized with any of the gums. The investigators suggested that this failure may be related to the large molecular sizes, complex structures, and extensive intermolecular associations in solutions of gums.[67]

MUTAGENICITY

Tragacanth Gum (in acetone) was evaluated for genetic activity in a series of in vitro microbial assays both with and without metabolic activation. Tragacanth Gum at concentrations ranging from 1.25 to 5.0% was nonmutagenic in suspension tests with *Saccharomyces cerevisiae* strain D4. Tragacanth Gum at concentrations ranging from 1.1 to 4.4% also was nonmutagenic in plate and suspension tests with *Salmonella typhimurium* strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100. The highest dose tested for both the yeast and the bacteria was equivalent to the 50% survival concentration as determined by survival curves.[68]

Tragacanth Gum was negative when tested (without metabolic activation) for chromosomal aberrations in WI-38 human embryonic lung cells and for base-pair substitution in *Salmonella typhimurium* strains G-46 and TA-1530. Questionable results were obtained when Tragacanth Gum was tested for mitotic recombinations in *Saccharomyces cerevisiae*.[69]

Tragacanth Gum also was evaluated for mutagenicity in three mammalian test systems: a host-mediated assay (in vitro and in vivo), cytogenetics studies (in vitro and in vivo), and a dominant lethal assay. Flow laboratories ICR male mice were used in the in vivo cytogenetic study, and Sprague-Dawley CD strain rats were used in the in vivo host-mediated and dominant lethal assays. Each of the in vivo and dominant lethal assays was conducted with acute (single dose) and subacute oral exposures (dosed once daily for 5 consecutive days). Three doses were used for these in vivo and dominant lethal assays: 30.0, 2500.0, and 5000.0 mg/kg (LD_{50}). The in vitro host-mediated assay was conducted with doses at the 50% survival concentration or above. The in vitro cytogenetic studies were conducted with doses of 5, 50, and 500 μg/ml. Saline or water was used as the negative control, and either triethylene melamine, ethyl methane sulfonate, or dimethylnitrosamine served as the positive control. Tragacanth Gum was nonmutagenic in *Salmonella typhimurium* TA-1530 and G-46 at the doses tested in the host-mediated assay. However, *Saccharomyces cerevisiae* D3 had increased recombinant frequencies in the subacute studies only. Ratios of the mean number of recombinants in a test group compared to the number in the negative control group ranged from 1.50 to 2.09 in the acute studies and from 4.39 to 6.36 in the subacute studies. These latter figures were considered significant when the population size difference was taken into consideration (a mean of 4.0×10^4/animal in the negative control versus means of 1.0×10^4, 2.3×10^4, and 2.6×10^4/animal for the low, intermediate, and high subacute doses, respectively). In the in vivo cytogenetic study, Tragacanth Gum administered orally produced no detectable significant aberration of the bone marrow metaphase chromosomes of rats. Similarly, in the in vitro study, Tragacanth Gum pro-

duced no significant aberration in the anaphase chromosomes of human tissue culture cells. Tragacanth Gum was nonmutagenic in rats when tested by the dominant lethal assay.[49]

CARCINOGENICITY

A study was conducted to determine the carcinogenicity of constituents of spermicidal contraceptive preparations in the genital tract of female mice. Tragacanth Gum was the solvent of choice. As solvent controls, 30 female mice (BALB/c) were administered intravaginally 0.1 ml Tragacanth Gum twice weekly for a total of 100 instillations. Tissues were examined microscopically. None had tumors of the genital tract and the number of type of tumors elsewhere were no different than those seen in the untreated control mice.[70]

CLINICAL ASSESSMENT OF SAFETY

Oral Toxicity

Eastwood et al.[71] studied the effects of dietary Tragacanth Gum in man. Five male volunteers participated in the study, which consisted of a 7-day control period followed by a 21-day treatment period. To simulate the mode of ingestion of Tragacanth Gum present in foods, each volunteer consumed three portions of 3.3 g Tragacanth Gum per day. Each portion of Tragacanth Gum was hydrated for 24 h prior to consumption, resulting in a thick fluid gel. This daily intake was judged to be very high in relation to the estimated 2 g Tragacanth Gum per person per year ingested as a food additive (in the United Kingdom). The Tragacanth Gum was well tolerated, and no adverse effects were noted in the volunteers. Analyses were made before and at the end of the test period. Tragacanth Gum did not sigificantly affect plasma biochemistry, hematological indices, urinalysis parameters, glucose tolerance, serum cholesterol, triglycerides and phospholipids, or breath hydrogen and methane concentrations. A decrease in intestinal transit time and an increase in fecal fat concentration were statistically significant in four subjects. Fecal wet and dry weights were significantly increased in all subjects. These changes may be of possible nutritional and physiological interest but were not considered to be an indication of any adverse toxicological effects due to the ingestion of large daily doses of Tragacanth Gum.

Irritation and Sensitization

A styling gel containing 1.25% Tragacanth Gum was evaluated for primary irritation using a panel of 100 females. An occlusive patch containing 0.1 ml of the gel was applied to the back of each subject for 48 h. Sites were scored 15 minutes and 24 h after patch removal. No erythema or edema was observed. The styling gel was not a primary irritant.[72] (Results of clinical irritation and sensitization studies are reported in Table 7.)

A modified Draize-Shelanski repeated insult patch test (RIPT) was conducted to evaluate the irritation and sensitization potential of two hair gels. Each gel

TABLE 7. Clinical Irritation, Sensitization, Phototoxicity, and Photoallergenicity

Ingredient	*Method*	*No. of subjects*	*Results*	*Reference*
Tragacanth Gum				
1.25% in a styling gel	Single occlusive patch	100	No erythema or edema; nonirritating	72
1.5% in a hair gel	Modified Draize-Shelanski RIPT[a]	207	One score of 1 at induction, one score of 2 at challenge; nonirritating and nonsensitizing	73
1.5% in a hair gel	Modified Draize-Shelanski RIPT	207	No reactions; nonirritating and nonsensitizing	74
1.5% in a hair gel	21-day cumulative irritation	10	Total score of 40 (max = 630); essentially no irritation, mild material	75
1.5% in a hair gel	21-day cumulative irritation	12	Total score of 190 (max = 630); slight potential for mild cumulative irritation, "probably mild" in normal use	76
10% in mixture of water and alcohol	Phototoxicity test: semiocclusive patch, UVA exposure	10	No contact dermal phototoxic response	77
10% in mixture of water and alcohol	Photoallergy test: semiocclusive patches, UVA and UVB exposure	29	No contact dermal photoallergy or contact dermal sensitization	78

[a]RIPT, Repeated Insult Patch Test.

contained 1.5% Tragacanth Gum. A 0.1 ml dose of each product was applied to the back of the subject using an occlusive patch. Patches were left in place for 24 h. A total of 10 induction patches was applied to the same site on Mondays, Wednesdays, and Fridays. Sites were scored (scale of 0–4) before the next patch application. After a 2-week rest period, a challenge patch was applied for 48 h to a previously unpatched site. Irritation responses were scored 48 and 72 h after application. Of the 207 subjects who completed the study, 2 had reactions to the first gel; 1 had a score of 1 after the first induction patch, and the second had a score of 2 at 72 h after the challenge patch. These reactions were considered to be irritant in nature and not of clinical significance. No reactions to the second gel were observed during induction or challenge. It was concluded that these hair gels were neither primary irritants nor allergic contact sensitizers.[73,74]

Two hair gels, each containing 1.5% Tragacanth Gum, were evaluated for cumulative irritation. Each panelist received an occlusive patch containing 0.2

ml of the hair gel applied for 23 h daily for 21 days. Patches were applied to the same site on the back each day, and reactions were scored at 24 h. Ten subjects completed the first study, giving a total score of 40 (max = 630). This gel was classified as a mild material, producing essentially no irritation.[75] Twelve subjects completed the second study, giving a total score of 190 (based on 10 subjects; max = 630). This gel gave evidence of a slight potential for very mild cumulative irritation under conditions of the test and was concluded to be "probably mild" in normal use.[76]

Phototoxicity and Photoallergenicity

Tragacanth Gum, at a concentration of 10% in an equal mixture of water and SD Alcohol 40, was evaluated for phototoxicity in 10 people. The light source consisted of four F40BL fluorescent tubes with an output at 360 nm of approximately 1.23 W per 10 nm of wavelength (dose of 0.22 J/cm^2 per minute at a distance of 10 cm). Semiocclusive patches, each containing 0.2 ml of the test solution, were applied to both volar forearms of each subject. The patches were removed after 24 h, and the reactions were graded (scale 0–4). One forearm of each subject was then irradiated with UVA, and the reactions were graded immediately. The unpatched part of this forearm served as the irradiated control. The reactions were graded again at 48 and 72 h. No reactions were observed on either the irradiated or nonirradiated sites. The investigators concluded that Tragacanth Gum did not induce a contact dermal phototoxic response in humans[77] (Table 7).

Tragacanth Gum, at a concentration of 10% in an equal mixture of water and SD Alcohol 40, was also evaluated for photoallergenicity in 29 subjects. The UVA light source consisted of four F40BL fluorescent tubes with an output at 360 nm of approximately 1.23 W per 10 nm of wavelength (dose of 0.22 J/cm^2 per minute at a distance of 10 cm). Each UVA irradiation was for 15 minutes, giving a dose of 3.3 J. The UVB light source was the Solarium 300 lamp, with a dose of approximately 1.2 mJ/cm^2 per second at a distance of 20 cm. The UVB irradiation was based on each subject's MED (minimal erythemal dose) as determined on the control arm (the lesser of two determinations). The approximate doses ranged from 90 to 126 mJ. Semiocclusive patches, each containing 0.2 ml of the test solution, were applied to both volar forearms of each subject. The patches were removed after 24 h, and the reactions were graded (scale 0–4). One forearm of each subject was then irradiated with both UVA and UVB, and the reactions were graded immediately. These procedures were repeated on Mondays, Wednesdays, and Thursdays for 3 weeks to give a total of nine inductions. To avoid irradiating the same test site 2 consecutive days, the subjects were patched on an adjacent site following the second irradiation (Thursday) for the week. After a 2-week rest period, similar challenge patches were applied to previously untreated sites on both forearms of each subject. Patches were removed after 24 h, and the reactions were scored. The designated forearm of each subject was then irradiated with UVA only, and reactions were scored immediately. The reactions were scored again at 48 and 72 h. During the induction phase, nine subjects had slight erythema scores (±) at the irradiated test sites containing Tragacanth Gum, and one subject had a score of 1 (erythema and/or slight edema). A similar number of subjects had slight scores (±) at the nonpatched

irradiated sites. The irradiated sites (with and without test material) were observed to have slight tanning responses. No reactions were observed at the non-irradiated patch test sites. The original patch sites had no reactions during rest or at challenge. Furthermore, no reactions were observed at the challenge sites. The investigators concluded that Tragacanth Gum did not induce contact dermal photoallergy or contact dermal sensitization in human subjects[78] (Table 7).

Case Reports

Numerous case reports of hypersensitivity reactions to Tragacanth Gum have been recorded. One man with a history of allergy to coal-tar drugs and aspirin was allergic to the Tragacanth Gum contained in pyribenzamine placebos.[79] One confirmed case of sensitivity to Tragacanth Gum has been reported in kidney transplant patients receiving prednisone tablets formulated with Tragacanth Gum as the tablet adhesive.[80] Sensitivity to Tragacanth Gum in a hand lotion and in an electrode jelly was found in a woman and a 4-year old boy, respectively.[81,82] One woman working in a commercial gum factory developed severe asthma due to Tragacanth Gum.[83]

Gelfand[84] carried out ingestion experiments with Tragacanth Gum, karaya, and arabic gums in five sensitive subjects. Each subject ingested a mixture of the three gums or foods known to contain these vegetable gums. The major symptoms of allergy included bronchial asthma, urticaria, angioedema, vasomotor rhinitis, and gastrointestinal problems. Symptoms appeared either rapidly or up to 4 h later, and the duration ranged from 1 to 24 h and longer. Tragacanth Gum was the dominant antigen by direct skin test in one subject, Tragacanth Gum and karaya gum were simultaneously dominant in two subjects, and arabic gum was the dominant antigen in the remaining two.

Gelfand[83] also studied the incidence of gum sensitivity in workers in a commercial gum factory. From the results of this study, it was concluded that gum sensitization is an occupational risk for predisposed persons, symptoms develop over a period of time (usually 1 year) after the first exposure, Tragacanth Gum is an allergen capable of causing extremely severe reactions, and some workers who become sensitized may later spontaneously develop tolerance.

SUMMARY

Tragacanth Gum is the dried exudate of small, thorny scrubs (species *Astragalus*) growing wild in the mountainous, semidesert regions of Iran, Syria, Turkey, and other areas of Asia Minor. The gum is collected after a series of incisions in the tap root and the bark of the branches. It dries in the form of ribbons or flakes and, after processing, can be sold in the form of ribbons, flakes, granules, or powder.

Tragacanth Gum is a complex polysaccharide composed of D-galacturonic acid, D-galactose, D-xylose, and L-arabinose, with associated calcium, magnesium, and potassium cations. Tragacanth is considered to have two primary constituents: bassorin and tragacanthin. Bassorin comprises 60–70% percent of the gum and is insoluble in water but swells to form a gel. Tragacanthin comprises 30–40% of the gum and is soluble in water.

Tragacanth Gum is odorless and white to yellow-brown. It is insoluble in alcohol and other organic solvents. Aqueous solutions of Tragacanth Gum are extremely viscous; viscosity is, in fact, used as a measure of the quality and uniformity of the gum. The viscosity of Tragacanth Gum solutions can, however, be altered by various factors. Tragacanth Gum solutions also are heat and acid stable, although very susceptible to microbial degradation.

Tragacanth Gum is used in cosmetics as a fixative, suspending and thickening agent, emulsifier, film former, and viscosity builder. Tragacanth Gum was reportedly used in 29 formulations (of those formulated before 1982) including eye and facial makeups, coloring and noncoloring hair preparations, oral hygiene products, shaving and skin care preparations. The concentration of use can vary up to 10%. However, Tragacanth Gum is most frequently used at concentrations of >0.1–1%.

Tragacanth Gum is used extensively in the pharmaceutical industry as an emulsifier, suspending agent, adhesive, lubricant, demulcent, and tablet binder. As a direct food substance with a maximum usage concentration of 1.3% (for fats and oils), Tragacanth Gum is considered GRAS (Generally Recognized As Safe). The gum is used primarily as a stabilizer in low pH salad dressings and ice cream and as a thickener and binder in confectionaries and bakery products.

Repeated oral administration of Tragacanth Gum to rats for 4 weeks produced an early severe damage to cardiac cell mitochondria, although this effect disappeared upon continued administration of gum, a cumulative reduction in oxidative phosphorylation in hepatic mitochondria, and no adverse effects on hepatic cell mixed function oxidases. Rats fed a diet containing Tragacanth Gum for 13 weeks had no abnormalities in the organelles of the heart and liver as determined by electron microscopy. No pathological changes were observed. Assays of hepatic cell microsomal protein and cytochrome P-450 content were negative for inductive effects.

Tragacanth Gum produced some cytopathic effects on human embryonic lung cells growing in culture, although it did not affect mitoses.

In acute toxicity studies, Tragacanth Gum was practically nontoxic when administered orally to mice, rats, hamsters, and rabbits.

In subchronic studies, a diet containing 2% Tragacanth Gum produced a significant reduction in growth in chickens. However, no significant reductions in average body weights were noted in quail, rats, or insect larvae. In a chronic study, six baboons receiving Tragacanth Gum (as the vehicle control) had no significant adverse effects over 26 weeks of oral administration.

Cosmetic products containing from 0.61 to 1.5% Tragacanth Gum were slightly to mildly irritating when applied topically to rabbits and nonirritating to mildly irritating to rabbit eyes.

No significant toxic or teratogenic effects were produced by oral administration of Tragacanth Gum to pregnant mice at a dose of 1200 mg/kg, rats at a dose of 210 mg/kg, hamsters at a dose of 900 mg/kg, and rabbits at a dose of 33 mg/kg. Significant maternal toxicity was, however, noted in rats and rabbits receiving greater doses of Tragacanth Gum; administration of 1200 mg/kg Tragacanth Gum to rats produced 25% mortality, whereas 150 and 700 mg/kg Tragacanth Gum administered to rabbits produced 40 and 60% mortality, respectively. Death was preceded by severe diarrhea, increased urination, and anorexia. Ani-

mals surviving at these doses carried their offspring to full term and appeared normal in all respects. Tragracanth Gum produced no teratogenic effects in chick embryos, although it was highly embryotoxic.

Tragacanth Gum produced an antigen-specific delayed hypersensitivity reaction (as measured by footpad swelling) in mice previously immunized with the gum, although no antibodies were detected in the sera.

Tragacanth Gum was essentially nonmutagenic in human embryonic lung cells and in *Salmonella typhimurium* strains G-46 and TA-1530 (without metabolic activation) and TA-1535, TA-1537, TA-1538, TA-98, and TA-100 (with and without metabolic activation). Inconclusive as well as negative results were obtained when Tragacanth Gum was tested for mutagenicity in *Saccharomyces cerevisiae* both with and without metabolic activation. Tragacanth Gum was also evaluated in three mammalian test systems: a host-mediated assay, cytogenetic studies, and a dominant lethal assay. All results were negative with one exception: *Saccharomyces cerevisiae* D3 had increased recombinant frequencies in the subacute host-mediated assay (one dose per day for 5 days).

Tragacanth Gum, as the solvent control in a carcinogenicity study, was administered intravaginally twice weekly to 30 female mice for 50 weeks. None had tumors of the genital tract, and the number and type of other tumors were no different than those seen in the untreated control mice.

In clinical studies, large oral doses of Tragacanth Gum over a period of 21 days produced no adverse effects in five male subjects. Cosmetic products containing up to 1.5% Tragacanth Gum were essentially nonirritating and nonsensitizing when evaluated by single patch test (100 subjects), RIPT (207 subjects), and a cumulative irritation test (10 subjects); results of one cumulative irritation test (12 subjects) indicated a slight potential for mild irritation. Tragacanth Gum, at a concentration of 10%, did not induce a contact dermal phototoxic response when tested in 10 humans. Ten percent Tragacanth Gum also did not induce contact dermal photoallergy or contact dermal sensitization in 29 subjects. Hypersensitivity reactions to Tragacanth Gum seem to be rare but can cause severe symptoms in susceptible individuals.

CONCLUSION

On the basis of the available animal and clinical data, the CIR Expert Panel concludes that Tragacanth Gum is safe as a cosmetic ingredient in the present practices of use and concentration.

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