Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	May 22, 2026
Panel Meeting Date:	June 15-16, 2026

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: David E. Cohen, M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Regina Tucker, M.S., former Scientific Analyst/Writer, and Thushara Diyabalanage, Ph.D., former Scientific Analyst/Writer, CIR.

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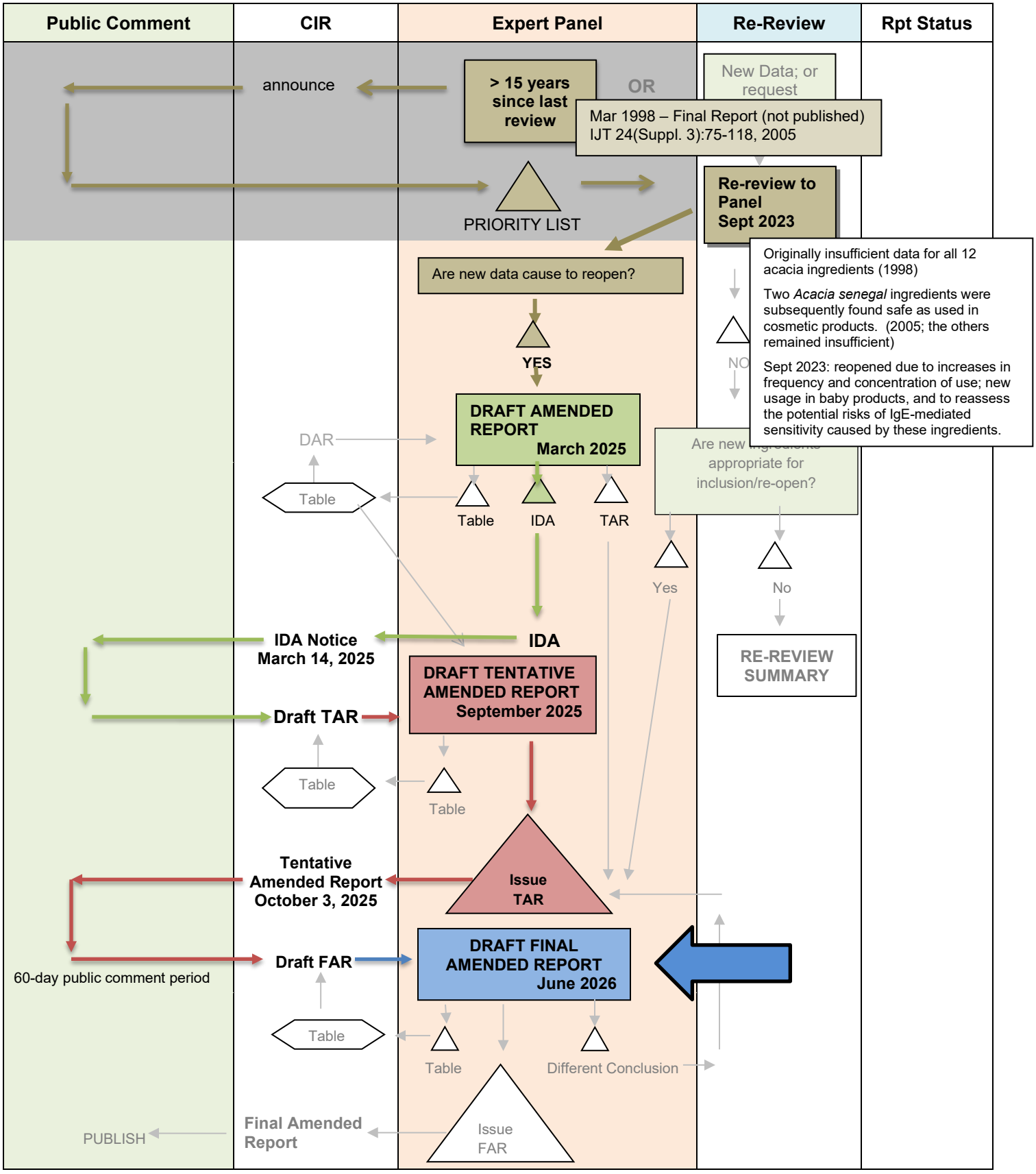
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Acacia Senegal Gum and Acacia Senegal Gum Extract

MEETING June 2026



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice Fiume, M.B.A.
Senior Director, CIR
Date: May 22, 2026
Subject: Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics

Enclosed is the Draft Final Amended Report on the Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics (identified as *report_AcaciaSenegal_062026* in the pdf document.) At the September 2025 meeting, the Panel issued a Tentative Amended Report, reaffirming the conclusion that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Since the September meeting, CIR has updated the report with use data obtained in 2025 from the FDA RLD. Frequencies of use have increased since reported in 2024. In 2024, Acacia Senegal Gum was reported to have 1833 uses, and Acacia Senegal Gum Extract 92; in 2025, Acacia Senegal Gum has 2938 uses and Acacia Senegal Gum Extract has 149.

The RLD for Acacia Senegal Gum lists 54 products under category (17) "other preparations (i.e., those preparations that do not fit another category)." In our analysis of these products, 5 were co-categorized with eye makeup preparations, 18 with non-coloring hair preparations, 1 with personal cleanliness products, and 3 with skin care preparations. The 27 remaining formulations were only listed as category 17, and the product names were useful in determining some (but not all) of the product types; e.g., 4 were face masks, 6 were skin care preparations, 1 was an eye cream, 1 was a mascara, and 10 were face paint products. However, for 5 of the products, the product type nor the area/route of exposure is obvious from the information submitted to the RLD, and some of those submitted products might not be considered to be cosmetic products in the US. We have sent a request to our colleagues in the FDA's OCAC for clarification.

For Acacia Senegal Gum Extract, 12 products reported in the RLD were listed under category (17). In our analysis of these products, all but one were co-categorized: 8 with non-coloring hair preparations, 1 with personal cleanliness products, and 2 with skin care preparations. The product type and the area/route of exposure, or whether it is a cosmetic product, is not clear for the 1 remaining category 17 entry.

No additional data have been received. However, comments were submitted by the Council on both the Draft Tentative Amended Report prior to the September 2025 meeting and on the Tentative Amended Report, and these have been addressed (*PCPCcomments_AcaciaSenegal_062026_1; PCPCcomments_AcaciaSenegal_062026_2*; *response-PCPCcomments_AcaciaSenegal_062026_1; response-PCPCcomments_AcaciaSenegal_062026_2*, respectively).

The original report that was issued in 1998 (*originalreport1998_AcaciaSenegal_062026*) and the amended report that was published in 2005 (*amendedreport2005_AcaciaSenegal_062026*) are included for your reference. Additional supporting documents for this report package include the following:

- flow chart (*flow_AcaciaSenegal_062026*)
- report history (*history_AcaciaSenegal_062026*)
- search strategy (*search_AcaciaSenegal_062026*)
- data profile (*dataprofile_AcaciaSenegal_062026*)
- minutes from past meetings at which *Acacia senegal*-derived ingredients were originally discussed (*originalminutes_AcaciaSenegal_062026*)
- transcripts from the previous meeting at which this amended report was reviewed (*transcripts_AcaciaSenegal_062026*)

The Panel should carefully review the Abstract, Discussion, and Conclusion, and issue a Final Amended Report.

Acacia senegal-derived Ingredients History

1998– The Panel issues a final report with an insufficient data conclusion for the entire group of acacia ingredients reviewed at that time, including Acacia Senegal Gum and Acacia Senegal Gum Extract.

2005 – Data were received, and an amended report was issued. However, the Panel's data needs were met for only Acacia Senegal Gum and Acacia Senegal Gum Extract. At that time, the Panel concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe as used in cosmetic products.

2023- An extensive search of the world's literature was performed for studies dated 2000 forward. New non-cosmetic use data that consists of current European Union regulations regarding use as a food additive were identified. Data which cover reproductive toxicity and occupational case studies were also found. At the September meeting, the panel decided to open this safety assessment due to the increases in frequency and concentration of use and new product category usage in baby products. The Panel also wanted to reassess the risks of IgE mediated sensitivity caused by these ingredients.

March 2025 Panel Meeting
A Draft Amended report was submitted to the Panel. An Insufficient Data Announcement (IDA) was issued

Data received:

- Institute for In Vitro Sciences Inc. 2014. Tissue equivalent assay with EpiOcular™ cultures (1% Acacia Senegal gum in a mascara).
- Anonymous. 2025. Information on Acacia Senegal Gum (UV absorption and ocular irritation).
- Reliance Clinical Testing Services, Inc. 2023. Four Week Safety-In-Use Test for Eye Area (Mascara with 3% Acacia Senegal Gum Extract)
- Institute for In Vitro Sciences, Inc. 2023. Topical Application Ocular Irritation Screening Assay Using EpiOcularTM Human Cell Construct.
- Farcoderm. 2013. In Vitro Product Safety Study: In vitro evaluation of the eye irritation potential of cosmetic products (mascara containing 2.9% Acacia Senegal Gum).
- Farcoderm. 2013. Clinical test aimed at evaluating the tolerability and safety of a cosmetic product used around the eyes (mascara containing 2.9% Acacia Senegal Gum).
- Anonymous. 2025. Summary information: Eye irritation studies of a mascara containing 6% Acacia Senegal Gum

September 2025 Panel Meeting
A Tentative Amended Report was issued with the conclusion that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe in cosmetics in the present practices of use and concentration as described in the safety assessment.

June 2026 Panel Meeting
FDA RLD were updated with values obtained in 2025 A draft Final Amended Report was submitted to the Panel for finalization.

Acacia Senegal Gum and Acacia Senegal Gum Extract * – June 2026																																	
					Toxico-kinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation			Clinical Studies	
	Method of Mfg	Composition/Impurities	UVAbsorption	Food Use	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Human	Retrospective/ Multicenter	Case Reports
Acacia Senegal Gum	**XO**	XO	**XO**	X			O		O			XO			XO	O	O		O			O			O		X		X			XO
Acacia Senegal Gum Extract																												X		X			

* "X" indicates that new data were available in this category for the ingredient; "O" indicates that data from the original assessment were available

Acacia Senegal Gum and Acacia Senegal Gum Extract

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Acacia Senegal Gum and Acacia Senegal Gum Extract	9000-01-5	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy (from 2000 on)

PubMed

(((“Acacia Senegal Gum”) OR (9000-01-5[CAS No.])) AND (("2000"[Date - Publication]: "3000"[Date – Publication]))) – 83 hits; 9 useful hits

(((“Acacia Senegal Gum Extract”-11”) OR (9000-01-5[CAS No.])) AND (("2000"[Date - Publication]: "3000"[Date – Publication]))) – 83 hits; 9 useful hits

(((“Gum arabic”) OR (9000-01-5[CAS No.])) AND (("2000"[Date - Publication]: "3000"[Date – Publication]))) – 1,721;7 useful hit

The following qualifiers were used in the search of Gum arabic: absorption, acute, allergy, allergic, allergenic, cancer, carcinogen, chronic, development, developmental excretion, genotoxic, irritation, metabolism, mutagen, mutagenic, penetration, percutaneous, pharmacokinetic, repeated dose, reproduction, reproductive, sensitization, skin, subchronic, teratogen, teratogenic, toxic, toxicity, toxicokinetic, toxicology, tumor.

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/;
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/ rganisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Kimberly Norman, Ph.D., DABT, ERT
Industry Liaison to the CIR Expert Panel

DATE: September 2, 2025

SUBJECT: Draft Tentative Amended Report: Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics (draft prepared for the September 8-9, 2025, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative amended report, Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics.

Abstract – As two ingredients are being reviewed in this report, "this ingredient" needs to be corrected to "these ingredients"

Cosmetic Use – As these ingredients are reported to be used in hair sprays, it is not clear why it says that they "may be used" in products that may be inhaled. They are used in products with potential inhalation exposure.

Developmental and Reproductive Toxicity, old report summary – Please check: "Rats fed with 5% gum Arabic solution (days 6-17 of gestation) showed no effects on estrus cycle or external skeletal or external skeletal or soft tissue malformations were observed." If the rats were only treated during gestation, it is not clear how they looked at estrus cycle effects.

Developmental and Reproductive Toxicity, Oral – In the study cited to reference 20 (titled: "Comparative efficacy of Gum Arabic (*Acacia Senegal*) and *Tribulus terrestris* on male fertility"), were the female mice really treated? If they were looking for effects on male fertility, it was likely that only the males were treated, and each male was mated with 2 untreated females. The report currently states: "Groups of 1 male and 2 female Balb/c mice were dosed with tap water or 5% (w/v) gum Arabic in tap water (5 g/100 ml) 21d."

Developmental and Reproductive Toxicity, Oral; Summary – Please correct: "The number of offspring living offspring"

Genotoxicity, In Vitro, old report summary – Please provide some indication of the doses/concentrations tested in these studies. At least the highest negative non-cytotoxic concentration/dose tested in each type of assay would be helpful.

Case Reports – Does sensitization to the carbohydrate portion really occur "casually", or should this be "occasionally"?

Case Reports; Table 5 – The text suggests that reference 18 indicated that sensitization might also be to the polypeptide portion of gum Arabic, but this is not stated in the summary for reference 18 in Table 5.

Summary – Since the RLD and the 2025 Council survey were collected using the same cosmetic product categories, it is not clear why these two are not discussed together. The Summary currently mentions the VCRP data and the 2025 Council survey which were completed using different product categories.

Summary – In the Summary, it would also help to note that one case reported antibodies directed to the polypeptide chain.

Discussion – As analytical methods can measure smaller amounts, please do not say that "aflatoxin should not be present", please state that aflatoxins should be minimized or controlled. It already says that it should follow USDA limits which is not zero (it is 15 ppb for peanuts).

Acacia Senegal Gum and Acacia Senegal Gum Extract – June 2026	
Comment Submitter: Kimberly Norman, Ph.D., DABT, ERT; Personal Care Products Council **Subject:** Draft Tentative Amended Report: Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics (draft prepared for the September 8-9, 2025, meeting) **Date of Submission:** September 2, 2025	
Comment	**Response/Action**
Abstract – As two ingredients are being reviewed in this report, "this ingredient" needs to be corrected to "these ingredients"	Addressed.
Cosmetic Use – As these ingredients are reported to be used in hair sprays, it is not clear why it says that they "may be used" in products that may be inhaled. They are used in products with potential inhalation exposure.	Addressed.
Developmental and Reproductive Toxicity, old report summary – Please check: "Rats fed with 5% gum Arabic solution (days 6-17 of gestation) showed no effects on estrus cycle or external skeletal or external skeletal or soft tissue malformations were observed." If the rats were only treated during gestation, it is not clear how they looked at estrus cycle effects.	Addressed.
Developmental and Reproductive Toxicity, Oral – In the study cited to reference 20 (titled: "Comparative efficacy of Gum Arabic (Acacia Senegal) and Tribulus terrestris on male fertility"), were the female mice really treated? If they were looking for effects on male fertility, it was likely that only the males were treated, and each male was mated with 2 untreated females. The report currently states: "Groups of 1 male and 2 female Balb/c mice were dosed with tap water or 5% (w/v) gum Arabic in tap water (5 g/100 ml) 21d."	Presented as described in the study.
Developmental and Reproductive Toxicity, Oral; Summary – Please correct: "The number of offspring living offspring"	Addressed.
Genotoxicity, In Vitro, old report summary – Please provide some indication of the doses/concentrations tested in these studies. At least the highest negative non-cytotoxic concentration/dose tested in each type of assay would be helpful.	Addressed.
Case Reports – Does sensitization to the carbohydrate portion really occur "casually", or should this be "occasionally"?	Stated as described in the study.
Case Reports; Table 5 – The text suggests that reference 18 indicated that sensitization might also be to the polypeptide portion of gum Arabic, but this is not stated in the summary for reference 18 in Table 5.	Addressed.
Summary – Since the RLD and the 2025 Council survey were collected using the same cosmetic product categories, it is not clear why these two are not discussed together. The Summary currently mentions the VCRP data and the 2025 Council survey which were completed using different product categories.	Addressed.
Summary – In the Summary, it would also help to note that one case reported antibodies directed to the polypeptide chain.	Addressed.
Discussion – As analytical methods can measure smaller amounts, please do not say that "aflatoxin should not be present", please state that aflatoxins should be minimized or controlled. It already says that it should follow USDA limits which is not zero (it is 15 ppb for peanuts).	Addressed.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Kimberly Norman, Ph.D., DABT, ERT
Industry Liaison to the CIR Expert Panel

DATE: October 9, 2025

SUBJECT: Tentative Amended Report: Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics (release date: October 3, 2025)

The Personal Care Products Council respectfully submits the following comments on the tentative amended report, Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics.

Key Issue

According to Table 3, the maximum concentrations of use for Acacia Senegal Gum were 9% in 2000 and 4% in 2025. Therefore, it is not clear why the Introduction, Summary and Discussion all say the report was re-opened "due to increases in frequency and concentration of use". Although the frequency may have increased, the maximum concentration of use decreased.

Additional Considerations

Abbreviations – The definitions of abbreviations should be consistent in all CIR reports. LD_{50} is usually defined as median lethal dose. In this report it is defined as "lethal dose for 50% of the population".

Introduction; Summary – These sections currently state: "emulsion stabilizer film former". Please add a comma between these two functions to make it clear that they are two different possible functions.

Method of Manufacture – Please correct: "in the powder [to] not more than 0.05 colony-forming units per gram) (add "to")

Composition/Impurities – Please correct "glucouronic" (should be "glucuronic" delete first "o")

Since more than one amino acid is listed, "is" should be corrected to "are". Please add "acid" after "aspartic".

The complete USP specifications should be included (add total ash not more than 0.5% and insoluble residue not more than 50 mg/5 g).

ADME, Human, Oral, old report summary – Although the original CIR report says that in the study in infants given gum arabic in milk, there was no evidence of absorption and no significant of excretion of gum arabic in the stools. This does not make sense. If the orally administered gum arabic was not absorbed and it was not in the feces, where did it go? The original reference (1973 FASEB review) was checked. The original reference says: "In this study, 22 infants 1 to 15 months old were fed 15 to 20 g per day of gum arabic in milk. No urinary pentose excretion was observed, while significant excretion of gum arabic occurred in the stools." Please correct the current CIR report to indicate that gum arabic was excreted in the feces in these infants.

Subchronic, Oral – It is not necessary to state "a diet containing" and "in feed" in the same sentence. One should be deleted.

Please include all the endpoints that were examined. The abstract of reference 19 also indicates ophthalmologic examinations and blood biochemistry were completed.

Developmental and Reproductive Toxicity, old report summary – On what gestation days were mice treated with doses up to 1600 mg/kg?

Please correct: "went he test article" (should be "when the test article")

When during gestation were female rats treated with 15% gum arabic? Was this a dietary concentration?

Please correct: "in rats s."

When during gestation were mice treated intraperitoneally with a 1% aqueous suspension of gum arabic?

Genotoxicity, In Vitro, old report summary – Please revise the last sentence of this section ("in mice" needs to be added before the word "dosed").

Anti-Carcinogenicity – In the study described in reference 21, were the mice treated daily for 12 weeks?

Case Reports; Table 5 – Please make it clear what is meant by "sIgE" (abstract of reference 19 says specific IgE).

Tables 2 and 5 – Please correct "ug" to "μg".

Acacia Senegal Gum and Acacia Senegal Gum Extract – June 2026	
Comment Submitter: Kimberly Norman, Ph.D., DABT, ERT; Personal Care Products Council **Subject:** Tentative Amended Report: Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics (release date: October 3, 2025) **Date of Submission:** October 9, 2025	
Comment	**Response/Action**
Key Issue: According to Table 3, the maximum concentrations of use for Acacia Senegal Gum were 9% in 2000 and 4% in 2025. Therefore, it is not clear why the Introduction, Summary and Discussion all say the report was re-opened "due to increases in frequency and concentration of use". Although the frequency may have increased, the maximum concentration of use decreased.	Addressed.
Abbreviations – The definitions of abbreviations should be consistent in all CIR reports. LD50 is usually defined as median lethal dose. In this report it is defined as "lethal dose for 50% of the population".	Addressed.
Introduction; Summary – These sections currently state: "emulsion stabilizer film former". Please add a comma between these two functions to make it clear that they are two different possible functions.	Addressed.
Method of Manufacture – Please correct: "in the powder [to] not more than 0.05 colony-forming units per gram) (add "to")	Addressed.
Method of Manufacture – Please correct: "in the powder [to] not more than 0.05 colony-forming units per gram) (add "to")	Addressed.
Composition/Impurities – Please correct "glucouronic" (should be "glucuronic" delete first "o")	Addressed.
Since more than one amino acid is listed, "is" should be corrected to "are". Please add "acid" after "aspartic".	Addressed.
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Subchronic, Oral – It is not necessary to state "a diet containing" and "in feed" in the same sentence. One should be deleted.	Addressed.
Please include all the endpoints that were examined. The abstract of reference 19 also indicates ophthalmologic examinations and blood biochemistry were completed.	Addressed.
Developmental and Reproductive Toxicity, old report summary – On what gestation days were mice treated with doses up to 1600 mg/kg?	Addressed.
Please correct: "went he test article" (should be "when the test article")	Addressed.
When during gestation were female rats treated with 15% gum arabic? Was this a dietary concentration?	Addressed.
Please correct: "in rats s."	Addressed.
When during gestation were mice treated intraperitoneally with a 1% aqueous suspension of gum arabic?	Addressed.
Genotoxicity, In Vitro, old report summary – Please revise the last sentence of this section ("in mice" needs to be added before the word "dosed").	Addressed.
Anti-Carcinogenicity – In the study described in reference 21, were the mice treated daily for 12 weeks?	Addressed.
Case Reports; Table 5 – Please make it clear what is meant by "sIgE" (abstract of reference 19 says specific IgE).	Addressed.
Tables 2 and 5 – Please correct "ug" to "µg".	Addressed.

SEPTEMBER 2023 PANEL MEETING –RE-REVIEW

Belsito's Team Meeting – September 11, 2023

DR. BELSITO: Acacia, open. I just had one question when I was looking at this. So the original report had all of these other acacias, acacia catechu gum, concinna fruit extract, yada, yada, yada, where we said the available data are insufficient to support the safety of these ingredients. That was done before we made this rule that, if things aren't addressed within two years, they become unsupported. Did that rule become retroactive so all of these other acacia species are considered unsupported? Because we're not looking at them in this report.

MS. FIUME: Right. I need to look back at the table that goes out that shows all the conclusions. I think they were all retroactively changed, but I cannot speak --

DR. EISENMANN: They should be.

MS. FIUME: Yeah. They should have been changed. If they are insufficient, we've never considered them for a rereview.

DR. BELSITO: Okay. I just wanted to make sure that, not only were they insufficient, but as a result of being insufficient back whenever, they became subject to that rule, that if they weren't supported within two years, they became not supported.

MS. FIUME: Yeah. I'm trying to think back to when we announced it. I honestly can't remember how it was announced, but I believe that they were all retroactively changed.

DR. BELSITO: I think we need to make sure of that because we're not reopen. We're obviously not looking at those here, so it's GRAS. So we're not worried about the systemic. The maximum leave on was covered by the age max of eight percent in the old report. Old report had no inhalation exposure, and now we do. We have additional occupational IgE cases. We had them in the old report, but I thought they were poorly dealt with in that report. They were almost dealt with as contact sensitization.

And we have no inhalation toxicity. So do we need to reopen the safety assessment for inhalation based upon the limited number of anaphylactic slash IgE asthma attacks or not? Just raising a question here, folks. That was my only concern because, when you read the old report, we mention them. So they're in the old report, but we almost deal with them like they're cutaneous sensitization, which they're not.

DR. SNYDER: Right.

DR. BELSITO: And we have no inhalation here, and you can't cover an IgE mediated --

DR. SNYDER: In an inhalation study anyway.

DR. BELSITO: -- with an inhalation study because we don't care if it reaches the alveoli. It just needs to get into your trachea.

DR. SNYDER: How do we address it in the discussion, then, in that old report?

DR. BELSITO: In the old report?

DR. SNYDER: Yeah.

DR. BELSITO: We addressed it almost like dermal sensitization rather than IgE.

DR. SNYDER: Mediated by contact instead of a person.

DR. BELSITO: Yeah. Basically, what we said, Panel noted the potential for allergic responses to gum arabic. However, because of the negative results for all 25 subjects in a human maximization test, mascara containing eight percent, and the expected slow rate of dermal absorption of gum arabic, not likely of normal use in cosmetic products would result in sensitization. We sort of totally ignored -- that was the sensitization. And we sort of transferred it over to dermal rather than addressing the respiratory.

DR. SNYDER: It's like 0.001 or something for inhalation potential. It's pretty low; isn't it?

DR. BELSITO: Yeah.

DR. SNYDER: Yeah.

DR. BELSITO: But, depending upon what your IgE levels are --

DR. SNYDER: I know, can be bad.

MS. FIUME: 0.003.

DR. SNYDER: 0.003, okay.

MS. FIUME: For a spray. 0.03 for a powder.

DR. BELSITO: I'm just pointing this out. Do we need to reopen to take a closer look at that? I just think we poorly addressed it in our discussion the last go around.

DR. SNYDER: It wasn't poorly addressed. It was incorrectly addressed --

DR. BELSITO: Yeah.

DR. SNYDER: -- I think.

DR. RETTIE: Well, if you feel like that, it seems to me like we should reopen to correct it.

DR. BELSITO: I hate to say that I was a member of the Panel at the time we did that. I don't know how that happened.

MS. FIUME: Is it something you need to reopen to address or can it be addressed in the rereview summary?

DR. BELSITO: I think it can be addressed in the rereview summary because the data isn't new. It's in the report. I just think we poorly addressed it. But I'm trying to think, Monice, because we've addressed ingredients like peanut, et cetera, where there have been limited numbers of IgE mediated allergy. And we're not talking about the oligopeptides where you had to reach a certain length.

Peanut oil, we said there would be no protein. But how have we dealt with things like soy and wheat and other things that have been reported to cause IgE mediated allergy?

MS. FIUME: Is that when we talked about the SOD?

DR. BELSITO: Pardon? No, that was with the oligopeptides --

MS. FIUME: Oh, okay.

DR. BELSITO: -- that we talked about SODs and had to reach over a certain number of daltons to be able to bind the IgE receptors.

DR. SNYDER: Crosslinking, yeah.

DR. BELSITO: But here we're talking about whole proteinaceous substances. So you can clearly activate, but we've dealt with that with other food-related allergens, like wheat, soy.

DR. SNYDER: I think we can address it in the review summary.

DR. BELSITO: Yeah. I know.

DR. SNYDER: There's no new case report.

DR. BELSITO: How do we address it is the question? How have we historically addressed that issue?

DR. SNYDER: We just have to see. Look at the wheat report.

DR. EISENMANN: That was based on size.

DR. SNYDER: Was it?

DR. EISENMANN: Hydrolyzed wheat, yes.

DR. BELSITO: Hydrolyzed, but what about when we looked at -- I mean, we must have looked at some whole soy ingredients or wheat or oat or anything, any other food derived where there have been IgE mediated reports.

MS. FIUME: So, for soy, the concern was alleviated because the reactions would not be induced by dermal exposure because the soy proteins are water soluble, would not penetrate the skin, and have molecular weights that are well below that which would cause IgE crosslinking. And there were no reported cases of type one immediate hypersensitivity reactions. That's what the soy report had to say.

DR. BELSITO: But this gum arabic is used in an aerosol product, right?

MS. FIUME: It also addressed that there was no concern for the asthmatic responses of soy because of the levels. It wouldn't be resulting from a cosmetic use. Let's see if wheat said anything.

DR. BELSITO: In this case, we have incidental inhalation spray up to 44 percent. It's pretty high.

MS. FIUME: So that would've meant face and neck preparations, those 43 uses.

DR. BELSITO: Which would go right into your nose and mouth.

MS. FIUME: Right.

DR. SNYDER: Mm-hmm.

MS. FIUME: So we also had IgE in that discussion, but that was restricting the peptides.

DR. EISENMANN: Yeah, I don't know. Do we know what is the sensitizer in this case? Is it proteins, or is it the polysaccharide itself?

DR. KLAASSEN: Probably has to been a protein.

DR. RETTIE: Why'd you say that?

DR. KLAASSEN: That's what it usually is.

DR. RETTIE: Is there evidence that polysaccharides --

DR. KLAASSEN: I don't know.

DR. RETTIE: I would have thought that's what we would have had here, but I don't know.

DR. SNYDER: I think we need to reopen it and look at it. There's a lot of stuff in here. There's a clinical study where there are eight male employees that reacted --

DR. EISENMANN: Isn't it mostly occupational, though?

DR. SNYDER: Yeah, it was. Yeah.

DR. EISENMANN: So it's probably from chronic exposure --

DR. SNYDER: Yeah.

DR. EISENMANN: It was longer term --

DR. BELSITO: We really need to decide --

DR. RETTIE: Paul, a motion to --

DR. SNYDER: Well, Carol correctly pointed out that most of it's all occupational because there are case studies where they have these type one reactions, all occupational. It's based of the occupational exposures, probably not relevant. And here it says that with the bark, the gum, and the gum arabic and the gum tragacanth.

DR. BELSITO: What page are you, Paul?

DR. SNYDER: Page 41.

DR. RETTIE: 48.

DR. SNYDER: Or 112. Or wait --

DR. KLAASSEN: 48. Oh, you're looking at -- okay. go ahead.

DR. SNYDER: Yeah. Page 48, yeah. They did a RAST test.

DR. KLAASSEN: Right here.

DR. BELSITO: So how are you thinking we can address this?

DR. SNYDER: Well, it's concerning that it caused rhinitis and asthma.

DR. RETTIE: This is the 1949 study.

DR. SNYDER: 1980.

DR. RETTIE: Yeah.

DR. BELSITO: Actually, this is not gum arabic. So why is it in the study because we're looking at gum arabic, right?

DR. SNYDER: Well, yeah.

DR. BELSITO: So there's --

DR. SNYDER: Not gum arabic. That may be why --

DR. BELSITO: Acacia, not gum arabic. And, then, there are reports of gum arabic. But the acacia gum arabic, this in our old report.

DR. SNYDER: Yeah. The gum arabic did cause a contact.

DR. BELSITO: Yeah.

DR. SNYDER: Yeah.

DR. BELSITO: And generalized urticaria vasomotor rhinitis. These were from gum-containing foods. I don't know. We have no inhalation data.

DR. SNYDER: But that's not going to help us because it's --

DR. BELSITO: Right.

DR. SNYDER: Yeah. So it's not inhalation data we're going to ask.

DR. BELSITO: Right.

DR. SNYDER: We're just going to try to understand the type one reactions. It's in the report that they can occur.

DR. BELSITO: Right.

DR. SNYDER: So there's no real difference, then.

DR. BELSITO: I know, but we didn't really address it very well in our discussion, did we? We addressed it sort of like sensitization, saying --

DR. SNYDER: Well, I'm sure it's because the right one did cause sensitization. We'll, let's just discuss it tomorrow with the others and see what they say.

DR. RETTIE: Yeah.

DR. BELSITO: But we've done whole proteins before, like wheat, that we obviously must have had to deal with this.

MS. FIUME: So, in the wheat discussion, it says, the Panel noted that it had previously concluded that hydrolyzed wheat protein and hydrolyzed wheat gluten were safe for use in cosmetics when formulated to restrict the peptide size to 3500 daltons. This conclusion was in response to reports of type one IgE mediated immediate hypersensitivity reactions that occurred in sensitized individuals following exposure to cosmetic products that contained one of these two ingredients with molecular weights greater than this limit.

However, based on the available information, none of the wheat-derived ingredients in this report are hydrolyzed, and most are not even proteins. Coupled with the lack of reports to contrary experience with such reactions to ingredients in the clinical setting, concern over such reactions to these ingredients was mitigated.

DR. BELSITO: We can't say that with gum arabic because what's the molecular size?

DR. SNYDER: (Inaudible) going to the composition.

DR. BELSITO: What?

DR. SNYDER: That's where I was going, to the composition data.

DR. BELSITO: We don't have all that, do we?

DR. SNYDER: Uh-uh.

DR. BELSITO: And this is an old report that includes all acacia species.

DR. SNYDER: Yeah.

DR. BELSITO: Does it say which Acacia species? Is it possible it's not the species we're looking at?

DR. EISENMANN: Maybe you want to open it just to make it on that one species, on gum arabic, rather than having all of them in there, too.

MS. FIUME: So we did it only on the -- I did look, but the others are reported as no reported uses. That's what they are categorized as now.

DR. BELSITO: Okay.

MS. FIUME: So they didn't get recategorized with the conclusion.

DR. BELSITO: What were you saying? Reopen it to do what?

DR. EISENMANN: So you have a clean report on gum arabic and not the other species and so you can deal with this issue that you're concerned about.

DR. BELSITO: It's probably reasonable.

DR. SNYDER: I think so. It could be a quick thing.

DR. BELSITO: Yeah.

DR. SNYDER: It's not appropriately addressed in the Discussion.

DR. BELSITO: That's for sure.

DR. SNYDER: Yeah.

DR. BELSITO: Okay. So we've got to reopen, get rid of all the data that's not acacia senegal slash gum arabic, and look to address this IgE mediated hypersensitivity issue.

MS. FIUME: But I thought all the data are acacia senegal. Aren't they?

DR. BELSITO: No.

DR. SNYDER: No.

MS. FIUME: No? There's others? Okay.

DR. BELSITO: A huge amount of data on other ones. It's all sort of intermixed.

DR. SNYDER: I'd like to see our discussion of why we cut all those out from the original report. We had all those other constituents in the original report.

MS. FIUME: So the report that is attached, the amended report, is the original report plus the data that were received. So it's all inclusive. So the amended report that was included with the rereview package is what the old report was.

DR. BELSITO: Right. And it has data on a whole bunch of non-gum arabic acacias. And what Carol is saying is reopen it, get rid of the data that's not relevant to the ingredient we're looking at, and then readdress and address appropriately the IgE mediated hypersensitivity.

MS. FIUME: Okay. I'm sorry, I thought you were meaning that the new data weren't only on the senegal.

DR. SNYDER: No.

DR. BELSITO: No.

MS. FIUME: Okay. Yeah. No, but what I was meaning for Paul was that maybe there's something in that report because it says why they were originally -- at first, all were insufficient. And then data were submitted that made these too.

DR. SNYDER: Right.

MS. FIUME: So there may be some case in the original report.

DR. SNYDER: Of our reasoning, yeah.

MS. FIUME: Yeah. But, then, when this comes back as a draft amended report, you will have the minutes from the original discussion.

DR. BELSITO: Yeah.

DR. RETTIE: Okay.

DR. BELSITO: So we're going to reopen, remove data on the other gums other than gum arabic, and discuss the IgE mediated hypersensitivity in some way that makes sense. That fair?

DR. SNYDER: Mm-hmm

Cohen's Team – September 11, 2023

DR. COHEN: Let's move on to Acacia. Acacia Senegal Gum and Acacia Senegal Gum Extract. These were part of a larger group of ingredients from the acacia plant. In 1998 the Panel issued a final report of insufficient data conclusion. And subsequently, some data needs were met, and an amended final report was published in 2005, that the gum and the gum extract are safe for use in cosmetic products. Please note that the other ingredients in the larger group had insufficient data and those data needs were not met so it's not being included in this re-review.

A literature search was performed. No non-cosmetic use data -- excuse me one second. Okay, so the EU has its use as a food additive and the frequency and concentration of use has increased for both ingredients since the amended report. The gum is now reported in 287 formulations at up to 26.7 percent. And in oral hygiene products as well, so it may be incidentally ingested. And in 2001, it was reported in one formulation at up to 9 percent and it's being used in baby products now. So, there's been a lot of change in the use of this product. A very large use change and a large concentration change.

Comments on reopening?

DR. TILTON: I have a question just about if this were to be reopened, would it automatically bring in the other ingredients that are not included here because they previously had insufficient data, and so they haven't been reviewed to see if they have any data available?

DR. COHEN: That would be our choice, right?

DR. HELDRETH: So typically, if something gets a final conclusion of insufficient data, unless someone petitions the Panel or CIR with data to fill the gaps that were announced, we don't look at that ingredient again. It just remains out there in its -- now, if the panel feels that there's some useful information by bringing that ingredient back or group of ingredients back to help with the others in the report, that absolutely is their prerogative. But we don't automatically reassess ingredients that have a final conclusion of insufficient data or the final conclusion of unsafe.

DR. COHEN: So, knowing that, Susan, what's your vote?

DR. TILTON: So, my recommendation was to not reopen. So even though the frequency of use in the max concentration reported the increase, the data that have been provided doesn't show any toxicological concern. And we also now have it approved as a food additive with no safety concerns, and that includes for infants below 16 weeks of age. Also, safe as an additive for animal feed. There were really no observed sub-chronic toxicity except at highest concentrations tested. No new reproductive and developmental data.

There was new data to suggest anti-carcinogenic effects, so reduction of adverse occurrence in colorectal cancer, but not data of concern. And there were some evidence of allergic reports to occupational exposures, but again those would be different than in the formulations. So, my recommendation was to not open.

DR. COHEN: Tom?

DR. SLAGA: I agree. Do not reopen.

DR. ROSS: I thought we were going to be quick with this one, but I guess I was on the other side of this. I mean, I went backwards and forwards with it. And I had it down as a reopen, basically because increased number of uses concentration. There was a new generation of gum, which I didn't quite understand because I didn't go back and read the full citation. But they referred to it as a super gum from trees and I didn't really know what that meant. But anyhow, one of the sub-chronic studies with this stuff had a NOAEL in rats of 5 percent in a sub-chronic toxicity study which got my attention.

So that was arguing for me to reopen it. On the downside of that, the don't reopen, yes, you have the EU data on use as a food additive, the food additive for animals. And there was no concerns, I think as Susan pointed out, with use in infants. But base it on that new data, I sort of came down just on the side of reopen it.

DR. COHEN: I had this as a reopen. I thought that reported use, of course, that by itself is not always a reason, but we had a tripling in the max use, right, and we have baby use. And so, I think for all the reasons that you came to a conclusion not to reopen, were sort of the mechanisms and metrics we would use during adjudication of reopen. Right?

So, I think you've probably come to a conclusion after we would've looked at all this data, that it's very similar. But, I don't know, I think we need to see more. Just because it's cleared for oral use doesn't mean it's not going to cause allergic contact dermatitis in a substantial way. I'd like to know that.

DR. BERGFELD: The highest use at 26 percent was in soap and detergents, which is basically a rinse off.

DR. COHEN: Well, it's also in an oral product as well, so lips will get exposed, right?

DR. BERGFELD: I didn't see that. I thought the highest was --

DR. HELDRETH: So, in a product in an eye area, up to 20 percent.

DR. COHEN: Yeah. I see we have a split decision here. Any objectives to re- --

DR. TILTON: I was going to say, I don't have an objection to reopening. So, as you said, going through evaluating this data in a whole review with the increased use and increased concentrations, we can fully review it in a reopen.

DR. COHEN: Okay.

DR. TILTON: I did not notice the super gum.

DR. ROSS: Yeah, I think I'm quoting that correctly per the citation, but I'm still not sure what it means.

DR. COHEN: Okay. Let's move on. We can have that discussion tomorrow. I think I present it anyway, so we'll see how this goes.

Full Panel – September 12, 2023

DR. COHEN: So Acacia Senegal Gum and Acacia Senegal Gum Extract was reviewed as part of a larger group of ingredients from the Acacia plant. And in 1998, the Panel had an insufficient data conclusion for the entire group. Subsequently, some Panel data needs were met for Senegal Gum and Acacia Senegal Gum Extract. And an amended report was issued in 2005, with a conclusion of safe is used.

Because these other ingredients in the larger group were insufficient, at the original report, they would not be considered in this re-review. We've had a frequency of use increase. We've had a higher concentration of use, and we've had some use in baby products.

Before I make a motion, there was just a technical issue that I wanted to discuss with Susan and Tom. David and I met afterwards, we reviewed the molecular weight of the product and we didn't think there'd be a change in the conclusion. Are you okay if we have a do not reopen vote? I couldn't communicate with you yesterday about it. I don't know if it'll carry, but I just wanted to make sure it was okay.

DR. TILTON: Yes, I agree with that. We had a discussion and sort of a split conclusion about the use in new products, but no concern about the toxicity data,

DR. COHEN: Tom?

DR. SLAGA: I agree.

DR. COHEN: Okay, so then our motion will be not to reopen.

DR. BERGFELD: Is there a second?

DR. BELSITO: No.

DR. COHEN: Okay.

DR. BERGFELD: Not a second. Okay.

DR. COHEN: After all of that.

DR. BELSITO: We had a slightly different conclusion. First of all, we confirmed that the other Acacia ingredients that were found insufficient in the prior report have been moved over to materials that are not supported -- no reported use. Because we were just concerned about what those danglers were. We noted, as you noted, that there was increased concentrations of use, increased uses.

We were a little bit concerned about the IgE-mediated hypersensitivity, and the way we dealt with that in the discussion, which seemed to be more akin to dealing with dermal sensitization rather than IgE-mediated. And we felt that we wanted this report reopened, remove all of the data in the report that had to deal with other Acacia species and re-look at it in terms of the needs to reassess that IgE-mediated safety.

And also to dig into some of the reports, because we've looked at things like hydrolyzed wheat where we've been able to reduce molecular size so it wouldn't bind IgE receptors. But that's not the case here. And we want to see if we can at least look at other reports where we may have dealt with whole proteins that have been reported to cause urticaria as well.

DR. SNYDER: And we wanted to reopen to limit it to Gum Acacia Senegal only. Correct?

DR. BELSITO: Right.

DR. COHEN: Not the extract?

DR. BELSITO: Well, yeah. I mean, all of the Gum Acacia product, but to get rid of all the extraneous data in the report that was related to the other Acacia species in that original report. To get a much clearer look at the information that we have on the products we're looking at, or the ingredients we're looking at.

DR. COHEN: Very big molecular weight, right, so it wasn't going to be a contact sensitizer. Could we not deal with those reports of immediate type hypersensitivity in the re-review summary?

DR. BELSITO: But how are you going to deal with them, because it's used reportedly in aerosols up to 50 percent, or potential aerosols.

DR. COHEN: Not 26 percent?

DR. BELSITO: Well still it's not trivial.

DR. COHEN: Okay, I think you guys are taking a conservative approach to it. I will amend my motion back to our original one, which was reopen.

DR. BERGFELD: Okay. And so, we have a motion that's been made and seconded. I'll call for the vote, all those to reopen? Unanimous. Thank you.

DR. BELSITO: Paul, believe me, I wish I were there.

DR. SNYDER: Oh, tonight you will be sadly missed. Tonight you'll be sadly missed at dinner. It's always one of my favorite times, interacting with the Panel. All right. We'll see you at 1:00.

DR. BELSITO: Okay. Take care.

MARCH 2025 PANEL MEETING – DRAFT AMENDED REPORT

Belsito Team – March 13, 2025

DR. SNYDER: Okay. So, we're going to move on to Acacia. There's Acacia Senegal gum and Acacia Senegal gum extract. This is a Draft Amended Report. In 1998, there was an IDA for a larger group of Acacia ingredients. We are dealing with Acacia gum and Acacia gum extract. An amended final report was published in 2005. September of 2023, we reopened for these two ingredients because of increased frequency and increased concentration of use and a potential risk for IgE-mediated sensitivity.

So, we received 2024 data on these two. And the gum is used in 1,833 formulations. The largest group is mascara use with 555. So, I'll open that up for discussion.

DR. BELSITO: First comment I have is, on PDF Page 23, method of manufacturer. I'm sure that it's for Acacia, not for *Nelumbo nucifera*-derived ingredients, first sentence.

DR. SNYDER: Yeah. Yeah. Is that a typo?

DR. BELSITO: Yeah. I presume it'd because the table looked like it was for Acacia and not *Nelumbo*. And then, I can't recall. This is PDF Page 24. When we mentioned the potential for aflatoxins, is there a slightly different botanical boilerplate when we're concerned about aflatoxins? I can't recall.

DR. RETTIE: You mean one specific to mycotoxins?

DR. BELSITO: Yeah. I mean, Ron Shank used to always do the aflatoxins, so I don't recall. Do we have a slightly different boilerplate when aflatoxins could be an issue?

MS. FIUME: So, we haven't used that in a while. Let me take a look at it right now. So, we do have it for the Discussion, to include an aflatoxin boilerplate. But it may be something that, as it's used, needs discussion because it does state what the designation is by USDA as less than 15 parts per billion. So, I don't know if we'd have to check and make sure that that number hasn't changed.

Or the Panel could choose to do like they've done in the others, where they just refer to a source and take the value out. But it lists what the aflatoxin content should -- what means negative aflatoxin.

DR. BELSITO: We would just need to decide how to do that, whether we put a number in or refer to the regulation.

MS. FIUME: Yeah. I mean. Right now it's less than or equal to 15 parts per billion to indicate negative aflatoxin content.

DR. BELSITO: But we would just have to add that to the botanical boilerplate. And the UV absorption on PDF Page 24 I didn't understand at all. It says that there's increased absorbance between 400 nm and approximately 260 nm, reaching a plateau ranging from 270 to 250, which essentially means to me that this is absorbing through the UVA region. Right?

DR. RETTIE: Yeah. That's how I read it. They did it back to front, starting up at 460 going down.

DR. BELSITO: Yeah. I mean, it's backwards.

DR. RETTIE: Yeah.

DR. BELSITO: But, if that's the case, then we need photo data on this. Right?

DR. SNYDER: Yep. Yeah.

DR. BELSITO: I just have to walk away for one minute. I'll be back.

DR. SNYDER: Okay.

DR. RETTIE: I mean, is it okay to switch the text when it's in italics and text from an old report?

MS. FIUME: Yes, because it's the Panel's work

DR. SNYDER: Yeah, our purview. It’s purview. Yeah.

DR. RETTIE: It just would make more sense to me to just switch the wavelengths there and start at 260.

DR. SNYDER: Okay.

DR. RETTIE: Good. That's how we always do it in other things. Then you have to switch the next sentence too because it's talking about a rapid increase as you go down. So, they're scanning down. I don't know how it's best to do it. It doesn't matter.

DR. KLAASSEN: It would be nice if we could see these UV absorptions instead of describing them. I mean, this is one place where a picture is worth a thousand words.

MS. FIUME: So, this is the information that was in the old report, the 2005 amended report. And it was only wording in there. We don't have the picture.

DR. SNYDER: Spectrum.

DR. RETTIE: Yes. The primary reference that it was taken from

MS. FIUME: It’s unpublished data. So, we can look and see if we can access it or not.

DR. RETTIE: Yeah.

MS. FIUME: So we can check it.

DR. KLAASSEN: That's all I'm suggesting. It's much, much better.

DR. RETTIE: I mean if we had that and then we had a scale for absorbency --

DR. KLAASSEN: Exactly.

DR. RETTIE: -- we might be able to guesstimate whether what the molar absorptivity was even with that number and the concentration is. Yeah. Pictures are worth a thousand words in this.

DR. SNYDER: Wait for Don.

DR. RETTIE: So, while we're waiting for him, is this GRAS? Is that how we're viewing this? It's GRAS?

DR. KLAASSEN: Yes.

DR. SNYDER: Yeah.

DR. RETTIE: That's going to help us a little bit.

DR. SNYDER: Okay, Don.

MS. FIUME: Yeah. This information was submitted in 2000, so we may be able to find it, depending on how good our files are.

DR. BELSITO: Not sure what I missed while I was gone. I'm sorry.

DR. SNYDER: Nothing. We didn't discuss anything other than Allan asked if this was GRAS, and it is.

DR. BELSITO: Well, it certainly is. And it's used, like, 85 percent in some candies? I have a note here someplace. Yeah. It's 85 percent in soft candy, PDF Page 25 under non-cosmetic use.

DR. RETTIE: Some very specific numbers there, 46.5 percent in hard candy.

DR. SNYDER: Yes. Yeah. Hard candy, yeah. So, is the UV enough to go insufficient?

DR. BELSITO: Yeah. I mean, I think that's a huge issue. Isn't it?

DR. SNYDER: Yeah. I think so.

DR. BELSITO: I mean, otherwise, I think all the tox data is good.

DR. SNYDER: Yep. Yep. Yep.

DR. BELSITO: We have 90-day oral tox.

DR. RETTIE: We didn't have any ocular irritation, but I don't know that we need it. Well, we've got mascaras so maybe we do need ocular tox.

DR. BELSITO: And I think the only thing that we need to address other than the photo are these rare IgE-mediated responses. But they appear to be very few, and almost all of them are occupational, suggesting that it's a very high level of exposure that is responsible, beyond what a consumer would see. That's how I read it.

DR. SNYDER: Yeah.

DR. BELSITO: I don't know what other people thought.

DR. SNYDER: I agree. Especially combined with it being a GRAS ingredient, you would expect it to be much, much higher.

DR. BELSITO: Right. Yeah.

DR. SNYDER: Yeah. Yeah.

DR. BELSITO: And I think it should be in the discussion –

DR. SNYDER: Sure.

DR. BELSITO: -- given the seriousness of the IgE and then the botanical boilerplate. But I think we need clarification on the UV before we do? And that's the big holdout. Right?

DR. SNYDER: Good with that?

DR. RETTIE: Yeah. Yeah.

DR. SNYDER: Okay. Anything else?

DR. BELSITO: That was what I had.

DR. SNYDER: That's quick for -- Allan, go ahead.

DR. RETTIE: I've got a couple of points.

DR. SNYDER: Sure.

DR. RETTIE: One was you had it in the old report, you had a structure. When I read through the description of this thing, 1, 3-linked Beta-D-galac, and on and on and on, again, a picture would paint a thousand words. I found it helpful to look back in the structure from the old report, wondered if that could be brought in into the chemistry section.

MS. FIUME: So, is the structure a constituent? Is that correct?

DR. RETTIE: It's the structure of the polymeric complex.

DR. DIYABALANAGE: Actually, when I looked at the literature because when they published the old report they did not have a definitive structure because this structure is actually what we are describing here, it includes a protein moiety.

DR. SNYDER: More than a gum. More than a gum. Yeah. Yeah. Yeah.

DR. DIYABALANAGE: It has a fatty acid, and it has a sugar part too. So, I don't think that we have like any structure that is actually very definitive and drawn.

DR. SNYDER: The gum, yeah.

DR. DIYABALANAGE: Yeah.

DR. SNYDER: Okay. Good point.

DR. DIYABALANAGE: Yeah.

DR. RETTIE: Fair enough.

DR. SNYDER: Yeah. All right. Anything else? So, we're going to go IDA for UV absorption. And, if the UV absorption data is correct, then we're going to need phototoxin and photosensitization.

DR. BELSITO: Correct. And then, in the discussion, the boilerplate botanical with aflatoxin, however, we decide to do the aflatoxin.

DR. RETTIE: You don't want information on ocular irritation since it's used in mascaras? Just a question.

DR. BELSITO: I thought we had ocular irritation from the original report. No?

DR. RETTIE: I have ocular irritation studies were not found. It's in sprays and powders as well. So, maybe we want some inhalational tox.

MS. FIUME: PDF Page 28 for the ocular, Don.

DR. BELSITO: 28?

MS. FIUME: 28, two, eight.

DR. SNYDER: Yeah. There were none found in the published literature and not included in the original report.

DR. BELSITO: I mean, if we're going --

DR. SNYDER: Insufficient, we can ask for it.

DR. BELSITO: I mean, we can ask for it, particularly since there are in vitro models now for ocular irritation. We're not asking them to do anything in animals.

DR. SNYDER: Animal study. Yeah. okay.

DR. RETTIE: We got no pesticide info. Is that something we care about?

DR. BELSITO: That's botanical boilerplate.

DR. SNYDER: It's all botanical boilerplate stuff. Yeah.

DR. RETTIE: Got it. And then, the only other thing I had a question about was needing to define the extract. Is it aqueous or alcoholic? I'm not sure where I read that.

DR. DIYABALANAGE: There was no information about the extract or the extraction methods.

DR. RETTIE: Yeah.

DR. DIYABALANAGE: So, it's a completely unknown quantity.

DR. RETTIE: Yeah. We could ask for that at this stage.

MS. FIUME: So, method of manufacture of the extract?

DR. RETTIE: Yeah.

DR. SNYDER: Aqueous?

DR. RETTIE: Aqueous or ethanol or whatever. Wasn't great.

DR. SNYDER: Yeah. I didn't see that. I didn't pick up on that aerosolized use. Did you, Don?

DR. BELSITO: No. I thought it could be covered by a boilerplate.

DR. SNYDER: Okay.

DR. BELSITO: 2024 RLD data, there's VCRP data, but then there are no -- we do have concentrations of use for inhalation for spray for 2022. Oh, that's 0.003.

DR. SNYDER: Yeah. Very low.

DR. BELSITO: 0.03.

DR. SNYDER: Yeah.

MS. FIUME: And they're not definitive sprays.

DR. SNYDER: Yeah. Right. Yeah. Yeah.

MS. FIUME: They're possible products that could possibly be sprays. They're not definitive.

DR. SNYDER: Where was that aerosol use covered at? In what page?

DR. RETTIE: Could go onto a table.

DR. BELSITO: So, PDF 31 is for the RLDS and the combinations.

DR. SNYDER: Okay. Okay. Thank you. Yeah. 0.003 is the highest. Okay. All right.

MS. FIUME: I mean, yeah.

DR. SNYDER: Okay. We good?

DR. RETTIE: Yeah.

DR. SNYDER: All right. Thank you. All right.

CohenTeam – March 13, 2025

DR. DAVID COHEN: This is a Draft Amended Report on the safety assessment of the *Acacia senegal* gum and *Acacia senegal* gum extract.

We previously reviewed the safety of these as part of a larger group of ingredients for the *Acacia* plant. In 1998, the Panel issued a final report with an Insufficient Data Conclusion for the entire group including gum and gum extract. And this was never published. Subsequently, data was submitted, and the Panel's needs were met only for gum and gum extract. And an amended report was published in 2005, and that conclusion was safe as used.

In September 2023, the Panel reopened the safety assessment for the two ingredients, just those two, because of increased frequency and concentration of use, and use in baby products. We also wanted further information about immediate type hypersensitivity reactions.

According to the 2023 VCRP and the results of the Council survey in 2022, gum was reported in 287 formulations at up to 26.7 percent in "other oral hygiene products." The RLD in 2024 had it in over 1,800 products. And by the way, historically, in 2001, it was in a concentration of 9 percent in mascara. I think I got that, right.

Gum and gum extract are used in sprays and powders that could potentially be inhaled. And it's in face powder. And there's a discussion about immediate type hypersensitivity reactions in the report. So let's open it up. Sam, you want to start?

DR. SAMUEL COHEN: Yeah. I thought for the most part there was a fair amount of tox data, and it was pretty much negative, especially the oral tox. Up to 45 days, it was up to 15 percent of the diet, which is above the amount that is acceptable, but the FDA usually will limit it to 5 percent of the diet.

In human data, there was a 21-day trial that showed no toxicity. There was none present in the feces, which was presumed that it's all digestive and absorbed from the GI tract. The only real toxicity was in rats in the secal enlargement, which to be perfectly frank, has nothing to do with human toxicity. Genotox was negative.

Carcinogenicity data, they actually had two-year bioassays in rats and mice orally, and it was negative. It's in co-carcinogenicity data, which claimed gastric cancer, but I think it was forced on that. We don't have to worry about that.

There was no evaluation that I could pick up of ocular irritation. And there was some indication of allergenicity, which I'll leave to you for interpreting.

DR. DAVID COHEN: The IgE type?

DR. SAMUEL COHEN: Yeah, the IgE. I just wasn't sure how to interpret that. So overall, I thought some of these are -- the use levels were reasonable, and it's a safe product.

DR. DAVID COHEN: Susan? That was great. That was great, comprehensive.

DR. TILTON: In general, I didn't have a lot of concerns about the toxicity either. I was trying to go back because I did not -- I made note that there was no ocular irritation data.

DR. ROSS: There's not?

DR. TILTON: There was not, no. So that was in terms of an insufficiency. That was just because of the use around the eye, ocular irritation was one request to make at this point.

DR. DAVID COHEN: Yeah. David?

DR. ROSS: Yeah, I sort of echo the comments made by Sam and Susan, but I'll just go through this in case there's anything else.

Yeah, GRAS and foods at 85 percent in soft candies, don't -- really no tox concerns apart from one or two things. So here we go. I didn't see general irritation on the gum, the sensitization. Yeah. Irritation, I didn't see. The ocular irritation, the ocular uses are quite high. The RLD comes in at 555 uses in mascaras. So I think even the ocular irritation data at max, which for the gum is 3.8 percent. We need an opinion on the IgE-mediated allergenic reactions, which I asked Dave and Wilma to give us in a minute.

The other issue is gum extract. That's 92 uses, mainly in hair products and makeup. We have no data at all for that. But if it's coming from the gum, then it's probably going to be okay. But I think what we do need there is a method of manufacture in how it's constructed.

DR. DAVID COHEN: For the gum?

DR. ROSS: For the gum extract. I guess a few issues are dermal irritation on the gum, ocular irritation data for the gum at max, the opinion on the allergenic reactions, and method of manufacture for the extract.

DR. DAVID COHEN: I mean, I think the rare cases of immediate type hypersensitivity could be mentioned and discussed. It's not disqualifying thing for the thing to be cleared.

DR. ROSS: That was my summary.

DR. DAVID COHEN: Yeah. I mean, some people, not surprisingly, that any plant can have a potential for immediate hypersensitivity depending on the constituents of it. I think we covered it, and we would just mention it again in the discussion. Hold on.

DR. SAMUEL COHEN: For IgE hypersensitivity, do we take into account the threshold idea that some are assigning that 1 milligram can be a threshold for that kind of reaction?

DR. DAVID COHEN: I don't know what the sensitizing event would be for. For a IgE immediate type hypersensitivity to foods occur through skin desensitization. But I don't know what the thresholds are. Well, are you suggesting a threshold clearance? I don't know how I could do it with the data that's here.

DR. BERGFELD: The gum has protein in it.

DR. DAVID COHEN: Yeah.

DR. SAMUEL COHEN: Yeah.

DR. DAVID COHEN: That's why it can do it.

DR. SAMUEL COHEN: But it's already been GRAS from what I understand. So as a food for --

DR. BERGFELD: I was just looking to see if it's called -- it's called -- was it -- yes, it was called GRAS. Here it is, yeah.

DR. DAVID COHEN: This is gum arabic, right?

DR. SAMUEL COHEN: Yeah.

DR. DAVID COHEN: So, I mean, people have been chewing on this for a long time, right?

DR. ROSS: So what's the summary of the current?

DR. BERGFELD: Well, if it's GRAS, then if you stick with the behavior of this group, you're going to just get human sensitization and irritation. The tox is okay.

DR. ROSS: So it's just dermal and ocular?

DR. DAVID COHEN: Dermal and ocular.

DR. ROSS: And composition on the extract.

DR. DAVID COHEN: I didn't write that down. Composition of the extract. Hold on. Let me just make sure I have everything.

DR. ROSS: Basically, it's a method of manufacture for the extract.

DR. DAVID COHEN: All right. We don't have composition on the extract, right?

DR. ROSS: I mean, if it's coming from the gum, it's going to be all right. But the bare minimum we need in there is how it's made from --

DR. DAVID COHEN: But they may concentrate things differently now. Well, it could be an issue from what Sam's bringing up. Do you concentrate protein, or do you concentrate other things?

DR. SAMUEL COHEN: Right.

DR. ROSS: Yeah. We just need to see how it's made.

DR. DAVID COHEN: Okay.

MR. ZHU: I think it's one large molecule, right, unless you break it down. I don't think that individual parts would be concentrated because it is made by the protein, the sugar, and it has fatty acids too. It's a combination of all these things.

DR. DAVID COHEN: Yes. I get your point.

DR. BERGFELD: I think that we need to discuss the previous discussions in these that are being re-reviewed to make sure that we want to include that information or not. This one has to do with particle size. I think all the botanicals has a pesticide in it. There's the sprays, and you have the inhalation. So all that has to be added.

But this one has to do with sensitization and absorption. It's unlikely that gum would cause sensitization.

DR. DAVID COHEN: I agree with that.

DR. BERGFELD: You want to include that?

DR. DAVID COHEN: Yeah.

DR. BERGFELD: Are we going to keep the old discussion in the final product, or are we going to modify the discussion?

DR. HELDRETH: Typically, we draft something new based on the Panel's discussion.

DR. BERGFELD: Something new. I think it's good to have it in here.

DR. DAVID COHEN: Okay.

DR. BERGFELD: You're going to have to call it GRAS in the Discussion.

DR. DAVID COHEN: It's GRAS, or is it --

DR. BERGFELD: It said GRAS here.

DR. HELDRETH: It's GRAS.

DR. ROSS: It's GRAS.

DR. DAVID COHEN: So it's GRAS, yeah.

DR. ROSS: So it's just ocular and dermal.

DR. BERGFELD: Anyone have problems with the impurities? I have a note to myself.

DR. SAMUEL COHEN: Yeah, and there was that one study with up to 8 percent of the product.

DR. DAVID COHEN: You mean the heavy metals? Is that what you're talking about?

DR. BERGFELD: Protein fraction? The European Food Safety said it was -- protein content was up to 2.7.

DR. DAVID COHEN: Anyone have any issues with that?

DR. SAMUEL COHEN: But there also was -- toward enhancing our confidence in safety is that there is that one study in using mascara up to 88 percent that were totally negative for skin sensitization.

DR. DAVID COHEN: Right. But we still need the ocular tox because they're putting it right near their eyes, right?

DR. ROSS: There's a lot of uses.

DR. DAVID COHEN: Yeah. Yeah. I'm going back and forth on the dermal irritation. We have the sensitization. I mean, I'm okay. I'm okay asking for it. The ocular tox is negative and we have negative sensitization, probably okay clearing it.

DR. ROSS: Ocular, yes.

DR. DAVID COHEN: I have it in the IDA. Are we good?

DR. BERGFELD: This one was easier.

DR. DAVID COHEN: Well, this was only two things.

Full Panel, March 14, 2025

DR. SNYDER: Acacia senegal-derived ingredients, particularly the Gum and the Gum Extract. In 1998, it was part of a larger group of acacia ingredients which there was an Insufficient Data Announcement. The Panel's needs were only met for Acacia Gum and Gum Extract. Amended Final Report was published in 2005.

In 2023 of September meeting we reopened for these two ingredients due to increase frequency of use and increase concentration of use, and a potential risk for IgE mediated hyposensitivity. We received new RLD data. And the Belsito Team motions that we go with an Insufficient Data Announcement. And then I can get those needs, so, an Insufficient Data Announcement.

DR. BERGFELD: Are you going to second it?

DR. DAVID COHEN: It's an IDA, I second the IDA.

DR. BERGFELD: Okay.

DR. DAVID COHEN: And then we can talk about our needs.

DR. SNYDER: So we said we thought that there was UV absorption, or clarification of UV absorption, and the potential for needs of phototox and photosensitization. We did find that the IgE responses were rare and almost all occupational, suggesting high concentration of exposures. We can deal with that in the Discussion. We need the boilerplate for aflatoxins. And that was it.

DR. DAVID COHEN: Those are great IDA components. We wanted ocular irritation since there's a lot of ocular use. For the Gum Extract, method of manufacturing and composition, since we really don't know what the extract is.

DR. SNYDER: I'm sorry, we actually have that on ours also. But, I'll amend it and say that we want to add that also, ocular irritation.

DR. DAVID COHEN: And, we don't have irritation on the Gum. I know we have sensitization. We might ask for irritation. And we don't have irritation and sensitization on the extract. Now, I understand the reply will be, if the extract is from the gum why do we need that? But we just don't know what the extract is.

DR. SNYDER: I think both teams have the same philosophy that when we go insufficient data announcement, let's ask for it so we get clarification. And then we can address it as we --

DR. DAVID COHEN: Right, because one piece of information may nullify the need for the other, but we just don't know what that's going to look like.

DR. SNYDER: We totally agree.

DR. DAVID COHEN: So, we have ocular irritation, method of manufacturing and composition and impurities on the extract, irritation on the gum, and irritation and sensitization on the extract.

DR. BERGFELD: Any additions to that or modifications?

DR. SNYDER: No, I don't think so. Don, I think that's consistent with our conclusion?

DR. BELSITO: So you wanted the sensitization and irritation on the gum, not --

DR. DAVID COHEN: Well, we have --

DR. BELSITO: On the gum, or the extract?

DR. DAVID COHEN: We wanted irritation on the gum. And we wanted irritation and sensitization on the extract. Understanding --

DR. BELSITO: But, if you have a sensitization study that's negative, David, you would have seen irritation. No? So why do you need irritation if you have a negative sensitization study?

DR. DAVID COHEN: I got to go back to look at the method of the study. Standby, one second.

DR. BELSITO: That would be in the original report.

DR. DAVID COHEN: Just a sec. Do you remember, Don, the methods?

DR. BELSITO: I don't off the top of my head, David. I'm sorry.

DR. DAVID COHEN: Wait, here we go.

DR. BELSITO: Skin sensitization, it's PDF Page 71.

DR. DAVID COHEN: Yes, I'm on it now.

DR. BELSITO: SLS was used, I mean, this is a really stressful test here. It says if skin irritation is not observed in occlusive patch da-da-da-da.

DR. DAVID COHEN: It was on for -- there's an induction phase.

DR. SNYDER: Five induction exposures and a 10-day non-treatment period.

DR. BELSITO: And there's an HRIPT using SLS.

DR. DAVID COHEN: Okay, yes. Okay, we're fine with that.

DR. SNYDER: Okay.

DR. BERGFELD: So you are --

DR. DAVID COHEN: We're pulling the irritation on the gum.

DR. BERGFELD: Okay.

DR. BELSITO: Okay, thank you.

DR. BERGFELD: So we have an understanding what the needs will be on this insufficient conclusion at this point in time?

DR. DAVID COHEN: We should.

DR. BERGFELD: I'm going to ask for the vote then. All those in favor of this insufficient report? Unanimous. Okay, moving to the Other Items, Dr. Cohen, Glyceryl Monoesters.

SEPTEMBER 2025 PANEL MEETING – DRAFT TENTATIVE AMENDED REPORT

Belsito Team – September 8, 2025

DR. BELSITO: Okay. Great. Okay. So, then we're moving on to Acacia Senegal. Okay. So, in '98, the Panel initially issued a Final Report with an Insufficient Data Conclusion for the entire group of Acacia ingredients, including the Senegal gum and Senegal extract. The report was never published. Subsequently, data were submitted that met our needs for the gum and the gum extract.

An amended report was published in 2005, with the conclusion that the gum and the gum extract were safe as used in cosmetics. In 2023, we reopened the safety assessment for the two ingredients. The decision to reopen the assessment, the Panel considered increases in frequency and concentration of use and new product categories that included baby products. We wanted to reassess the potential risk of IgE-mediated sensitivity.

In March of 2025, we reviewed the safety data of the two ingredients and decided to issue an insufficient data announcement. The data that were needed were for both ingredients, UV absorption and, if absorbed, phototox and photosensitization, ocular irritation, and for the gum extract, composition, impurities, method of manufacture, sensitization and irritation. And again, we received a bit of data in response to this announcement.

Updated concentration of use data was also obtained from the Council. So, now we're looking at this. So, we received UV on Senegal gum. We got ocular toxicity on both. We have no UV, impurities, manufacture, or sensitization and irritation on the gum extract. But, regarding the extract, is there anything in the gum, if concentrated down, that would give us concern?

I'm assuming gum extract is going to have all the same thing as the gum has. It would be nice to have manufacture and impurities on the extract. So, maybe that's still insufficient. But I thought we could drop UV and sensitization and irritation. The max use is reported to be 0.041 percent in rinse offs and 0.021 percent in leave ons. And no baby products are reported for the extract. So, I'm opening up for discussion.

DR. SNYDER: I had that all the data needs were met for the gum and they were not all met for the gum extract, unless, like you said, caveat, the gum can cover the gum extract. So, the same thing you said, Don.

DR. BELSITO: Right.

DR. SNYDER: But we don't have any data to suggest whether that's different, the gum extract, whether it concentrates down versus the gum. So, I think we're still insufficient, aren't we then?

DR. BELSITO: For all of them?

DR. SNYDER: For the gum extract. I thought we were safe for the gum.

DR. BELSITO: Right. Well, I just thought, except for manufacture and impurities, I wasn't so worried about the UV and sensitization and irritation. We have no composition, right? If you look, Acacia gum, it's basically sugars, galactose, arabinose, rhamnose, and then glucuronic acid and protein. What are we concerned about in the gum Acacia, other than heavy metals, pesticides, and aflatoxins?

DR. RETTIE: It's a good point that you bring up, since it's just a polysaccharide linked to a protein in a couple of positions. Might be helpful to have a structure in there under Chemistry as the glycoprotein molecular structure has been elucidated recently, so we know what that is.

DR. BELSITO: Also we have ocular data on the extract. It's non-irritating. And, I would think that, if it's going to be irritating on the skin, it would be irritating to the eye. There are really no clinical reports of sensitization to speak of. I think, except for manufacture and impurities, if we want to go down that rabbit hole, I think the extract is fine.

Curt, you haven't said anything. Where are you here? Curt, are you with us? I don't know, Paul. What are you thinking? You think we still need all of the data we have asked for in the extract?

DR. SNYDER: That's what my notes summed up for me. I said that they're all met for the gum but not met for the gum extract. And then, question mark about the gum extract versus the gum. But I can go either way.

DR. BELSITO: Who's reporting on this tomorrow?

DR. SNYDER: David reports on it.

MS. FIUME: No, I think you do, Don. Oh, no, I'm sorry, you're right. It is David.

DR. SNYDER: Yeah. Yeah.

DR. KLAASSEN: Can you hear me now?

DR. BELSITO: Yeah.

DR. KLAASSEN: Yes, I think it's good. I don't think we need any more information. And one of the things that makes me feel that way is the GRAS, Generally Recognized As Safe. It's a food.

DR. BELSITO: Yeah. It's used up to 85 percent in soft candies.

DR. KLAASSEN: So, if you can put it in your mouth, you're surely safe on the skin.

DR. SNYDER: You're on mute, Don.

DR. BELSITO: I know. They're jackhammering outside of my building. At 85 percent, if you put it in your mouth as a soft candy, if it were a sensitizer, I'd expect to see a lot of lip dermatitis. And, again, we don't have a lot of clinical reports.

DR. SNYDER: All right. Let's go safe as used for both.

DR. BELSITO: Yeah. See what the Cohen Team says. I mean if anything, if the extract is unsafe, it's manufacture and impurities. But, again, I think we cover that with the pesticide boilerplate and aflatoxin. Well, Cohen reports first. So, if they're going insufficient, we can not second it and have a discussion, right, and then come to terms?

DR. SNYDER: That's the way it works.

DR. BELSITO: Okay. Good. So, safe as used. All right. Okay. Should we take like a five or ten-minute break to stretch?

DR. KLAASSEN: Sure.

DR. RETTIE: Yes, please.

DR. BELSITO: So, it's 3:42 Eastern, so 3:52 Eastern, 12:52 Pacific, 2:52 Central. Okay.

DR. RETTIE: Okay.

Cohen Team – September 8, 2025

DR. DAVID COHEN: All right, we'll move on. We're moving on to the Acacia Senegal. A lot of extracts that I'm presenting. This is a Draft Tentative Amended Report on the safety of the Acacia Senegal gum and gum extract. The Panel originally reviewed the safety of the gum and the gum extract as part of a larger group of ingredients derived from acacia plant.

In 1998, the Panel initially issued a final report with an Insufficient Data Conclusion for the entire group of acacia ingredients reviewed at the time, including gum and gum extract. This report was never published. Subsequently, data was submitted, but the Panel's needs were met only for Acacia Senegal gum and gum extract, and an amended final report was published in 2005, with a conclusion of safe as used.

In September 2023, the Panel reopened the safety assessment for these two ingredients. Our decision to reopen was considered increases in frequency and concentration of use and new product category in baby products. The Panel also wanted to reassess the potential risk for IGE-mediated sensitivity caused by these ingredients.

In March, the Panel reviewed the safety data of the two ingredients and decided to issue an IDA with the following needs for the gum and the gum extract, UV absorption data and if absorbed, phototox, ocular irritation. For the gum that extract, composition and impurities, method of manufacturing, irritation and sensitization. I think we have a max use of 4 percent. For the gum we have HRIPT at 8 percent.

So, we received our data needs for the gum. We received ocular irritation for the gum extract, but none of the others. And in the chemistry section, it says Acacia Senegal gum extract is defined as the extract of the gum of acacia. So, what are your thoughts about clearing?

DR. ROSS: Clear the gum. Insufficient on the extracts because of method of manufacture and lack of skin sensitization data.

DR. DAVID COHEN: Well, okay.

DR. ROSS: That's one option.

DR. DAVID COHEN: Yeah, no, no. And it's a fine option. But if the gum extract is an extract of the gum and we're clearing the gum, are you concerned that we're going to hyper-concentrate a component that we're concerned about that we can't clear the whole thing?

DR. ROSS: Yes. My notes say option one, which I've just given you. Option two, we can give the extract a pass because it's derived from the gum. But there are no details on methods of extraction or impurities, so we really don't know what's in it. But I'm willing to be dissuaded from that.

DR. DAVID COHEN: We have composition of secondary metabolites of Acacia Senegal gum. We know what's in it, right?

DR. ROSS: Extract?

DR. DAVID COHEN: No, the gum.

DR. ROSS: Yeah, I know.

DR. DAVID COHEN: Right. So, what are we going to take from the gum by extracting it?

DR. ROSS: You would hope you're not going to put anything else into it, so if it's an extract you're just going to concentrate what's already in it. I mean, as I said, I present these two options, we can go either way.

DR. SAM COHEN: I tended to lean towards your option two. But it would still be nice to know what the processes of producing the extract. What are the extract with and that. But I would not be worried about the irritation and sensitization because anything that's in there should be in the gum itself.

DR. DAVID COHEN: So, Sam, what was your conclusion, if you had one?

DR. SAM COHEN: The conclusion I had was that we could clear it on irritation and sensitization, but I think we still need process of manufacturer because we need to know what it's extracted with.

DR. DAVID COHEN: Isn't that David's number one, not number two?

DR. ROSS: Numero uno. And I don't know, I flipped flopped between them, and it's a tough call. I mean, we've held things up before for method of manufacturer and method of extraction. And there are examples we can pull out where we've not held it up.

DR. SAM COHEN: So, I guess I mixed up the options. The only thing I think that's left that we don't know is the method of manufacture. I'm not concerned about irritation or sensitization.

DR. DAVID COHEN: To me, this was like if we have the whole plant extract, we would have cleared all the other components. But, Susan, try to break this tie for us.

DR. TILTON: Well, I unfortunately had the exact same two conclusions as Dave. And then my final question is, is just what do we do about the lack of method of manufacturing? So that was my last thought is -- I mean, one is derived from the other, so we presumably could use that to clear some of these endpoints. We have plenty of ocular irritation showing that it's non-irritating. So there doesn't seem to be at least something additional in the extract that would be causing ocular irritation.

DR. ROSS: Do we have that for the extract? I'm just looking at table. I think we have it, if I go through my notes, but I'm just looking at the table up front and it says we don't have it.

DR. SAM COHEN: Have we got ocular irritation data for the gum and the extract?

DR. TILTON: So, it came after the IDA.

DR. ROSS: I'm looking at dermal irritation and sensitization, yeah. We got ocular irritation and sensitization, in vitro and everything, yeah.

Yeah, no, the ocular looks okay. Got a mascara at 3 percent, gum extract five days a week. So even though we don't have an actual concentration used around the eye, I think it's okay because that's the maximum concentration overall, 3 percent. So, you can get away with this (audio skip) the ocular.

DR. DAVID COHEN: David, I see the 3 percent. I can't find where 3 percent is actually used or even comes close.

DR. ROSS: Sorry David, your point being?

DR. DAVID COHEN: So, on Table 3, maximum concentration of use of 3 percent, and I cannot find a product that has anywhere near that concentration.

DR. TILTON: Yeah, I agree.

DR. ROSS: Yeah.

DR. DAVID COHEN: So where is that coming from?

DR. EISENMANN: I thought in 2022, I had a 3 percent in mascara of the gum extract. But I'm not looking at the table. I'm not looking at the table right this minute.

DR. DAVID COHEN: I'm looking at the 2025 table.

DR. EISENMANN: It's what I have in my notes. I don't think it was reported in 2025. But I think in the 2022, which is why you might be getting the data, the safety data on 3 percent in a mascara.

DR. DAVID COHEN: Well then Table 3 is not correct.

DR. ROSS: All right, hang on. Hang on. You're right.

DR. TILTON: Yes, sometimes that max concentration of use column includes both 2025, and 2022 data, I believe, combined.

DR. SAM COHEN: But on that Table 3 in the bottom, under skin care preparations, face and neck, it has 0.17-3.

DR. DAVID COHEN: Where?

DR. SAM COHEN: Under skin care preparations, face and neck, 0.17-3; and under cleansing is 3.4.

DR. DAVID COHEN: No, but you're looking at the gum, not the extract.

DR. ROSS: Yeah, that's the extract. Yeah, I'm not seeing that 3 either, David.

DR. BERGFELD: It's on the bottom of the table on the second page, I think.

DR. DAVID COHEN: I don't see it.

DR. ROSS: I'm not seeing it.

DR. BERGFELD: It's under gum.

DR. DAVID COHEN: It's not under the gum.

MS. BURNETT: I'm sorry, the concentration of use for face and neck, 0.17-3 as a leave on.

DR. DAVID COHEN: Wait, where?

DR. HELDRETH: That's the gum.

DR. ROSS: That's the gum, not the extract.

DR. DAVID COHEN: That's the gum. We're talking about the extract. I mean that there's nothing.

DR. BERGFELD: Extract doesn't even come close.

DR. DAVID COHEN: Right. Doesn't even come close, which means Table 3 is a problem -- with the table.

DR. ROSS: There is a problem with the table.

DR. DAVID COHEN: There's a problem with the table. And if the content of the table I'm having more faith in, then the gum extract is used in very low concentrations.

DR. ROSS: But even if it was 3 percent, I would clear it at ocular given the data I've got.

DR. DAVID COHEN: I just wanted to make everyone feel better with the concentration, but the table needs to be fixed.

DR. ROSS: Yeah. And so, we're back to this issue of no method of manufacture, no impurities, and I have no dermal sensitization data. Am I missing that for the gum extract?

DR. DAVID COHEN: You, I don't think, are missing that.

DR. TILTON: No. I mean it's not included for the gum extract. But we discussed, I guess, if the extract is just an extract of the gum, we wouldn't necessarily expect --

DR. SAM COHEN: You don't need it.

DR. TILTON: -- a different response.

DR. ROSS: Well, you do if you don't know what's -- I mean, yeah, option one, you don't need it. Option two, well, you don't know what's in it, so therefore you do need it. So, we need we need a tiebreaker, as David says, on this. And we're going to have to have to stop being so balanced about it and come to a decision, and then let David argue it out tomorrow.

DR. DAVID COHEN: Yeah, no, I'm just looking.

DR. SAM COHEN: I'm still voting for not needing the dermal sensitization for the extract.

DR. DAVID COHEN: I'm voting to clear the whole report.

DR. ROSS: Okay, let's go with it. I can get behind that based on the extract is prepared from the gum, but this could be precedent setting for botanicals.

DR. DAVID COHEN: No. David, don't you think that -- do you agree that we have gotten whole plant extracts, cleared the individual component based on a whole plant extract?

DR. ROSS: Sorry I didn't get the first part of that question. Can you repeat it?

DR. DAVID COHEN: If in Nelumbo, we had a whole plant, we had data on irritation and sensitization of the whole plant, right, and an extract of the whole plant, might be clear everything maybe other than the cultured components?

DR. ROSS: You are probably correct. And, in fact, we have just done that, I guess.

DR. SAM COHEN: Yes.

DR. DAVID COHEN: Right, so what's the precedent here?

DR. ROSS Yeah. Okay.

DR. DAVID COHEN: I don't think there's a precedent setting here. That's my opinion.

DR. ROSS: You're following precedent, then.

DR. DAVID COHEN: I'm following precedent.

DR. SAM COHEN: Now you're starting to sound like a lawyer.

DR. DAVID COHEN: All right.

DR. ROSS: Please stop me here.

DR. TILTON: And so, is the conclusion on Table 3, that the max concentration of use at the top will be updated to reflect the content in the table? Or will the content in the table will be updated to include the 2022 use?

DR. HELDRETH: I'm going to look back through the surveys that we received from PCPC and find out which numbers are correct. And so, I'll update you to whichever one is what we received.

DR. EISENMANN: We received two, 2022 and 2025.

DR. HELDRETH: All right, so then the 2025 was meant to replace the 2022, because sometimes it's just an addition or replacement.

DR. TILTON: Okay. So, then the max concentration of use for the extract is a hundredfold lower than for the gum. Overall, like, big picture.

DR. DAVID COHEN: Yeah.

DR. ROSS: A hundredfold LOAEL. You got that from the new use concentration?

DR. TILTON: Well, if you look in the table, the highest concentration of the extract is 0.041 percent.

DR. ROSS: Assuming the 3 is erroneous.

DR. DAVID COHEN: I think the 3 is erroneous. Bart, will you have that by tomorrow, perhaps, so we can --

DR. HELDRETH: Yes, I absolutely will. I'll have it in a few minutes; I'm just trying to get it to load.

DR. DAVID COHEN: Let's move on to something that we can really spend some time talking about.

Full Panel – September 9, 2025

DR. DAVID COHEN: Yes, so this is a Draft Tentative Amended Report on the safety assessment of Acacia Senegal Gum, and Acacia Senegal Gum Extract. Our motion is safe as used.

DR. BELSITO: Second.

DR. BERGFELD: Any discussion regarding this ingredient, or edits, or added information to the Discussion. Anything?

DR. DAVID COHEN: The use table for the extract needs to be corrected. Because it's showing -- I'm doing this by memory, I haven't pulled it up, but it showed maximum concentration of use of 3 percent. But nowhere on the table was there anything used at 3 percent. So, we just need to make sure that's corrected.

DR. BELSITO: Yeah, I had the same comment, David. The ranges were .000005 to .041.

DR. DAVID COHEN: We got nowhere near 3 percent.

DR. BELSITO: Right.

DR. HELDRETH: That's right. Yeah, that was old data, and that was our mistake. We'll fix that, no problem.

DR. BERGFELD: Okay, any other edits or comments? I'll call the question, those that disapprove? Abstaining? This ingredient is approved and moved forward as safe. Okay, our next biggie is Dr. Belsito, the Fatty Amphocarboxylates.

APRIL 1997 PANEL MEETING-DRAFT REPORT

After reviewing the Draft Report, the Panel determined that the available data are insufficient for arriving at a conclusion on the safety of these ingredients. Considering that data were not received in response to the informal data request issued at the December 1996 Panel meeting, the Panel voted unanimously in favor of issuing an Insufficient Data Announcement with the following data requests (on all of the Acacias being reviewed):

(1) Concentration of use; (2) Identify the specific chemical constituents, and clarify the relationship between crude Acacias and their extracts and the Acacias and their extracts that are used as cosmetic ingredients; (3) Data on contaminanats, particularly relating to the presence of pesticide residues. Additionally, determine whether Acacia melanoxylon is used in cosmetics, and whether acamelin (a quinone) and melacacidin (a flavin) are present in the Acacias that are being used; (4) Skin sensitization study (i.e. dose response to be determined); (5) Contact urticaria study at use concentration; and (6) UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then a photosensitization study may be needed. Note: Other studies may be requested after clarification of the chemical constituents of the Acacias.

SEPTEMBER 1997 PANEL MEETING TENTATIVE REPORT W/ INSUFFICIENT DATA CONCLUSION

The Panel voted unanimously in favor of issuing a Tentative Report with an insufficient data conclusion. The data needed for completion of this safety assessment will be listed in the report discussion as follows:

(1) Concentration of use

(2) Identify the specific chemical constituents, and clarify the relationship between crude Acacias and their extracts and the Acacias and their extracts that are used as cosmetic ingredients

(3) Data on contaminants, particularly relating to the presence of pesticide residues. Additionally, determine whether Acacia melanoxylon is used in cosmetics, and whether acamelin (a quinone) and melacacidin (a flavin) are present in the Acacias that are being used

(4) Skin sensitization study (dose response to be determined)

(5) Contact urticaria study at use concentrations

(6) UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then a photosensitization study may be needed

Note: In the absence of information on the chemical constituents of the various Acacias, the test data is needed on all species. Other studies may be required after clarification of the chemical constituents of the Acacias.

The Panel also agreed to delete all studies on Acacias other than those listed on the cover page of the Tentative Report. Material from all studies removed will be saved in a WordPerfect file for future use.

Regarding a comment (from Carlisle International Corporation) to the Insufficient Data Announcement that was issued at April 3-4, 1997 Panel meeting, Dr. Andersen noted that CIR will respond in writing. The purpose of the written response is that of seeking documentation for the various conclusions on the safety of Acacia Concinna that are stated in the comment.

Furthermore, because cosmetic uses of Acacia Concinna are implied in the comment, the addition of this ingredient to the present review was recommended.

Dr. McEwen noted that uses of Acacia, with no mention of the species, are reported to FDA, and that Industry has petitioned FDA to use both the genus and species of a cosmetic ingredient (botanical) in reporting frequency of use data.

MARCH 1998 PANEL MEETING-FINAL REPORT W/ INSUFFICIENT DATA CONCLUSION

Dr. Belsito noted that a Tentative Report with an insufficient data conclusion was issued at the September 22-23, 1997 Panel meeting, and that report comments (but no supporting data) were received from Carlisle International Corporation. Dr. Belsito added that, to date, the Panel has not received the data needed for completion of this safety assessment. The Panel voted unanimously in favor of issuing a Final Report with an insufficient data conclusion. The data needed in order for the Panel to complete its safety assessment of this group of ingredients are listed in the discussion section of the report as follows:

(1) Concentration of use

(2) Identify the specific chemical constituents, and clarify the relationship between crude Acacias and their extracts and the Acacias and their extracts that are used as cosmetic ingredients

(3) Data on contaminants, particularly relating to the presence of pesticide residues. Additionally, determine whether Acacia Melanoxylon is used in cosmetics, and whether acamelin (a quinone) and melacacidin (a flavin) are present in the Acacias that are being used

(4) Skin sensitization study (dose response to be determined)

(5) Contact urticaria study at use concentration

(6) UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then a photosensitization study may be needed

Dr. Belsito noted that the preceding data requests are for each of the various Acacia species reviewed in this report.

Dr. Schroeter recalled the Panel=s review of data indicating that Acacia Melanoxylon is a sensitizer. He also noted that FDA frequency of use data indicate that Gum Arabic (Acacia) is used in mascara, which is used in the area of the eye.

Dr. Belsito said that Acacia Melanoxylon is not listed as one of the species of Acacia that is used in cosmetics. He also said that the Panel does not know whether the sensitizing chemicals in this particular species of Acacia are also present in the other Acacias.

Dr. McEwen said that the preceding statement by Dr. Belsito supports the need for industry to supply chemical characterization data on cosmetic ingredients, particularly on botanicals.

SEPTEMBER 2000 PANEL MEETING-NEW DATA RECIEVED

Dr. Schroeter stated that the Panel issued a Final Report with an insufficient data conclusion on these ingredients at the March 19-20, 1998 Panel meeting, and that the Panel's data needs are listed in the report discussion as follows:

(1) Concentration of use

(2) Identify the specific chemical constituents, and clarify the relationship between crude Acacias and their extracts and the Acacias and their extracts that are used as cosmetic ingredients

(3) Data on contaminants, particularly relating to the presence of pesticide residues. Additionally, determine whether Acacia Melanoxylon is used in cosmetics, and whether acamelin (a quinone) and melacacidin (a flavin) are present in the Acacias that are being used

(4) Skin sensitization study (dose response to be determined)

(5) Contact urticaria study at use concentration

(6) UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then a photosensitization study may be needed

Since the issuance of the Final Report, the identity of various ingredients in this family has been described in the International Cosmetic Ingredient Dictionary and Handbook, two new ingredients in this family have been added to the dictionary, and the following information was received in response to the Panel's data requests: (1) an evaluation of the contact-sensitization potential of a topical coded product (mascara containing 8% Acacia Senegal) on human skin by means of the maximization assay, (2) pesticide residue analysis of Acacia Senegal, (3) UV absorption spectra on Acacia Senegal, and (4) product information (physical and chemical properties included) on Gum Arabic.

The following information on Acacia Concinna Fruit Extract was also received: (1) recommended use concentration range [previously submitted], (2) relationship between crude Acacia Concinna and its extract [previously submitted] , (3) impurities analysis for pesticides [previously submitted; results, but no data], (4) human skin tolerance test [skin irritation evaluated], and (5) skin sensitization study [results, but no data], contact urticaria study [results, but no data], and UV spectral analysis [results, but no data].

It was agreed that the Panel needs to determine whether the additional new data received and clarification of the cosmetic ingredient description of Gum Arabic represent a sufficient basis for amending the Panel's original insufficient data conclusion on the Acacia ingredient family.

Dr. Schroeter noted that based on the clarification of terminology used in the dictionary, Gum Arabic is now clearly identified as being the gummy exudate from acacia plants in Africa (e.g. Acacia Senegal Gum from *Acacia senegal*). He added that this definition should be included in the report introduction.

Drs. Schroeter and Shank noted that because it has been determined that Acacia Melanoxylon is a non-African species of Acacia, the request for information relating to this Acacia species in item 3 should be deleted. It was also noted that data on pesticide residues in Acacia Senegal have been received from industry.

Dr. Eisenmann noted that Acacia melanoxylon is an Australian species of Acacia.

Dr. Schroeter said that the human maximization test data (28 subjects) may be sufficient for evaluating the skin sensitization potential of Acacia Senegal. He also stated that his Team expressed concern over the contact urticaria potential of species of Acacia. However, in the absence of these data, Dr. Schroeter noted that Gum Arabic is generally recognized as safe for use as a direct additive in foods designated for human consumption and that it is metabolized in the gut to basic sugars. He also noted that, because of its molecular size and water solubility, Gum Arabic is absorbed very slowly through the epidermis.

Dr. Schroeter said that his Team determined that Acacia Senegal Extract, Acacia Senegal Gum, and Acacia Senegal Gum Extract are safe as used, that UV absorption data only are needed to arrive at a conclusion on the safety of Acacia Concinna Fruit Extract, and that all of the data requests listed at the beginning of this section are needed in order to arrive at a conclusion on the safety of the following ingredients: Acacia Catechu Gum, Acacia Dealbata Leaf Extract, Acacia Decurrens Extract, Acacia Farnesiana Extract, and Acacia Farnesiana Gum.

Dr. Belsito noted that the conclusions for a UV spectral analysis, skin sensitization study, and contact urticaria study on Acacia Concinna Fruit Extract are included in a letter (to Dr. Eisenmann) from Carlisle International Corporation, but that data supporting these conclusions were not provided. With this in mind, he wanted to know why only UV absorption data on Acacia Concinna Fruit Extract are being requested.

Dr. Shank said that Acacia Concinna Fruit Extract is used only in rinse-off products, except for use in a small number of eye make-up products. He noted that Dr. Schroeter's Team determined that this ingredient is safe as used in rinse-off products, because it would be very slowly absorbed due to its large molecular size and water solubility.

Dr. Belsito wanted to know how the use of Acacia Concinna Fruit Extract in leave-on products should be addressed.

Dr. Shank said that it is not his understanding that Acacia Concinna Fruit Extract is being used in leave-on products.

Dr. Belsito noted that Acacia is used in mascara products.

Dr. Eisenmann said that the only use data for Acacia Concinna are from a supplier, and these data indicate use of this ingredient in hair products. She also noted that the use frequency data submitted to FDA refer to Acacia, with no indication of the species of Acacia.

Dr. Belsito agreed that the data on Acacia Senegal are sufficient for arriving at a conclusion on the safety of this ingredient. He also said that if the data referred to in the letter form Carlisle International Corporation exist, then these data may be sufficient for arriving at a conclusion on the safety of Acacia Concinna as well. Dr. Belsito favored tabling the current report, pending details from the UV spectral analysis of Acacia Concinna Fruit Extract and studies evaluating the skin sensitization and contact urticaria potential of this ingredient. He noted that it is not possible for the Panel to issue an amended conclusion on the safety of the Acacias at this Panel meeting.

The Panel voted unanimously in favor of tabling the report on the Acacia ingredient family, pending details from the UV spectral analysis of Acacia Concinna Fruit Extract and studies evaluating the skin sensitization and contact urticaria potential of this ingredient.

Dr. Andersen said that it should be captured for the record that the Panel agrees that Acacia Senegal Gum can be ruled safe as used. He said that the intent is not to return to that issue substantially at the December 4-5, 2000 Panel meeting, because there is the sense that Acacia Senegal Gum is Gum Arabic and can be ruled safe as used.

Dr. Bergfield asked Dr. Belsito to describe the ideal study for contact urticaria.

Dr. Belsito's comments were as follows: (1) Simply place the material (under a patch) on intact skin. (2) Remove the patch at 30 minutes and evaluate. The positive control is usually histamine (1 mg/ml), and the negative control is usually saline.

Referring to the Clinical Assessment of Safety section of the report, Dr. Bergfeld asked whether there is any concern over the contact urticaria potential of Acacia Gum. She noted that in a study involving ten subjects, generalized urticaria was reported after ingestion of various gum-containing foods (Gum Arabic included).

Dr. Belsito said that the study results need to be discussed.

FEBRUARY 2001 PANEL MEETING- TENTATIVE AMENDED FINAL REPORT

Dr. Belsito said that his Team had reached a tentative conclusion on the safety of these ingredients at yesterday's Team meetings, but that this conclusion may need to be revised based on information indicating that *Acacia farnesiana* is not an African species of Acacia. Specifically, according to the Germplasm Research Information Network of the U. S. Department of Agriculture, *Acacia farnesiana* is native to North America and South America. Dr. Belsito noted that it is not likely that *Acacia farnesiana* would be considered Gum Arabic because it is not an African species of Acacia.

Dr. Belsito noted that after reviewing all of the available information, his Team concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe as used in cosmetic products and that the data are insufficient to assess the safety of the following ingredients: Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, and Acacia Senegal Extract. It was determined that the following data are needed for completion of the safety assessment on these ingredients:

(1) Concentration of use in cosmetics

(2) Identify the chemical constituents; if they are sufficiently different from those of Acacia Senegal Gum, then the following data would be needed:

(a) UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then phototoxicity and photosensitization studies may be needed

(b) With the exception of Acacia Farnesiana Extract, sensitization and irritation data are needed

(c) Two genotoxicity assays, one in a mammalian system; if positive, then a 2- year dermal carcinogenicity study using NTP methods may be needed

(d) Dermal absorption data; if there is any evidence of significant dermal absorption, then reproductive and developmental toxicity data may be needed

Additionally, Dr. Belsito's Team agreed that both pesticide and heavy metal components of Acacia Senegal Gum and Acacia Senegal Gum Extract should be restricted to the levels specified in the CIR Final Report on Lanolin, and that these restrictions should be incorporated into the report discussion.

Dr. Bergfeld stated that the restrictions on pesticides and heavy metals should be included in the discussion section of all CIR reports on botanical ingredients.

Dr. Belsito noted that genotoxicity data are being requested because all of the genotoxicity data included in the report are on Gum Arabic and are not applicable to the other acacia-derived ingredients. Dr. Belsito added that dermal absorption data are being requested for the same reason (i.e., lack of dermal absorption data on the remaining ingredients).

The Panel voted unanimously in favor of issuing a Tentative Amended Final Report with the following conclusion: Based on the available animal and clinical data included in this report, the CIR Expert Panel concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe as used in cosmetic products. The Panel also concluded that the available data are insufficient to support the safety of the following ingredients in cosmetic products: Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, and Acacia Senegal Extract.

The Panel also agreed that the data needed for completion of the safety assessment on ingredients with an insufficient data conclusion will be listed in the report discussion. The data needs are listed on the preceding page.

SEPTEMBER 2001-TABLED

Dr. Marks stated that his Team determined that the Final Report draft on this ingredient family should be tabled for 90 days, so that the Panel can gather more information on the semi-quantitative composition of each ingredient (gums included).

Dr. Belsito noted that his Team reviewed the following information that was submitted: (1) published information on the composition of Acacias that was compiled by the European Federation for Cosmetic Ingredients), (2) skin irritation and acute oral toxicity animal studies on Acacia Dealbata Leaf Wax, and (3) skin irritation and acute oral toxicity animal studies on Acacia Farnesiana Flower Wax. He also noted that the current report on the Acacia ingredient family has been under review by the Panel for quite some time, and that questions relating to the composition of these ingredients remain unanswered. Specifically, item 1 consists of lists of components of some of the Acacias, but the data are not sufficient for determining whether or not similarities exist.

Dr. Belsito was not in favor of tabling the report. He said that a Final Report should be issued at this meeting, and that any interested parties will have an opportunity to submit the data that are needed in the future.

Dr. Slaga said that Dr. Mark's Team had hoped that there would be some type of standardization of a way to present the complex mixtures, a way to reorganize so that different types of similar mixtures could be compared quantitatively.

Dr. Belsito expressed concern over the fact that most of the data on composition were obtained from the internet. He said that unless published documents are associated with these data, it is possible that the information may not be credible.

Dr. Shank said that his Team agreed that the chemists who generated the qualitative data probably have the ability to make a semi-quantitative report. He added that tabling the report would give the chemists an opportunity to submit a semi-quantitative report and specify the composition of the gums.

Dr. McEwen said that the Panel had not previously requested composition data, but had requested identification of the constituents of Acacias. He said that it should be made clear that the Panel needs semi-quantitative composition data, not a listing of constituents, and that interested parties should be given an opportunity to provide the data.

Dr. Belsito agreed that data on the % composition of constituents are needed.

The Panel voted unanimously in favor of tabling the Final Report draft on the Acacia ingredient family for 90 days, pending the submission of semi-quantitative composition data.

NOVEMBER 2001-AMENDED FINAL REPORT

The Panel voted unanimously in favor of issuing an Amended Final Report on the Acacia ingredient family with the following conclusion: Based on the available animal and clinical data included in this report, the CIR Expert Panel concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe as used in cosmetic products. The Panel also concluded that the available data are insufficient to support the safety of the following ingredients in cosmetic products: Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, and Acacia Senegal Extract.

The Panel's data needs relative to the following ingredients are stated below: Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, and Acacia Senegal Extract.

(1) Concentration of use in cosmetics

(2) Identify the chemical composition; if they are sufficiently different from those of Acacia Senegal Gum, then the following data would be needed:

(a) UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then phototoxicity and photosensitization studies may be needed

(b) With the exception of Acacia Farnesiana Extract, sensitization and irritation data are needed

(c) Two genotoxicity assays, one in a mammalian system; if positive, then a 2- year dermal carcinogenicity study using NTP methods may be needed

(d) Dermal absorption data; if there is any evidence of significant dermal absorption, then reproductive and developmental toxicity data may be needed

Dr. Belsito noted that the table of qualitative data on Acacias that was presented to the Panel should be incorporated into the report text.

Amended Safety Assessment of Acacia Senegal Gum and Acacia Senegal Gum Extract as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: May 22, 2026
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: David E. Cohen, M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Regina Tucker, M.S., former Scientific Analyst/Writer, and Thushara Diyabalanage, Ph.D., former Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

BCOP	bovine corneal opacity and permeability
CFR	Code of Federal Regulations
cfu	colony forming units
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary*
DMH	1,2-dimethylhydrazine
DSS	dextran sodium sulfate
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV	forced expiratory volume
GRAS	generally recognized as safe
HET-CAM	hen's egg test on the chorioallantoic membrane
HPLC	high-performance liquid chromatography
IgE	immunoglobulin E
IVIS	in vitro irritation score
LD_{50}	median lethal dose
LOQ	limit of quantification
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MTT	3-[4,5-dimethylthiazol-2yl]-2,5-diphenyltetrazolium bromide
NOAEL	no-observed-adverse-effect-level
OECD	Organisation of Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate buffered saline
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-*p*-dioxins
PCDF	polychlorinated dibenzofurans
RLD	Registration and Listing Data
SLS	sodium lauryl sulfate
SPT	skin prick test
TGFβ1	transforming growth factor β1
US	United States
USDA	United States Department of Agriculture
UV	ultraviolet
VCRP	Voluntary Cosmetic Registration Program
WHO-TEQ	World Health Organization-toxic equivalent

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of Acacia Senegal Gum and Acacia Senegal Gum Extract. Acacia Senegal Gum has several reported functions in cosmetics (i.e., adhesive, binder, emulsion stabilizer, film former, and fragrance ingredient), but no function is reported for Acacia Senegal Gum Extract. Industry should minimize impurities in these ingredients, such as heavy metals and pesticide residues, according to limits set by the US Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA). The Panel reviewed the relevant data to determine the safety of these ingredients, and issued an amended report reaffirming the previous conclusion that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

According to the *International Cosmetic Ingredient Dictionary* (*Dictionary*), Acacia Senegal Gum is reported to function in cosmetics as an adhesive, binder, emulsion stabilizer, film former, and fragrance ingredient; no function is reported for Acacia Senegal Gum Extract.[1] These ingredients were first reviewed as part of a larger group of ingredients derived from several species of the acacia plant. In 1998, the Expert Panel for Cosmetic Ingredient Safety (Panel) issued a final report with an insufficient data conclusion for a group of 11 acacia ingredients, including Acacia Senegal Gum and Acacia Senegal Gum Extract.[2] Subsequently, the Panel's data needs were met for Acacia Senegal Gum and Acacia Senegal Gum Extract, but none of the other acacia-derived ingredients (including Acacia Senegal Extract, now named Acacia Senegal Flower/Stem Extract according to the *Dictionary*), and an amended final report was published in 2005.[3] At that time, the Panel concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe as used in cosmetic based on the animal and clinical data included in that report. (Both of these reports are available on the Cosmetic Ingredient Review (CIR) website (https://cir-reports.cir-safety.org/).)

In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In September 2023, the Panel determined that this safety assessment should be reopened to reassess the risks of immunoglobulin E (IgE)-mediated hypersensitivity caused by these ingredients.

Botanicals, such as *Acacia senegal*, may contain hundreds of constituents. In this assessment, the Panel is evaluating the potential toxicity of these ingredients as whole, complex substances; toxicity from single components might not predict the potential toxicity of botanical ingredients.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted in April 2026. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties. Please note that because the other ingredients included in the larger group had an insufficient data conclusion, they are not included in the review.

Excerpts of data from the previous report on the acacia-derived ingredients that are relevant to Acacia Senegal Gum and Acacia Senegal Gum Extract are disseminated throughout the text of this re-review document, as appropriate, and are identified by italicized text. (This information is not included in the tables or the summary section.)

The cosmetic ingredient names, according to the *Dictionary*, are written as depicted in the title of this report, without italics and without abbreviations. When referring to the genus and species from which the ingredients are derived, the standard taxonomic practice of using italics is followed (i.e., *Acacia senegal*). Often in published literature, the general names acacia, acacia gum, and gum arabic are used, and it is not known how the substance being tested compares to the ingredient as used in cosmetics. Therefore, if it is not known whether the substance being discussed is equivalent to the cosmetic ingredient, the test substance will be identified by the name used in the publication that is being cited (which is the case throughout most of this report, as well as in the data excerpted from the previous report). However, if it is known that the substance is a cosmetic ingredient, the naming convention provided in the *Dictionary* (e.g., Acacia Senegal Gum) will be used.

CHEMISTRY

Definition and Plant Identification

According to the *Dictionary*, Acacia Senegal Gum (CAS No. 9000-01-5) is the dried, gummy exudate obtained from plant *Acacia senegal*; the accepted scientific name for *Acacia senegal* is *Senegalia senegal*.[1] Acacia Senegal Gum is often referred to as gum arabic in the published literature. Acacia Senegal Gum Extract is defined as the extract of the gum of the acacia, *Acacia senegal*.

Structurally, gum arabic is an arabinogalactan-protein complex (glycoprotein) composed of magnesium, calcium, and potassium salts of arabic acid.[4] The structure of arabic acid is made of 1,3-linked β-D-galactopyranosyl units along with branches that consist of two to five β-D-galactopyranosyl residues linked together via 1,3-ether linkages and connected to the fundamental β-

D-galactopyranosyl chain by 1,6-linkages. The main component of this gum (approximately 90%) is an arabinogalactan fraction with a molecular weight 250 kDa.[5,6] An example structure of this fraction is drawn in Figure 1.

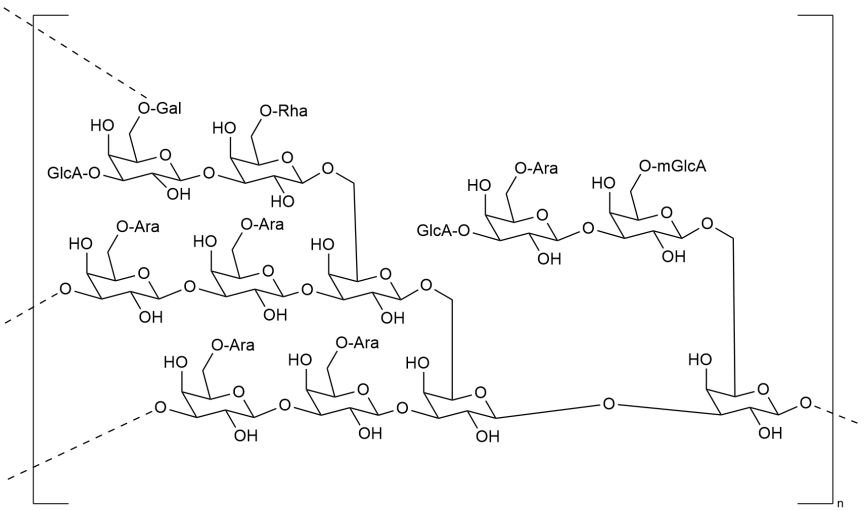

Figure 1. An example arabinogalactan faction (Gal is galactose; Rha is rhamnose; Ara is arabinose; GlcA is glucouronic acid; and mGlcA is 4-*O*-methyl-D-glucouronic acid)

The minor component of the gum consists of hydrophobic proteins with a molecular weight range of 1000 - 2000 kDa. This protein component is associated with the arabinogalactan via covalent bonds at hydroxy proline, serine and threonine amino acid units.

Upon further investigations conducted using high-performance size exclusion chromatography, multi-angle laser light scattering, single-angled x-ray scattering, synchrotron radiation circular dichroism and transmission electron microscopy, the glycoprotein molecular structure has been elucidated as mixture of spheroidal monomers and more anisotropic oligomers.[7] These studies have shown that the molecular architecture of Acacia Senegal Gum is an assembly of ring-like glycoproteins modules which have been explained as hydroxyproline and arabinogalactan subunits.

Glycosylphosphatidylinositol lipid units are also present in the acacia gum superstructure. These lipid units are composed of saturated fatty acids (C_{22} - C_{25}) some of which are hydroxylated at the second carbon.[6] The glycosyl component is oligosaccharide in nature.

Chemical Properties

Gum arabic is a pale white to orange-brown solid which breaks with a glassy fracture.[8] The best grades are in the form of spheroidal tears of varying size with matte surface texture. When ground, the resultant pieces are paler and have a glassy appearance. Additional chemical properties are listed in Table 1.

Method of Manufacture

Gum arabic is produced when the Acacia tree is stressed by infection, poor nutrition, heat, or lack of moisture.[3] The gum exudes through wounds in the bark that occur naturally or are purposely made to stimulate production. The exudate dries rapidly, is collected as hardened drops or tears, sorted, graded, and marketed. The gum becomes harder during storage. The removal of the bark that adheres to the tears is critical to the production of quality gum arabic.

Acacia gum is in the form of tears or nodules when it is collected from the trees.[6] It then undergoes sorting and grading based on their color and impurities. The gum which is light in color is considered best in quality. It can deteriorate during storage due to the presence of enzymes. Therefore, the deterioration is prevented by temperature control during the storage period.

Raw gum is a blend of gum nodules with different mesh sizes, containing vegetable and mineral impurities and fluctuating bacteriological contamination.[5] The level of impurities can be reduced slightly using dry purifications steps, such as kibbling, sieving and pulverization. Kibbling is a mechanical treatment of nodules or tears for the preparation of acacia gum powder of different particle/mesh size. This kibbled gum has more solubility as compared to nodules or tears of acacia gum. For the preparation of food grade acacia gum, the best quality gum nodules are selected. However, the bacteriological contamination cannot be improved, and often raw gum does not meet the specifications for acacia gum.

The dry methods of purification have been substituted by purification in an aqueous solution as they have proven to be more efficient. The gum is fully dissolved in water and all the impurities removed by a cascade of filtration steps reducing the levels of insoluble matter in the finished product (as low as 0.02%). Bacterial contamination is also reduced by treatment in a heat exchanger plate and the gum syrup is concentrated and dried, reducing the level of microbial contamination in the powder to not more than 0.05 colony-forming units per gram (cfu/g).

Different processes are used for recovering purified, powdered Acacia Senegal Gum from the syrup. Roller-drying is used to produce gum in powder form with good hydration properties. However, the drastic thermal treatment employed at the drying step can have undesirable effects which reduce emulsifying properties. Spray drying has been able to address this successfully to retain good physical and functional properties. The spray drying techniques have been further improved by using a multi-stage spray drying process where fine particles of gum produced during drying are recycled at the top of the dryer. Agglomerated gum particles are obtained, keeping the entire properties of the raw gum, but containing no dust or particles below 75 µm and giving unique hydration and dissolution properties, without any lump formation up to the maximum level of solubility in water of 45 - 50%.

Composition/Impurities

Three grades of gum arabic have been noted in the published literature: (1) processed gum arabic recovered by spray-drying from a solution of commercial food-grade gum arabic after filtration to remove sand, and after heat treatment to effect pasteurization; (2) finely powdered natural gum arabic of poor commercial quality, giving solutions of a dark reddish-brown color; (3) finely powdered natural gum arabic of very high quality, giving essentially colorless solutions.[3]

Acacia gum contains galactose (37 – 53%), arabinose (20 – 30%), rhamnose (10 – 16%), glucuronic acid (6 – 14%), 4-*O*-methyl-D-glucouronic acid (1.5%), and protein 2%.[6] According to a documentation provided to the European Food Safety Authority (EFSA), the protein content was in a range of 0.99 - 2.7% in three samples analyzed in duplicate.[5] The principal amino acids found in acacia gum arabic are hydroxy proline, serine, aspartic acid, glycine and leucine.[6]

The protein fraction in acacia gum is known to contain oxidizing enzymes, particularly oxidases and peroxidases which may oxidize some secondary metabolites present in the gum.[5] In fact, it is thought that the oxidation of amines and phenols may form the colored compounds. However, it has been noted that heating acacia gum to a high temperature during manufacturing may destroy these enzymes before the start of their actions.

According to *United States Pharmacopeia* monographs, *acacia* has following specifications: loss on drying (15% maximum); arsenic (3 ppm); lead (0.001%), heavy metals (0.004%); total ash (not more than 0.5%); and insoluble residue (not more than 50 mg/5 g).[9]

Five batches each of two acacia gum exudates were analyzed (after hydrolysis) for molar distribution of the sugars.[10] Galactose was in the range 28.3 – 37.1%, arabinose 31.7 – 53.6%, rhamnose 1.9 – 16.3%, and glucuronic acid 5.3 – 16.3%. The same batches showed also concentrations of arabinogalactoprotein in the range 6.8 – 36.9%, and concentrations of arabinogalactan plus glycoprotein fraction ranging from 63.1 - 93.2 %; the molecular weights varied between 373,000 and 1,071,100 Da.

During an analysis of five additional batches acacia gum (gum arabic) for impurities and contaminants, lead concentration varied between < 0.02 (limit of quantification (LOQ)) and 0.036 mg/kg; mercury, cadmium and arsenic were below the respective LOQs.[10] Aluminum concentration was in the range 3.7 – 14.7 mg/kg, iron 3.2 – 16.5 mg/kg, copper 1.1 – 1.59 mg/kg, and zinc and tin below the respective LOQs. Presence of mycotoxin ochratoxin A, in acacia gum (gum arabic) was below the LOQ (0.5 µg/kg in four batches and 0.02 µg/kg in one batch). Aflatoxins B1, B2, G1 and G2 were detected at < 0.01 µg/kg (all of them in four batches) and < 0.02 µg/kg (one batch). The sum of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) was in the range of 0.032 – 0.13 ng PCDD/F World Health Organization *polychlorinated dibenzo*-p-*dioxins and furans toxic equivalence* (WHO-TEQ)/kg, dioxin-like polychlorinated biphenyls (PCBs) were in the range 0.015 – 0.06 ng WHO-TEQ/kg, and the sum of dioxins and dioxins-like PCBs in the range 0.047 – 0.19 ng PCDD/F + PCB WHO-TEQ/kg. The pesticides were not detected in a multiresidue analysis (> 30 compounds of different groups). *Escherichia coli* (in 5 g) and *Salmonella* spp. (in 25 g) were absent in all the batches.

The chemical composition of a sample of gum acacia dissolved in water was determined via high-performance liquid chromatography (HPLC).[11] The results showed the presence of a variety of phenolic compounds and flavonoids. The major phenolic compounds were identified as *p*-coumaric and ferulic acid (10.14 µg/ml and 11.09 µg/ml, respectively), and the major flavonoid was luteolin (10.22 µg/ml). The results obtained using HPLC are also shown in Table 2.

UV Absorption

An increase in absorbance for Acacia Senegal was observed between 400 nm and approximately 260 nm, reaching a plateau at wavelengths ranging from 270 to ~250 nm.[3] *A rapid increase in absorbance was observed at wavelengths less than 250 nm. UV absorption spectra provided on two other lots of Acacia gum (Acacia Senegal) were both similar to the preceding UV spectral analysis.*

The UV absorption spectrum of a mixture (202 µg/ml) containing Acacia Senegal Gum (51 - 59%) was submitted.[12] It was observed that the absorbance over the wavelength range 290 - 700 nm was negligible.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US FDA and the cosmetics industry on the expected use of Acacia Senegal Gum and Acacia Senegal Gum Extract in cosmetics. Registration

and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[13] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

According to RLD obtained from FDA in 2025, Acacia Senegal Gum is used in 2938 formulations, and Acacia Senegal Gum Extract in 149 formulations (Table 3).[14,15] According to the results of the concentration of use survey conducted by the Council in 2025, Acacia Senegal Gum has the highest maximum concentration of use at 4% in mascaras and in eyelash and eyebrow preparations.[16]

As stated above, cosmetic products containing these ingredients may incidentally come in contact with the eyes, and they are also used in products that could be incidentally ingested and come in contact with mucous membranes (e.g., up to 2.9 % Acacia Senegal Gum in dentifrices). Additionally, Acacia Senegal Gum and Acacia Senegal Gum Extract are used in cosmetic formulations that are sprays and Acacia Senegal Gum in powders, and could possibly be inhaled; for example, Acacia Senegal Gum is used in hair sprays and other fragrance preparations at 0.19 and 0.42%, respectively, and in face powders (concentration not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

It is possible that some products containing Acacia Senegal Gum or Acacia Senegal Gum Extract may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined therein, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. None of the reported product categories for these ingredients as listed in the RLD include a designation indicating airbrush application, so it is possible that these ingredients are used with airbrush delivery systems, but not reported as such. Additionally, concentration of use surveys are conducted based on product categories as stated in the RLD; airbrush use was not reported in response to the survey. No consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with airbrush technology, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. If these ingredients were to be used in airbrush formulations, the data are insufficient to evaluate the exposure resulting from cosmetics applied in such a manner.

Non-Cosmetic

Gum arabic is a direct food substance generally recognized as safe (GRAS) under the provisions of Section 184.1330 of the Code of Federal Regulations (CFR). It is approved for use in various food categories at the following maximum permitted usage levels (21CFR184.1330) and (21CFR172.780) : 2.0% (beverage and beverage bases), 5.6% (chewing gum), 12.4% (confections and frostings), 1.3% (dairy product analogs), 1.5% (fats and oils), 2.5% (gelatins, puddings, and fillings), 46.5% (hard candy and cough drops), 8.3% (nuts and nut products), 6.0% (quiescently frozen confection products), 4.0% (snack foods), 85.0% (soft candy), and 1% (all other food categories).

Uses of Acacia Senegal Gum in the various food categories include emulsifier and emulsifier salt, flavoring agent and adjuvant, formulation aid, stabilizer and thickener, humectant, surface-finishing agent, processing aid, microencapsulating agent and powder. Acacia Senegal Gum is used in the food, textile, pottery, lithography, and pharmaceutical industries.[6,17]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Oral

In a study using rats, an apparent decrease in the caloric value of gum arabic with increasing administered dose was noted. gum arabic was incorporated into the diet at concentrations of 5, 10, and 17%. Digestibility data indicated that up to 80% of the gum arabic was absorbed. Following a 48-h fast, 20 young male rats were fed 10 mg of a mixture consisting of 34% white,

powdered gum arabic and 66% cacao butter. The difference in glycogen content between the rats who were fed gum arabic, and the rats in the control did not show a significant difference. It was concluded that gum arabic was not metabolized by enzymes of the rat digestive tract. The metabolism of gum arabic was evaluated using albino Wistar male rats. One group of animals was fed standard diet only, and the other diet plus 200 g gum arabic/kg, ad libitum, for 4 wk. In rats fed gum arabic in their diet, a white flocculent precipitate typical of gum arabic was detected in contents from the stomach and small intestine, but not from the cecum, distal colon, or in the feces. This suggests that the metabolism of gum arabic is mediated by bacteria in the cecum. In animals in which the cecum was resected, precipitable gum arabic was detected along the length of the entire residual intestine. This observation suggests that in the absence of the bacterial mass resident in the cecum, there is no degradation of gum arabic. No precipitate typical of gum arabic was found in the gastrointestinal tract of the control rats that received only the standard diet. In a guinea pig study, it was determined that gum arabic was highly digestible (90%) when administered in the diet at a concentration of 15% for 10 d.

Human

Oral

In a study with 22 infants, 1 to 15-mo-old, that were given gum arabic (15 to 20 g/d) in milk, no evidence of absorption was found.[3] No urinary pentose excretion was observed, while significant excretion of gum arabic occurred in the stools. The excretion of gum arabic and its effect on glucose absorption and routine hematological and biochemical measurements in 5 healthy male volunteers (30 to 55-yr-old) was examined. No significant effect on the mean concentration of serum lipids, mean blood glucose concentration, or mean insulin concentration was noted; a significant decrease in serum cholesterol was observed.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

In an acute oral toxicity study using rabbits (weights and strain not stated), an LD_{50} of 80 g/kg gum arabic was reported.[3]

Short-Term Toxicity Studies

Animal

Oral

The oral toxicity of gum arabic (dose not stated) using Sprague-Dawley rats (16 males, 16 females) was assessed.[3] The animals were fed the test article daily for 28 d. No treatment-related behavioral effects were noted. All values for serum chemistry and mean red blood cell volume were within the normal range. No toxicologically significant lesions were noted at microscopic examination. Wistar albino rats (number of rats not stated) were fed 10% (w/w) gum arabic daily for 45 d. Portions of the jejunum, ileum, and cecum were excised and the ultrastructure of each was evaluated using transmission electron microscopy. No abnormalities in organelles were observed within cells of the jejunum, ileum, or cecum. No significant ultrastructural differences occurred between experimental and control rats. Groups of rats (number and weights not stated) were fed 15% gum arabic in the diet for 62 d. A cathartic effect was noted. Weight gain, feed efficiency, hematological findings, and organ weights were normal. Diet containing 15-20% gum arabic was fed to 133 guinea pigs for 3 - 9 wk. No toxic effects resulted from the administration of gum arabic.

Human

Oral

Five healthy male subjects (30 to 55-yr-old) ingested 25 g gum arabic daily for 21 d.[3] Toxic effects were not observed during the 21-d period. The fact that gum arabic was not recovered from the feces suggested that it is degraded extensively in in the human colon.

Subchronic Toxicity Studies

Oral

The oral toxicity of gum arabic was examined in two experiments using albino Wistar rats.[3] In the first experiment, test groups of 15 male and 15 female rats were fed 0.91 – 8.6% and 0.75 – 7.5% gum arabic, respectively, for 13 wk. In the second experiment, groups of 15 male and 15 female rats were fed gum arabic at an average concentration of 18.6 and 18.1%, respectively, for 13 wk. No differences or alterations were found that were attributable to the ingestion of gum arabic. The only treatment-related alteration noted at necropsy was cecal enlargement in rats of the highest dose group. In another study, 4 groups of 5 male albino Wistar rats were fed diets containing 0.5, 1.5, 2.5, and 3.5% (w/w) gum arabic daily for 91 d. Electron microscopy reported no abnormalities in cardiac muscle or the liver.

In a 90-d oral toxicity study, male and female F344/DuCrj rats (6 animals/sex/group) were administered a diet containing gum arabic, a naturally processed polysaccharide exudate from gum acacia trees (*Acacia senegal*), at doses of 0, 1.25, 2.5 and 5.0% (equivalent to 770, 1505, and 3117 mg/kg bw/d for males, respectively, and 839, 1666, and 3296 mg/kg bw/d, respectively for females).[18] The treatment diet was mixed with an irradiated powder diet. Animals were observed daily. Body weights and feed and water consumption were measured during the study, ophthalmologic examinations were made, and urinalysis, hematology,

blood biochemistry, and histopathological examinations were all carried out. At the end of week 13, all rats were euthanized. During the 90 d on the diet, no clinical signs of effect of toxicity were noted in any of the treated animals. Overall, the study results indicated no adverse effects on any parameter examined. The no-observed-adverse-effect-level (NOAEL was determined to 3117 mg/kg bw/d for males and 3296 mg/kg bw/d for females.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral administration of gum arabic did not cause antifertility effects in female rats or the suppression of spermatogenesis in male rats.[3] *Gum arabic was not teratogenic when administered orally to mice at doses up to 1600 mg/kg on days 6 – 15 of gestation. Oral doses of gum arabic up to 1600 mg/kg also were not teratogenic in rats (days 6 - 15 of gestation) and hamsters (days 6-10 of gestation), and oral doses up to 800 mg/kg were not teratogenic in rabbits (days 6 - 18 of gestation). No fetal malformations were observed when rats were given 5% gum arabic solution orally (days 6 - 17 of gestation in one study; 14 d prior to mating, throughout mating, and until day 21 of gestation in another); additionally, no effects on estrus cycle were observed when the test article was given pre-mating through lactation. In a dietary study in which Osborne-Mendel rats were fed the test article starting at 13 wk prior to mating, reproductive and developmental effects were not observed. No effect on spermatogenesis was observed in male Sprague-Dawley rats that were fed a diet containing 30% gum arabic 30% for 82 d. Effects on fetuses were not observed with a 1% aqueous suspension or mucilage prepared from gum arabic in mice that were dosed orally (5 times), subcutaneously (5 injections), or intraperitoneally (as a single injection or a series of 5 injections between days 11 – 15 of gestation.*

Oral

A study was conducted to examine the effects of gum arabic (*Acacia senegal*) on male fertility.[19] Groups of 1 male and 2 female Balb/c mice were given with tap water or 5% (w/v) gum arabic in tap water (5 g/100 ml) for 21 d. Two weeks after the females delivered, blood was obtained from the males for testosterone measurements by immunoassay for the quantitative determination of testosterone. The males were then killed and the testes were removed and examined. The number of living offspring was higher in the test group than the controls. The testosterone concentration was statistically significantly greater in the test group (1.35 ng/ml) compared to the controls (0.85 ng/ml). Histopathological analysis showed the gum arabic group had normal seminiferous tubules with increased spermatogenesis.

GENOTOXICITY STUDIES

In Vitro

Gum arabic was not mutagenic in numerous in vitro mutagenicity tests using Salmonella typhimurium.[3] *In an in vitro cytogenetics assay, although results were classified as slightly positive, gum arabic (tested at up to 1000 µg/ml culture) did not induce definite abnormal anaphase figures in diploid human embryonic lung (WI-38) fibroblasts (test methods not given). The mutagenicity of gum arabic was also evaluated in numerous in vivo assays, the results of which were mostly negative. However, statistically significant positive results were noted in a dominant lethal test in rats (gum arabic in feed at up to 4% w/w prior to mating), but not in 2 dominant lethal assays in mice (one with 1% given orally and one with up to 20% in feed). In acute and short-term in vivo cytogenetics assays (rats), the results may have indicated a slight positive response, but no significant positive responses were observed; it was stated that further tests and a detailed statistical evaluation are needed to confirm this possibility. Negative results were also reported in micronucleus tests (mouse bone marrow smears) in mice dosed intraperitoneally with 3% gum arabic and in other in vivo assays.*

CARCINOGENICITY STUDIES

Oral

The carcinogenicity of gum arabic was studied using F344 rats (50 males, 50 females) and B6C3F1 mice (50 males, 50 females) in a 2-yr study.[3] *Both male and female rats were divided into high- and low-dose groups. Low-dose animals were fed gum arabic at a concentration of 25,000 ppm in the diet and high-dose animals were fed 50,000 ppm for 103 wk, followed by 1-2 wk of basal diet. The control mice (50 males and 50 females) and rats (50 males and 50 females) were given the basal diet according to the same schedule. The investigators concluded that gum arabic was not carcinogenic in F344 rats or B6C3F1 mice of either sex.*

Parenteral

No evidence of carcinogenicity was observed in rats dosed intraperitoneally with gum arabic (1.75 or 7.0% in saline or water) 3x/wk for up to 15 wk. [3] *In another study, tumors were not observed in guinea pigs injected intramediastinally with 0.1 ml of a gruel of gum arabic (single dose).*

Co-Carcinogenicity

Gum arabic has been reported to have increased the number of metastases in mice injected intraperitonially with Ehrlich ascites carcinoma cells.[3] *The carcinoma cells were injected 6 or 24 h after the mice were injected with gum arabic intravenously. However, it was noted that ascites tumor formation was inhibited under the same conditions.*

ANTI-CARCINOGENICITY STUDIES

The ability of gum arabic to reduce induced colorectal carcinogenesis were studied by investigating the effect of gum arabic on the formation of aberrant crypts, local, hepatic and systemic genotoxicity and oxidative stress.[20] Colorectal carcinogenesis was induced in Swiss male mice which were then given water or 2.5 or 5% gum arabic daily, via gavage at 5 ml/kg, for 12 wk. Proximal and distal colon, liver, blood, and bone marrow samples were obtained. The number of aberrant crypts in the of gum arabic-treated animals was lower than in the control groups.

In a study to investigate the effect of gum arabic (from *Acacia senegal*) on colonic tissues, a group of mice was treated with 10% wt/vol gum arabic in drinking water, and gene array was performed.[21] Chemical carcinogenesis was induced by intraperitoneal injection of 20 mg/kg 1,2-dimethylhydrazine (DMH) followed by 3 cycles of 3% dextran sodium sulfate (DSS) in drinking water with or without gum arabic treatment for 7 d, followed by distilled water for subsequent 14 d (one cycle - 21 d). Within 4 d, dosing with gum arabic (10% wt/wt) in drinking water decreased the colonic transcript levels of the angiogenetic factors angiogenin 1 (by 78%), angiogenin 3 (by 88%), and angiogenin 4 (by 92). According to Western blotting, gum arabic treatment also decreased angiogenin protein expression, and based on immunohistochemistry, ss-catenin expression was also decreased. Chemical carcinogenesis resulted in multiple colonic tumors in untreated groups within 12 wk; treatment with gum arabic in drinking water significantly decreased the number of tumors by 70%.

OTHER RELEVANT STUDIES

Immunological Effects

A study was conducted to evaluate the anti-inflammatory and antifibrotic effects of gum arabic in treating ulcerative colitis.[22] DSS was used to induce colitis in C57BL/6 mice and the animals were then switched to normal drinking water to monitor recovery. Mice received 140 g/l gum arabic before (pre-gum arabic treated group) or after (post-gum arabic treated group) induction of colitis. Disease activity and recovery were assessed by changes in body weight, disease activity index, and histological assessment. Gene expressions of proinflammatory, anti-inflammatory, and fibrotic markers were measured in colonic tissues.

Mice in the pre-gum arabic treated group showed an increase in body weight, with no differences in disease activity index scores, during the recovery phase and had lower histological colitis scores than mice in the post-gum arabic group, which showed higher disease activity scores and histological scores during the recovery phase. During the recovery phase, mice in the pre-gum arabic treated group showed increased expression of proinflammatory markers, while gene expression of the fibrotic markers, transforming growth factor β1 (TGFβ1) and procollagen I, were reduced. The reduced fibrotic marker expression was associated with reduced collagen staining and increased epithelial cell proliferation. The researchers concluded that administration of gum arabic had protective and alleviative effects on the severity of DSS-induced colitis, with a reduction in colonic fibrosis and TGFβ1 expression.

Effect on Cisplatin-Induced Infertility

The co-treatment effect of gum acacia/arabic (*Acacia senegal*) on cisplatin-related spermatogenesis dysfunction was investigated.[11] Cisplatin has several harmful effects on spermatogenesis. Daily administration of aqueous gum acacia/arabic, 7.5 mg/kg orally via a stomach tube, alleviated the adverse effects of cisplatin on spermatogenesis and reversed testicular damage, reduced oxidative stress induced by cisplatin, elevated testosterone and luteinizing hormone levels in blood sera, elevated germ cells, and ameliorated sperm quality.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Sensitization

The skin sensitization potential of a mascara containing 8.0% Acacia Senegal was evaluated in the maximization test using 28 healthy adult volunteers.[3] It was concluded that, under the conditions of the test, the mascara containing 8.0% Acacia Senegal did not possess a detectable contact-sensitizing potential and is not likely to cause contact sensitivity reactions under normal use conditions.

OCULAR IRRITATION STUDIES

Details on ocular irritation studies summarized below can be found in Table 4.

Potential ocular irritancy of mascaras containing 1% Acacia Senegal Gum[23] and 3% Acacia Senegal Gum Extract[24] was investigated in EpiOcular™ assays; both formulations were predicted to be non-irritant.[24] The ocular irritation potential of a mixture of Acacia Senegal Gum (51 - 59%) studied by bovine corneal opacity and permeability test method, was not classified for eye irritation or serious eye damage.[12].A hen's egg test on the chorioallantoic membrane (HET-CAM) was performed for this test material indicated that the test item was non-irritant.[12] An in vitro cytotoxicity assay by neutral red uptake performed on cell model fibroblasts by human skin (ATTC-CRL-2703) showed no ocular irritation potential of a mascara containing 2.9% Acacia Senegal Gum.[25] The results of a bovine corneal opacity and permeability assay and a neutral red release assay conducted on a mascara containing 6% Acacia Senegal Gum indicated that it was well-tolerated.[26]

In a clinical study conducted with 20 subjects, a mascara containing 2.9% Acacia Senegal Gum was applied to the periocular area, at least 1x/d for 1 mo.[27] No significant alteration of palpebral skin and mucosa were noticed. In another clinical study performed on 29 subjects for a 4-wk use period with a mascara containing 6% Acacia Senegal Gum, good ocular and peri-ocular acceptability were reported.[28] Ocular irritation potential of a mascara with 3% Acacia Senegal Gum Extract was evaluated in 50 female subjects.[29] The product was applied at least 5x/wk for 4 wk and a potential to elicit an ophthalmic irritation was not observed. It was well tolerated by subjects who were contact lens wearers and who had self-perceived sensitive eyes.

CLINICAL STUDIES

Case Reports

A number of case reports of gum arabic allergenicity have been identified in the published literature.[3] *Positive skin reactions were observed in 10 subjects who ingested gum arabic. The results of serologic studies (sera from 4 subjects) indicated that gum arabic was the dominant gum antigen in 2 subjects. Cross-reactivity between gum arabic and gum tragacanth was reported for a 24-yr old patient who developed sensitization to Quillaja bark (Quillaja saponaria) dust which led to rhinitis and asthma.*

In the case reports of exposures to gum arabic, a skin prick test (SPT) was performed for initial diagnosis and if positive for IgE, generally it was followed by testing for specific to gum arabic.[17,30-32] Food workers in direct contact with gum arabic on a regular basis also showed allergic symptoms. These case reports are summarized in Table 5.

Further analysis of the immunological reaction of gum arabic showed that the sensitization to its carbohydrate structural components occur casually in atopic patients with pollen sensitization without apparent exposure to the gum.[17] The study suggested that the allergy to gum arabic is mediated preferentially by IgE antibodies directed to its polypeptide chain.

SUMMARY

According to the *Dictionary*, Acacia Senegal Gum is reported to function in cosmetics as an adhesive, binder, emulsion stabilizer, film former, and fragrance ingredient; no function is reported for Acacia Senegal Gum Extract. These ingredients were first reviewed in 1998 as part of a larger group of ingredients derived from the acacia plants. At that time, the Panel issued a final report with an insufficient data conclusion for the entire group of 11 acacia ingredients, including Acacia Senegal Gum and Acacia Senegal Gum Extract. Subsequently, data were submitted that met the data needs for Acacia Senegal Gum and Acacia Senegal Gum Extract; in the amended report that was published in 2005, the Panel concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe as used in cosmetic products.

In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In September 2023, the Panel determined that this safety assessment should be re-opened in order to reassess the risks of IgE-mediated sensitivity caused by these ingredients.

According to RLD submitted to CIR in 2025, Acacia Senegal Gum is not used, and Acacia Senegal Gum Extract in 149 formulations. According to the results of the concentration of use survey conducted by the Council in 2025, Acacia Senegal Gum has the highest maximum concentration of use at 4% Acacia Senegal Gum in mascaras and in eyelash and eyebrow preparations.

Male and female F344/DuCrj rats (6 animals/sex/group) were fed a diet containing 0, 1.25, 2.5, and 5.0% (equivalent to 770, 1505, and 3117 mg/kg bw/d for males, respectively, and 839, 1666, and 3296 mg/kg bw/d, respectively for females). The NOAEL was determined to be 3117 mg/kg/d for males and 3296 mg/kg/d for females.

In a study in which groups of 1 male and 2 female Balb/c mice were dosed with tap water or 5% (w/v) gum arabic in tap water (5 g/100 ml) for 21 d, the number of living offspring was higher in the test group than the controls. Compared to controls, the testosterone concentration was statistically significantly greater and seminiferous tubules showed increased spermatogenesis in the male given gum arabic.

Treatment with gum arabic at concentrations of 2.5 and 5% reduced the formation of aberrant crypts in the colon of mice. In another study, gum acacia led to marked down regulation of several angiogenins and further genes relevant for tumor growth.

In a study examining the effect of gum arabic on ulcerative colitis, administration of gum arabic to mice had protective and alleviative effects on the severity of DSS-induced colitis, with a reduction in colonic fibrosis and TGFβ1 expression. Administration of gum acacia/arabic alleviated spermatogenesis and reversed testicular damage, reduced oxidative stress induced by cisplatin, elevated testosterone and luteinizing hormone levels in blood sera, elevated germ cells, and ameliorated sperm quality.

Potential ocular irritancy of mascaras containing 1% Acacia Senegal Gum[23] and 3% Acacia Senegal Gum Extract was investigated in EpiOcular™ assays; both formulations were predicted to be non-irritant. The ocular irritation potential of a mixture of Acacia Senegal Gum (51 - 59%) was evaluated using the bovine corneal opacity and permeability test; the test article was not classified for eye irritation or serious eye damage. A HET-CAM assay that was performed for this test material indicated that the test item was non-irritant An in vitro cytotoxicity assay by neutral red uptake performed on cell model fibroblasts by human skin (ATTC-CRL-2703) showed no ocular irritation potential of a mascara containing 2.9% Acacia Senegal Gum The results of a bovine corneal opacity and permeability assay and a neutral red release assay conducted on a mascara containing 6% Acacia Senegal Gum indicated that it was well-tolerated.

In a clinical study conducted with 20 subjects, a mascara containing 2.9% Acacia Senegal Gum was applied to the periocular area, at least 1x/d for 1 mo. No significant alteration of palpebral skin and mucosa were noticed. In another clinical study performed on 29 subjects for a 4-wk use period with a mascara containing 6% Acacia Senegal Gum, good ocular and peri-ocular acceptability were reported. Ocular irritation potential of a mascara with 3% Acacia Senegal Gum Extract was evaluated in 50 female subjects. The product was applied at least 5x/wk for 4 wk and a potential to elicit an ophthalmic irritation was not observed. It was well tolerated by subjects that were contact lens wearers and who had self-perceived sensitive eyes.

Cases of food workers in direct contact with gum arabic on a regular basis having allergic symptoms have been reported. In one study, analysis of the immunological reaction of gum arabic showed that the sensitization to its carbohydrate structural components occur casually in atopic patients with pollen sensitization without apparent exposure to the gum, and allergy to gum arabic is mediated preferentially by IgE antibodies directed to its polypeptide chain.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusions of previously-issued reports approximately every 15 years. In 1998, the Panel published a final report on 11 acacia ingredients, including Acacia Senegal Gum and Acacia Senegal Gum Extract, and concluded that the available data were insufficient to determine safety of the acacia ingredients. Subsequently, the Panel's data needs were met for Acacia Senegal Gum and Acacia Senegal Gum Extract, and a Final Amended Report was published in 2005. At the September 2023 meeting, since more than 15 years have passed since the last review, the Panel considered another re-review and determined to reopen the safety assessment to reassess the risk of IgE mediated sensitivity caused by these ingredients. However, the Panel subsequently stated that the reports of IgE responses to these ingredients are rare, and that almost all that do occur are occupational and related to exposure to high concentrations. Accordingly, the Panel concluded that both ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

The Panel found that a robust data profile was available for Acacia Senegal Gum. Also, the Panel noted that gum arabic is a direct food substance that is GRAS, particularly noting the maximum permitted usage level of 85% in soft candy, and Acacia Senegal Gum is often referred to as gum arabic in the published literature. Although the profile of Acacia Senegal Gum Extract was not as robust, the Panel stated that the safety of the two ingredients was likely equivalent.

Aflatoxin has been detected in *Acacia senegal*, and accordingly, the Panel stated that aflatoxin should be minimized in Acacia Senegal Gum and Acacia Senegal Gum Extract. The Panel has adopted the limits set by the US Department of Agriculture (USDA) corresponding to "negative" aflatoxin content. The Panel also expressed concern about heavy metals, pesticide residues, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to minimize impurities in cosmetic formulations according to limits set by the US FDA and the EPA.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., hair sprays and other fragrance preparations and face powders). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded that if these ingredients are used in airbrush formulations, the data are insufficient to support safe use when applied with such delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Chemical properties of Acacia Senegal Gum

Property	Value	Reference
Physical Form	solid which breaks with a glassy fracture	[8]
Color	Pale white to orange-brown	[8]
Molecular Weight (kDa)	330-940	[6]
UV absorption λ (nm)	negligible absorbance at 290 - 700 (mixture containing 51 – 59% Acacia Senegal Gum)	[12]
Specific Gravity	1.35-1.49	
Viscosity (ml/g)	16-24	[6]
Optical rotation	-34 to -37	[33]
Water Solubility	Readily soluble	[6]
Other Solubility	Insoluble in alcohol	[6]

Table 2. Composition of secondary metabolites in Acacia Senegal Gum[11]

Acacia Senegal Gum			
Phenolic Compounds	**Concentration (µg/ml)**	**Flavonoid Compounds**	**Concentration (µg/g)**
chlorogenic acid	7.88	7-OH flavone	6.11
catechol	3.45	naringin	9.14
syringenic	3.56	rutin	7.02
p-coumaric	10.14	quercetin	6.88
cinnamic acid	9.79	kaempferols	3.88
caffeic acid	3.69	luteolin	10.22
pyrogallol	9.77	apigenin	2.33
gallic acid	2.56	catechin	1.98
protoatechulic	2.31		
ferulic acid	11.09		
salicylic acid	2.17		
ellagic acid	3.09		
benzoic acid	4.19		

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category

	Acacia Senegal Gum		Acacia Senegal Gum Extract	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)[14,15]	% (2025)[16]	RLD (2025)[14,15]	% (2025)[16]
Totals*	**2938**	**0.00005-4**	**149**	**0.000005-0.041**
summarized by likely duration and exposure**				
Duration of Use				
Leave-On	*2508*	*0.00005-4*	*84*	*0.000005-0.021*
Rinse-Off	*677*	*0.00005-3.4*	*110*	*0.021-0.041*
Diluted for (Bath) Use	*13*	*NR*	*NR*	*0.005*
Unknown	*54*	*NR*	*12*	*NR*
Exposure Type				
Baby Products	4	NR	NR	NR
Children's Makeup	55	NR	NR	NR
Eye Area	991	0.15-4	5	NR
Incidental Ingestion	61	0.24-2.9	NR	0.000005
Mucous Membrane	136	0.003-2.9	9	0.000005-0.041
Incidental Inhalation-Spray	8; 481[a]; 759[b]	0.19-0.42 0.0055-0.083[a] 0.003-2.9[b]	5; 68[a]; 47[b]	0.021[b]
Incidental Inhalation-Airbrush	NR	NR	NR	NR
Incidental Inhalation-Powder	25; 759[b]; 1[c]	0.003-2.9[b] 0.00005-3[c]	47[b]	0.021[b]
Dermal Contact	1938	0.00005-4	79	0.05-0.041
Deodorant (underarm)	7 (not spray)	NR	NR	NR
Hair - Non-Coloring	400	0.000075-0.2	83	0.021
Hair-Coloring	42	NR	39	0.021
Nail	8	NR	NR	0.001
Other Preparations (Unknown Exposure Type)	54	NR	12	NR
as reported by product category				
Baby Products				
Baby Shampoos	3	NR		
Baby Lotions, Oils. Powders, Creams	1	NR		
Bath Preparations				
Bath Oils, Tablets, and Salts	2	NR		
Bubble Baths	1	NR		
Bath Capsules	3	NR	NR	0.005
Other Bath Preparations	7	NR		
Eye Makeup Preparations (not children's)				
Eyebrow Pencil	10	NR		
Eyeliner	45	0.44		
Eye Shadow	47	NR		
Eye Lotion	10	0.37		
Eye Makeup Remover	2	NR		
False Eyelashes	4	NR		
Mascara	763	0.15-4	1	NR
Eyelash and Eyebrow Adhesives, Glues, and Sealants	4	NR	1	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	53	2.5-4	1	NR
Other Eye Makeup Preparations	53	NR	2	NR
Fragrance Preparations				
Other Fragrance Preparation	NR	0.42		
Hair Preparations (non-coloring)				
Hair Conditioners	13 (l.o.); 115 (r.o.)	0.003 (l.o.) 0.0005 (r.o.)	5 (l.o.); 14 (r.o.)	0.021 (r.o.)
Hair Sprays (aerosol fixatives)	8	0.19	5	NR
Hair Straighteners	6	NR	2	NR
Rinses (non-coloring)	13	NR	6	NR
Shampoos (non-coloring)	1 (l.o.); 103 (r.o.)	0.000075 (r.o.)	8 (r.o.)	0.021 (r.o.)
Tonics, Dressings, Other Hair Grooming Aids	46	0.003-0.2	13	NR
Other Hair Preparations	41 (l.o..); 51 (r.o.)	0.04	12 (l.o.); 18 (r.o.)	NR
Hair Coloring Preparations				
Hair Dyes and Colors (all types requiring caution statements and patch tests)	8	NR	8	NR
Hair Bleaches	5	NR	5	NR
Other Hair Coloring Preparation	2 (l.o.); 27 (r.o.)	NR	26 (r.o.)	0.021 (l.o.)
Makeup Preparations (not eye or children's)				
Blushers and Rouges (all types)	7	NR		
Face Powders	24	NR		
Foundations	148 (traditional)	0.44 (traditional)		
Leg and Body Paints	68 (traditional)	NR		
Lipstick and Lip Glosses	55	0.3	NR	0.000005

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category

	Acacia Senegal Gum		Acacia Senegal Gum Extract	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)[14,15]	% (2025)[16]	RLD (2025)[14,15]	% (2025)[16]
Makeup Bases	24 (traditional)	NR		
Makeup Fixatives	5	NR		
Other Makeup Preparations	54 (traditional)	NR	1 (traditional)	NR
Makeup Preparations for Children (not eye)				
Children's Face Paints	52	NR		
Other Children's Makeup	3	NR		
Manicuring Preparations				
Nail Polish and Enamel	6	NR		
Other Manicuring Preparations	2	NR	NR	0.001
Oral Hygiene Products				
Dentifrices	2	2.9		
Other Oral Hygiene Products	4	0.24		
Personal Cleanliness				
Bath Soaps and Body Washes	37	0.003-0.052	3	0.041
Deodorants (underarm)	7 (not spray)	NR		
Douches	1	NR		
Disposable Wipes	1	NR		
Other Personal Cleanliness Products	7 (l.o.); 16 (r.o.)	NR	1 (l.o.); 5 (r.o.)	NR
Shaving Preparations				
Aftershave Lotions	NR	0.028		
Men's Talcum	1	NR		
Pre-shave Lotions (all types)	3	NR		
Shaving Creams (aerosol/brushless/lather)	1	NR		
Shaving Soap (cakes, sticks, etc.)	1	NR		
Other Shaving Preparations	1	NR		
Skin Care Preparations				
Cleansing	123	3.4	18	NR
Depilatories	6	NR		
Face and Neck (excluding shaving preps)	530 (l.o.); 90 (r.o.)	0.17-3 (l.o.; not spray) 0.00006 (r.o.; not spray)	17 (l.o.); 2 (r.o.)	NR
Body and Hand (excluding shaving preps)	45 (l.o.); 15 (r.o.)	0.00005 (l.o.; notpsray)	2 (l.o.); 1 (r.o.)	NR
Moisturizing	230	0.0055-0.083	19	NR
Night	23	0.0055		
Paste Masks (mud packs)	35	0.00005-3.3		
Skin Fresheners	13	NR		
Other Skin Care Preparations	92 (l.o.); 28 (r.o.)	0.63 (l.o.)	3 (l.o.); 2 (r.o.)	NR
Suntan Preparations				
Suntan Gels, Creams, and Liquids	4	0.26 (not spray)		
Indoor Tanning Preparations	6 (traditional)	NR	1 (traditional)	NR
Other Preparations (i.e., those preparations that do not fit another category)	54	NR	12	NR

NR – not reported
l.o. – leave-on; r.o. – rinse-off
*The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.
**Likely duration and exposure are derived from survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 4. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
IN VITRO						
1% Acacia Senegal Gum in mascara	None	Neat	EpiOcular™ human cell construct	EpiOcular™ assay. Duration of exposure to result 50% decrease in MTT conversion in the test article related-human cell construct was determined	50% toxicity was not observed in 12.9 h, longest possible exposure. Non-ocular irritant	[23]
2.9% Acacia Senegal Gum in a mascara	Culture medium	0.03 - 2 mg/ml	Cell model fibroblasts by human skin (ATTC-CRL-2703)	In vitro cytotoxicity assay by neutral red uptake	Non-ocular irritant	[25]
Mascara containing 6% Acacia Senegal Gum	none	neat	Isolated bovine cornea	BCOP and neutral red release assay	Well tolerated	[26]
mixture of Acacia Senegal Gum (51 - 59%)	0.9% NaCl	20%	Isolated bovine cornea	BCOP in accord with OECD TG 437. Test material left in contact with isolated corneas for 4 h.	In Vitro Irritancy score (IVIS) was -2.2. Non-ocular irritant.	[12]
Acacia Senegal Gum (51-59%)	None	Neat	chorion-allantoïc membrane of fertilized Leghorn hens' eggs	HET-CAM.	Non-ocular irritant	[12]
Mascara containing 3% Acacia Senegal Gum Extract	none	Neat	EpiOcular™ human cells construct	EpiOcular™ assay. Topical application ocular irritation screening assay to determine 50% decrease of MTT	ET_{50} > 8 h. Non-ocular irritant	[24]
HUMAN						
Mascara containing 2.9% Acacia Senegal Gum	none	neat	20 subjects; 50% wearing contact lenses)	Applied on periocular area, at least once a day for 1 mo.	No significant alteration or palpebral skin and mucosa were noticed.	[27]
Mascara containing 6% Acacia Senegal Gum	none	neat	29 subjects	4-wk use study	Good ocular and peri-ocular acceptability reported	[28]
Mascara with 3% Acacia Senegal Gum Extract	none	neat	54 subjects; 50% had self-perceived sensitive eyes and 50% wore contact lenses	In-use test. Product was applied at least 5x/wk for 4 wk.	No ophthalmic irritation	[29]

Table 5. Case reports of occupational exposures to gum arabic

Description	Reference
-Eight male employees aged 23-52 yr were exposed to a powder mixture composed of 10% thaumatin and 90% gum arabic, which led to allergic symptoms in the upper airways. -Three individuals with rhinitis but without lower respiratory symptoms underwent spirometric and plethysmographic testing. SPT were performed. Anterior rhinoscopy was used to assess the state of the turbinates. A positive SPT for pure thaumatin was obtained in all 4 individuals with rhinitis of whom also had a positive skin prick test result for pure gum arabic and gum arabic-specific IgE.	[31]
In 2002 a 30-yr-old male pharmaceutical industry worker was admitted for medical advice after experiencing workplace-related shortness of breath, chest tightness, runny nose, itching, swelling, redness of the eyes and redness of the face and neck. He was exposed to dust from a variety of drugs and additives in the tablet coating plant that he worked in and in 1994 his symptoms began to worsen. -Symptoms occurred mainly during weighing of gum arabic or another substance at his workplace. The case was studied further to identify specific IgE-binding components responsible for the work-related symptoms. - SPT was performed with gum arabic (1% w/v, protein concentration 40 µg/ml; material from the patient's workplace) and a panel of environmental allergens. SPT with extracts of materials from the patient's workplace in PBS showed negative reactions, with the exception of gum arabic which produced a 4 mm wheal/20 mm flare with the 1% (w/v) extract and a 2 mm wheal/8 mm flare with a diluted 0.1% (w/v) extract. Total IgE was 80 kU/l. Lung function and challenge tests were performed. Nebulizations were performed for 0.6 s during each of 10 slow total lung capacity breaths with doubling concentrations up to 10 mg gum arabic/ml (maximal cumulative dose 0.45 mg; this corresponds to a maximal protein dose of 1.8 µg/ml). After the bronchial challenge with gum arabic, the patient complained of chest tightness. A 36% decrease in FEV 1 (from 3,690 to 2,340 ml PBS) was documented 10 min after the maximal dose-The study showed that gum arabic may cause occupational allergic rhinitis and asthma with urticaria symptoms in some patients	[17]
119 patients (control) underwent SPT with gum arabic (1% w/v, protein concentration 40 µg/ml; material from the patients' workplace) and environmental allergens. - Thirty-six subjects with total IgE ≥ 100 kU/l or at least 1 positive SPT were tested for IgE to gum arabic. Additionally, the sera of 7 highly atopic patients without occupational exposure to gum arabic were selected to complete the control group for in vitro tests. - Only 3 subjects showed IgE specific to gum arabic: one control with positive SPT, one control with negative SPT, and the patient that came to the clinic. - it appeared that the allergy to gum arabic is mediated preferentially by IgE antibodies directed to its polypeptide chain	[17]
-Eleven candy factory workers with respiratory and/or skin symptoms referred to the hospital reported some of the following symptoms: hives, erythema of the hands, dyspnea, rhinitis, eye symptoms, redness of the skin, itching of the skin, cough, nasal congestion, and secretion. -Six candy factory workers had occupational allergic disease, in which 4 of the cases were confirmed to be occupational asthma caused by gum arabic with contact urticaria. -Contact urticaria was verified in 2 of the workers via cutaneous exposure test. One worker underwent a specific bronchial provocation test to gum arabic and was found to be positive.	[30]
A 35-yr-old male presented with a 5-yr history of recurrent bilateral nasal obstruction; since the previous year, it had been followed by the onset of wheals on his arms. His job involved making candies with gum arabic. -SPTs were performed with 10% wt/vol gum arabic in physiological saline, yielding a 9-mm wheal. Open patch testing was performed by applying 10% wt/vol gum arabic in saline solution on his back and leaving it under occlusion for 20 min; this also produced multiple wheals. -ImmunoCAP tests resulted in positive results at a level of 0.33 kU/l. The level of total IgE was 85 kU/l. A nasal provocation test with (200 AU/ml) gave a positive result.	[32]

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FINAL REPORT

SAFETY ASSESSMENT OF ACACIA CATECHU, ACACIA CONCINNA, ACACIA CONCINNA EXTRACT, ACACIA DEALBATA, ACACIA DEALBATA EXTRACT, ACACIA DECURRENS, ACACIA DECURRENS EXTRACT, ACACIA FARNESIANA, ACACIA FARNESIANA EXTRACT, ACACIA SENEGAL, ACACIA SENEGAL EXTRACT, and ACACIA SENEGAL GUM EXTRACT

ABSTRACT

These ingredients are derived from various species of the acacia plant. The concentration at which these ingredients are reported to be used ranges from 9% in mascara to 1% in shampoos. Gum arabic is the common name for Acacia Catechu, Acacia Farnesiana, or Acacia Senegal, and describes material that exudes from the bark of the plant when it has been stressed by infection, poor nutrition, heat or drought. Gum arabic is comprised of various sugars, and glucuronic acid residues in a long chain of galactosyl units with branched oligosaccharides. Gum arabic is generally recognized as safe as a direct food addltive. Little information is available to characterize the extracts, however. Acacia Concinna Extract was generally described as containing saponins, alkaloids, and malic acid with parabens and potassium sorbate added as preservatives. The use of these ingredients categorized as biological additives, but no information was available to describe what function they serve in cosmetic formulations. Toxicity data on gum arabic indicates little or no acute, short-term or subchronic toxicity. Gum arabic is negative in several genotoxicity assays, is not a reproductive or developmental toxin, and is not carcinogenic when given intraperitoneally or orally. Clinical testing indicated some evidence of skin sensitization with gum arabic. While there is extensive safety test data on gum arabic, it was not possible to relate these data to the crude Acacias and their extracts that are used in cosmetic formulations. Therefore, the available data were considered insufficient to support the safety of this family of ingredients in cosmetic products. The additional data need to complete the safety assessment include: (1) Concentration of use; (2) Identify the specific chemical constituents, and clarify the relationship between crude Acacias and their extracts and the Acacias and their extracts that are used as cosmetic ingredients; (3) Data on contaminants, particularly relating to the presence of pesticide residues. Additionally, determine whether Acacia melanoxylon is used in cosmetics, and whether acamelin (a quinone) and melacacidin (a flavin) are present in the Acacias that are being used; (4) Skin sensitization study (i.e. dose response to be determined); (5) Contact urticaria study at use concentration; and (6) UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then a photosensitization study may be needed. It was also noted that other studies may be needed after clarification of the chemical constituents of the Acacias.

INTRODUCTION

The safety for use in cosmetics of ingredients derived from species of Acacia and listed in the International Cosmetic Ingredient Dictionary and (Wenninger and McEwen, 1995a) is reviewed in this report. The ingredients and the Acacia species from which they are derived include: Acacia Catechu, Acacia Concinna, Acacia Concinna Extract, Acacia Dealbata, Acacia Dealbata Extract, Acacia Decurrens, Acacia Decurrens Extract, Acacia Farnesiana, Acacia Farnesiana Extract, Acacia Senegal, Acacia

and Acacia Senegal.

Gum Arabic is a substance that is generally recognized as safe (GRAS) for direct addition to human food under the provisions of Section 1884.1330 of the Code of Federal Regulations (21 CFR 1884.1330). A report, prepared for the Food and Drug Administration, summarizing all available scientific data (1920 to 1972) related to the safety of Gum Arabic as a food ingredient has been published (Informatics Inc., 1972). Studies from that report are referenced in the text of this report.

In a subsequent report (prepared for FDA) evaluating the safety of Gum Arabic as a food ingredient, the Select Committee on GRAS Substances (of the Life Sciences Research Office, Federation of American Societies for Experimental Biology (FASEB) concluded the following (FASEB, 1973): "There is no evidence in the available information on gum arabic that demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard."

The Select Committee also determined that additional experiments should be undertaken to evaluate the significance of Gum Arabic allergenicity to the population as a whole, and that it may be advisable to conduct feeding studies in several animal species (including pregnant animals) at dosage levels that approximate and exceed the current maximum daily human intake (See **NONCOSMETIC USE** section for maximum values for possible daily human intake).

Studies from the 1973 FASEB report are summarized in the text of this report. Studies on Acacia Senegal and other species of Acacia (listed in International Cosmetic Ingredient Dictionary and those not listed) that have been published since the FASEB report was issued are also included. To ensure that the information in the present report is representative of the published chemistry and toxicity data on species of Acacia, the data presented involve various parts/components of the Acacia tree as well as the gummy exudate.

CHEMISTRY

Chemical And Physical Properties

The International Cosmetic Ingredient Dictionary (Wenninger and McEwen, 1997) is the source of the following descriptions of various species of Acacia:

Acacia Catechu - also known as Catechu and Gum Arabic, is the dried, crushed core of *Acacia catechu*. It is also defined as the plant material derived from *Acacia catechu*.

Acacia Concinna - defined as the plant material derived from *Acacia concinna*.

Acacia Concinna Extract - also Extract of Acacia Concinna, is an extract of the fruit of *Acacia concinna*.

Acacia Dealbata - defined as the plant material derived from *Acacia dealbata*.

Acacia Dealbata Extract - an extract of the leaves of the wattle, *Acacia dealbata*. This ingredient is also known as Extract of Acacia Dealbata, Extract of Wattle, and Wattle Extract.

Acacia Decurrens - defined as the plant material derived from *Acacia decurrens*.

Acacia Decurrens Extract - an extract of the acacia, *Acacia decurrens*.

Acacia Farnesiana - (CAS No. 9000-01-5), also known as Acacia and Gum Arabic, is a plant material that is derived from the dried, gummy exudate of the acacia, *Acacia farnesiana*. It is also defined as the plant material derived from *Acacia farnesiana*.

Acacia Farnesiana Extract - an extract of the flowers and stems of the acacia, *Acacia farnesiana*. This ingredient is also known as Extract of Acacia Farnesiana and Acacia Extract.

Acacia Senegal - (CAS No. 9000-01-5), also known as Acacia and Gum Arabic, is a plant material derived from the dried, gummy exudate of the acacia, *Acacia senegal*. It is also defined as the plant material derived from *Acacia senegal*.

Acacia Senegal Extract - also known as Acacia Extract and Extract of Acacia Senegal, is an extract of the flowers and stems of the acacia, *Acacia senegal*.

Acacia Senegal Gum Extract - an extract of the gum of the acacia, *Acacia senegal*. Synonyms for this ingredient include Acacia Gum Extract and Extract of Acacia Senegal Gum (Wenninger and McEwen, 1997).

In the preceding definitions from the International Cosmetic Ingredient Dictionary, Gum Arabic is another name for Acacia Catechu, Acacia Farnesiana, and Acacia Senegal. Information from another source defines Gum Arabic as the dried gummy exudate from the stems and branches of *Acacia senegal*, *Acacia arabica*, and other species of Acacia (Anonymous, 1993). The gummy exudate from Acacia Senegal has been described as a proteinaceous polysaccharide, with protein content ranging from approximately 1.5% to 3% for samples from various producing areas (World Health Organization, 1990).

Data on physical properties indicate that Gum Arabic is a white powder that is readily soluble in water, but insoluble in alcohol (Anonymous, 1993). It has a molecular weight of approximately 850,000 (Ross et al., 1984) and a density of 1.35 to 1.49 (Anonymous, 1981). The aqueous solution is acid to litmus (Lewis, 1993a). Other names for Gum Arabic include: Acacia, Acacia Gum, Acacia Dealbata Gum, Acacia Senegal, Acacia Syrup, Arabic Gum, Australian Gum, Gum Ovaline, Gum Senegal, Indian Gum, Senegal Gum, and Wattle Gum (Anonymous, 1981).

The structure of Gum Arabic has been defined as follows: "Gum Arabic is composed of D-galactose, L-rhamnose, L-arabinose, and D-glucuronic acid residues in an arrangement of a main chain of galactosyl units joined by β-D-(1→ 3) linkages and side chains or branched oligosaccharides linked to the main chain by β-D-(1→ 6) linkages. The oligosaccharides may contain terminal rhamnosyl units linked (1→ 3) or terminal arabinofuranosyl units linked (1→ 4) to internal galactosyl or glucuronosyl units." (Pazur et al., 1986)

Based on methylation and degradation studies of Gum Arabic (*Acacia senegal*) along with periodate oxidation and other confirmatory reactions, a structure (Figure 1) for this gum has been proposed (Informatics Inc., 1972).

METHODS OF PRODUCTION

Gum Arabic is produced when the Acacia tree is stressed by infection, poor nutrition, heat, or lack of moisture. The gum exudes through wounds in the bark that occur naturally or are purposely made to stimulate production. The exudate dries rapidly, is collected as hardened drops or tears, sorted, graded, and marketed. The gum becomes harder during storage; market preferences exist for both the harder (old) and softer (new) gum (FASEB, 1973).

Gum Arabic in solid form is imported from the Sudan. According to one source, the solid is converted to a liquid form and the preservatives Proxel GXL (0.13%) and sodium benzoate are then added. Proxel GXL consists of 20% 1,2-benzisothiazolin-3-one (BIT) in aqueous dipropylene glycol (Freeman, 1984).

Crude Acacia Concinna results from the drying and pulverization of the pods of *Acacia concinna*. The extract of these pods (Acacia Concinna Extract) is drawn by cold processing (Carlisle International Corporation, 1997a).

COMPOSITION, ANALYTICAL METHODS, AND IMPURITIES

Acacia Senegal has been described as the major commercial Acacia gum (Anderson, 1988). The following three grades of Gum Arabic have been noted in the published literature: (1) processed Gum Arabic recovered by spray-drying from a solution of commercial food grade Gum Arabic after filtration to remove sand, etc., and after heat treatment to effect pasteurization. (2) finely powdered natural Gum Arabic of poor commercial quality, giving solutions of a dark reddish brown color. (3) finely powdered natural Gum Arabic of very high quality, giving essentially colorless solutions (Strobel et al., 1982). Gum Arabic has been analyzed by gas chromatography (Lawrence and Iyengar, 1985) and has been identified by microelectrophoresis (Informatics Inc., 1972).

The following specifications exist for United States Pharmacopoeia (USP) grade Acacia: loss on drying (15% max), total ash (4% max), arsenic (3 ppm), lead (0.001%), and heavy metals (0.004%) (United States Pharmacopeial Convention, Inc., 1995).

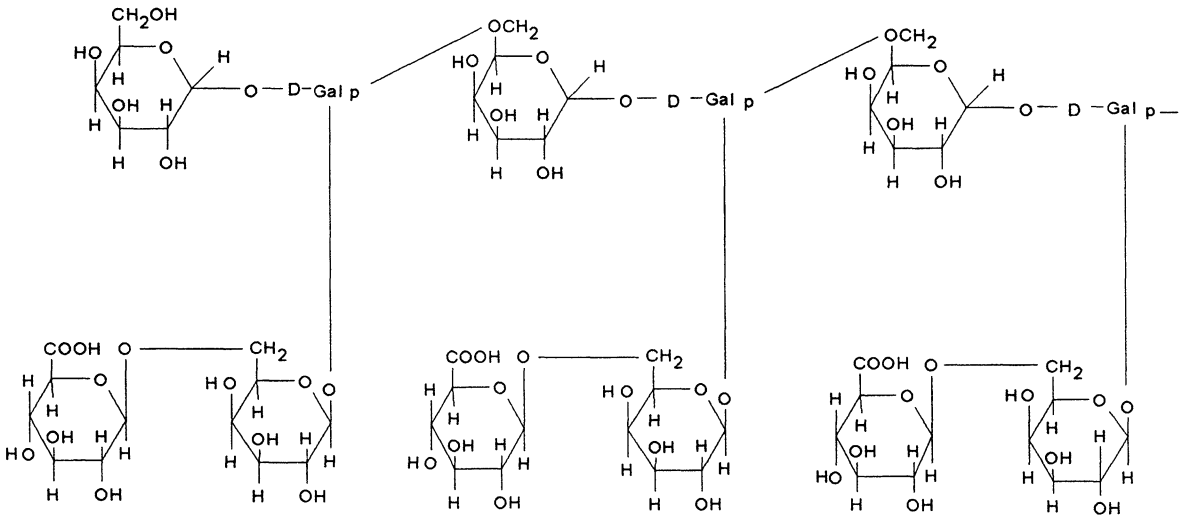

Figure 1. Proposed structure of Gum Arabic (Informatics, 1972).

FDA has listed Acacia (Gum Arabic) as a direct food addltive that meets the specifications of the "Food Chemicals Codex" (21 CFR 184.1330). The specifications for food grade Acacia include: arsenic (3 mg/kg max); ash, acid-insoluble (0.5% max); ash, total (4% max); heavy metals, as Pb (0.002% max); insoluble matter (1% max); lead (5 mg/kg max); and loss on drying (15% max) (Food Chemicals Codex, 1996). Data on the composition (impurities data included) of Acacia Senegal are included in Tables 1 through 4.

Information on the composition of various species of Acacia is included in Table 5. The Acacia species that are listed in the International Cosmetic Ingredient Dictionary are identified with an asterisk.

As noted in Table 5, aflatoxin has been detected in the bark and seeds of *Acacia catechu.* Furthermore, Gum-yielding *Acacia* twigs from the Sudan (supplier of Acacia Senegal) have been described as a source of aflatoxin (81 to > 1000 μg/kg) (Abdalla, 1988). However, the results of an enzyme-linked immunosorbent assay indicated no detectable aflatoxin in either of two samples of Gum Arabic. Absorbencies for both samples were equivalent to less than 2 ppb, the lowest detectable level. The assay system was capable of determining aflatoxin in the concentration range of 2.0 to 200.0 ppb in the presence of Gum Arabic (Smith et al., 1990).

The following information on Acacia Concinna Extract was received: Acacia Concinna Extract consists of 1 part of extract obtained from 1 part of dry pods of *Acacia concinna*. It contains the active

Table 1. Analytical Data for Natural Gum Arabic (*Acacia Senegal*) Samples provided by Importers in 1990/91 (Anderson et al.,1991)

Sample No.	Sample Sent by	Date received	% H_2O	% Ash	% N	Specific rotation[a] (degrees)	Conforms to revised JECFA Spec. (1990)[b]	Confirmation from NMR spectrum
N1	American importer A	12/90	13.2	3.8	0.34	-29	yes	Good *Acacia senegal*
N2	American importer A	12/90	13.9	4.0	0.36	-31	yes	Good *Acacia senegal*
N3	Italian importer B	12/90	14.4	3.3	0.31	-30	yes	Good *Acacia senegal*
N4	British importer C	12/90	14.5	3.6	0.37	-31	yes	Good *Acacia senegal*
N5	British importer D	12/90	12.2	3.5	0.35	-33	yes	Good *Acacia senegal*
N6	British importer E	12/90	14.9	2.0	0.38	-33	yes	Good *Acacia senegal*
N7	German importer A	1/91	14.4	4.0	0.26	-34	yes	Good *Acacia senegal*
N8	American importer G	1/91	15.0	3.2	0.29	-26	yes	Good *Acacia senegal*
N9	American importer H	1/91	13.9	3.9	0.33	-32	yes	Good *Acacia senegal*
N10	British importer K	2/91	13.3	3.7	0.34	-28	yes	Good *Acacia senegal*
N11	Italianimporter L	2/91	14.8	3.4	0.30	-29	yes	Good *Acacia senegal*
Mean Values			14.0	3.6	0.33	-30.5		

[a] Dry-weight basis, as specified (Food and Agriculture Organization of the United Nations, 1990).
[b]All samples conformed to the Revised (1990) JECFA (Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives) Specification in respect of solubility (complete in cold water); acid-insoluble ash (> 0.5%) and matter (> 1%); starch/dextrin (absent); tannin (absent); arsenic (> 3 ppm), lead (> 10 ppm), heavy metals (> 40 ppm).

constituents of the pods of *Acacia concinna*, such as vegetable saponins. The raw material (*Acacia concinna*) from which Acacia Concinna Extract is derived is from wild, crafted sources. Thus, reportedly, there is no contamination of the raw material with pesticide residues (Carlisle International Corporation, 1997a). Specifications for Acacia Concinna Extract are listed in Table 6, and the analytical profile of this ingredient is included in Table 7.

REACTIVITY

When Gum Acacia was weakly hydrolyzed by hydrochloric acid at room temperature, pentose is split off (Marrack and Carpenter, 1938). Partial acid hydrolysis has also yielded galactose and complex sugar acids (Heidelberger et al., 1929).

Gum Acacia emits acrid smoke when heated to decomposition (Lewis, 1993b). Heating a solution of Acacia for a few minutes at 100° destroys peroxidase (oxidizing agent) present in the gum and the colored derivatives produced (Gennaro, 1990).

USE

PURPOSE IN COSMETICS

The following species of Acacia function as biological additives in cosmetics: Acacia Catechu, Acacia Concinna Extract, Acacia Dealbata Extract, Acacia Decurrens Extract,

Table 2. Analytical Data For Sudanese and Nigerian Gum Arabic Samples of *Acacia senegal* (Anderson et al., 1990)

	Acacia senegal	
Properties/Composition	Sudanese samples Mean Values (13 years total between 1904 and 1989)	Nigerian samples Mean Values (9 years total between 1905 and 1967)
Equiv. weight - Corrected for moisture and protein contents	1050 ± 95	980 ± 56
Intrinsic viscosity (ml/g) - Corrected for moisture and protein contents	16 ± 2	18 ± 2
Brookfield viscosity, 25% (cp)	78 ± 13	84 ± 19
Specific rotation (degrees) - Corrected for moisture and protein contents	-30 ± 1.4	-30 ± 2
pH, 25% aqueous solution, at 25°C	4.4 ± 0.5	4.3 ± 0.03
Loss on drying, 105°C (%)	13 ± 0.8	13 ± 1
Total ash, 550°C (%)	3.6 ± 0.4	3.7 ± 0.3
Nitrogen (%)	0.34 ± 0.03	0.34 ± 0.03
Hence protein (%) - Corrected for loss on drying	2.3 ± 0.2	2.3 ± 0.4
Hence uronic anhydride (If all acidity arises from uronic acids)	17 ± 2	18 ± 1
Methoxyl (%) - Corrected for moisture and protein contents	0.25 ± 0.06	0.23 ± 0.03
4-O-Methylglucuronic Acid[a] (If all methoxyl content present in this acid)	1.5 ± 0.5	1.5 ± 0.3
Glucuronic Acid[a]	16 ± 1.7	16.6 ± 0.8
Galactose[a]	44 ± 6	47 ± 6
Arabinose[a]	25 ± 3	23 ± 4
Rhamnose[a]	14 ± 2	12 ± 2

[a]Sugar composition after hydrolysis (%) - Corrected for moisture and protein contents

Acacia Farnesiana, Acacia Farnesiana Extract, Acacia Senegal, Acacia Senegal Extract, and Acacia Senegal Gum Extract. The functions of Acacia Concinna, Acacia Dealbata, and Acacia Decurrens in cosmetics are not listed (Wenninger and McEwen, 1997).

Reportedly, *Acacia concinna* pods is a useful hair wash, in that it promotes hair growth, kills lice, and removes dandruff. The active constituents of *Acacia concinna* pods (saponins, alkaloids, tannins, and malic acid) are said to have cleansing, stimulating, and astringent properties. The astringent action provides toning of the scalp and conditioning of the hair.

Additionally, the active constituents are said to offer effective skin and scalp exfoliation (Carlisle International Corporation, 1997b).

SCOPE AND EXTENT OF USE IN COSMETICS

The product formulation data submitted to the Food and Drug Administration (FDA) in 1997

Table 3. The Amino Acid Composition of Sudanese and Nigerian Gum Arabic Samples of *Acacia senegal* (Anderson et al., 1990)

	Acacia senegal	
Amino Acid	Sudanese samples Mean Values[a] (13 years total between 1904 and 1989)	Nigerian samples Mean Values[a] (9 years total between 1905 and 1967)
Alanine	27 ± 3	24 ± 4
Arginine	13 ± 4	12 ± 1
Aspartic Acid	68 ± 13	61 ± 16
Cystine	2 ± 4	0
Glutamic Acid	42 ± 10	42 ± 15
Glycine	50 ± 5	50 ± 6
Histidine	44 ± 8	48 ± 5
Hydroxyproline	304 ± 47	331 ± 73
Isoleucine	12 ± 3	13 ± 3
Leucine	66 ± 7	69 ± 8
Lysine	25 ± 3	24 ± 6
Methionine	2 ± 2	1
Phenylalanine	33 ± 5	29 ± 10
Proline	63 ± 14	55 ± 9
Serine	129 ± 11	129 ± 13
Threonine	68 ± 9	67 ± 8
Tyrosine	14 ± 5	14 ± 4
Valine	35 ± 8	32 ± 6

[a] (residues per 1000 residues)

indicated that Acacia was used in a total of 22 cosmetic products (Table 8) (FDA, 1997).

The following use concentration data on Acacia for various product categories were received from the cosmetics industry: Mascara (9%), Blush (1%), Make-up (1%), and Hair Mousse (1%) (CTFA, 1995).

Reportedly, recommended use concentrations of Acacia Concinna Extract are 0.5 to 5.0% w/w (Carlisle International Corporation, 1997a) and 1.0 to 2.0% for use in shampoos, hair packs, hair conditioners, and hair rinses (Carlisle International Corporation, 1997b).

Cosmetic products containing Acacia are applied to most parts of the body and could come in contact with the ocular and nasal mucosae. These products could be used on a daily basis, and could be applied frequently over a period of several years.

INTERNATIONAL USE

Acacia Senegal is listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category* (*CLS*) (Rempe and Santucci, 1997). Acacia Senegal, which conforms to the specifications of the Japanese Cosmetic Ingredients Codex, has precedent for use without

Table 4. Cationic Composition of the Ash from Sudanese and Nigerian Gum Arabic Samples of *Acacia senegal* (Anderson et al., 1990)

	Acacia senegal	
Cation	Sudanese samples Mean Values[a] (15 years total between 1904 and 1989)	Nigerian samples Mean Values[a] (9 years total between 1905 and 1967)
Aluminum	190 ± 53	311 ± 156 (Mean = 266 [n = 8] if one value, 675, is treated as an outlier)
Calcium	256,000 ± 34,000	316,000 ± 56,000
Chromium	47 ± 22	34 ± 26
Copper	52 ± 27	66 ± 65 (Mean = 47, if one value, 225, is treated as an outlier)
Iron	128 ± 84	110 ± 33
Lead	6 ± 2	11 ± 7
Magnesium	38,000 ± 15,000	39,000 ± 15,000
Manganese	100 ± 95	57 ± 27
Nickel	10 ± 11	12 ± 17
Potassium	237,000 ± 37,000	221,000 ± 43,000
Sodium	9,400 ± 4,480	10,200 ± 5,200
Zinc	24 ± 10	40 ± 49 (Mean = 25, if one value, 159, is treated as an outlier)
Arsenic	< 1 ppm	< 1 ppm
Cadmium	< 1 ppm	< 1 ppm
Cobalt	< 1 ppm	< 1 ppm
Molybdenum	< 1 ppm	< 1 ppm

[a] μg/g ash, unless expressed as ppm.

restriction in all CLS categories.

Acacia is not included among the substances listed as prohibited from use in cosmetic products that are marketed in the European Union (EEC, 1995).

NONCOSMETIC USE

Gum Arabic is a substance that is generally recognized as safe (GRAS) for direct addition to human food under the provisions of Section 1884.1330 of the Code of Federal Regulations (CFR). It is approved for use in various food categories at the following maximum permitted usage levels: 2.0% (beverage and beverage bases), 5.6% (chewing gum), 12.4% (confections and frostings), 1.3% (dairy product analogs), 1.5% (fats and oils), 2.5% (gelatins, puddings, and fillings), 46.5% (hard candy and cough drops), 8.3% (nuts and nut products), 6.0% (quiescently frozen confection products), 4.0% (snack foods), 85.0% (soft candy), and 1% (all other food categories).

Uses of Gum Arabic in the various food categories include: emulsifier and emulsifier salt, flavoring agent and adjuvant, formulation aid, stabilizer and

Table 5. Composition Data on Various Species of Acacia

Acacia Species	Analytical Method	Components	Reference
*Acacia farnesiana** (pod, leaf, stem, old stem, and flower)	Phytochemical screening	Carbohydrates and/or glycosides, reducing sugars, hydrolyzable tannins, alkaloids and nitrogenous bases, unsaturated sterols, and/or terpenes, and coumarins (all organs). Flavonoids (all organs except stem). Cyanogenic glycosides (in pod, leaf, and stem). Volatiles (flower)	Wassel et al., 1992
*Acacia farnesiana** oil	Thin layer chromatography	Anisaldehyde, benzalcohol, benzaldehyde, cuminicalcohol, farnesol, cuminicaldehyde, geraniol, geranyl acetate, ionone, linalool, linalyl acetate, nerolidol, terpineol, and methyl salicylate	El-Hamid and Sidrak, 1970
Acacia nilotica (pod, leaf, stem, old stem, and flower)	Phytochemical screening	Carbohydrates and/or glycosides, reducing sugars, hydrolyzable tannins, condensed tannins, saponins, alkaloids and nitrogenous bases, unsaturated sterols, and/or terpenes, and coumarins (all organs). Volatiles (flower). Flavonoids (all organs except stem). Cyanogenic glycosides (pod and stem)	Wassel et al., 1992
Acacia latifolia (flowers)	Standard spectral, hydrolytic, and chromatographic data used	Flavonoids detected: quercetin 7-O-β-D-glucoside, quercetin 3-O-β-D-galactoside, quercetin 3-O-β-glucoside, quercetin 3-O-rutinoside, quercetin 3-O-trioside with galactose and glucose as sugars, myricetin 3-O-β-D-galactoside, myricetin 3-O-β-glucoside, taxifolin 7-O-α-D-glucoside, and isorhamnetin (after hydrolysis)	Voirin et al., 1986
Acacia leucophloea (stem bark)	- - -	n-hexacosanol, β-sitosterol, and β-amyrin	Khan et al., 1991
Acacia leucophloea (flower)	Column chromatography	Behenic ester, β-sitosterol, quercetin-3-glucoside, and mannitol	Khan et al., 1991
Acacia leucophloea (seed)	Column chromatography	Total free phenols (0.90 ± 0.03 g/100 g seed flour); tannins (0.68 ± 0.02 g/100 g seed flour)	Vijayakumari et al., 1994
Acacia leucophloea Wild. (leaves and pods)	Acid titration method	Hydrocyanic acid	Gupta and Nauriyal, 1966
*Acacia catechu** (bark)	Thin-layer chromatography and spectrophotometry	Aflatoxin B_1 (0.09 μg/g)	Roy and Kumari, 1991
*Acacia catechu** (seed)	Thin-layer chromatography and spectrophotometry	Aflatoxin B_1 (0.01 to 0.76 μg/g)	Roy and Kumari, 1991
Acacia berlandieri (leaf extract)	Paper chromatography	N-methyl beta-phenylethylamine (sympathomimetic)	Camp et al., 1963
Acacia berlandieri (leaves)	Paper, thin layer, and gas chromatography	Phenolic amines: tyramine, N-methyl-tyramine, and hordenine	Adams and Camp, 1966
Acacia berlandieri (leaves)	High performance liquid chromatography	Tyramine, N-methyltyramine, and hordenine	Pemberton et al., 1993
Acacia honey (species not stated)	Flame absorption spectrometry	Chromium (0.52 μg/g weight); ash (0.121%)	Petrovic et al., 1994

Acacia Species	Analytical Method	Components	Reference
Acacia tortilis (gum and bark extracts)	High performance liquid chromatography	Smooth muscle relaxants: quaracol A and B (in gum) and (+)-fisetinidol (in gum and bark)	Hagos and Samuelson, 1988
Acacia modesta (stem bark, heartwood, and leaf extracts)	Thin layer chromatography	α-amyrin, betulin, octacosanol and ε-sitosterol (in stem bark); γ-sitosterol and pinitol (in heartwood); octacosane, hentriacontane, octacosanol, and hentriacontanol (leaves)	Joshi et al., 1975
Acacia georginae (seeds)	Extractive and chromatographic procedures	Fluoroacetic acid	Oelrichs and McEwan, 1962
Acacia atramen-taria and *Acacia tortuosa* (leaves)	Gas chromatography and NMR spectroscopy	Proacacipetalin (cyanogenic glucoside)	Seigler et al., 1983
Acacia aroma (leaves)	Gas chromatography and NMR spectroscopy	Linamarin and lotaustralin (cyanogenic glucosides)	Seigler et al., 1983
Acacia globulifera (leaves	Gas chromatography and NMR spectroscopy	Epiproacacipetalin (cyanogenic glucoside)	Seigler et al., 1983
Acacia mollissima, Acacia confusa, Acacia longifolia, Acacia decur-rence, Acacia dealbata*, Acacia baileyana, and Acacia verticillata* (leaves)	Amino acid autoanalyzer used	(-)-trans-4-hydroxypipecolic acid	Marakesh et al., 1969
Acacia albida, Acacia ataxa-cantha, Acacia catechu, Acacia confusa, Acacia coulteri, Acacia erubescens, Acacia ferruginea, Acacia galpinii, Acacia hamulosa, Acacia mellifera, Acacia modesta, Acacia nigrescens, Acacia polyacantha, Acacia rovumae, Acacia senegal*, Acacia venosa, and Acacia welwitschii* (seeds)	Ion exchange chromatography	α-amino-β-oxalylaminopropionic acid (neurotoxic lathyrogen)	Quereshi et al., 1977

*Acacia species listed in International Cosmetic Ingredient Dictionary

thickener, humectant, surface-finishing agent, processing aid, and texturizer (21 CFR 184.1330). Gum Arabic is also listed as one of the optional blending ingredients of vanilla powder (21 CFR 169.179) and vanilla-vanillin powder (21 CFR 169.182).

The following maximum values for possible daily human intake (g/kg body weight) of Gum Arabic in the total diet have been calculated for various age groups by the Select Committee on GRAS Substances using data from the National Research Council: 115 mg/kg (0 to 5 months), 322 mg/kg (6 to 11 months), 329 mg/kg (12 to 23 months), and 113 mg/kg (2 to 65 + years) (FASEB, 1973).

At the thirty-fifth meeting of the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA), which was held in Rome from May 29 to June 7, 1989, JECFA confirmed its ADI (acceptable daily intake) "not specified" classification of Gum Arabic. Here, Gum Arabic (a.k.a. Gum Acacia) is defined as the dried gummy exudate from tropical and subtropical *Acacia senegal* trees.

The category ADI "not specified" is explained as follows: "This term is applicable to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological, and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect, and from its acceptable background in food does not, in the opinion of the JECFA, represent a hazard to

Table 6. Specifications for Acacia Concinna Extract (Carlisle International Corporation, 1997a)

Aspect	Brown, clear liquid
pH	4 to 6
Specific Gravity	1.01 to 1.1
Refractive Index (at 20°C)	1.1 to 1.4
Dried Residue (2 h /110°C)	5 to 10%
Water	60 to 65%
Propylene Glycol	35 to 40%
Water Solubility	Soluble
Preservatives	Parabens and Potassium Sorbate
Heavy Metal	< 10 ppm
Other Constituents	Saponins (detected by HPTLC)
UV/VIS Spectrophotometry (Absorbance at 220 nm of a 0.20% aqueous solution)	2.0 ± 0.20
Maximum Total Bacterial Count	100/g
Maximum Yeasts and Moulds	0/g

Table 7. Analytical Profile of Acacia Concinna Extract (Carlisle International Corporation, 1997a)

SPECIFICATION	STANDARD	SAMPLE
Aspect	Brown	Brown
pH	4 to 6	Passes
Specific Gravity (at 25°C)	1.0 to 1.10	Passes
Refractive Index (at 20°C)	1.1 to 1.4	Passes
Dried Residue (2 h/110°C)	10 to 20%	Passes
Water	60 to 65%	Passes
Propylene Glycol (%)	35 to 40%	Passes
Water Solubility	Soluble	Passes
Preservatives	Present	Passes
Heavy Metal	< 10 ppm	Passes
UV/VIS Spectrophotometry (Absorbance at 220 nm of a 0.1% aqueous solution)	1.0 ± 0.25	Conforms
HPTLC Method	Saponins, alkaloids, malic acid	Conforms
Maximum Total Bacterial Count	100/g	Passes
Maximum Yeasts and Moulds	0/g	Passes

Table 8. Product Formulation Data on Acacia (FDA, 1997)

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient
Bath Oils, Tablets, and Salts	141	1
Mascara	158	12
Other Eye Make-up Preparations	116	2
Other Hair Coloring Preparations	56	1
Foundations	283	1
Lipstick	758	1
Body and Hand Skin Care Preparations (Excl. Shaving)	776	2
Moisturizing Skin Care Preparations	743	1
Paste Masks (Mud Packs)	247	1
1997 Totals		22

health. For that reason, and for reasons stated in individual evaluations, the establishment of an acceptable daily intake expressed in numerical form is not deemed necessary. An addltive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect; it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance." (World Health Organization, 1990)

Gum Arabic (Acacia Senegal) is used in the pharmaceutical industry to stabilize emulsions during the preparation of tablets (Collins et al., 1987). It is also used for its demulcent action in the treatment of throat or gastric inflammation (Gennaro, 1990). Furthermore, the therapeutic efficacy of Acacia Catechu in the treatment of lepromatous leprosy has been reported (Ojha et al., 1969).

Gum Arabic has also been used in glues, lithographic solutions, and matches (tip and binder in striking surface), and polisher and textile finishes (van Ketel, 1984).

The following uses of Acacia Concinna in folk medicine have been reported: A chutney (pungent relish of fruits, spices, and herbs) made of the tender leaves of *Acacia concinna*, salt tamarind, and chillies is administered for the treatment of bilious affections such as jaundice. An infusion of the leaves is used in the treatment of malarial fever; it checks flatulence and serves as a mild laxative. Furthermore, repeated, large doses of a decoction of the *Acacia concinna* pods act as an emetic and purgative (Carlisle International Corporation, 1997b).

An ointment made from the pods reportedly is used in the treatment of skin diseases (Carlisle International Corporation, 1997b).

BIOLOGICAL PROPERTIES

ABSORPTION, DISTRIBUTION, AND METABOLISM

The weight gain for rats fed Gum Arabic at a dietary concentration of 16% was 75% of that reported for control rats. It was determined that approximately 80% of the Gum Arabic was absorbed (Informatics, 1972).

In a study using rats, an apparent decrease in the caloric value of Gum Arabic with increasing administered dose was noted. Gum Arabic was incorporated into the diet at concentrations of 5%, 10%, and 17%. Digestibility data indicated that up to 80% of the Gum Arabic was absorbed (Informatics Inc., 1972).

Following a 48 h fast, 20 young male rats were fed 10 mg of a mixture consisting of 34% white, powdered Gum Arabic and 66% cacao butter. At 72 h after feeding, the rats were anesthetized and the liver was removed and analyzed for glycogen content. The difference in glycogen concentration between control and fed rats was insignificant. Therefore, it was concluded that the Gum Arabic molecule was not metabolized by enzymes of the rat digestive tract (Informatics Inc., 1972; FASEB, 1973).

Other studies have indicated that Gum Arabic is partially digested in the rat. In one study, weight gain and feed efficiency were determined using groups of six rats fed 15% Gum Arabic for 62 days. Feed efficiency was identical between experimental and control groups. However, compared to the control group (mean weight gain = 199 g), rats fed Gum Arabic had a mean weight gain of 224 g. In another study, groups of five rats were pair-fed Gum Arabic (0.75 g/day; added to 5 g basal diet). Results indicated that the digestibility of Gum Arabic was 71% (Informatics Inc., 1972).

The metabolism of Gum Arabic was evaluated using albino Wistar male rats (3 months old; weights ≈ 350 g). The number of animals used in the study was not stated. Two groups of animals were fed Oxoid breeders diet only and Oxoid breeders diet plus 200 g Gum Arabic/kg *ad lib*, respectively, for four weeks. Oxoid breeders diet was described as a reconstituted diet that allowed the ready incorporation of Gum Arabic into pellet form.

Feces were collected during the 24 h period before animals were killed. Following *ad libitum* overnight feeding, the animals were killed using a combination of diethyl ether anesthesia and cervical dislocation and contents from the stomach, small bowel, cecum, and distal colon were removed.

For rats fed Gum Arabic in the diet, a white flocculent precipitate typical of Gum Arabic was detected in contents from the stomach and small intestine, but not from the cecum, distal colon, or in the feces. The fact that precipitable Gum Arabic was detected along the GI tract as far as the terminal ileum, but not in the cecum, suggests that the metabolism of Gum Arabic is mediated by bacteria in the cecum.

In animals in which the cecum was resected, precipitable Gum Arabic was detected along the length of the entire residual intestine. This observation suggests that in the absence of the bacterial mass resident in the cecum, there is no degradation of Gum Arabic. No precipitate typical of Gum Arabic was found in the GI tract of control rats that received the Oxoid breeders diet only (Ross et al., 1984).

While the preceding study suggested that Gum Arabic was metabolized by bacteria in the cecum, the fate of undigested gum was not determined in earlier feeding studies involving rats and guinea pigs (Informatics, 1972).

A total caloric intake slightly greater than that for starch has been reported for Gum Arabic in rabbits. Evidence of glycogenesis was also demonstrated in this study. Thus, it appears that rabbits are able to utilize Gum Arabic (FASEB, 1973).

In a study involving guinea pigs, it was determined that Gum Arabic was highly digestible (90%) when administered in the diet at a concentration of 15% for ten days (Informatics, 1972).

Results of studies in which dogs and rabbits were injected intravenously with Gum Arabic indicated that Gum Arabic or some other product associated with it accumulated in the liver and remained in the tissues for several months. Non-lethal effects included serious disturbances in hemoglobin, white blood cells, and serum proteins (FASEB, 1973).

Using many of the studies summarized above, the Select Committee on GRAS Substances determined in 1973 that Gum Arabic can be digested to simple sugars. However, it was also determined that conclusive evidence indicating that the intact Gum Arabic molecule is absorbed under normal conditions was lacking (FASEB, 1973). It should also be noted that data on the fate of undigested Gum Arabic in male rats (Ross et al., 1984) have been published since the FASEB report was issued. The results of this previously summarized study suggest that the

bacterial mass resident in the cecum is responsible for the metabolism of Gum Arabic. [See section under Clinical Assessment of Safety for human studies on absorption, distribution and excretion.]

HYPOTENSIVE ACTIVITY

The hypotensive activity of *Acacia catechu* (aqueous extract of branches) was evaluated using four groups of four anesthetized dogs (males and females; weights = 8 to 12 kg). The right femoral artery was cannulated for blood pressure recordings and, the right femoral vein, for intravenous injection. After a 30 min equilibration period, *Acacia catechu* was injected (bolus injection) into dogs from each of the four groups. Doses ranged from <1 to ~2 mg/kg. Changes in mean arterial blood pressure (MAP) were recognized as differences between the steady MAP before injection and the lowest MAP after injection.

The results were presented as a log-dose response curve. *Acacia catechu* induced dose-related hypotensive responses. At high doses, the hypotensive effect lasted approximately 30 min. Based on experimentation with various blocking agents, it was determined that this effect was not mediated through α- and β-adrenergic, cholinergic, or histaminergic receptors, or related to autonomic ganglion transmission (Sham et al., 1984).

The hypotensive activity of *Acacia catechu* (aqueous extract of branches) was also evaluated using four groups of five male Sprague-Dawley rats (weights between 170 and 250 g) according to the procedure in the preceding paragraph; however, in this experiment, the left carotid artery and jugular vein were cannulated.

Acacia catechu induced dose-related hypotensive responses in rats over the range of doses tested (1 to 2 mg/kg). It was also determined that the hypotensive responses were not mediated through α- and β- adrenergic, cholinergic, or histaminergic receptors, or related to autonomic ganglion transmission (Sham et al., 1984).

In an *in vitro* experiment, *Acacia catechu* induced a dose-dependent relaxation of helical strips of rat tail artery that had been pre-constricted with the vasoconstrictors arginine vasopressin and methoxamine, respectively. In the presence of arginine vasopressin, *Acacia catechu* was tested at concentrations of 0.01, 0.03, and 0.1 mg/ml. *Acacia catechu* was tested at concentrations of 0.1, 0.3, and 1 mg/ml in the presence of methoxamine (Sham et al., 1984).

HYPOCHOLESTEROLEMIC ACTIVITY

The hypocholesterolemic activity of the dried water extract of *Acacia catechu*, also known as katha in India, was evaluated using three groups of ten male albino rats (weights = 100 to 125 g). One group was fed stock diet thoroughly mixed with 1% cholesterol, and a second group was fed stock diet thoroughly mixed with 1% cholesterol plus 0.2% katha. The control group was fed stock diet only. The diets were fed *ad libitum*. Half of the animals in each group was killed after six weeks of feeding, and the remaining animals were killed after twelve weeks of feeding. The cholesterol content of the serum and liver was determined for each rat.

A progressive increase in serum and liver cholesterol content was observed in animals fed the stock diet supplemented with cholesterol for six months. In animals fed stock diet supplemented with cholesterol and katha for six months, the elevation of serum and liver cholesterol levels was significantly lower ($p = 0.001$) when compared to rats fed stock diet supplemented with cholesterol.

However, at the end of twelve weeks, the increase in serum and liver cholesterol concentrations in rats fed stock diet supplemented with cholesterol and katha was elevated by approximately 50% when compared to rats fed stock diet supplemented with cholesterol only. It was also determined that there was substantially less deposition of lipids in the liver of katha-fed rats. It was concluded that katha had hypocholesterolemic activity in this study, and that it helped prevent fatty degeneration of the liver (Chaudhari and Hatwalne, 1973).

HYPOGLYCEMIC ACTIVITY

The hypoglycemic activity of ethanolic extracts of the pod, leaf, stem, old stem, and flower of *Acacia farnesiana L. Wild* was evaluated using groups of 11 alloxanized diabetic albino rats (weights = 150 to 200 g). To prevent the development of fatal hypoglycemia during the first 12 h after alloxan administration, a 25% glucose solution (5 to 10 ml) was subcutaneously injected at 2 to 3 h intervals. Extract from each plant part

(dose = 30 or 50 mg/kg in polysorbate 80) was administered orally to a group of 11 rats, and blood samples were taken at 2 h post-administration. Blood samples were collected prior to treatment in order to estimate the normal blood glucose level of fasting rats. The hypoglycemic activity of ethanolic extracts of *Acacia farnesiana* stem and pod was considerable following the administration of a 50 mg/kg dose. *Acacia farnesiana* stem and pod caused 21% and 36% reductions in the normal fasting blood sugar level, respectively (Wassel et al., 1992).

EFFECTS ON SMOOTH MUSCLE

The effect of ethanolic extracts of the pod, leaf, stem, old stem, and flower of *Acacia farnesiana L. Wiild* on uterine motility was evaluated. Rat uteri at various stages of the estrous cycle were suspended in 50 ml baths containing oxygenated Krebs solution; uteri were equilibrated in the solution for at least 90 min. Drugs were added to the water bath and were retained until the highest contraction was achieved.

Normal rhythmic contractions of the isolated uteri were first recorded using a T_2 isotonic transducer and two channel MD_2 oscillograph. Subsequently, the organ extracts (in polysorbate 80) were added to organ water baths, respectively. Organ extracts were administered at a dose of 50 or 75 mg/ 50 ml bath. The drug used to induce uterine contraction was then removed by washing the preparation with fresh Krebs solution.

Most of the Acacia ethanolic extracts stimulated uterine muscular contraction during the estrous cycle and pregnancy. However, some of the extracts had a stimulatory effect on uterine contraction, followed by inhibition (i.e. leaf extract on non-estrus uteri and pod extract on pregnant uterus). The stem extract of *Acacia farnesiana* inhibited contraction of the pregnant uterus (Wassel et al., 1992).

The bronchodilator activity of *Acacia farnesiana* was evaluated using the perfused, isolated guinea pig lung. The control guinea pig lung preparation was treated with saline. The unripe pods of *Acacia farnesiana* were collected and dried at room temperature. The glycosidal fraction of the ethyl alcohol extract of coarsely powdered Acacia pods was then isolated, and an aqueous solution of this fraction was tested.

Doses of 2, 5, and 10 μg of the aqueous solution increased outflow in the isolated lung perfusion preparation, indicating that the glycosidal fraction induced a smooth muscle relaxant effect. The same doses also increased outflow following histamine (10 μg) -induced contraction, and the bronchodilator effect was not blocked by propranolol (400 μg). These results suggested that the glycosidal fraction exerted a direct relaxant action on the bronchial muscles. The investigators noted that this effect is not mediated through β-adrenergic receptors (Trivedi et al., 1986).

The vasodilator activity of *Acacia farnesiana* was evaluated *in vitro*. The glycosidal fraction of the ethyl alcohol extract of coarsely powdered Acacia pods was isolated, and an aqueous solution of this fraction was tested. The hind limb of dogs was perfused through the femoral artery with oxygenated, defibrinated blood in Ringer solution. Femoral venous outflow was recorded periodically. The control preparation was treated with normal saline.

The aqueous glycosidal fraction induced vasodilation at doses of 2, 5, and 10 μg (% increases in blood flow/min of 21.4, 20.86, and 24.3, respectively; n = 5). Vasodilation was not blocked following the addition of any of the following agents: chlorphenaramine maleate (20 μg), atropine (20 μg), or propranolol (400 μg). Study results indicated that the glycosidal fraction of *Acacia farnesiana* had a smooth muscle relaxant effect. The investigators noted that this effect was not mediated through cholinergic or H_1 receptors (Trivedi et al., 1986).

ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory activity of *Acacia farnesiana* was evaluated *in vitro*. The glycosidal fraction of the ethyl alcohol extract of coarsely powdered Acacia pods was isolated, and an aqueous solution of this fraction was tested. The effect of this fraction on chemically-induced edema of the rat hind paw was evaluated according to the method of Winter et al. (1962). The glycosidal fraction inhibited carrageenin and formaldehyde induced inflammation of the rat hind paw *in vitro* (% inhibition of 38.2 and 26.26, respectively; $P < 0.001$, n = 10). It was concluded that this fraction has a promising anti-inflammatory

effect (Trivedi et al., 1986).

BIOCHEMICAL EFFECTS

Gum Arabic was administered twice daily to groups of four rats (weights = 100 to 110 g) at concentrations of 1, 2, and 10%, respectively, five days per week for four weeks. The test substance was suspended in distilled water and administered orally at a dose volume of 0.2 ml/100 g body weight; control rats were given equal volumes of distilled water. The actual doses of Gum Arabic administered were 2 x 20, 2 x 40, and 2 x 200 mg/kg/day, respectively. Groups of four rats were killed by cervical dislocation 16 h after administration of the last dose. Following maceration and homogenization, heart and liver mitochondria were isolated by differential centrifugation. Electron transfer reactions (oxygen consumption) and oxidative phosphorylation were measured polarographically. The hydroxylation of biphenyl was chosen as the assay system for measuring mixed function oxidases of hepatic cell endoplasmic reticulum.

Dose-dependent uncoupling of oxidative phosphorylation was the primary effect on cardiac and hepatic cell mitochondrial function. The damage to cardiac mitochondria progressed as dosing continued. However, hepatic cell mitochondrial function seemed to have gradually returned to normal during the fourth week of dosing.

At the highest administered dose (2 x 200 mg/kg/day) marked uncoupling of oxidative phosphorylation was observed in the heart and liver after two days of dosing. Partial recovery was reported for cardiac mitochondria after the first week of dosing; however, the same degree of uncoupling was noted up to the end of the experiment. Hepatic cell mitochondria were said to have recovered slowly as the experiment progressed. Gum Arabic also caused a progressive inhibition of the biphenylhydroxylase system in the hepatic microsomal fraction (Bachmann et al., 1978).

Lutz et al. (1978) considered the study results in the preceding paragraph and decided to investigate whether comparable biochemical effects of Gum Arabic could also be demonstrated *in vivo*. The measurement of maximal aminopyrine demethylation as expired CO_2 was deemed a suitable approach for this investigation, which was conducted using female rats of the ZUR SIV-Z strain (weights = 152 to 180 g). Oral dosing with 10% (w/v) Gum Arabic had no effect on the *in vivo* demethylation of 4-dimethyl(^{14}C)-aminoantipyrine (Lutz et al., 1978).

Trypsin inhibitor has been isolated from the seeds of *Acacia confusa* (Lin and Lin, 1985; Lin et al., 1991).

ANTIMICROBIAL ACTIVITY

The antimicrobial activity of ethanolic extracts of plant organs from *Acacia farnesiana* was evaluated. Extracts were made from the following plant parts: the pod, leaf, stem, old stem, and flower. Bacteria and fungi were cultured and filter paper disks were impregnated with 10 μl of each extract. Each disk (one extract per disk) was then dried and placed on the surface of the inoculated agar medium, and cultures were incubated for 48 h and observed for zones of inhibition. All plant extracts were inhibitory to *Bacillus subtilis* and *Staphylococcus aureus.* Additionally, most of the extracts were inhibitory to *Sarcina lutea*, *Pseudomonas aeruginosa*, and *Escherichia coli.* The plant extracts had no effect on *Mycobacterium phlei* or *Candida albicans* (Wassel et al., 1992).

TOXICOLOGY

ACUTE ORAL TOXICITY

In an acute oral toxicity study using rabbits (weights and strain not stated), an Acacia Gum LD50 of 80 g/kg was reported (Dangerous Properties of Industrial Materials Report, 1981).

ACUTE INTRAPERITONEAL TOXICITY

In a study using dogs (number and weights not stated), the intraperitoneal injection of 4.8 g/kg Gum Arabic did not induce toxicity. However, the same dose killed dehydrated dogs (highest no-effect-level = 1.9 g/kg) (FASEB, 1973).

SHORT-TERM ORAL TOXICITY

The oral toxicity of Gum Arabic was evaluated using three-week-old Sprague-Dawley rats (16 males, 16 females). Three days before dosing, mean body weights were 122 g and 125 g for males and females, respectively. The animals were fed Gum Arabic (dose not stated) daily for

28 days and then killed by exsanguination. Blood samples were obtained for hematological examination and serum analysis the day before animals were killed. Microscopic examination of most organs was performed, which included examination of any tissues that appeared abnormal.

No treatment-related behavioral effects were noted. All values for serum chemistry parameters were within the normal limits for laboratory rats. Mean cell volume values were said to have been within the normal range for Sprague-Dawley rats. No toxicologically significant lesions were noted at microscopic examination (Cook et al., 1992).

Groups of rats (number and weights not stated) were fed 15% Gum Arabic in the diet for 62 days. A cathartic effect was noted. Weight gain, feed efficiency, hematological findings, and organ weights were normal (World Health Organization, 1974).

In another study, 10% (w/w) Gum Arabic (Acacia Senegal) was fed to Wistar albino rats (no. not stated; weights = 99 to 120 g) daily for 45 days. The rats were then killed by cervical dislocation while under ether anesthesia. Portions of the jejunum, ileum, and cecum were excised and the ultrastructure of each was evaluated using transmission electron microscopy.

No abnormalities in organelles were observed within cells of the jejunum, ileum, or cecum of rats fed Gum Arabic. Additionally, neither inclusions nor other pathological changes were detected. It was concluded that no significant ultrastructural differences occurred between experimental and control rats (Anderson et al., 1986).

Three groups of three male Albino Wistar rats (weights = 140 to 160 g) were fed diets containing 1%, 4%, and 8% (w/w) Gum Arabic (Acacia Senegal), respectively, daily for 28 days. A fourth group served as the negative control. At necropsy, hepatic and cardiac tissues were obtained for electron microscopy and microsomal P-450 assays.

No discernible ultrastructural differences were observed between the livers of test (all dietary groups) and control rats; particularly, the mitochondria were normal. Also, no discernible ultrastructural differences were found between the hearts of test (all dietary groups) and control rats. Particularly, both the appearance and concentration of the mitochondria and myofibrils were identical in this comparison. The results of assays of hepatic microsomal protein and cytochrome P-450 for each dietary group indicated that Gum Arabic did not cause inductive effects. The investi-gators noted that when induction by active agents (e.g. phenobarbitone) takes place, cytochrome P-450 values are increased by several-fold within a few days (Anderson et al., 1984).

Diets containing Gum Arabic were fed to 133 guinea pigs. Twenty-two of the diets contained 15% Gum Arabic and one contained 20% Gum Arabic. The animals were fed for periods ranging from three to nine weeks. No toxic effects resulted from the administration of Gum Arabic (Informatics Inc., 1972).

SHORT-TERM INTRAVENOUS TOXICITY

Acacia (Gum Arabic) was administered intravenously to three dogs (weights not stated) over a period of 76 days. The number of intravenous injections ranged from 32 to 35 over this period, and the range for the total cumulative dose was 15.7 to 47.7 g/kg. An enlarged liver was observed in the dog that received the highest dose; death occurred four months after the last injection. The cause of death was not determined. The remaining two dogs remained in good condition. The results of biopsies performed on the two animals indicated that Acacia was present in the liver 26 months after the last injection (World Health Organization, 1974).

In another study, Gum Arabic was administered intravenously to dogs (number and weights not stated) over a period ranging from 1 to 84 days. Doses ranged from 1 to 2 g/kg. Enlarged livers and swollen kidneys were the most characteristic changes. Similar doses were fatal when administered to two rabbits (weights not stated) (FASEB, 1973).

SUBCHRONIC ORAL TOXICITY

The subchronic oral toxicity of Gum Arabic (Acacia Senegal) was evaluated in two experiments using albino Wistar rats (24 to 28 days old). Body weights prior to initiation of the study were not included.

In the first experiment, groups of 15 male rats were fed Gum Arabic at concentrations of 0.91%

(dietary level = 0.53 g/kg/day), 2.0% (1.08 g/kg/day), 4.3% (2.55 g/kg/day), and 8.6% (5.22 g/kg/day), respectively, for 13 weeks. Groups of 15 female rats were fed concentrations of 0.75% (0.5 g/kg/day), 1.7% (1.05 g/kg/day), 3.7% (2.6 g/kg/day), and 7.5% (5.31/g/kg/day), respectively. Fifteen males and fifteen females served as controls.

In the second experiment, 15 male rats were fed Gum Arabic at an average concentration of 18.6% (14 g/kg/day) for 13 weeks. Fifteen females were fed an average concentration of 18.1% (13.8 g/kg/day). The two control groups consisted of 15 males and 15 females, respectively. Urine and blood samples were obtained during the study. The animals were killed under anesthesia by cervical dislocation at the end of the treatment period and prepared for necropsy.

The combined results for the two experiments included the reported deaths of two control female rats. Growth rates were not reduced for male or female rats at dietary doses up to 5 g/kg/day (~ 8.5%Gum Arabic in diet). At a concentration of approximately 18% in the diet (14 g/kg/day), male rats had a reduced growth rate and smaller final body weight ($P < 0.01$). The average weight gain for male rats was 78% of that of controls.

Following the ingestion of Gum Arabic, 5 g/kg/day, by male rats, kidney weights (absolute and relative to body weight) were reduced ($P < 0.05$). At the highest dietary doses tested (~ 18%, 14 g/kg/day), kidney weights for male and female rats were significantly reduced ($P < 0.01$). Liver weight was reduced in a dose-dependent manner in male rats; the difference between experimental and control groups was not significant at doses of Gum Arabic less than 5 g/kg/day. No significant differences were observed in urine volume or composition between control and test groups at any of the dietary concentrations of Gum Arabic tested. Similarly, no significant hematological changes were observed between test and control groups. At microscopic examination, no alterations were found that were attributable to the ingestion of Gum Arabic. The only treatment-related alteration noted at necropsy was cecal enlargement in rats of the highest-dose groups (Anderson et al., 1982).

In another study, four groups of five male Albino Wistar rats (weights = 40 to 60 g) were fed diets containing 0.5, 1.5, 2.5, and 3.5% (w/w) Gum Arabic (Acacia Senegal), respectively, daily for 91 days. A fifth group served as the negative control. At the end of the feeding period, the animals were killed by cervical dislocation for necropsy. Samples of liver and heart from each treatment group were obtained for transmission electron microscopy. Livers from the remaining rats (2 per group) were used for assays of microsomal protein and cytochrome P-450.

Electron microscopic findings for cardiac muscle included no abnormality of myofilaments, no depletion of glycogen reserves, no abnormality of the intracytoplasmic mitochondria or endoplasmic reticulum, no excessive infiltration with lipid, and no evidence of interstitial infiltration. Additionally, no abnormalities were observed with respect to the size, chromatin content, or nucleoli of nuclei. Electron microscopic findings for the liver included no abnormalities in hepatocytes, Kupffer cells, or lining cells of the biliary passages. The mitochondria and nuclei were normal both in appearance and internal structure, and no abnormalities were observed in intracytoplasmic glycogen stores (Anderson et al, 1984).

IMMUNOLOGICAL RESPONSES

Studies on immunological responses to Gum Arabic are summarized in Table 9.

The allergenicity of Acacia solution (exact composition not stated) was evaluated using six rabbits (12 weeks old). The rabbits were injected intravenously with 50 cc Acacia, and this dose was repeated 5, 12, and 17 days later. At 4 weeks after the last injection, each rabbit was injected intravenously with 2 cc of Acacia.

The rabbits appeared normal during a 1 h observation period following this injection. On the same day, one of the rabbits was injected intravenously with 2 cc of a 50% egg white solution to determine whether exposure to a foreign protein would result in greater sensitivity to Acacia. Acacia (2 cc) was injected intravenously three weeks later, and then three weeks after this injection at a dose of 15 cc. No signs of anaphylaxis were observed in this animal (Maytum and Magath, 1932).

In a second experiment (same study) evaluating the allergenicity of Acacia solution (exact composition not stated), eight guinea pigs (weights = 300 g) were injected intraperitoneally with a dose of 10 cc, and this dose was repeated 5, 12,

Table 9. Immunological Responses

Test Substance	Animals Tested	Test Procedure	Test Results	References
Acacia solution	6 rabbits (12 weeks old)	Four i.v. injections (50 cc) on days 0, 5, 12, and 17, followed by single i.v. injection (2 cc) 4 weeks after fourth injection	No signs of anaphylaxis	Maytum and Magath, 1932
Acacia solution	8 guinea pigs (weights = 300 g)	Four i.p. injections (10 cc) on days 0, 5, 12, and 17 followed by single i.v. injection (0.5 cc) 4 weeks after fourth injection	Anaphylactic signs (sneezing, coughing, dyspnea) in 8 animals; 2 deaths. Milder signs noted in two surviving animals injected intracardially (0.5 cc); one died. Mild signs also in two of remaining four survivors injected intraperitoneally (0.5 cc). In a follow-up experiment involving guinea pigs, it was concluded that Acacia was capable of inducing peritonitis (followed by death) regardless of the route of administration, i.p. or i.v.	Maytum and Magath, 1932
Acacia solution	19 guinea pigs (8 guinea pigs in preceding study included)	Parenteral administration	No anaphylactic signs (10 animals); Mild and fairly severe anaphylactic signs in four and three animals, respectively; extremely severe signs in two animals; three of 19 died	Maytum and Magath, 1932
Anti-Gum Acacia rabbit serum	5 guinea pigs (weights 300 to 450 g)	Passive sensitization with 2 ml of serum (i.p. injection), followed by i.v. dose of a homologous gum (1 mg).	Three animals died at 2 to 3 min post-injection. The remaining two recovered from anaphylactic shock slowly.	Partridge and Morgan, 1942
7% Gum Acacia solution	Two groups of 10 guinea pigs (weights 600 to 1000 g)	Injected subcutaneously (5 ml) repeatedly over seven-week period. After two weeks of dosing, animals injected with 1 ml *Brucella abortus* vaccine.	No deleterious effects on antibody production resulted, as judged by the development of agglutinative and complement-fixing activity in the serum to *Brucella abortus*.	Rice, 1954a
7% Gum Acacia solution	4 rabbits (weight range 1800 to 2650 g)	Injected subcutaneously (10 ml) repeatedly over four-week period. Injected with Brucella abortus vaccine 4 days (2 ml) and 8 days (3 ml) later	No deleterious effects on antibody production resulted, as judged by the development of agglutinative and complement-fixing activity in the serum to *Brucella abortus*.	Rice, 1954a
7% Gum Acacia solution	Two groups of 10 guinea pigs	Group 1: Injected subcutaneously (5 ml) repeatedly over 16-day period. Actively sensitized after seven doses and challenged in three weeks. Group 2: Received 11 subcutaneous injections. Passively sensitized and challenged 48 h later	Group 1: One animal with signs of asphyxia; Eight animals with shock signs; two died. Group 2: Typical respiratory signs developed; no deaths. Both groups: No significant decline in serum-complement activity	Rice, 1954b
6% Acacia solution	12 guinea pigs (weights ≈ 300 g)	Twelve animals sensitized via single intra-abdominal injections of 600 mg Acacia (6 % solution, 10 ml). Challenged 1 month later with i.v. injection of solution or other samples of Acacia. Two additional guinea pigs tested subsequently with Acacia from different lot	Twelve animals with anaphylactic shock; 10 died. Two additional guinea pigs sensitized by intra-abdominal injection of 160 mg Acacia with Freund's adjuvant (2 ml of emulsion containing two parts 20% Acacia), followed by i.v. challenge with 60 mg Acacia one month later, died of anaphylactic shock	Silvette et al., 1955

Test Substance	Animals Tested	Test Procedure	Test Results	References
Three grades of Gum Arabic (dissolved in 0.15 M NaCl at concentration of 4 mg/ml)	Groups of 6 to 8 female CBA mice (6 weeks old)	Mice immunized by injection of the antigen (0.1 mg in 0.05 ml Freund's adjuvant) into footpad. Delayed-type hypersensitivity measured 21 days after primary immunization.	Compared to controls, no significant increase in footpad thickness. Antigen-specific hypersensitivity reaction noted for all three grades of Gum Arabic.	Strobel et al., 1982
Gum Arabic (dissolved in 0.15 M saline at concentration of 400 mg/ml)	Two groups of 8 female BDF1 [(C57BL/6] x DBA/2 F_1] mice (6 to 8 weeks old)	Initially dosed with Gum Arabic (80 mg) by intragastric administration. Mice then immunized by injection of 100 μg Gum Arabic in saline and Freund's complete adjuvant (FCA) into hindpaw. Delayed hypersensitivity measured at 3 weeks post-immunization	Compared to controls, footpad swelling significantly suppressed. Systemic immunological hyporesponsiveness (oral tolerance) developed in mice fed Gum Arabic	Strobel and Ferguson, 1986
Five different samples of Gum Arabic (*Acacia senegal*)	5 groups of 6 to 8 male [(C57BL/6J] x DBA/2 F_1] (BDF_1) mice	Footpad swelling test. Non-immunized male mice injected intradermally with each sample	All but one sample induced footpad swelling at 24 h. Footpad swelling said to have been indicative of non-specific irritant effect	Strobel et al., 1986
Five different samples of Gum Arabic (*Acacia senegal*), each emulsified in FCA	5 groups of 30 to 40 [(C57BL/6J] x DBA/2 F_1] mice	Footpad swelling test. Initially, mice immunized with each sample (200 μg per sample) in left hind footpad. Presence of delayed-type hypersensitivity measured	All samples found to be immunogenic. Intradermal challenge after immunization caused significant increase in footpad thickness at 24 h.	Strobel et al., 1986
Five different samples of Gum Arabic (*Acacia senegal*), each emulsified in FCA	5 groups of 30 to 40 [(C57BL/6J] x DBA/2 F_1] mice	Test for cross-reactivity. Blood samples obtained from mice in preceding experiment at 3 weeks post-immunization. Antibodies assayed using enzyme-linked immunosorbent assay (ELISA)	Except for one sample, assay results indicated that antigens were shared between the samples tested	Strobel et al., 1986
Acacia Extract	Germ-free and conventional guinea pigs of Hartley strain	Acacia Extract (40 mg/ml) applied topically to the right eye.	Microscopic examination results: Severe inflammatory response observed in germ-free and conventional guinea pigs (14 animals total, 8 days old). Minimal inflammatory response in germ-free and conventional guinea pigs (13 animals total, 12 weeks old). Inflammatory response most severe in conjunctiva.	Aronson and McMaster, 1972

and 17 days later. At four weeks after the last dose, two of the animals were injected intravenously with 0.5 cc Acacia.

Typical anaphylactic signs (sneezing and coughing, scratching the nose, and dyspnea) were noted in both guinea pigs after approximately 30 sec. The two animals died approximately three minutes after signs were first noted. Two other guinea pigs were injected intracardially with Acacia solution (0.5 cc; exact composition not stated), after which both had milder signs of anaphylaxis. One animal recovered, and the other died after 1 h. The remaining four guinea pigs each received an intraperitoneal injection of Acacia solution (0.5 cc). Mild reactions were noted in two of the animals, and no signs were reported for the remaining two (Maytum and Magath, 1932).

A follow-up experiment to the preceding study was performed to determine whether the deaths reported were due to the intravenous method of test substance administration in the first experiment (rabbits). Four guinea pigs were injected intravenously with 0.5 cc Acacia solution (exact composition not stated), and no deleterious effects were noted. Acacia solution (10 cc) was

administered intraperitoneally to eight guinea pigs; four of the animals died within five days after injection.

Seven days later, the four remaining guinea pigs that were injected intraperitoneally, the four guinea pigs that were injected intravenously in the first experiment, and four new guinea pigs were injected intraperitoneally with Acacia solution (10 cc). Of the four new guinea pigs, two died from peritonitis within four days.

Seven days after intraperitoneal injection, the remaining ten animals from the third experiment were injected intraperitoneally with 10 cc Acacia. Four of the ten died of peritonitis on the next day. Therefore, Acacia was capable of inducing peritonitis (followed by death) only after intraperitoneal administration (Maytum and Magath, 1932).

The results of studies involving a total of 19 guinea pigs (8 guinea pigs from preceding experiment included) include sensitization induced by Acacia solution (administered parenterally; exact composition not stated) in a total of 19 guinea pigs, and no anaphylactic signs developed in seven of the animals. Mild and moderate anaphylactic signs developed in four and three guinea pigs, respectively, and severe signs were noted in two guinea pigs. Three of the 19 guinea pigs died. In addressing the results from the preceding experiments, the investigators noted that anaphylactic sensitivity to Acacia can develop under certain unusual conditions. It was also stated that no danger was associated with an initial dose of Acacia if the solution was properly prepared.

However, subsequent doses administered after at least three weeks should be given cautiously because of the possibility of anaphylactic reactions (Maytum and Magath, 1932).

Five guinea pigs (weights = 300 to 450 g) were passively sensitized with 2 ml of anti-Gum Acacia rabbit serum via intraperitoneal injection. At 24 to 36 h post-injection, an intravenous dose of a homologous gum (1 mg) was administered to each animal, and the animals were observed for signs of anaphylaxis. Three guinea pigs died 2 to 3 min after intravenous administration, and the remaining two slowly recovered from shock during the following 2 to 3 h (Partridge and Morgan, 1942).

The effect of Gum Acacia on complement and antibody production was evaluated using two groups of ten guinea pigs (strain not stated; weights = 600 to 1000 g). The animals were injected subcutaneously with Gum Arabic (7% solution, 5 ml) on alternate days prior to and during immunization; Gum Arabic was injected repeatedly over a period of seven weeks. After two weeks of dosing, the animals were bled and injected intraperitoneally with 1 ml of *Brucella abortus* vaccine. Three additional injections of this vaccine were made 4 days (2 ml injection), 8 days (3 ml) , and 21 days (3 ml) later.

The guinea pigs were bled again one week after the third and fourth doses of vaccine, and all sera were titrated for hemolytic complement and for agglutinative and complement-fixing activity with *Brucella abortus* antigens. Surviving animals were retested for six weeks, bled again, injected with a fifth dose of vaccine, and bled for a fourth time seven days later. Twenty guinea pigs of comparable weight were included in each of the control groups (immunized and non-immunized).

A sharp decline in complement titers was noted in both groups of guinea pigs injected with Gum Acacia. Following seven injections, only two of 18 surviving guinea pigs had complement titers over 1000 units per ml (minimum titer = 455). After 14 injections, one of the remaining animals had a titer that approached normal (minimum titer = 385). During the ensuing period, a rise in complement titer to over 1000 units per ml was noted for five guinea pigs and complement titers below 500 units were noted for eight guinea pigs; the reason for these changes in titer was undetermined.

In addition to the reductions in complement titer noted in the two groups, both antibody and total serum protein production were also reduced. It was determined that no deleterious effects on antibody production resulted, as judged by the development of agglutinative and complement-fixing activity in the sera to the bacterial antigen *Brucella abortus* (Rice, 1954a).

The effect of Gum Acacia on complement and antibody production was also evaluated using four rabbits (weight range = 1800 to 2650 g). This experiment is from the study in the preceding paragraph. The rabbits were injected subcutaneously with a 7% solution of Gum Acacia (10 ml) every second day for four weeks. All rabbits were bled on the fifteenth day and injected

with 1 ml *Brucella abortus* vaccine. The vaccine was also injected 4 and 8 days later in 2 ml and 3 ml volumes, respectively. The rabbits were bled again seven days after the third dose of vaccine. Untreated rabbits (immunized) and non-immunized rabbits served as controls.

In contrast to the effects noted in guinea pigs in the preceding study, Gum Acacia did not appreciably lower complement activity. The authors concluded that no deleterious effects on antibody production resulted, as judged by the development of agglutinative and complement-fixing activity in the sera to the bacterial antigen *Brucella abortus* (Rice, 1954a).

In another study, complement titers were evaluated in guinea pigs (strain and weights not stated) that were either actively or passively sensitized to a 7% solution of Gum Acacia. Ten guinea pigs were injected subcutaneously with 16 doses (5 ml per dose) of a 7% Gum Acacia solution over a period of 16 days. The animals were actively sensitized after 7 doses, and the nine survivors were bled, challenged, and re-bled in three weeks.

Signs of asphyxia were reported for one of the nine survivors; this animal survived for more than 3 h. The other guinea pigs became very excited shortly after challenge, running around wildly and squealing (shock signs); two eventually died. An additional ten guinea pigs that had received eleven injections of Gum Acacia solution were passively sensitized, bled, and challenged 48 h later. Typical respiratory signs developed; none of the animals died. No significant decline in serum-complement activity was detected in animals challenged shortly after passive sensitization or in actively-sensitized Gum Acacia-treated guinea pigs; however, a decline in this activity was noted. Additionally, in both sensitized groups, initial excitement followed by fatigue and weakness were the most striking clinical signs (Rice, 1954b).

Twelve guinea pigs (strain not stated; weights ≈ 300 g) were sensitized via single intra-abdominal injections of 600 mg Acacia (6% solution, 10 m; exact composition of solution not stated). The animals were challenged one month later with an intravenous injection of 60 mg of the sensitizing sample or other samples of Acacia.

Anaphylactic shock resulted in each of the twelve guinea pigs, ten of which died. Two additional guinea pigs were sensitized via intra-abdominal injection of 160 mg Acacia with Freund's complete adjuvant (FCA) (2 ml of emulsion containing two parts 20% Acacia). This Acacia sample was from another lot. The animals were challenged intravenously with 60 mg Acacia one month later. Typical anaphylactic death was reported for both guinea pigs.

The results of this experiment as well as additional experiments (rabbits and guinea pigs) in this study collectively indicated that four different lots of Gum Acacia were equally effective as immunizing, sensitizing, and anaphylactogenic and desensitizing antigens, based on the results of cross-precipitin tests and cross-anaphylaxis experiments (Silvette et al., 1955).

Antibodies directed against Gum Arabic have been isolated using affinity chromatography on AH-Sepharose 4B containing Gum Arabic ligands. These antibodies were induced in rabbits immunized with Gum Arabic in FCA. It was determined that the antibodies were anti-carbohydrate antibodies with specificity for certain carbohydrate units of the Gum Arabic. The results of chemical modification and inhibition experiments indicated that 4-α-L-arabinofuranosyl-D-glucuronic acid units of the polysaccharide were the major immunodeterminant groups (Pazur et al., 1986).

Blood group antigens have been demonstrated in Gum Arabic. The following substances were identified using an agglutinin inhibition test of mild hydrolyzed Gum Arabic: B, C (of ABO blood group system) and H substances (of H blood group system) and Le^a (Lewis ^{a} antigen, in Lewis blood group system). The results of a revised latex agglutination technique indicated the presence of P and S (of MN blood group system) as well as the substances mentioned in the preceding statement. Elution processes, using sensitized and agglutinated latex or kaolin particles, resulted in the identification of B, H, and Le^a substances in Gum Arabic; the elution of anti-P and anti-S did not occur (Matsuzawa, 1968).

Additionally, Narita (1985) reported the isolation of high-titer anti-Gum Arabic sera were obtained from rabbits injected with Gum Arabic. The antisera had cross-reactivity with the Lewis^a antigen (Le^a) antigen, as measured by both a single diffusion tube test and the Ouchterlony test (Narita, 1985).

The allergenicity of three grades of Gum Arabic

was evaluated using female CBA mice (6 weeks old; 6 to 8 mice per group). The grades of Gum Arabic tested were as follows: (1) processed Gum Arabic recovered by spray-drying from a solution of commercial food grade Gum Arabic after filtration to remove sand etc. and after heat treatment to effect pasteurization. (2) finely powdered natural Gum Arabic of poor commercial quality giving solutions of a dark red-brown color. (3) finely powdered natural Gum Arabic of very high quality, giving essentially colorless solutions.

The gum exudates were dissolved in 0.15 M NaCl at a concentration of 4 mg/ml by incubation at 37°C for 16 h. The resulting solution was sterilized by irradiation. The mice were immunized by injection of the antigen (0.1 mg in 0.05 ml of FCA) into the left hind footpad. At 21 days after primary immunization, delayed-type hypersensitivity was measured using a skin test. In this test, the antigen (0.1 mg dissolved in 0.15 M saline in volume of 0.05 ml) was injected intradermally into the plantar side of the right footpad of anesthetized mice. Using a micro caliper, footpad thickness was measured in triplicate immediately before intradermal injection and 24 h later. For controls, footpad swelling was measured before and after antigen injection into the footpad of nonimmunized mice, and before and after saline injection into the footpad of immunized mice. All mice were killed one week after the skin tests. The animals were bled and serum separated and decomplemented.

The intradermal injection of antigen into nonimmunized mice (4 mice per antigen) did not induce significant footpad swelling at 24 h. Similarly, the intradermal injection of saline into immunized mice did not cause a significant increase in footpad thickness. However, compared to the control, significant positive responses were noted ($P < 0.01$), indicating an antigen-specific hypersensitivity reaction for all three Gum Arabic specimens that were tested. A comparison of results for the three grades of Gum Arabic indicated that footpad swelling in mice immunized and tested with the dark, red-brown grade was significantly greater ($P < 0.005$) when compared to the colorless grade (Strobel et al., 1982).

The immunological activity of Gum Arabic was evaluated using two groups of eight female BDF1 [(C57BL/6] x DBA/2)F_1] mice (6 to 8 weeks old). A finely powdered sample of Gum Arabic was dissolved in 0.15 M saline at a concentration of 400 mg/ml. Each of eight mice was then dosed with Gum Arabic (80 mg) by intragastric administration. Control mice were dosed with saline. At seven days post-dosing, the mice were immunized by injecting a saline solution of 100 μg Gum Arabic emulsified in an equal volume of FCA (total volume injected = 0.05 ml) into the left hind footpad.

Control mice were immunized with 0.15 M saline in FCA. Prior to and three weeks after immunization all mice were bled and decomplemented sera were tested for anti-Gum Arabic antibodies by a micro-ELISA technique (Strobel et al., 1982). Delayed-type hypersensitivity was also measured (skin test) at three weeks post-immunization. The mice were anesthetized and 0.1 mg Gum Arabic (in volume of 0.05 ml) was injected intradermally into the right footpad. Footpad thickness was measured in triplicate immediately before intradermal injection and 24 h later. As controls, footpad swelling was measured before and after Gum Arabic was injected into the footpad of saline/adjuvant-immunized animals, as well as before and after saline was injected into the footpad of mice immunized with Gum Arabic.

Footpad swelling was negligible in both control groups. Antibodies were not detected in the serum of mice that were bled before systemic immunization. Serum antibodies were identified in five of eight control (saline pre-fed) mice after systemic immunization. However, antibodies were not detected in the serum of mice that were pre-fed with Gum Arabic. Regarding delayed type hypersensitivity, a similar pattern was noted. Positive skin tests were reported for all saline-pre-fed mice. However, footpad swelling in mice pre-fed with Gum Arabic was significantly suppressed. Test results indicated that systemic immunological hypo-responsiveness (oral tolerance) developed in mice that were fed Gum Arabic (Strobel and Ferguson, 1986).

The immunogenicity, cross-reactivity, and non-specific irritant properties of Gum Arabic (*Acacia senegal*) were evaluated using male mice (6 to 8 weeks old) of the [(C57BL/6J x DBA/2F_1] (BDF_1) strain. Non-specific irritant properties were assessed in the foot pad swelling test using control groups of non-immunized mice. Immunogenicity was evaluated in an *in vivo* footpad swelling test, and cross-reactivity was

assessed by secondary antibody response. The following Gum Arabic samples (identified as samples A, B, C, D, and E) were tested in each experiment: (1) Sample A (sodium arabate) resulted from the neutralization of Sample C with sodium hydroxide. (2) Sample B resulted from three successive precipitations of Sample C from aqueous solution with acidified ethanol. (3) Sample C, Gum Arabic, was a water-soluble polysaccharide containing rhamnose, arabinose, glucuronic acid, and galactose. (4) Sample D was defined as powdered food grade natural Gum Arabic. (5) Sample E was obtained by exhaustive ethanolic extraction of Sample D. In the non-specific footpad swelling test, five groups (6 to 8 mice per group) of nonimmunized male mice were injected intradermally with the five samples, respectively.

Sample A did not induce significant swelling at 24 h; however, samples B, C, and D increased, but only slightly, non-specific swelling ($P < 0.05$). Sample E induced the greatest extent of footpad swelling. These results (footpad swelling) were indicative of a non-specific irritant effect (Strobel et al., 1986).

In the second experiment, five groups (30 to 40 mice per group) of mice were immunized with the five Gum Arabic samples (200 μg per sample), respectively, in the left hind footpad. Each Gum Arabic sample was emulsified in Freund's complete adjuvant prior to immunization. Control mice (30 to 40 mice) were immunized with saline in Freund's complete adjuvant. At 21 days post-immunization, the presence of delayed-type hypersensitivity (specific cell mediated immunity) was measured in the footpad swelling skin test. All Gum Arabic samples were immunogenic in this test.

In each case, intradermal challenge after immunization caused a significant increase in footpad thickness at 24 h. In the test for cross-reactivity, blood samples were obtained from mice that had been immunized and tested (footpad swelling test) three weeks after immunization. Antibodies were assayed by an enzyme-linked immunosorbent assay (ELISA). Assay results indicated that antigens were shared between all of the samples, except for Sample E. Mice immunized with Sample A had significant reactions when tested with Samples A, B, C, and D. The greatest non-specific swelling was produced by Samples B and C (Strobel et al., 1986).

The nonnecrotizing toxicity of Acacia extract was evaluated using germ-free and conventional guinea pigs of the Hartley strain. The ages of the germ-free animals tested were as follows: Group A (12 animals, 8 days old), Group B (9 animals, 3 weeks old), and Group C (6 animals, 12 weeks old). The test substance (40 mg/ml) was suspended in phosphate buffer (pH 7.4, 0.1 M) and applied topically to the cornea of the right eye; phosphate buffer was applied to the cornea of the left eye. For both substances, one drop was applied every half hour for a total of seven applications.

The following three groups of conventional guinea pigs were also treated according to the same procedure: Group 1 (six animals, 8 days old), Group 2 (seven animals, 12 weeks old), and Group 3 (2 animals, 7 months old). These animals were killed 30 min after application of the last drop. Additionally, phosphate buffer was instilled into both eyes of two animals (killed when 8 days old), and the same was true for two other animals (killed when 3 weeks old). The eyes were enucleated immediately after all animals were killed. The animals were bled prior to killing, and serum samples were subsequently obtained for determination of antibody or γ-globulin. At microscopic examination, a severe inflammatory response was observed in both germ-free and conventional 8-day-old guinea pigs. The inflammatory response was described as minimal in 12-week-old germ free and conventional guinea pigs. In the 7-month-old conventional animals, the responses were much more severe than that noted for 12-week-old germ free animals. This comparison was made because 7-month-old germ-free animals were not available.

The inflammatory response to Acacia was most severe in the conjunctiva and the subconjunctival tissues were relatively free of inflammatory changes. Swelling of superficial epithelial cells of the central cornea and necrosis of a few of these cells were also observed. The severity of inflammatory responses was correlated with serum γ-globulin concentrations. The extent of the inflammation induced by Acacia paralleled γ-globulin concentrations in germ-free guinea pigs more closely than in conventional guinea pigs (Aronson and McMaster, 1972).

MUTAGENICITY

Both *in vitro* and *in vivo* studies on the mutagenicity of Gum Arabic are summarized in Table 10. While a few positive results are described, most studies were negative for mutagenic activity.

ANTIMUTAGENICITY

The antimutagenic activity of *Acacia arabica* was evaluated using the WP-2 strain of *Escherichia coli*. UV light was used as the mutagen. Cultures were irradiated with UV light (1.5 J/m^2/ sec) for 15 sec, with intermittent stirring. The bark of *Acacia arabica* was extracted with methanol and the extract was added to cultures at a concentration of 5 mg/plate. The revertants and viable cells were counted after incubation for two days at a temperature of 37°C.

Compared to control cultures exposed to UV light (mean number of revertants per plate = 216), the mutagenic activity of UV light was reduced in cultures dosed with *Acacia arabica* extract. The mean number of revertants per plate in test cultures was 34. The % survival for control and test cultures was 100% and 70.6%, respectively. The investigators stated that the decrease in UV-induced mutagenicity in the presence of Acacia could have been due to some enzymatic action that reverted the formation of pyrimidine dimers (Jain et al., 1987).

ENHANCEMENT OF MUTAGENICITY

The effect of 3%Gum Arabic (solvent) on the mutagenicity of 4-nitroquinoline-N-oxide was evaluated using results from the bone marrow micronucleus assay. Based on an analysis of time-response and dose-response data on 4-nitro-quinoline-N-oxide, it was determined that the mutagenicity of this chemical was six times greater in Gum Arabic when compared to test results for the chemical in DMSO. When the mutagenicity of other chemicals, such as mitomycin C, was evaluated using different solvents, no solvent effect on mutagenicity was observed. The investigators concluded that no clear relationship existed between the solvent used and the mutagenicity observed (Katz et al., 1981).

CARCINOGENICITY

No evidence of carcinogenicity was noted in rats dosed intraperitoneally with Gum Arabic (1.75 or 7% in saline or water) three times per week for up to 15 weeks. Based on the data presented, it was difficult to ascertain the size of the dose administered. The doses administered were on the order of several hundred mg/kg. Also, no evidence of carcinogenicity was found in a similar study using mice (doses injected not stated) (FASEB, 1973).

Gum Arabic gruel was injected intramediastinally (single dose) into five (0.5 ml dose of test substance) and 10 (1 ml dose) guinea pigs. The animals (strain not specified) ranged in weight from 220 to 450 g and were four to ten months old. Neoplasms were not observed in any of the guinea pigs either at necropsy or at microscopic examination of tissue. On the average, the animals survived from 1200 to 1490 days (Tlolka-Pluszczyk, 1970).

The carcinogenicity of Gum Arabic was evaluated using four-week-old F344 rats (50 males, 50 females) and four to five-week-old B6C3F$_1$ mice (50 males, 50 females) in a two-year chronic study. Both male and female rats were divided into high and low dose groups. Low dose animals were fed Gum Arabic at a concentration of 25,000 ppm in the diet and high dose animals were fed 50,000 ppm. Test diets were fed for 103 consecutive weeks, followed by one-to-two weeks of feeding of the basal diet. Control mice (50 males, 50 females) and rats (50 males, 50 females) were fed the basal diet only according to the same schedule. Moribund animals and animals that survived to the end of the study were killed using carbon dioxide and necropsied. Tissues were preserved for histopathologic evaluation. Study results are summarized below (Melnick et al., 1983):

Changes in mean body weight for male and female rats were comparable to those of the respective control groups throughout the study. Slight decreases in body weight (7 to 13%) were observed in female rats. Compared to controls, consistent differences in mean body weight were noted for female mice of the high dose group (50,000 ppm in diet). No significant differences were found in survival between experimental mice or rats when compared to the respective control groups (Melnick et al., 1983).

Neoplasms were observed only in male rats, and were diagnosed as malignant lymphomas or leukemia/lymphoma. The incidences of malignant lymphomas for control, low dose (25,000 ppm Gum Arabic), and high dose

Table 10. *In vitro* and *in vivo* mutagenicity of Gum Arabic and *Acacia belandieri*.

Test Substance	Bacterial strains/cells Tested	Test Procedure	Test Results	References
Gum Arabic (in 0.067 M potassium or phosphate buffer)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538. *Escherichia coli* WP2.	*Salmonella* strains tested in plate incorporation assay (Ames et al., 1975) with and without metabolic activation; doses up to 10 mg/plate. *E. coli* tested according to modification of plate incorporation assay at same doses	Not mutagenic with or without metabolic activation	Prival et al., 1991
Gum Arabic	*Salmonella typhimurium* TA100, TA1535, TA1537, TA97, and TA98.	Modification of preincubation procedure by Haworth et al., (1983) with and without metabolic activation. Cultures incubated with 0.05 ml Gum Arabic	Not mutagenic with or without metabolic activation	Zeiger et al., 1992
Gum Arabic	*Salmonella typhimurium* G-46 and TA-1530	Ames test (Ames, 1971)	Not mutagenic	Maxwell and Newell, 1973
Gum Arabic (in 0.067 M sodium phosphate buffer)	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, and TA 100. *E. coli* WP2 (uvrA)	*Salmonella*/microsome assay with and without metabolic activation; concentrations up to 10,000 μg/plate	Not toxic or mutagenic	SRI International, 1980
Gum Arabic (in DMSO)	*Salmonella typhimurium* TA1535, TA1537, and TA1538. *Saccharomyces cerevisiae* D4.	Plate and suspension assays with and without metabolic activation. Plate test concentrations up to 3.3%. Suspension assay concentrations up to 0.36%.	Not mutagenic with or without metabolic activation	Litton Bionetics, Inc., 1975
Gum Arabic	*Saccharomyces cerevisiae* D4.	Host-mediated assay for mitotic recombination (Gabridge and Legator, 1969); test concentration of 5% w/v if no lethal effects observed	Not mutagenic	Maxwell and Newell, 1973
Gum Arabic	*Saccharomyces cerevisiae* D3	Plate test (Brusick, 1973)	Not mutagenic	Green, 1977
Gum Arabic	Diploid human embryonic lung (WI-38) cells	Cytogenetics assay; concentrations up to 1000 μg/ml culture if no cytotoxicity observed at this level. Anaphase analyses according to procedure of Nichols et al. 1971	Slightly positive. Further tests and detailed statistical evaluation needed to confirm classification	Maxwell and Newell, 1973
Gum Arabic	WI-38 human embryonic lung cells	Test methodology not stated	Chromosomal aberrations induced in anaphase	Green, 1977
Gum Arabic (in water)	*Bacillus subtilis* M 45 Rec$^-$ and H 17 Rec$^+$	Spore rec-assay (with and without metabolic activation) for DNA-damaging activity	Not mutagenic	Ishizaki and Ueno, 1987)
Gum Arabic	Male and female Sprague-Dawley rats (males: 6 to 8 weeks old; females: 10 to 12 weeks old)	Dominant lethal test. Male rats fed concentrations up to 4% w/w Gum Arabic prior to mating. Number of live and dead implants counted 14 days after midweek of mating	Statistically significant dominant lethal effects in male rats. Biological significance of these data could be questioned	Sheu et al., 1986
Gum Arabic	(SEC X C57BL)F1 and (C3H X C57BL)F1 female mice (10 to 12 weeks old. (101 X C3H)F1 male mice (8 weeks old)	Dominant lethal test. Male rats fed diets containing up to 20% Gum Arabic prior to mating	No evidence of dominant lethal effect	Sheu et al., 1986
Gum Arabic	Male and female Swiss mice (10 to 12 weeks old; weights = 25 to 30 g)	Dominant lethal test. Male rats dosed orally with 1% Gum Arabic prior to mating	No dominant lethal effect	Kar et al., 1984

Test Substance	Bacterial strains/cells Tested	Test Procedure	Test Results	References
Gum Arabic	(SEC X C57BL)F1 female mice (10 to 12 weeks old. (101 X C3H)F1 male mice (8 weeks old)	Heritable translocation test. Male mice fed test diet containing 15% w/w Gum Arabic prior to mating	No reduction in average litter size. Number of translocation-carrying male progeny in test group was comparable to that of control group	Sheu et al., 1986
Gum Arabic	Male albino rats (weights 200 g)	Acute and short-term *in vivo* cytogenetics assays. Doses up to maximum tolerated dose administered. Cytogenetic evaluations on bone marrow cells in metaphase	Results slightly positive in acute and short-term assays. Further tests and detailed statistical evaluation needed to confirm this possibility	Maxwell and Newell, 1973
Gum Acacia	Male Swiss mice (6 to 8 weeks old)	Chromosomal aberrations and sperm-head morphology assays. Mice dosed with 5% Gum Acacia by gavage (volume per dose = 0.5 ml)	No statistically significant differences in frequency of chromosomal aberrations and incidence of sperm head abnormalities, compared to control (distilled water) group.	Prasad et al., 1987
Acacia	Male ICR mice (7 weeks old; weights between 28 and 32 g)	Micronucleus test (bone marrow smears). Mice dosed with 10% Acacia by gavage (volume per dose = 0.02 ml/g body weight.	Not genotoxic	Parton et al., 1988
Acacia	Male ICR mice	Micronucleus test (bone marrow smears). Mice dosed with 10% Acacia by gavage (volume per dose = 20 ml/kg)	Not genotoxic	Parton et al., 1990
Gum Acacia	Male Swiss albino mice (8 weeks old)	Micronucleus test (bone marrow smears). Mice dosed orally with 5% Gum Acacia	The ratio of polychromatic erythrocytes to monochromatic erythrocytes (P/N ratio) was slightly higher, compared to mice dosed with water	Pentiah et al., 1989
Gum Arabic	NMRI mice (weights between 30 to 35 g)	Micronucleus test (bone marrow smears). Mice dosed i.p. with 3% Gum Arabic	Not genotoxic	Wild et al., 1985
Acacia (in water)	Male Swiss-Webster mice (6 weeks old; mean weights between 16 to 32 g)	Micronucleus test (bone marrow smears). Mice dosed with 2% Acacia in water	Not genotoxic	MacGregor et al., 1983
Acacia	Inbred female Chinese hamsters (*Cricetulus griseus*) (weight range, 26 to 32 g)	Assay for sister chromatid exchanges. Hamsters dosed i.p. or orally with 10% Acacia (dose volume = 10 ml/kg)	Mean number of sister chromatid exchanges not significantly different, compared to control hamsters dosed with 0.9% normal saline	Neal and Probst, 1983
Gum Arabic	Male NMRI mice (weights between 30 to 35 g)	Intrasanguineous host-mediated assay. *Salmonella typhimurium* strain TA 98 culture (0.1 ml) injected into tail vein. Intravenous injection followed by oral dose of 3% Gum Arabic	Not mutagenic to strain TA 98	Wild et al., 1985
Gum Arabic	C57BL virgin female mice	Mouse coat color spot test (transplacental mutagenicity test). Gum Arabic (3%) injected i.p. after mating. Spots classified as relevant caused by mutations at heterozygous coat-color loci	Not mutagenic	Wild et al., 1985
Gum Arabic	C57BL mice	Mouse melanocyte test - Used to detect somatic mutations that affect the morphology of pigment cells. Pregnant females received i.p. injections of 3% Gum Arabic on 16th day after detection of vaginal plug	Not genotoxic	Wild et al., 1985

(50,000 ppm Gum Arabic) experimental groups of male rats were as follows: 4/50 (low dose), 1/50 (high dose), 8/50 (concurrent controls) and 31/1066 (historical controls). Compared to the concurrent control group, a significant decrease ($P < 0.05$) in tumor incidence was observed in the high dose group, and this was the only statistically significant finding for this neoplasm (Melnick et al., 1983).

The incidences of neoplasms classified as leukemia/lymphoma in control, low dose (25,000 ppm Gum Arabic), and high dose (50,000 ppm Gum Arabic) groups of male rats were: 19/50 (low dose), 16/50 (high dose), 18/50 (concurrent controls), and 238/1066 (historical controls). Compared to concurrent controls, no statistically significant differences were observed in the incidence of tumors of this type (Melnick et al., 1983).

No significant changes were observed in the incidence of primary neoplasms in mice that were fed Gum Arabic in the diet at concentrations of 25,000 or 50,000 ppm. Based on the preceding results, the investigators concluded that Gum Arabic was not carcinogenic in F344 rats or $B6C3F_1$ mice of either sex (Melnick et al., 1983).

COCARCINOGENICITY

The cocarcinogenicity of Gum Acacia was evaluated using male rats of the Buffalo strain (6 to 10 weeks old). Thirty-four rats were exposed to fission neutrons (single exposure of 300 to 364 rads; whole-body irradiation), followed by three intraperitoneal injections (0.5 ml per injection) of a 7% solution of Gum Acacia in 0.85% sodium chloride weekly for 23 weeks. A second test group (30 rats) was irradiated after treatment with Gum Acacia according to the same procedure. Three groups of rats served as controls: One of the control groups (50 rats) was exposed to fission neutrons only. Two additional control groups consisted of 40 rats injected intraperitoneally with 7% Gum Acacia only (according to test group protocol) and an untreated control group of 79 rats.

No significant neoplasm incidence was present in the two control groups. However, the survival time for the 40 control rats injected with Gum Acacia (554.8 ± 39.4 days, $n = 30$) was significantly shortened when compared to untreated controls (669.2 ± 19.0 days, $n = 58$). Increases in hepatic, gastric, and intestinal neoplasms were noted in the first test group (34 rats; neutron exposure followed by Gum Acacia injections), when compared to the group of 50 rats exposed to fission neutrons only. Except for gastric neoplasms, these differences in neoplasm incidence were considered small and probably not significant. It is important to note that no gastric neoplasms were observed in the 50 rats exposed to fission neutrons only, whereas, 20% of the 34 test rats had gastric cancers. No explanation for this difference was given. Tissues of 28 of the 34 test rats in this group were subjected to complete histopathological analysis after necropsy. Similarly (compared to fission neutrons control group), no gastric neoplasms were noted in the group of 30 rats treated with Gum Acacia and then exposed to fission neutrons. The investigators stated that this finding could have been due to the small number of rats ($n = 14$, compared to $n = 28$ in other test group) subjected to complete histopathological examination after necropsy. The data presented in this study suggest that Gum Acacia might be considered a "potentiator" for carcinogenesis (Vogel and Zaldivar, 1971).

Gum Arabic has been reported to increase the number of metastases in mice injected intraperitoneally with Ehrlich ascites carcinoma cells. The carcinoma cells were injected six or 24 h after the mice were injected intravenously with Gum Arabic. However, under some conditions, ascites tumor formation was inhibited (Osswald, 1968).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Studies on the reproductive and developmental toxicity of Gum Arabic are summarized in Table 11.

The antifertility activity of Gum Acacia (1 ml in water) was evaluated using ten female rats (strain and weights not stated). The test substance was administered by stomach tube daily for a period of five days after mating. After performing laparotomy on anesthetized dams, the number of fetuses was counted on the tenth day of pregnancy. The average number of implants per rat was 7.8. The percentage of rats with no implant was 0 (Sabir and Razdan, 1970).

The reproductive toxicity of Gum Acacia was evaluated using two groups of five male albino

Table 11. Reproductive and Developmental Toxicity Studies

Test Substance	Animals/cells Tested	Test Procedure	Test Results	References
Gum Acacia	10 female rats	Gum Acacia (1 ml in water) administered orally during 5-day period after mating	No antifertility activity. Average number of implants per rat = 7.8	Sabir and Razdan, 1970
Gum Acacia	Two groups of 5 male albino Wistar rats (4 months old; weights between 180 to 200 g)	First group dosed orally (dose = 1 ml) daily for 24 days. Second group dosed orally (dose = 1 ml) for 48 days.	No suppression of spermatogenesis	Akbarsha and Manivannan, 1973
Gum Arabic	Adult female albino CD-1 outbred mice (4 groups). Most groups contained 22 to 23 mice	The four groups of mated mice received oral doses of 16, 75, 350, and 1600 mg/kg on days 6 through 15 of gestation	The number of abnormalities observed in soft or skeletal tissues of fetuses did not differ from the number occurring spontaneously in sham-treated controls	Food and Drug Re-search Laboratories, 1972
Gum Arabic	Groups of female rats, rabbits, and hamsters	Oral doses of 16, 75, 350, and 1600 mg/kg on days 6 through 10 of gestation (hamsters and rats). Oral doses of 8, 37, 173, and 800 mg/kg in corn oil on days 6 through 18 of gestation (rabbits).	The number of abnormalities observed in soft or skeletal tissues of fetuses did not differ from the number occurring spontaneously in sham-treated controls	Food and Drug Re-search Laboratories, 1972
Gum Arabic (Acacia Senegal)	Groups of 4-week-old Osborne-Mendel (FDA strain) rats	Groups fed dietary concentrations up to 15% beginning at week 13 prior to mating	Gum Arabic not classified as a reproductive or developmental toxicant in rats	Collins et al., 1987
10% aqueous Acacia solution	9 Little Dutch female rabbits (average weight between 2.1 kg)	After mating, 10% aqueous Acacia solution administered orally on day 0 and the following six days.	Normal microscopic variations in blastocysts reported: minor trophoblastic vacuolation, trophoblastic degeneration granules, and trophoblastic knob formations	Schardein et al., 1965
5% aqueous Gum Arabic solution	36 female Sprague-Dawley Crl:CDBR rats (~ 9 months; weights between 207 to 314 g)	Solution administered orally once daily (5 ml/kg/day) on days 6 through 17 of gestation	External, visceral, and skeletal malformations observed were unrelated to dosing with Acacia	Morseth and Ihara, 1989a
5% aqueous Gum Arabic solution	30 male Sprague-Dawley Crl:CDBR male rats (6 weeks old; weights between 181.9 to 226.3 g). 30 female rats of same strain (10 weeks old; weights between 210.9 to 309.9 g)	Solution administered orally to females once daily (5 ml/kg/day) for 14 days prior to mating, throughout the mating period, and through day 19 of gestation or day 21 of lactation. Solution also administered to males prior to and during mating and until animals killed.	No treatment-related abnormal estrous cycles. No external, skeletal, or soft tissue malformations.	Morseth and Ihara, 1989b
5% Gum Acacia	9 Syrian golden hamsters (8 weeks old; weights between 80 to 100 g)	Dosed orally with 5% Gum Acacia (dose volume = 0.1 ml/10 g body weight) daily for 54 days	All of the hamsters produced morphologically normal sperm	Waller et al., 1983
4% Gum Acacia	6 Haffkine albino rabbits (weights between 175 to 225 g)	Males dosed orally daily for 28 days and mated with untreated females for total of 12 weeks	No statistically significant difference in number of pregnant females between experimental and control groups. No anti-fertility effect in males	Yegnanarayan and Joglekar, 1978

Test Substance	Animals/cells Tested	Test Procedure	Test Results	References
4% Gum Acacia	Adult female rabbits (weights between 1 to 2 g)	Dosed orally with 4% Gum Acacia for two days	No inhibitory effect on ovulation	Yegnanarayan and Joglekar, 1978
4% Gum Acacia	Female albino rats (weights between 150 to 200 g)	4% Gum Acacia administered orally to 10 females over period of two estrus cycles, followed by mating with males during pro-estrus phase of third estrus cycle (short-term experiment). 4% Gum Acacia administered orally to 6 females over period of 6 estrus cycles, followed by mating during pro-estrus stage of seventh estrus cycle	No significant differences in mating (number of females inseminated) between experimental and control groups. No significant changes in duration of estrus cycles after dosing	Yegnanarayan and Joglekar, 1978
4% Gum Acacia	10 female rats (weights between 150 to 200 g)	Females dosed orally with 4% Gum Arabic on days 1 to 7 of pregnancy	No statistically significant difference in average litter sizes between experimental and control groups, indicating that fetal resorption did not occur	Yegnanarayan and Joglekar, 1978
4% Gum Arabic	10 female rats(weights between 150 to 200 g)	Females dosed orally with 4% Gum Arabic on days 10 to 16 of pregnancy	No statistically significant differences in number of pups delivered between experimental and control groups	Yegnanarayan and Joglekar, 1978
1% aqueous suspension or mucilage prepared from Gum Arabic	NMRI mice	1% aqueous suspension or mucilage prepared from Gum Arabic injected intraperitoneally (single injection or series of 5 injections), subcutaneously (5 injections), and administered orally (5 times) between the 11th and 15th day of gestation	No lethal effects on fetuses	Frohberg et al., 1969
1% Gum Acacia	10 female Charles Foster rats (90 days old; weights between 200 ± 20 g)	Administered daily at dose of 50 mg/kg/day during the period of organogenesis	No gross or visceral defects	Sethi et al., 1989

rats of the Wistar strain (4 months old; weights between 180 to 200 g). The test substance was administered orally (dose = 1 ml) to the first group daily for 24 days. The second group was dosed (dose = 1 ml) daily for 48 days. Rats in both groups were necropsied 24 h after the last dose.

The following tissues were excised, homogenized, and centrifuged: testis, epididymis (divided into caput and cauda), seminal vesicle, ventral prostate, and coagulating gland. The supernatant was used for determination of total protein and acid phosphatase (ACPase) and alkaline phosphatase (ALPase) activities. Supernatant obtained from the testes was also used for the determination of glycogen and cholesterol, and lactate dehydrogenase (LDH) activity. Increased glycogen and LDH in the testis are both consequences of spermatogenic arrest. Decreased ACPase and increased ALPase activities in the testis also reflect the suppression of spermatogenesis. Gum Acacia did not induce suppression of spermatogenesis in this study (Akbarsha and Manivannan, 1993).

The teratogenicity of Gum Arabic was evaluated using six groups of mated adult female albino CD-1 outbred mice. Three of the test groups consisted of 22 to 23 mice per group and received doses of 16, 75, and 350 mg/kg, respectively, on days 6 through 15 of gestation. Doses were administered by oral intubation. The fourth test group of 31 mice was dosed with Gum Arabic (1600 mg/kg) according to the same procedure. Sham-treated mice (28) served as negative controls, and positive control mice were dosed with aspirin (150 mg/kg). Mean body weights for the test groups ranged from 30 to 39.7 g and were 31.2 g and 31.8 g for negative and positive controls, respectively.

On day 17, all dams were placed under anesthesia and Caesarean section was performed. The numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The urogenital tract of each dam was examined in detail for anatomical normality. Gross examinations for the presence of external congenital abnormalities were performed on all fetuses. Detailed visceral examinations employing 10X magnification were performed on one-third of the fetuses from each litter. The remaining two-thirds were examined for skeletal defects. The administration of Gum Arabic to pregnant mice at doses up to 1600 mg/kg had no clearly discernible effect on nidation or maternal or fetal survival. The number of abnormalities observed in either soft or skeletal tissues of fetuses from test groups did not differ from the number occurring spontaneously in sham-treated controls (Food and Drug Research Laboratories, 1972).

In the above study, groups of rats, rabbits, and hamsters were dosed with Gum Arabic according to the following modifications of the above test procedure: Doses (indicated above) were administered to hamsters on gestation days 6 through 10. C-sections were performed earlier on hamsters (day 14) and later on rats (day 20). Positive control rats and hamsters received a higher dose of aspirin (250 mg/kg). Rabbits were dosed with Gum Arabic in corn oil (8, 37, 173, and 800 mg/kg, respectively) on days 6 through 18 of gestation; C-sections were performed on day 29. Rabbits were injected with human chorionic gonadotropin (day 0) and artificially inseminated. Mean weights for the dams tested were as follows: 200 to 216 g (24 rats per group), 104.6 to 118.4 g (21 to 24 hamsters per group), and 2.01 to 2.43 kg (15 rabbits per group). Positive control hamsters and rats received 250 mg aspirin.

The conclusion in the preceding paragraph was found to be applicable to all test groups of rats and hamsters. However it was concluded that the administration of Gum Arabic, in corn oil, to pregnant rabbits at doses up to 37 mg/kg (highest dose tested = 800 mg/kg) had no clear effect on nidation or maternal or fetal survival. The number and types of abnormalities observed in fetal soft or skeletal tissues from this group did not differ from the number occurring spontaneously in the sham-treated controls. Maternal toxicity was noted at doses of 173 and 800 mg/kg; for surviving rabbits at these doses, the offspring were normal in all respects (Food and Drug Research Laboratories, 1972).

The teratogenicity of Gum Arabic (Acacia Senegal) was evaluated using groups of four-week-old Osborne-Mendel (FDA strain) rats. Beginning at thirteen weeks prior to mating, the rats were fed Gum Arabic at concentrations of 1, 2, 4, 7.5 or 15%, respectively. Another group of rats was fed a control diet. Control and test diets were also fed throughout mating and gestation. After mating was confirmed, females were placed in groups of 41 to 47. The dams were killed on day 20 of gestation.

One female rat (1% dietary group) died during the study. External observations of the dams were unremarkable, and included one female (7.5% dietary group) with a cystic ovary and one with lung nodules (15% dietary group). Sporadic non-significant increases in body weight were observed in all experimental groups (Collins et al., 1987). Additional results, summarized below, indicate that Gum Arabic was not a reproductive or developmental toxicant in rats at dietary concentrations of 1, 2, 4, 7.5 or 15%:

The percentage of pregnant females was approximately the same in all experimental groups and controls. Mean numbers of corpora lutea and implants per female were also similar to control values, and the average number of viable fetuses was similar in all groups. No effect was seen in any group with respect to the mean number of viable males and females. Three litters were totally resorbed, one litter from the control, 1%, and 4% dietary groups. Gum Arabic in the diet had no effect on the percentage of females with at least one resorption or with at least two resorptions. The numbers of early and late deaths, singly or combined (as average percentage of resorptions), were similar to control values (Collins et al., 1987).

The feeding of Gum Arabic had no effect on mean fetal body weights and crown-rump lengths. The ingestion of Gum Arabic also had no effect on the distribution of fetuses by sex. A significant decrease in mean female body weight in the 1% dietary group was noted; however, this observation was deemed a random occurrence. The significant increase in the length of females in the 4% and 7.5% dietary groups was not considered biologically significant.

The investigators stated that because of the large group of animals in this study, small variations in crown-rump length can result in significant effects. Similar numbers of runts were noted among male and female fetuses from all dietary groups, with the exception of no runts among male fetuses in

the 1% and 15% dietary groups (Collins et al., 1987).

Regarding external variations in live fetuses, spina bifida and exencephaly were observed in two fetuses from the control group. No other terata were observed, and the external variations were distributed randomly. Similar numbers of fetuses with hemorrhages were observed in all dietary groups (Collins et al., 1987).

The mean numbers of sternebral variations per litter varied from 4.18 (4% Gum Arabic dietary group) to 5.09 (15% dietary group) in experimental groups, and the mean number of sternebral variations per litter in the control group was 5.21. The variations included reduced ossification and bipartite, missing, and malaligned sternebrae. No dose-related increases were found with respect to any of the observed sternebral deficiencies, and no significant differences were found between experimental and control groups. The significant decrease in the average number of fetuses with one or more sternebral variations per litter that was observed in the 4% and 7.5% dietary groups was considered a random occurrence. Thus, the ingestion of Gum Arabic did not affect the incidence of litters with fetuses with sternebral variations (Collins et al., 1987).

Skeletal ossification deficiencies were observed in bones other than sternebrae; however, no dose-related differences were observed between experimental and control groups with respect to any variation. Furthermore, no dose-related effect was found on the incidence of variations, fetuses with variations, or litters affected in any of the dietary groups (Collins et al., 1987).

Also, no dose-related effect was observed on the incidence of any type of soft-tissue variation. Most of the soft tissue variations involved the kidneys. Additionally, the incidence of soft tissue variations in fetuses from experimental and control groups was similar. The mean numbers of soft tissue variations per litter ranged from 0.30 (15% dietary group) to 0.82 (7.5% dietary group), and the mean was 0.76 per litter in the control group (Collins et al., 1987).

A 10% aqueous *Acacia* solution was administered by gavage to two groups of nine Little Dutch strain mated female rabbits (average weight = 2.1 kg) at doses of 1.26 and 1.5 ml/kg, respectively. Doses were administered on day 0 and the following six days (7 doses per female). Nine untreated rabbits served as negative controls. Blastocysts were removed from the uterine horns at 6.5 days of age, prepared as flat mounts, and then evaluated.

The number of fertile rabbits with blastocysts recovered (8 of 9 rabbits) in the 1.26 and 1.5 ml/kg dose groups was the same as that noted for the untreated control group. The mean numbers of blastocysts per rabbit were as follows: untreated controls (5.3 ± 1.2), 1.26 ml/kg dose group (7.0 ± 1.7), and 1.5 ml/kg dose group (5.4 ± 2.2). Normal microscopic variations in blastocysts were reported for test and control groups, and included minor trophoblastic vacuolation, trophoblastic degeneration granules, and trophoblastic knob formations (Schardein et al., 1965).

The teratogenicity of a 5% solution of Gum Arabic (powder) in distilled water was evaluated using 36 female Crl: CDBR rats (~ 9 months old) for which mating had been confirmed. Body weights on gestation day 0 ranged from 207 to 314 g. The solution was administered by gavage once daily (5 ml/kg/day) on gestation days 6 through 17. The dams were necropsied on day 20 of gestation. Fetuses were subjected to external (303 fetuses), visceral (102 fetuses), and skeletal (201 fetuses) examinations.

External variations were not observed in any of the fetuses evaluated; however, external malformations, brachygnathia and rudimentary/short tail, were observed in one fetus. Visceral variations included only two fetuses with increased renal pelvic cavitation. At skeletal evaluation, one fetus had brachygnathia, tail short/rudimentary, abnormal fusion of sternebrae, and vertebral anomaly with/without associated rib anomaly. The external, visceral, and skeletal malformations observed were unrelated to dosing with Acacia (Morseth and Ihara, 1989a).

The effect of a 5% solution of Gum Arabic (powder) in distilled water on fertility and general reproductive performance was evaluated using 30 male (6 weeks old; weights = 181.9 to 226.3 g) and 30 female (10 weeks old; weights = 210.9 to 309.9 g) Sprague-Dawley Crl: CDBR rats. The solution was administered (oral intubation) to male and female rats once daily (5 ml/kg/day) for 63 days prior to mating, throughout the mating period, and until the animals were killed. Male rats were killed after the females had littered. The oral dosing schedule for female rats was daily for 14 days prior to mating, throughout the mating period, and through gestation day 19 or day 21 of lactation. Fifteen female rats were killed on day 20 of gestation, and the remaining females were assigned to the natural delivery phase to raise

their young to day 22 postpartum.

No abnormal estrous cycles that were considered treatment-related were observed in any of the females. Twenty-nine of the 30 females became pregnant; the male fertility index was 97%. Mean viability and mean weaning indices were 96% and 98%, respectively. No external, skeletal, or soft tissue malformations were observed (Morseth and Ihara, 1989b).

The reproductive toxicity of 5% Gum Acacia was evaluated using nine male Syrian golden hamsters (8 weeks old; weights = 80 to 100 g). The males were mated with female Syrian golden hamsters in order to confirm fertility. Subsequently, the males were dosed (oral gavage) with 5% Gum Acacia (dose volume = 0.1 ml/10 g body weight) daily for 54 days. The animals were killed three days after the last dose. As determined by analysis of testis sections, spermatogenesis was reported for all mice. All of the mice produced morphologically normal sperm, which were also observed in the epididymis (Waller et al., 1983).

Anti-fertility effects of 4% Gum Acacia were evaluated in a series of five experiments using male and female rats and female rabbits of the Haffkine strain. Six male albino rats (weights = 175 to 225 g) were tested In the first experiment. The rats were dosed orally daily for 28 days using a rubber catheter. Beginning on the first day of feeding, males were mated (1 male to 2 females) with females for twelve weeks. Females were replaced each week of feeding. Additional groups of females were mated with control males dosed with saline according to the same procedure. Vaginal smears were examined daily for the presence of spermatozoa. Pregnant females were surgically observed on the tenth day of pregnancy, and allowed to deliver normally.

The number of inseminated females (73) was the same in experimental and control groups. The total number of pregnant females in experimental and control groups was 24 and 37, respectively. However, this difference was not statistically significant (Yegnanarayan and Joglekar, 1978).

In the second experiment, the effect of 4% Gum Acacia on the estrus cycle and mating was evaluated using fertile female albino rats (weights = 150 to 200 g). The experiment was divided into two phases. In the first phase (short-term treatment), 4% Gum Acacia was administered orally to ten female rats over a period of two estrus cycles, beginning on the day of proestrus. The females were mated singly with males during the pro-estrus phase of the third estrus cycle. In the second phase (long-term treatment), 4% Gum Acacia was administered orally to six female rats over a period of six estrus cycles, beginning in the proestrus phase. Mating was allowed in the pro-estrus stage of the seventh estrus cycle.

In both the first and second experimental phases, control females dosed with saline were mated with males according to the same procedures, respectively. Results for the first and second phases of this experiment indicated no significant differences in mating (number of females inseminated) between experimental and control groups. Additionally, for both phases, no significant changes were observed in the duration of estrus cycles after dosing (Yegnanarayan and Joglekar, 1978).

The third experiment, for determining anti-implantation effects, involved 10 fertile rats (weight range from 150 to 200 g) that were mated in pro-estrus singly with fertile males. Females were dosed orally with 4% Gum Arabic on days 1 to 7 of pregnancy. The animals were allowed to deliver normally and litter sizes were recorded. Ten control females dosed with saline were mated according to the same procedure. No statistically significant differences were observed in average litter sizes between experimental and control groups, indicating that fetal resorption did not occur in litters of rats dosed with 4% Gum Arabic (Yegnanarayan and Joglekar, 1978).

The fourth experiment was performed to determine any post-implantation effect of 4% Gum Arabic using ten fertile rats (weights = 150 to 200 g). After mating, the uteri were surgically exposed on the tenth day of pregnancy and the number of implantation sites counted. Female rats were dosed orally with 4% Gum Arabic on days 10 to 16 and litter sizes determined. The rats were observed for vaginal bleeding, indicative of abortifacient activity during pregnancy. Control females were dosed with saline according to the same procedure. One of ten experimental rats did not have a litter. All control females had litters. No statistically significant differences were observed in the number of pups delivered between experimental and control groups (Yegnanarayan and Joglekar, 1978).

In the fifth experiment, the anti-ovulatory potential of 4% Gum Acacia was evaluated using adult female rabbits (number not stated; weights = 1 to 2 kg). The rabbits were dosed orally with 4% Gum Arabic for two days. Copper acetate (4

mg/kg) was then injected into the marginal ear vein in order to induce ovulation. At 48 h post-injection, laparotomy was performed; fresh bleeding points on the ovaries were indicative of ovulation. Control rabbits were pre-treated with saline according to the same procedure prior to the injection of copper acetate. After the injection of copper acetate, bleeding points on the ovaries were observed in all control and experimental rabbits. Therefore, 4% Gum Acacia did not have an inhibitory effect on ovulation (Yegnanarayan and Joglekar, 1978).

A 1% aqueous suspension or mucilage prepared from Gum Arabic had no lethal effects on fetuses of NMRI-mice injected intraperitoneally (single injection or series of 5 injections), subcutaneously (5 injections), or administered orally (5 times) between the 11th and 15th day of gestation (Frohberg et al., 1969).

The embryotoxicity of 1% Gum Acacia was evaluated using ten Charles Foster rats (90 days old; weights = 200 ± 20 g). The test substance was administered daily at a dose of 50 mg/kg/day during the period of organogenesis. The fetuses were delivered by Caesarean section on day 20 of gestation, fixed in Bouin's solution, and examined for visceral and skeletal defects. None of the fetuses had gross or visceral defects (Sethi et al., 1989).

CLINICAL ASSESSMENT OF SAFETY

ABSORPTION, DISTRIBUTION, AND EXCRETION

No evidence of the absorption of intact Gum Arabic was found in a study using infants. Twenty-two infants, 1 to 15 months old, were fed Gum Arabic (15 to 20 g per day) in milk. No urinary excretion of pentose or significant excretion of Gum Arabic was observed in the stools (FASEB, 1973).

In a nephrotic patient, 20% of the Gum Arabic injected intravenously over a period of six weeks was excreted in the urine (FASEB, 1973).

Other studies involving patients with nephrosis indicated that intravenously injected Gum Acacia or some product associated with it accumulated in the liver and remained in the tissues for several months. Serious disturbances in hemoglobin, white blood cells, and serum proteins, all non-lethal effects, were noted (FASEB, 1973).

The excretion of Gum Arabic and its effect on glucose absorption and routine hematological and biochemical measurements was evaluated using five healthy male volunteers (30 to 55 years old). All subjects were free of signs of gastrointestinal disease. The study was divided into two time periods, a 7-day control period that was followed by a 24-day treatment period. After an overnight fast, glucose (50 g in 200 ml H_20) was fed to each subject on the first day of the control period. During the 24-day treatment period, Gum Arabic (25 g in 125 ml 7% dextrose) was ingested daily by each subject. Urine was collected on one day of the control period and on one day during the third week of the treatment period. Complete 5-day fecal collections were made on days 2 to 6 of the control period and on days 16 to 20 of the treatment period. Pooled stool slurry samples from the five subjects were centrifuged. A precipitate typical of Gum Arabic was not detected in feces specimens collected before or after the administration of Gum Arabic. The marked increases in breath hydrogen production noted after Gum Arabic ingestion were indicative of bacterial breakdown of Gum Arabic in the cecum and colon after three weeks of administration. Additional study results are summarized in the following paragraph (Ross et al., 1983).

No significant differences in the mean concentration of serum lipids (phospholipids and triglycerides) were noted when concentrations before and after Gum Arabic ingestion were compared. However, a significant decrease in serum cholesterol (0.39 mmol/l reduction; $p < 0.05$) was noted. Also, no statistically significant differences were observed between the mean blood glucose concentration (control) and the glucose concentration after the administration of Gum Arabic.

Similarly, no significant differences were found in the mean insulin concentration (before vs. after Gum Arabic ingestion). Alanine amino transferase and aspartate amino transferase activities were significantly reduced ($p < 0.0025$; $p < 0.001$) after Gum Arabic ingestion; however, both mean values were within the normal limits for the population. Of the 13 biochemical measurements that were estimated in the plasma, these reductions in plasma enzyme concentrations represented the only noted significant changes (Ross et al., 1983).

SHORT-TERM ORAL TOXICITY

Five healthy male subjects (30 to 55 years old) ingested 25 g Gum Arabic (Acacia Senegal) daily for 21 days. Toxic effects were not observed during the 21-day period; breath hydrogen concentrations increased only after chronic administration. The fact that Gum Arabic was not recovered from the feces suggest that it is degraded extensively in the human colon (Anderson, 1986).

SHORT-TERM INTRAVENOUS TOXICITY

Acacia was administered to nine patients with nephrotic edema over periods up to eight weeks. The test substance was administered intravenously, and total doses ranged from 80 to 325 g. No signs or symptoms of hepatic enlargement or any other complications were observed. Five of the patients excreted 5.5% to 38% of a single dose in the urine during periods ranging from ten to 30 days, respectively (World Health Organization, 1974).

CLINICAL IMMUNOLOGY

Allergic disorders were reported for ten subjects (7 males, 3 females; 11 to 55 years old) who had ingested various gum-containing foods. Gum Arabic was among the gums present in each food ingested. Some of the allergic symptoms reported included bronchial asthma, generalized urticaria, and vasomotor rhinitis. Allergic symptoms were not observed upon removal of suspect gum-containing foods from the diet, and symptoms were reproduced when clinical trials were repeated.

Positive skin reactions (test procedure not stated) to Gum Arabic were observed in each of the ten subjects. The results of serologic studies (sera from 4 subjects) indicated that Gum Arabic was the dominant gum antigen in two subjects and that tragacanth and karaya were the dominant gum antigens in the remaining two subjects. The serological studies included passive transfer tests in serial dilutions and neutralization studies. It was determined that Gum Arabic and other vegetable gums could cause allergic disorders by ingestion in sensitive subjects (Gelfand, 1949).

Prick test results indicated that 24% of 228 subjects (ages not stated) with rhinitis and/or asthma who were patients at an allergy clinic in Australia had positive reactions to *Acacia longifolia*. A mean wheal size of 5.8 mm was reported. Two hundred of the patients had been studied for three years, whereas, the remaining 28 had been studied for six weeks (Kijvanit and Walls, 1986).

The skin sensitization potential of Acacia pollen extract (1000 protein nitrogen units/ml) was evaluated using a total of 36 patients in Brazil with asthma and/or rhinitis. The mean ages of the two test populations, from different parts of the country, were 25.7 years (20 patients) and 18.4 years (16 patients). All patients were tested intradermally (procedure not stated).

Of the 20 patients tested, three had mild intradermal skin test reactions to Acacia pollen extract. One of 16 patients in the remaining test population had a mild intradermal skin test reaction to Acacia pollen extract (Geller and Rosario, 1981).

Cross-reactivity between Gum Acacia and gum tragacanth was reported in a 24-year-old patient who developed sensitization to Quillaja bark (*Quillaja saponaria*) dust, which resulted in rhinitis and asthma. The CIR Expert Panel has previously evaluated the safety of Tragacanth Gum in cosmetics, and concluded that this ingredient is safe in the present practices of use and concentration (Elder, 1987). Specific IgE to pulverized Quillaja bark, Gum Arabic, and gum tragacanth were measured according to a modification of the radioallergosorbent test (RAST) (Wide et al., 1967). Each of the three antigens (20 mg/ml) was coupled directly to methyl cellulose disks that had been activated previously by cyanogen bromide dissolved in acetonitrile. Results were expressed as percent binding.

The amount of radioactivity bound by the patient's serum was compared with control sera from healthy, nonallergic volunteers (number not stated) who had never been exposed to Quillaja bark dust. The mean percent binding of IgE to Quillaja bark in patient sera was 22.4%, compared to 3.2% for the control. Compared to negligible binding in control sera, significant binding was reported for Gum Arabic (32.5% binding) and gum tragacanth (30.8% binding) (Raghuprasad et al., 1980).

CASE REPORTS

Case reports on Gum Arabic and other species of *Acacia* are summarized in Table 12. While two fatalities are reported, most case reports involve sensitization reactions.

Table 12. Case Reports on Gum Arabic and Other Species of Acacia

Ingredient Studied	Patients Evaluated	Procedure/Route of Exposure	Results	Reference
Acacia	78-year-old male with hard nodular mass in right upper quadrant (shock symptoms reported)	Subcutaneous injection of two doses of the drug tyramin (0.06 g/dose). Second dose followed by i.v. dose of 6% Acacia in saline (500 cc)	Death accelerated by intravenous administration of Acacia solution	Lee, 1922
Acacia	Male patient with pulmonary hemorrhage	Intravenous administration of 6% Acacia in saline (150 cc)	Patient's condition worsened immediately after injection, followed by death 2h 20 min later	Lee, 1922
Acacia	27-year-old female recovering from elephantiasis surgery	Intravenous administration of 6% Acacia solution (500 cc) and 500 cc of physiologic saline solution after initial surgery and after second operation 7 months later	No adverse effects after first infusion. Signs/symptoms noted after second infusion: nasal obstruction and lacrimation, followed by difficulty in breathing, coughing, and suggestion of laryngeal stridor. Symptoms disappeared rapidly after epinephrine administration	Maytum and Magath, 1932
Acacia	15 kidney transplant patients. Itching/rash in 3 patients	Patients had been treated with prednisone and azathioprine for 10 months to 5 years. Prednisone tablets contained Acacia and tragacanth gums as adhesives [Itching/rash not observed after tablets withdrawn.] Scratch tests performed	Scratch test results for 2 of 3 patients with reactions tested: Positive reactions to Acacia and tragacanth gums, respectively. Scratch test results negative in remaining transplant patients	Rubinger et al., 1978
Gum Arabic	65 -year-old male with allergic reactions	Four allergic accidents experienced after drinking coffee. Gum Arabic used to coat roasted coffee beans. Prick tests and human basophil degranulation tests performed	Dual sensitization to coffee and Gum Arabic	Moneret-Vautrin, 1993
Gum Arabic	57-year-old male with chronic alveolitis	Chronic alveolitis due to repeated and prolonged inhalation of sweets containing Gum Arabic.	Progress satisfactory in terms of clinical status and lung function measurement after exposure discontinued	De Fenoyl et al., 1987
Acacia (crude and purified forms)	53-year-old plaster molder in candy factory with bronchial asthma	Bronchial asthma due to inhalation of dust from factory environment. Scratch and intradermal injection tests performed	Markedly positive reaction to crude Acacia. Purified Acacia more reactive; induced positive reactions when tested at concentrations as low as 1:5000 dilution in scratch and intradermal injection tests	Spielman and Baldwin, 1933
Gum Arabic	53-year-old printer with asthma	Asthma due to exposure to offset spray containing Gum Arabic. Repeat cutaneous and intracutaneous tests performed	4+ reaction to Gum Arabic in repeat cutaneous and intracutaneous tests	Bohner et al., 1941
Gum Acacia	32 male printers with asthma	Exposure to spray (used in color-printing) containing Gum Acacia and isopropyl alcohol. Average duration of exposure = 4 to 8 years	Asthma developed after exposure to spray	Fowler, 1952
Gum Arabic	12 employees of gum processing factory (office and mill workers)	Sensitization test performed	Seven of 12 workers had positive skin reactions to Gum Arabic. All 12 had respiratory symptoms that were of an allergic nature	Gelfand, 1943
Gum Arabic (as supplied)	24-year-old printer with 3-month history of hand dermatitis	Exposure to Gum Arabic on the job. Patch tests (Finn chambers) performed	++ reaction to Gum Arabic	Freeman, 1984

Ingredient Studied	Patients Evaluated	Procedure/Route of Exposure	Results	Reference
Wet clay containing 5 to 7% Gum Arabic	45-year-old female with rash on hands	Exposure to wet clay for 2 years on the job. Patch tests performed	+ reaction to 1% and 5% aqueous Gum Arabic. ++ reaction to 25% aqueous Gum Arabic	Ilchyshyn and Smith, 1985
Gum Arabic	44-year-old litho-printer with 2-year history of hand eczema	Exposure to Gum Arabic (used to coat printing plates) on the job. Eczema worsened after exposure to Gum Arabic. Patch testing of 10% aqueous Gum Arabic	Positive patch test reaction to 10% aqueous Gum Arabic	van Ketel, 1984

SUMMARY

This safety assessment is on the following species of Acacia that are listed in the International Cosmetic Ingredient Dictionary: Acacia Catechu, Acacia Concinna, Acacia Concinna Extract, Acacia Dealbata, Acacia Dealbata Extract, Acacia Decurrens, Acacia Decurrens Extract, Acacia Farnesiana, Acacia Farnesiana Extract, Acacia Senegal, Acacia Senegal Extract, and Acacia Senegal Gum Extract. According to the International Cosmetic Ingredient Dictionary, Gum Arabic is another name for Acacia Catechu, Acacia Farnesiana, and Acacia Senegal. Gum Arabic is generally recognized as safe (GRAS) for direct addition to food for human ingestion. Acacia Senegal has been described as the major commercial Acacia gum.

Gum Arabic is composed of D-galactose, L-rhamnose, L-arabinose, and D-glucuronic acid residues in an arrangement of a main chain of galactosyl units joined by β-D-(1→ 3) linkages and side chains or branched oligosaccharides linked to the main chain by β-D-(1→ 6) linkages. It is produced when the Acacia tree is stressed by infection, poor nutrition, heat, or lack of moisture. The gum exudes through wounds in the bark that occur naturally or are purposely made to stimulate production.

Aflatoxin has been detected in the bark and seeds of Acacia Catechu (a.k.a. Gum Arabic). However, the results of an enzyme-linked immunosorbent assay indicated no detectable aflatoxin in either of two Gum Arabic samples analyzed. The limits of detection for aflatoxin in this assay system were in the concentration range of 2.0 to 200.0 ppb.

Information on Acacia Concinna Extract represents the only data on the Acacia ingredient family that were received from the cosmetics industry. These data indicate that Acacia Concinna Extract consists of 1 part of extract obtained from 1 part of dry pods of *Acacia concinna*. Active constituents in the pods include saponins, alkaloids, tannins, and malic acid. The raw material (*Acacia concinna*) from which Acacia Concinna Extract is derived is from wild, crafted sources. Thus, reportedly, there is no contamination of the raw material with pesticide residues.

According to an industry specification and analytical data sheet, Acacia Concinna Extract contains preservatives (e.g. parabens and potassium sorbate), saponins, alkaloids, and malic acid.

All of the species of Acacia reviewed in this report function as biological additives in cosmetics. Product formulation data submitted to the Food and Drug Administration in 1997 indicated that Acacia was used in 22 cosmetic products. Use concentrations of Acacia supplied by the cosmetics industry in 1995 included: Mascara (9%), Blush (1%), Make-up (1%), and Hair Mousse (1%).

Reportedly, *Acacia concinna* pods is a useful hair wash. The active constituents of *Acacia concinna* pods (saponins, alkaloids, tannins, and malic acid) are said to have cleansing and astringent properties. The astringent action provides toning of the scalp and conditioning of the hair. Additionally, the active constituents are said to offer effective skin and scalp exfoliation (Carlisle International Corporation, 1997b).

Recommended use concentrations of Acacia Concinna Extract, derived from *Acacia concinna* pods, that have been reported include: 1.0 to 2.0% (for use in shampoos, hair packs, hair conditioners, and hair rinses) and 0.5 to 5.0% w/w.

The weight gain for rats fed Gum Arabic at a dietary concentration of 16% was 75% of that reported for control rats. Approximately 80% of

the Gum Arabic was absorbed. Results from other studies involving rats suggest that the metabolism of Gum Arabic is mediated by bacteria in the cecum.

Results of studies in which dogs and rabbits were injected intravenously with Gum Arabic indicated that Gum Arabic or some other product associated with it accumulated in the liver and remained in the tissues for several months. Non-lethal effects included disturbances in hemoglobin values, white blood cells, and serum proteins.

Based on absorption and metabolism studies from a report, prepared for the Food and Drug Administration, affirming the GRAS status of Gum Arabic as a direct food addltive, it was determined that Gum Arabic is capable of being digested to simple sugars. It was also determined that conclusive evidence indicating that the intact Gum Arabic molecule is absorbed under normal conditions was lacking. Studies in the preceding two paragraphs were also used in this assessment.

Dose-dependent uncoupling of oxidative phosphorylation was noted in groups of rats dosed orally with Gum Arabic at concentrations of 1, 2, and 10% twice daily for four weeks. Effects on oxidative phosphorylation were determined *in vitro* using cardiac and hepatic mitochondria. Damage to cardiac mitochondria progressed as dosing continued; however, hepatic mitochondrial function seemed to have gradually returned to normal during the fourth week of dosing. It was concluded that comparable biochemical effects were not observed *in vivo*, based on negative results for *in vivo* demethylation of 4-dimethyl(^{14}C)-aminoantipyrine.

An acute oral LD50 of 8000 mg/kg was reported for Acacia Gum in rabbits.

Gum Arabic did not cause any abnormal changes in serum chemistry parameters or induce toxicologically significant lesions in rats that received oral doses daily for 28 days. Gum Arabic was also administered to rats in four other short-term oral toxicity studies. Collectively, test concentrations ranged from 1 to 20% and study durations ranged from 28 days to nine weeks.

No significant or discernible ultrastructural differences were found between tissues (heart, liver, small intestine) of control rats and test rats; hematological findings were normal. Gum Arabic was non-toxic, even at the highest concentration tested.

One of three dogs injected intravenously (32 to 35 injections) with Gum Arabic over a period of 76 days died. The range for the total cumulative dose was 15.7 to 47.7 g/kg, and death occurred at the highest dose (47.7 g/kg). An enlarged liver was observed in the animal that died, and the cause of death was not determined. Enlarged livers and swollen kidneys were also observed in dogs that received doses ranging from 1 to 2 g/kg.

In a subchronic (13 weeks) oral toxicity study on Acacia Senegal, the only treatment-related alteration noted in rats at necropsy was cecal enlargement in animals of the highest dose groups. The highest dose groups consisted of male rats fed an average dietary concen-tration of 18.6% (dose = 14 g/kg/day) and female rats fed an average dietary concentration of 18.1% (dose = 13.8 g/kg/day). Kidney weights were significantly reduced in male rats fed 8.6% Acacia Senegal (5.22 g/kg/day) and in male and female rats of the highest dose groups. The reduction in liver weight noted in male rats was not significant. No significant hematological changes were observed between test and control groups. At microscopic examination, no alterations attributable to the ingestion of Acacia Senegal were found.

Electron microscopic findings for samples of livers and kidneys from groups of five rats fed diets containing 0.5 to 3.5% w/w Acacia Senegal daily for 91 days were negative. Mitochondria and nuclei were ultrastructurally normal in appearance and internal structure.

In studies dating back as far as 1932, anaphylactic signs in guinea pigs injected with Acacia solution have been reported. In one of the studies, no signs of anaphylaxis were observed in rabbits injected with Acacia solution.

In rabbits and guinea pigs injected with 7% Gum Acacia solution, no deleterious effects on antibody production resulted. Effects on antibody production were judged by the development of agglutinative and complement-fixing activity in the serum to *Brucella abortus*.

Mouse footpad swelling test results indicated no significant increase in footpad thickness (compared to controls) in mice immunized by injection of Gum Arabic in saline and Freund's adjuvant. Antigen-specific hypersensitivity reactions were noted. In a similar test, footpad swelling was significantly suppressed (compared to controls) in mice dosed orally with Gum Arabic and then immunized by injection of Gum Arabic in

saline and Freund's adjuvant.

Footpad swelling was considered indicative of a non-specific irritant effect in non-immunized male mice injected with Acacia Senegal. In another test, intradermal challenge after immunization of mice with Acacia Senegal caused a significant increase in footpad thickness.

Gum Arabic was not mutagenic in numerous *in vitro* mutagenicity tests using *Salmonella typhimurium, Saccharomyces cerevisiae, and Bacillus subtilis* bacterial strains. Slightly positive results for Gum Arabic in diploid human embryonic lung (WI-38) cells were noted in the cytogenetics assay. It was stated that further tests and a detailed statistical evaluation are needed in order to confirm this classification. The results of a subsequent study indicated that Gum Arabic induced chromosome aberrations in WI-38 human embryonic lung cells.

The mutagenicity of Gum Arabic was also evaluated in numerous *in vivo* assays, the results of which were mostly negative. Statistically significant results were noted in one of the three dominant lethal tests that were performed. It was noted that the biological significance of the positive finding could be questioned. Results were slightly positive in acute and short-term *in vivo* cytogenetics assays (rats); however, it was stated that further tests and a detailed statistical evaluation are needed in order to confirm this possibility. There were no statistically significant findings in mouse chromosomal aberrations and sperm-head morphology assays. Negative results were also reported in micronucleus tests (mouse bone marrow smears) and other *in vivo* assays.

No evidence of carcinogenicity was observed in rats dosed intraperitoneally with Gum Arabic (1.75 or 7.0% in saline or water) three times per week for up to 15 weeks. In another study, tumors were not observed in guinea pigs injected intramediastinally with 0.1 ml of a gruel of Gum Arabic (single dose).

The carcinogenicity of Gum Arabic was also evaluated using four-week-old F344 rats (50 males, 50 females) and four to five-week-old $B6C3F_1$ mice (50 males, 50 females). Low dose animals were fed Gum Arabic at a concentration of 25 g/kg in the diet and high dose animals were fed 50 g/kg for 103 consecutive weeks. Neoplasms were observed only in male rats, and were diagnosed as malignant lymphomas or leukemia-lymphoma. Compared to controls, no significant increases were observed in the incidence of either type of neoplasm at either of the two test concentrations; Gum Arabic was classified as non-carcinogenic in rats and mice.

Oral administration of Gum Arabic (1 ml) did not cause antifertility effects in female rats or the suppression of spermatogenesis in male rats. Gum Arabic was not teratogenic when administered orally to mice at doses up to 1600 mg/kg. Oral doses of Gum Arabic up to 1600 mg/kg also were not teratogenic in rats and hamsters, and oral doses up to 800 mg/kg were not teratogenic in rabbits.

At lower test concentrations, no effects on fertility or ovulation (4%Gum Arabic), or any abnormal variations in blastocysts (10% Gum Arabic) were found in rabbits. Gum Arabic, at a concentration of 15% or in the 1 to 5% concentration range (oral doses), failed to induce teratogenicity or other reproductive effects in female rats. Gum Arabic (5%) also did not cause abnormal sperm development in hamsters. Embryo-toxicity was not noted in mice injected intraperitoneally with a 1% aqueous suspension or mucilage prepared from Gum Arabic.

No evidence of absorption of intact Gum Arabic was found in 22 infants (1 to 15 months) fed Gum Arabic in milk. In a patient with nephrosis, 20% of the Gum Arabic injected intravenously was excreted in the urine over a period of six weeks. Gum Arabic was not detected in feces specimens collected from five male volunteers before or after administration of the gum. In this study, Gum Arabic (25 g in 125 ml 7% dextrose) was ingested daily over a period of 24 days. Marked increases in breath hydrogen production noted after ingestion were said to have been indicative of bacterial breakdown of Gum Arabic in the cecum and colon.

Toxic effects were not observed in five male subjects who ingested 25 g of Gum Arabic daily for 21 days.

The results of a study involving ten subjects who had ingested various gum-containing foods, indicated that Gum Arabic could cause allergic disorders in sensitive subjects. Analyses of sera from four of the ten subjects indicated that Gum Arabic was the dominant gum antigen in two subjects. Cross reactivity between Gum Arabic and gum traga-canth was reported for a 24-year-old patient who developed sensitization to Quillaja bark (*Quillaja saponaria*) dust, which led to rhinitis and asthma.

A number of case reports on the allergenicity of

Gum Arabic have been identified in the published literature.

DISCUSSION

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be enough to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on Acacia Catechu, Acacia Concinna, Acacia Concinna Extract, Acacia Dealbata, Acacia Dealbata Extract, Acacia Decurrens, Acacia Decurrens Extract, Acacia Farnesiana, Acacia Farnesiana Extract, Acacia Senegal, Acacia Senegal Extract, and Acacia Senegal Gum Extract were insufficient to determine whether these ingredients, for purposes of cosmetic use, are either safe or unsafe. The Expert Panel released a 'Notice of Insufficient Data Announcement' on April 4, 1997 outlining the data needed to assess the safety of these ingredients. In the absence of information on the chemical constituents of the various Acacias, the following test data are needed on each of the ingredients in this review:

(1) Concentration of use

(2) Identify the specific chemical constituents, and clarify the relationship between crude Acacias and their extracts and the Acacias and their extracts that are used as cosmetic ingredients

(3) Data on contaminants, particularly relating to the presence of pesticide residues. Additionally, determine whether Acacia melanoxylon is used in cosmetics, and whether acamelin (a quinone) and melacacidin (a flavin) are present in the Acacias that are being used

(4) Skin sensitization study (i.e. dose response to be determined)

(5) Contact urticaria study at use concentration

(6) UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then a photosensitization study may be needed.

Note: Other studies may be requested after clarification of the chemical constituents of the Acacias

No offer to supply the data was received. In accordance with Section 45 of the CIR Procedures, the Expert Panel will issue a Final Report - Insufficient Data. When the requested data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

CONCLUSION

The Expert Panel concludes that the available data are insufficient to support the safety of Acacia Catechu, Acacia Concinna, Acacia Concinna Extract, Acacia Dealbata, Acacia Dealbata Extract, Acacia Decurrens, Acacia Decurrens Extract, Acacia Farnesiana, Acacia Farnesiana Extract, Acacia Senegal, Acacia Senegal Extract, and Acacia Senegal Gum Extract for use in cosmetic products.

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Final Report of the Safety Assessment of Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, Acacia Senegal Extract, Acacia Senegal Gum, and Acacia Senegal Gum Extract[1]

These ingredients are derived from various species of the acacia plant. Only material derived from *Acacia senegal* are in current use according to industry data. The concentration at which these ingredients are reported to be used ranges from 9% in mascara to 0.0001% in tonics, dressings, and other hair-grooming aids. Gum arabic is a technical name for Acacia Senegal Gum. Gum arabic is comprised of various sugars and glucuronic acid residues in a long chain of galactosyl units with branched oligosaccharides. Gum arabic is generally recognized as safe as a direct food additive. Little information is available to characterize the extracts of other Acacia plant parts or material from other species. Acacia Concinna Fruit Extract was generally described as containing saponins, alkaloids, and malic acid with parabens and potassium sorbate added as preservatives. Cosmetic ingredient functions have been reported for Acacia Decurrens Extract (astringent; skin-conditioning agent—occlusive) and Acacia Farnesiana Extract (astringent), but not for the other Acacias included in this review. Toxicity data on gum arabic indicates little or no acute, short-term, or subchronic toxicity. Gum arabic is negative in several genotoxicity assays, is not a reproductive or developmental toxin, and is not carcinogenic when given intraperitoneally or orally. Clinical testing indicated some evidence of skin sensitization with gum arabic. The extensive safety test data on gum arabic supports the safety of Acacia Senegal Gum and Acacia Senegal Gum Extract, and it was concluded that these two ingredients are safe as used in cosmetic formulations. It was not possible, however, to relate the data on gum arabic to the crude Acacias and their extracts from species other than *Acacia senegal*. Therefore, the available data were considered insufficient to support the safety of Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, and Acacia Senegal Extract in cosmetic products. The additional data needed to complete the safety assessment for these ingredients include (1) concentration of use; (2) identify the specific chemical constituents, and clarify the relationship between crude Acacias and their extracts and the Acacias and their extracts that are used as cosmetic ingredients; (3) data on contaminants, particularly relating to the presence of pesticide residues, and a determination of whether Acacia melanoxylon is used in cosmetics and whether acamelin (a quinone) and melacacidin (a flavin) are present in the Acacias that are being used; (4) skin sensitization study (i.e., dose response to be determined); (5) contact urticaria study at use concentration; and (6) ultraviolet (UV) absorption spectrum; if there is significant absorbance in the UVA or UVB range, then a photosensitization study may be needed. It was also noted that other data may be needed after clarification of the chemical constituents of the Acacia-derived ingredients.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel began developing a safety assessment of Acacia-derived ingredients in 1996. In 1998, a final safety assessment was issued with the conclusion that the available data were not sufficient to support the safety of these ingredients in cosmetics. The needed data included concentration of use; specific chemical constituents, including the relationship between crude Acacias and their extracts and the Acacias and their extracts that are used as cosmetic ingredients; contaminants, particularly relating to the presence of pesticide residues and a determination if Acacia melanoxylon is used in cosmetics, and whether acamelin (a quinone) and melacacidin (a flavin) are present in the Acacias that are being used; skin sensitization dose response; contact urticaria data use concentration; and ultraviolet (UV) absorption; if there is significant absorbance in the UVA or UVB range, then a photosensitization study may be needed. The Panel noted that other studies may be requested after clarification of the chemical constituents of the Acacias.

In 2000 and 2001, new data were received including use concentration data on Acacia Senegal and Acacia Senegal Extract;

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information on the composition of gum arabic and various Acacia species; UV spectral analyses on Acacia Senegal Gum and Acacia Concinna Fruit Extract; impurities analysis for pesticide residues in gum arabic; human skin tolerance test (skin irritation evaluated) on 2% Acacia Concinna Fruit Extract; and human maximization test data on a mascara containing 8% Acacia Senegal. Based on this new information, the Panel has prepared this amended safety assessment.

The terminology with which the cosmetics industry describes these ingredients has changed over the past several years. Table 1 shows the progression of terminology from the mid-1990s to 2004. In some cases (e.g., Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Wax, and Acacia Farnesiana Gum) the current name for the ingredient (Gottschalck and McEwen 2004) better reflects the source of the plant material. The current terminology will be used in this report.

A key factor in the determination that the current data are sufficient was the finding that gum arabic is the equivalent of Acacia Senegal Gum. Accordingly, the following is background information on gum arabic and its relationship to gum produced by the *Acacia senegal* plant.

Sudan is the world's largest producer of gum arabic, and it is the main source of gum in international trade. Nigeria is the second largest producer of gum arabic. In the Sudan, the term gum arabic is inclusive of two types of gum that are produced and marketed, "hashab" (from *Acacia senegal*) and "talha" (from *Acacia seyal*). Gum arabic (hashab) from the Sudan is considered to be of the highest quality, and sets the standard by which other "gum arabics" are judged. *Acacia senegal* intrinsically produces a high-quality exudate (pale to orange-brown-colored solid) with superior technical performance; and, in the Sudan, the collection, cleaning, sorting, and handling of it up to the time of export is well organized and highly efficient. In a wider sense, the name gum arabic often is understood to mean the gum from any *Acacia* species and is sometimes referred to as "Acacia gum." For example, gum arabic from Zimbabwe is derived from *Acacia karroo* (Food and Agriculture Organization of the United Nations 1999). Acacia Senegal Gum has been described as the major commercial Acacia gum (Anderson 1988).

Although most internationally traded gum arabic comes from *Acacia senegal*, the term "gum arabic" may not imply a particular botanical source. In a few cases, so-called gum arabic may not even have been collected from Acacia species, but may originate from *Combretum*, *Albizia*, or some other genus (Food and Agriculture Organization of the United Nations 1999).

In the *International Cosmetic Ingredient Dictionary and Handbook*, gum arabic is listed as a technical name for Acacia Catechu Gum, Acacia Farnesiana Gum, and Acacia Senegal Gum (Gottschalck and McEwen 2004). However, since this publication, the Cosmetic, Toiletry, and Fragrance Association (CTFA) determined that gum arabic does not apply to Acacia Catechu Gum or Acacia Farnesiana Gum and will no longer be listed in the *International Cosmetic Ingredient Dictionary and Handbook* as a technical/other name for these ingredients (CTFA 2000b).

According to CTFA, gum arabic applies to the dried gummy exudate from branches and stems of *Acacia senegal* and other Acacia species from Africa, and *Acacia catechu* and *Acacia farnesiana* are not African species (CTFA 2000b).

This definition is similar to the following definition of Acacia that is found in the *National Formulary* (United States Pharmacopeial Convention 2000): Acacia is the dried gummy exudate from the stems and branches of *Acacia senegal* (Linné) Wildenow or of other related African species of Acacia (Family Leguminosae). It has also been described as a complex mixture of calcium, magnesium, and potassium salts of arabic acid. Arabic acid is a complex of galactose, rhamnose, arabinose, and glucuronic acid (Frutarom Meer Corporation, no date).

Gum arabic is a substance that is generally recognized as safe (GRAS) for direct addition to human food under the provisions of Section 184.1330 of the Code of Federal Regulations (21 CFR 184.1330). A report, prepared for the Food and Drug Administration (FDA), summarizing all available scientific data (1920 to 1972) related to the safety of gum arabic as a food ingredient has been published (Informatics Inc. 1972). Studies from that report are referenced in the text of this report.

In a subsequent report (prepared for FDA) evaluating the safety of gum arabic as a food ingredient, the Select Committee on GRAS Substances of the Life Sciences Research Office, Federation of American Societies for Experimental Biology (FASEB), concluded that "there is no evidence in the available information on gum arabic that demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard" (FASEB 1973).

The Select Committee also determined that additional experiments should be undertaken to evaluate the significance of gum Arabic allergenicity to the population as a whole, and that it may be advisable to conduct feeding studies in several animal species (including pregnant animals) at dosage levels that approximate and exceed the current maximum daily human intake (see "Noncosmetic Use").

Studies from the 1973 FASEB report are summarized in the text of this report. Studies on Acacia Senegal Gum and other species of Acacia (listed in the *International Cosmetic Ingredient Dictionary and Handbook* and those not listed) that have been published since the FASEB report was issued are also included. To ensure that the information in the present report is representative of the published chemistry and toxicity data on species of Acacia, the data presented involve various parts/components of the Acacia tree as well as the gummy exudate.

CHEMISTRY

Definitions of various ingredients derived from Acacia species in the *International Cosmetic Ingredient Dictionary and*

TABLE 1
Acacia-derived cosmetic ingredient terminology, description, and function

1995–1997 Terminology (Wenninger and McEwen 1995, 1997)			2004 Terminology (Gottschalck and McEwen 2004)		
Name	Description	Cosmetics function	Name	Description	Cosmetics function
Acacia Catechu	Plant material derived from *Acacia catechu*	Biological additive	Acacia Catechu	EU term for Acacia Catechu Gum	N/A
Acacia Catechu	Dried, crushed core of *Acacia catechu*	Biological additive	Acacia Catechu Gum	Dried, crushed core of *Acacia catechu*	Not reported
Acacia Concinna	Plant material derived from *Acacia concinna*	Not reported	Acacia Concinna	EU term for Acacia Concinna Fruit Extract	N/A
Acacia Concinna Extract	Extract of the fruit of *Acacia concinna*	Biological additive	Acacia Concinna Fruit Extract	Extract of the fruit of *Acacia concinna*	Not reported
Acacia Dealbata	Plant material derived from *Acacia dealbata*	Not reported	Acacia Dealbata	EU term for Acacia Dealbata Leaf Extract	N/A
Acacia Dealbata Extract	Extract of the leaves of *Acacia dealbata*	Biological additive	Acacia Dealbata Leaf Extract	Extract of the leaves of the wattle, *Acacia dealbata*	Not reported
			Acacia Dealbata Leaf Wax	Wax obtained from the leaves of *Acacia dealbata*	Skin-conditioning agent—emollient; skin protectant
Acacia Decurrens	Plant material derived from *Acacia decurrens*	Not reported	Acacia Decurrens	EU term for Acacia Decurrens Extract	N/A
Acacia Decurrens Extract	Extract of the acacia, *Acacia decurrens*	Biological additive	Acacia Decurrens Extract	Extract of the acacia, *Acacia decurrens*	Astringent; Skin-conditioning agent—Occlusive
Acacia Farnesiana	Plant material derived from *Acacia farnesiana*	Not reported	Acacia Farnesiana	EU term for Acacia Farnesiana Extract, Flower Wax, and Gum	N/A
Acacia Farnesiana	Plant material derived from the dried, gummy exudate of the acacia, *Acacia farnesiana*	Not reported	Acacia Farnesiana Gum	Plant material derived from the dried, gummy exudate of the acacia, *Acacia farnesiana*	Not reported
Acacia Farnesiana Extract	Extract of the flowers and stems of the the acacia, *Acacia farnesiana*	Biological additive	Acacia Farnesiana Extract	Extract of the flowers and stems of the the acacia, *Acacia farnesiana*	Astringent
			Acacia Farnesiana Flower Wax	wax obtained from the flowers of *Acacia farnesiana*	Skin protectant
Acacia Senegal	Plant material derived from *Acacia senegal*	Not reported	Acacia Senegal	EU term for Acacia Senegal Extract, Gum, and Gum Extract	N/A

(Continued on next page)

TABLE 1
Acacia-derived cosmetic ingredient terminology, description, and function *(Continued)*

1995–1997 Terminology (Wenninger and McEwen 1995, 1997)			2004 Terminology (Gottschalck and McEwen 2004)		
Name	Description	Cosmetics function	Name	Description	Cosmetics function
Acacia senegal	Plant material derived from the dried, gummy exudate of the acacia, *Acacia senegal*	Not reported	Acacia Senegal Gum	Plant material derived from the dried, gummy exudate of the acacia, *Acacia senegal*	Not reported
Acacia Senegal Extract	Extract of the flowers and stems of the the acacia, *Acacia senegal*	Biological additive	Acacia Senegal Extract	Extract of the flowers and stems of the acacia, *Acacia senegal*	Not reported
Acacia Senegal Gum Extract	Extract of the gum of the acacia, *Acacia senegal*	Biological additive	Acacia Senegal Gum Extract	Extract of the gum of the acacia, *Acacia senegal*	Not reported

Handbook are included in Table 1 (Gottschalck and McEwen 2004). CAS numbers are listed for the following two: Acacia Catechu Gum (CAS no. 8001-76-1) and Acacia Senegal Gum (CAS no. 9000-01-5).

Chemical and Physical Properties

Gum Arabic

The gummy exudate from the *Acacia senegal* is a proteinaceous polysaccharide, with protein content ranging from approximately 1.5% to 3% for samples from various producing areas (World Health Organization 1990).

Gum arabic is a white powder that is readily soluble in water, but insoluble in alcohol (Anonymous 1993). Molecular weights of ~850,000 (Ross et al. 1984a, 1984b) and ~240,000 (Frutarom Meer Corporation no date), and a density of 1.35 to 1.49 (Dangerous Properties of Industrial Materials Report 1981) have been reported. An aqueous solution is acid to litmus (Lewis 1993a).

Pazur et al. (1986) indicated that gum arabic is composed of D-galactose, L-rhamnose, L-arabinose, and D-glucuronic acid residues in an arrangement of a main chain of galactosyl units joined by β-D-(1 $\rightarrow$ 3) linkages and side chains or branched oligosaccharides linked to the main chain by β-D-(1 $\rightarrow$ 6) linkages. The oligosaccharides may contain terminal rhamnosyl units linked (1 $\rightarrow$ 3) or terminal arabinofuranosyl units linked (1 $\rightarrow$ 4) to internal galactosyl or glucuronosyl units. Based on methylation and degradation studies of gum arabic (*Acacia senegal*) along with periodate oxidation and other confirmatory reactions, the structure for gum arabic shown in Figure 1 was proposed (Informatics Inc. 1972).

Gum arabic is almost completely soluble in twice its weight of cold water, and the viscosity of the gum increases slowly at concentrations up to 25%. At concentrations greater than 25%, the viscosity increases much more rapidly in proportion to the gum content (Frutarom Meer Corporation no date).

UV Absorption

An increase in absorbance for Acacia Senegal was observed between 400 nm and approximately 260 nm, reaching a plateau at wavelengths ranging from 270 to ~250 nm. A rapid increase in absorbance was observed at wavelengths less than 250 nm (Avon Products, Inc. 2000a). UV absorption spectra provided on two other lots of Acacia gum (Acacia Senegal) were both similar to the preceding UV spectral analysis (Avon Products, Inc. 2000b).

Methods of Production

Gum arabic is produced when the Acacia tree is stressed by infection, poor nutrition, heat, or lack of moisture. The gum exudes through wounds in the bark that occur naturally or are purposely made to stimulate production. The exudate dries rapidly, is collected as hardened drops or tears, sorted, graded, and marketed. The gum becomes harder during storage; market preferences exist for both the harder (old) and softer (new) gum (FASEB 1973).

According to another source, the removal of the bark that adheres to the tears is critical to the production of quality gum arabic. Additionally, in order to produce quality products, elaborate processes for the preclearing of milled gum and the centrifugation and filtration of feed solutions for spray dried gum must be followed. The major growing regions for gum arabic are in the Sudan and West Africa, and the Kordofan grade is considered the best (Frutarom Meer Corporation, no date).

Gum arabic in solid form is imported from the Sudan. According to one source, the solid is converted to a liquid form and

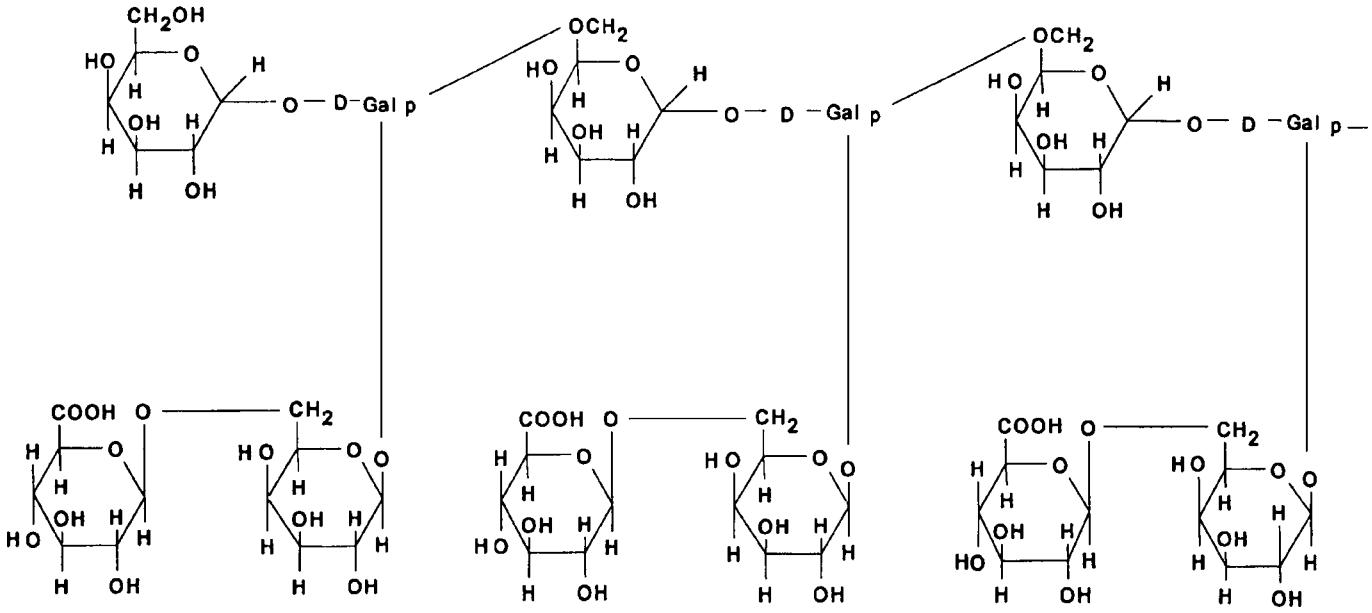

FIGURE 1
Proposed structure for Gum Arabic (Informatics 1972).

the preservatives Proxel GXL (0.13%) and sodium benzoate are then added. Proxel GXL consists of 20% 1,2-benzisothiazolin-3-one (BIT) in aqueous dipropylene glycol (Freeman 1984).

Crude Acacia Concinna results from the drying and pulverization of the pods of *Acacia concinna*. The extract of these pods (Acacia Concinna Fruit Extract) is drawn by cold processing (Carlisle International Corporation 1997a).

Composition, Analytical Methods, and Impurities

The following three grades of gum arabic have been noted in the published literature: (1) processed gum arabic recovered by spray-drying from a solution of commercial food grade gum arabic after filtration to remove sand, etc., and after heat treatment to effect pasteurization; (2) finely powdered natural gum arabic of poor commercial quality, giving solutions of a dark reddish brown color; (3) finely powdered natural gum arabic of very high quality, giving essentially colorless solutions (Strobel et al. 1982). Gum arabic has been analyzed by gas chromatography (Lawrence and Iyengar 1985) and has been identified by microelectrophoresis (Informatics Inc. 1972).

Powdered gum arabic contains moisture (15% maximum) and insoluble ash (0.5% maximum). The pH of a 10% solution is approximately 4.6 (Frutarom Meer Corporation, no date). The following specifications exist for United States Pharmacopoeia (USP) grade Acacia: loss on drying (15% maximum), total ash (4% maximum), arsenic (3 ppm), lead (0.001%), and heavy metals (0.004%) (United States Pharmacopeial Convention, Inc. 2000).

FDA has listed Acacia (Gum Arabic) as a direct food additive that meets the specifications of the *Food Chemicals Codex* (21 CFR 184.1330). The specifications for food grade Acacia include arsenic (3 mg/kg maximum); ash, acid-insoluble (0.5% maximum); ash, total (4% maximum); heavy metals (0.002% maximum); insoluble matter (1% maximum); lead (5 mg/kg maximum); and loss on drying (15% maximum) (Food Chemicals Codex 1996).

Anderson et al. (1990) compared the amino acid composition of Sudanese and Nigerian gum arabic. Analyses were done on samples collected over a 13-year period for samples from the Sudan and over 9 years for those from Nigeria. The data are presented in Table 2.

Anderson et al. (1991) analyzed gum arabic samples provided by importers shown in Table 3. All samples conformed to the revised Joint Food and Agriculture Organization of the United Nations/World Health Organization, Expert Committee on Food Additives (JECFA) specification in respect of solubility, complete in cold water; acid-insoluble ash, (>0.5%) and matter (>1%); starch/dextrin (absent); tannin (absent); arsenic (>3 ppm), lead (>10 ppm), heavy metals (>40 ppm) (JECFA 1990). All samples were confirmed by nuclear magnetic resonance (NMR) spectroscopy to be "good" *Acacia senegal*.

Anderson et al. (1990) also analyzed the ash from gum arabic samples from these same two countries. These data are given in Table 4.

West Coast Analytical Service, Inc. (1999) analyzed gum arabic for pesticide residues using USP methodology and found no detectable pesticide residues.

Other food additive specifications for gum arabic from the Food and Agriculture Organization (FAO) of the United Nations defined the material as a dried exudate obtained from the stems and branches of *Acacia senegal* (L.) Willdenow or *Acacia seyal*

TABLE 2
The amino acid composition of Sudanese and Nigerian Gum Arabic (*Acacia senegal*) (Anderson et al. 1990)

Amino acid	Sudanese samples Mean residues/1000 residues (13 years total between 1904 and 1989)	Nigerian samples Mean residues/1000 residues (9 years total between 1905 and 1967)
Alanine	27 ± 3	24 ± 4
Arginine	13 ± 4	12 ± 1
Aspartic acid	68 ± 13	61 ± 16
Cystine	2 ± 4	0
Glutamic Acid	42 ± 10	42 ± 15
Glycine	50 ± 5	50 ± 6
Histidine	44 ± 8	48 ± 5
Hydroxyproline	304 ± 47	331 ± 73
Isoleucine	12 ± 3	13 ± 3
Leucine	66 ± 7	69 ± 8
Lysine	25 ± 3	24 ± 6
Methionine	2 ± 2	1
Phenylalanine	33 ± 5	29 ± 10
Proline	63 ± 14	55 ± 9
Serine	129 ± 11	129 ± 13
Threonine	68 ± 9	67 ± 8
Tyrosine	14 ± 5	14 ± 4
Valine	35 ± 8	32 ± 6

(family Leguminosae), include the following: loss on drying (not more than 15% [105°C, 5 h] for granular and not more than 10% [105°C, 4 h] for spray dried material); total ash (not more than 4%), acid-insoluble ash (not more than 0.5%), acid-insoluble matter (not more than 1%); and lead (not more than 2 mg/kg) (FAO 1999).

TABLE 4
Cation composition of ash from Sudanese and Nigerian Gum Arabic (*Acacia senegal*) (Anderson et al. 1990)

Cation	Sudanese samples Mean μg/g ash unless expressed as ppm (15 years total between 1904 and 1989)	Nigerian samples Mean μg/g ash unless expressed as ppm (9 years total between 1905 and 1967)
Aluminum	190 ± 53	311 ± 156[a]
Calcium	256,000 ± 34,000	316,000 ± 56,000
Chromium	47 ± 22	34 ± 26
Copper	52 ± 27	66 ± 65[b]
Iron	128 ± 84	110 ± 33
Lead	6 ± 2	11 ± 7
Magnesium	38,000 ± 15,000	39,000 ± 15,000
Manganese	100 ± 95	57 ± 27
Nickel	10 ± 11	12 ± 17
Potassium	237,000 ± 37,000	221,000 ± 43,000
Sodium	9,400 ± 4,480	10,200 ± 5,200
Zinc	24 ± 10	40 ± 49[c]
Arsenic	<1 ppm	<1 ppm
Cadmium	<1 ppm	<1 ppm
Cobalt	<1 ppm	<1 ppm
Molybdenum	<1 ppm	<1 ppm

[a]Mean = 266 (n = 8) if one value, 675, is treated as an outlier.
[b]Mean = 47, if one value, 225, is treated as an outlier.
[c]Mean = 25, if one value, 159, is treated as an outlier.

Acacia Concinna Fruit Extract

Acacia Concinna Fruit Extract consists of 1 part of extract obtained from 1 part of dry pods of *Acacia concinna*. It contains the active constituents of the pods of *Acacia concinna*, such as

TABLE 3
Analytical data for natural Gum Arabic samples provided by importers in 1990/1991 (Anderson et al. 1991)

Sample no.	Sample sent by	Date received	% H_2O[a]	% Ash[a]	% N[a]	Specific rotation (degrees)
N1	American importer A	12/90	13.2	3.8	0.34	−29
N2	American importer A	12/90	13.9	4.0	0.36	−31
N3	Italian importer B	12/90	14.4	3.3	0.31	−30
N4	British importer C	12/90	14.5	3.6	0.37	−31
N5	British importer D	12/90	12.2	3.5	0.35	−33
N6	British importer E	12/90	14.9	2.0	0.38	−33
N7	German importer A	1/91	14.4	4.0	0.26	−34
N8	American importer G	1/91	15.0	3.2	0.29	−26
N9	American importer H	1/91	13.9	3.9	0.33	−32
N10	British importer K	2/91	13.3	3.7	0.34	−28
N11	Italian importer L	2/91	14.8	3.4	0.30	−29
Mean values			14.0	3.6	0.33	−30.5

[a]Dry-weight basis, as specified (Food and Agriculture Organization of the United Nations 1990).

TABLE 5
Acacia Concinna Fruit Extract specifications (Carlisle International Corporation 1997a)

Specification	Standard
Color	Brown
pH	4 to 6
Specific gravity (at 25°C)	1.0 to 1.10
Refractive index (at 20°C)	1.1 to 1.4
Dried residue (2 h/110°C)	10% to 20%
Water	60% to 65%
Propylene glycol	35% to 40%
Water solubility	Soluble
Preservatives	Parabens and potassium sorbate
Heavy metal	<10 ppm
UV/VIS spectrophotometry	
Absorbance at 220 nm of a 0.1% aqueous solution	1.0 ± 0.25
Absorbance at 220 nm of a 0.2% aqueous solution	2.0 ± 0.20
Other constituents (HPTLC method)	Saponins, alkaloids, malic acid
Maximum total bacterial count	100/g
Maximum yeasts and molds	0/g

vegetable saponins. The raw material (*Acacia concinna*) from which Acacia Concinna Fruit Extract is derived is from wild, crafted sources free of contamination with pesticide residues. The standard analytical profile of Acacia Concinna Fruit Extract is given in Table 5. A sample "passes" if it meets these specifications (Carlisle International Corporation 1997a).

Information on the composition and impurities of various species of Acacia and their contaminants is included in Table 6. The Acacia species that are listed in the *International Cosmetic Ingredient Dictionary and Handbook* are identified with an asterisk.

As noted in Table 6, aflatoxin has been detected in the bark and seeds of *Acacia catechu* (Roy and Kumari 1988, 1991). Abdalla (1988) also described gum-yielding Acacia twigs from the Sudan (supplier of Acacia Senegal Gum) as a source of aflatoxin (81 to >1000 μg/kg).

Smith et al. (1990), however, found no detectable aflatoxin in either of two samples of gum arabic analyzed using an enzyme-linked immunosorbent assay. The assay system was capable of determining aflatoxin in the concentration range of 2.0 to 200.0 ppb in gum arabic.

Data from the European Federation for Cosmetic Ingredients (EF*f*CI) describes the components of the plant material from various Acacia species. While there are some similarities, there are many differences in composition (EF*f*CI 2000). These data are given in Table 7.

Reactivity

When Gum Acacia is weakly hydrolyzed by hydrochloric acid at room temperature, pentose is split off (Marrack and Carpenter 1938). Partial acid hydrolysis has also yielded galactose and complex sugar acids (Heidelberger et al. 1929).

Gum Acacia emits acrid smoke when heated to decomposition (Lewis 1993b). Heating a solution of Acacia for a few minutes at 100°C destroys peroxidase (oxidizing agent) present in the gum and the colored derivatives produced (Gennaro 1990).

USE

Purpose in Cosmetics

The functions of these ingredients in cosmetics as described in the *International Cosmetic Ingredient Dictionary and Handbook* are given in Table 1 (Wenninger et al. 2000).

Reportedly, *Acacia concinna* pods are a useful hair wash, in that they promote hair growth, kill lice, and remove dandruff. The active constituents of *Acacia concinna* pods (saponins, alkaloids, tannins, and malic acid) are said to have cleansing, stimulating, and astringent properties. The astringent action provides toning of the scalp and conditioning of the hair. Additionally, the active constituents are said to offer effective skin and scalp exfoliation (Carlisle International Corporation 1997b).

Scope and Extent of Use in Cosmetics

The product formulation data submitted to the FDA in 2001 indicated that Acacia was used in 33 cosmetic products and that Acacia Senegal was used in 1 cosmetic product (Table 8) (FDA 2001). Neither the species nor the plant part was further delineated in the category "Acacia." It is assumed that Acacia Senegal is Acacia Senegal Gum.

Current concentration of use data are given in Table 8. These data from industry (CTFA 2000a) show the highest concentration of Acacia Senegal Gum (9%) in shampoos. Acacia Senegal Gum Extract was reported at a concentration of 0.001% in bath soaps and detergents. For many uses of these ingredients, information regarding use concentration for specific product categories is provided, but the number of such products is not known, but they must be assumed to be in use.

Recommended use concentrations of Acacia Concinna Fruit Extract are 0.5% to 5.0% (Carlisle International Corporation 1997a) and 1.0% to 2.0% for use in shampoos, hair packs, hair conditioners, and hair rinses (Carlisle International Corporation 1997b).

Cosmetic products containing Acacia are applied to most parts of the body and could come in contact with the ocular and nasal mucosae. These products could be used on a daily basis, and could be applied frequently over a period of several years.

Acacias are not included among the substances listed as prohibited from use in cosmetic products that are marketed in the European Union (EEC 2001). The European Union terminology

TABLE 6
Composition and impurities data on Various Species of Acacia

Acacia species (part/source)	Analytical method	Components	Reference
Acacia atramentaria and *Acacia tortuosa* (leaves)	Gas chromatography and NMR spectroscopy	Proacacipetalin (cyanogenic glucoside)	Seigler et al. 1983
*Acacia albida, Acacia ataxa-cantha, Acacia catechu**, *Acacia confusa, Acacia coulteri, Acacia erubescens, Acacia ferruginea, Acacia galpinii, Acacia hamulosa, Acacia mellifera, Acacia modesta, Acacia nigrescens, Acacia polyacantha, Acacia rovumae, Acacia senegal**, *Acacia venosa*, and *Acacia welwitschii* (seeds)	Ion exchange chromatography	α-Amino-β-oxalylaminopropionic acid (neurotoxic lathyrogen)	Quereshi et al. 1977
Acacia aroma (leaves)	Gas chromatography and NMR spectroscopy	Linamarin and lotaustralin (cyanogenic glucosides)	Seigler et al. 1983
*Acacia catechu** (seed)	Thin-layer chromatography and spectrophotometry	Aflatoxin B_1 (0.01 to 0.76 μg/g)	Roy and Kumari, 1991
*Acacia concinna** (pods)	—	Highly polar saponin mixture. Hydrolysis with alkali yields 5 triterpenoidal prosapogenols (concinnosides A, B, C, and D), 4 glycosides (acadiaside, julibroside A1, julibroside A3, albiziasaponin C), and aglycone, acacic acid lactone	Abul et al. 1997
*Acacia concinna** (fruit)	—	Kinmoonsides A–C (3 cytotoxic saponins)	Tezuka et al. 2000
*Acacia farnesiana** (pod, leaf, stem, old stem, and flower)	Phytochemical screening	Carbohydrates and/or glycosides, reducing sugars, hydrolyzable tannins, alkaloids and nitrogenous bases, unsaturated sterols, and/or terpenes, and coumarins (all organs)	Wassel et al. 1992
*Acacia farnesiana** (pod, leaf, old stem, and flower)	—	Flavonoids (all organs except stem)	Wassel et al. 1992
*Acacia farnesiana** (pod, leaf, stem)	—	Cyanogenic glycosides (in pod, leaf, and stem)	Wassel et al. 1992
*Acacia farnesiana** (flower)	—	Volatiles (flower)	Wassel et al. 1992
*Acacia farnesiana** oil	Thin layer chromatography	Anisaldehyde, benzalcohol, benzaldehyde, cuminicalcohol, farnesol, cuminicaldehyde, geraniol, geranyl acetate, ionone, linalool, linalyl acetate, nerolidol, terpineol, and methyl salicylate	El-Hamid and Sidrak 1970
*Acacia farnesiana** (leaves)	—	Total soluble phenols ranged from 10.27% to 35.46%. Condensed tannins ranged from 0.5% to 8.28% on dry matter basis	Sotohy et al. 1995
*Acacia farnesiana** (leaves)	—	Cyanogenic glycoside (linamarin or lotaustralin may be present)	Secor et al. 1976

(Continued on next page)

TABLE 6
Composition and impurities data on Various Species of Acacia *(Continued)*

Acacia species (part/source)	Analytical method	Components	Reference
Acacia tortilis (gum and bark extracts)	High-performance liquid chromatography	Smooth muscle relaxants: quaracol A and B (in gum) and (+)-fisetinidol (in gum and bark)	Hagos and Samuelson 1988
Acacia georginae (seeds)	Extractive and chromatographic procedures	Fluoroacetic acid	Oelrichs and McEwan 1962
Acacia globulifera (leaves)	Gas chromatography and NMR spectroscopy	Epiproacacipetalin (cyanogenic glucoside)	Seigler et al. 1983
Acacia modesta (stem bark, heartwood, and leaf extracts)	Thin-layer chromatography	α-amyrin, betulin, octacosanol and ε-sitosterol (in stem bark); γ-sitosterol and pinitol (in heartwood); octacosane, hentriacontane, octacosanol, and hentriacontanol (leaves)	Joshi et al. 1975
*Acacia mollissima, Acacia confusa, Acacia longifolia, Acacia decur-rence**, *Acacia dealbata**, *Acacia baileyana*, and *Acacia verticillata* (leaves)	Amino acid autoanalyzer used	(−)-*trans*-4-hydroxypipecolic acid	Marakesh et al. 1969

*The Acacia species listed in the *International Cosmetic Ingredient Dictionary.*

for these ingredients is described in Table 1, where the genus and species names are used to describe all of the plant material (e.g., gum, extract, etc.) derived from that particular genus/species, independent of the plant part from which the material is derived.

The Acacias reviewed in this report are not included on the list of ingredients that must not be combined in cosmetic products that are marketed in Japan (Ministry of Health, Labor and Welfare [MHLW] 2000a) or on the list of restricted ingredients for cosmetic products that are marketed in Japan (MHLW 2000b).

Noncosmetic Use

Gum arabic is a substance that is generally recognized as safe (GRAS) for direct addition to human food under the provisions of Section 184.1330 of the Code of Federal Regulations (CFR). It is approved for use in various food categories at the following maximum permitted usage levels: 2.0% (beverage and beverage bases), 5.6% (chewing gum), 12.4% (confections and frostings), 1.3% (dairy product analogs), 1.5% (fats and oils), 2.5% (gelatins, puddings, and fillings), 46.5% (hard candy and cough drops), 8.3% (nuts and nut products), 6.0% (quiescently frozen confection products), 4.0% (snack foods), 85.0% (soft candy), and 1% (all other food categories).

Uses of gum arabic in the various food categories include: emulsifier and emulsifier salt, flavoring agent and adjuvant, formulation aid, stabilizer and thickener, humectant, surface-finishing agent, processing aid, and texturizer (21 CFR 184.1330). Gum arabic is also listed as one of the optional blending ingredients of vanilla powder (21 CFR 169.179) and vanilla-vanillin powder (21 CFR 169.182).

The following maximum values for possible daily human intake (g/kg body weight) of gum arabic in the total diet have been calculated for various age groups by the Select Committee on GRAS Substances using data from the National Research Council: 115 mg/kg (0 to 5 months), 322 mg/kg (6 to 11 months), 329 mg/kg (12 to 23 months), and 113 mg/kg (2 to 65 + years) (FASEB 1973).

At the 35th meeting of the JECFA, held in Rome from May 29 to June 7, 1989, JECFA confirmed its acceptable daily intake (ADI) of gum arabic as "not specified." Here, gum arabic (a.k.a. gum Acacia) is defined as the dried gummy exudate from tropical and subtropical *Acacia senegal* trees.

ADI "not specified" is applicable to a food substance of very low toxicity, which, on the basis of the available data (chemical, biochemical, toxicological, and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect, and from its acceptable background in food does not, in the opinion of the JECFA, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect; it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance (JECFA 1990).

TABLE 7
Chemicals found in Acacia species (EF*f*CI 2000)

Acacia catechu plant	Acacia decurrens plant	Acacia farnesiana plant	Acacia senegal plant
(+)-afzelichin	(+)-catechin	(+)-catechol	4-methoxyglucuronic acid
3-(beta-L-arabopyranoside)-L-arabinose	3,3′,4′,5′,7-pentahydroxy-2-phenylchroman	(+)-gallocatechol	Arabic acid
3-methoxyflavones	3,3′,4,4′,7′-pentahydroxyflavin	Apigenin-6,8-bis-beta-D-glucopyranoside	Arabinose
4-(4-*O*-methyl-alpha-D-glucuronoside)-L-arabinose	3-methyl-L-rhamnose	Aromadendrin	Ascorbic acid
4-hydroxypipecolic acid	7,3′,4′,5-tetrahydroxyflavan-3-O-L-catechin	Aspartic acid	Aspartic acid
5-(beta-D-xylopyranoside)-L-arabinose	Acetic acid	Cresols	Beta sitosterol
7,3,4-trihydroxy-3,8-dimethoxyflavone	Aldobionic acid	Ellagic acid	Beta sitosterol-D-glucose
7,8,14′-trihydroxyflavonol	Alpha cellulose	Ethyl ester	Cysteine
7,8,4-trihydroxy-3-methoxyflavone	Anthocyanidin	Hydroxyacetophenone	D-galactose
8-methoxyfisetin	Anthocyanilidine	Isorhamnetin-3-rutinoside	D-glucoside
9-methoxyflavone-3,4-diones	Beta carotene	Kaempferol	Dimethyltryptamine
Acacatechin	Carbohydrates	Kaempferol-7-galloylglucose	Erythrodiol
Acetaldehyde	Cellulose	Kaempferol-7-glucoside	Galactoglucuronid acid
Aldobiuronic acid	D-galacturonic acid	Linamarin	Glucuronic acid
Alpha-amino-beta-oxalylaminopropionic acid	D-pinetol	Lotaustralin	HCN
Alpha catechin	Fiber	*m*-digallic acid	Hentriacontane
Beta catechin	Fisetinidin	Methyl gallate	Hentriacontanol
Boron	Fructose	Mucilage	Kaempferol
Catechuic acid	Gallocatechin	Myricetin-4′-methylether-3-rhamnoside	L-arabinose
Catechutannic acid	Indoleacetic acid	*N*-acetyl-djenkkolic acid	L-rhamnose
Cobalt	L-arabinose	Naringenin-7-glucoside	Leucine
D-galactose	L-rhamnose	Naringenin-7-rhamnoglucoside	Magnesium
D-glucuronic acid	Lignin	Pipecholic acid	Octacosanol
D-xylose	Mearnsitrin	Prunin-*O*-6′-gallate	Peroxidase
Diamino acid	Methanol	Quercetin-3-*O*-rutinoside	Potassium
Dihydrokaempferol	Methylsalicylic ester	Salicylic acid	Quercetin
DL-catechol	Pelargonidin	Tyramine	Rhamnose
DL-epicatechin	Phlobaphene		Rhamnose hydrate
Fisetin	Phlobaphene anhydride		Serine
Flavotannin	Phloroglucinol		Sitosterol
Formaldehyde	Proanthocyanidin		Sodium

(Continued on next page)

TABLE 7
Chemicals found in Acacia species (EF*f*CI, 2000) *(Continued)*

Acacia catechu plant	Acacia decurrens plant	Acacia farnesiana plant	Acacia senegal plant
Gallic acid	Protocatechuic acid		Sucrose
Gallotannin	Robinetin		Tannin
Gamma-catechin	Rutin		Uronic acid
Glucosyluronic acid	Xanthophyll		Valine
Gum			
Isocacatechin			
Isorhamnetin			
Isovaleraldehyde			
Kaempferol			
L-epicatechin			
L-leucomacluricglycol ether			
L-rhamnose			
Magnesium			
Malate dehydrogenase			
Manganese			
Peroxidase			
Phlobatannin			
Phosphatase			
Procyanidin			
Quercetagetin			
Quercetin			
Quercitrin			
Rutin			
Silicon			
Tannin			
Taxifolin			
Uronic acid			

Gum arabic (Acacia Senegal Gum) is used in the pharmaceutical industry to stabilize emulsions during the preparation of tablets (Collins et al. 1987). It is also used for its demulcent action in the treatment of throat or gastric inflammation (Gennaro 1990).

The therapeutic efficacy of Acacia Catechu in the treatment of lepromatous leprosy has been reported (Ojha et al. 1969).

Gum Arabic has also been used in glues, lithographic solutions, and matches (tip and binder in striking surface), and polisher and textile finishes (van Ketel 1984).

The following uses of Acacia Concinna in folk medicine have been reported: A chutney (pungent relish of fruits, spices, and herbs) made of the tender leaves of *Acacia concinna*, salt tamarind, and chilies is administered for the treatment of bilious affections such as jaundice. An infusion of the leaves is used in the treatment of malarial fever; it checks flatulence and serves as a mild laxative. Furthermore, repeated, large doses of a decoction of the *Acacia concinna* pods act as an emetic and purgative (Carlisle International Corporation 1997b).

An ointment made from the *Acacia concinna* pods reportedly is used in the treatment of skin diseases (Carlisle International Corporation 1997b).

BIOLOGICAL PROPERTIES

Absorption, Distribution, Metabolism, and Excretion

Gum Arabic

The weight gain for rats fed gum arabic at a dietary concentration of 16% was 75% of that reported for control rats. It was determined that approximately 80% of the gum arabic was absorbed (Informatics 1972).

In a study using rats, an apparent decrease in the caloric value of gum arabic with increasing administered dose was noted. Gum arabic was incorporated into the diet at concentrations of 5%, 10%, and 17%. Digestibility data indicated that up to 80% of the gum arabic was absorbed (Informatics Inc. 1972).

Following a 48 h fast, 20 young male rats were fed 10 mg of a mixture consisting of 34% white, powdered gum arabic and 66% cacao butter. At 72 h after feeding, the rats were anesthetized

TABLE 8
Product formulation data on Acacia and Acacia Senegal

Product category (total formulations in category) (FDA 2001)	Formulations with ingredient (FDA 2001)	Concentration of use (CTFA 2000a) (%)
Acacia		
Other bath preparations (193)	1	—
Mascara (187)	18	—
Other eye makeup preparations (151)	2	—
Hair tints (49)	1	—
Hair color sprays (Aerosol) (5)	1	—
Other hair-coloring preparations (59)	3	—
Foundations (319)	1	—
Lipstick (942)	1	—
Other makeup preparations (186)	1	—
Body and hand skin care preparations (excluding shaving) (827)	3	—
Paste masks (mud packs) (269)	1	—
2001 totals for Acacia	33	—
Acacia Senegal Gum		
Eyebrow pencil	—	1
Eyeliner	—	3
Mascara (187)	1	3–9
Powders (dusting and talcum; excluding aftershave talc)	—	0.5
Tonics, dressings, and other hair grooming aids	—	0.0001
Other skin care preparations	—	0.02
2001 totals for Acacia Senegal Gum	1	—
Acacia Senegal Gum Extract		
Bath soaps and detergents	—	0.001
2001 totals for Acacia Senegal Gum Extract	—	—

and the liver was removed and analyzed for glycogen content. The difference in glycogen concentration between control and fed rats was insignificant. Therefore, it was concluded that the gum arabic molecule was not metabolized by enzymes of the rat digestive tract (Informatics Inc. 1972; FASEB 1973).

Other studies have indicated that gum arabic is partially digested in the rat. In one study, weight gain and feed efficiency were determined using groups of six rats fed 15% gum arabic for 62 days. Feed efficiency was identical between experimental and control groups. However, compared to the control group (mean weight gain = 199 g), rats fed gum arabic had a mean weight gain of 224 g. In another study, groups of five rats were pair-fed gum arabic (0.75 g/day; added to 5 g basal diet). Results indicated that the digestibility of gum arabic was 71% (Informatics Inc. 1972).

Ross et al. (1984b) evaluated the metabolism of gum arabic using albino Wistar male rats (3 months old; weights = 350 g). The number of animals used in the study was not stated. Two groups of animals were fed Oxoid breeders diet only and Oxoid breeders diet plus 200 g gum arabic/kg ad libitum, respectively, for 4 weeks. Oxoid breeders diet was described as a reconstituted diet that allowed the ready incorporation of gum arabic into pellet form.

Feces were collected during the 24 h period before animals were killed. Following ad libitum overnight feeding, the animals were killed using a combination of diethyl ether anesthesia and cervical dislocation and contents from the stomach, small bowel, cecum, and distal colon were removed.

For rats fed gum arabic in the diet, a white flocculent precipitate typical of gum arabic was detected in contents from the stomach and small intestine, but not from the cecum, distal colon, or in the feces. The fact that precipitable gum arabic was detected along the gastrointestinal (GI) tract as far as the terminal ileum, but not in the cecum, suggests that the metabolism of gum arabic is mediated by bacteria in the cecum.

In animals in which the cecum was resected, precipitable gum arabic was detected along the length of the entire residual intestine. This observation suggests that in the absence of the bacterial mass resident in the cecum, there is no degradation of gum arabic. No precipitate typical of gum arabic was found in

the GI tract of control rats that received the Oxoid breeders diet only (Ross et al. 1984b).

A total caloric intake slightly greater than that for starch has been reported for gum arabic in rabbits. Evidence of glycogenesis was also demonstrated in this study. Thus, it appears that rabbits are able to utilize gum arabic (FASEB 1973).

In a study involving guinea pigs, it was determined that gum arabic was highly digestible (90%) when administered in the diet at a concentration of 15% for 10 days (Informatics 1972).

Results of studies in which dogs and rabbits were injected intravenously with gum arabic indicated that gum arabic or some other product associated with it accumulated in the liver and remained in the tissues for several months. Nonlethal effects included serious disturbances in hemoglobin, white blood cells, and serum proteins (FASEB 1973).

Using many of the studies summarized above, the Select Committee on GRAS Substances determined in 1973 that gum arabic can be digested to simple sugars. However, it was also determined that conclusive evidence indicating that the intact gum arabic molecule is absorbed under normal conditions was lacking (FASEB 1973). It should also be noted that data on the fate of undigested gum arabic in male rats (Ross et al. 1984b) have been published since the FASEB report was issued. The results of this previously summarized study suggest that the bacterial mass resident in the cecum is responsible for the metabolism of gum arabic.

Hypotensive Activity

Acacia (Not Gum Arabic)

Sham et al. (1984) evaluated the hypotensive activity of *Acacia catechu* (aqueous extract of branches) using four groups of four anesthetized dogs (males and females; weights = 8 to 12 kg). The right femoral artery and vein were cannulated for blood pressure recordings and intravenous injection. After a 30-min equilibration period, *Acacia catechu* was injected (bolus injection) into dogs from each of the four groups. Doses ranged from <1 to ~ 2 mg/kg. Changes in mean arterial blood pressure (MAP) were recognized as differences between the steady MAP before injection and the lowest MAP after injection.

The results were presented as a log dose-response curve. *Acacia catechu* induced dose-related hypotensive responses. At high doses, the hypotensive effect lasted approximately 30 min. Based on experimentation with various blocking agents, it was determined that this effect was not mediated through α- and β-adrenergic, cholinergic, or histaminergic receptors, or related to autonomic ganglion transmission.

The hypotensive activity of *Acacia catechu* (aqueous extract of branches) was also evaluated using four groups of five male Sprague-Dawley rats (weights between 170 and 250 g) according to the procedure in the preceding paragraph; however, in this experiment, the left carotid artery and jugular vein were cannulated.

Acacia catechu induced dose-related hypotensive responses in rats over the range of doses tested (1 to 2 mg/kg). It was also determined that the hypotensive responses were not mediated through α- and β-adrenergic, cholinergic, or histaminergic receptors, or related to autonomic ganglion transmission (Sham et al. 1984).

These same authors reported that, in an in vitro experiment, *Acacia catechu* induced a dose-dependent relaxation of helical strips of rat tail artery that had been preconstricted with the vasoconstrictors arginine vasopressin and methoxamine, respectively. In the presence of arginine vasopressin, *Acacia catechu* was tested at concentrations of 0.01, 0.03, and 0.1 mg/ml. *Acacia catechu* was tested at concentrations of 0.1, 0.3, and 1 mg/ml in the presence of methoxamine (Sham et al. 1984).

Hypocholesterolemic Activity

Acacia (Not Gum Arabic)

Chaudhari and Hatwalne (1973) determined the hypocholesterolemic activity of the dried water extract of *Acacia catechu*, also known as katha in India. They used three groups of 10 male albino rats (weights = 100 to 125 g). One group was fed stock diet thoroughly mixed with 1% cholesterol, and a second group was fed stock diet thoroughly mixed with 1% cholesterol plus 0.2% katha. The control group was fed stock diet only. The diets were fed ad libitum. Half of the animals in each group were killed after 6 weeks of feeding, and the remaining animals were killed after 12 weeks of feeding. The cholesterol content of the serum and liver was determined for each rat.

A progressive increase in serum and liver cholesterol content was observed in animals fed the stock diet supplemented with cholesterol for 6 months. In animals fed stock diet supplemented with cholesterol and katha for 6 months, the elevation of serum and liver cholesterol levels was significantly lower ($p = .001$) when compared to rats fed stock diet supplemented with cholesterol.

However, at the end of 12 weeks, the increase in serum and liver cholesterol concentrations in rats fed stock diet supplemented with cholesterol and katha was elevated by approximately 50% when compared to rats fed stock diet supplemented with cholesterol only. It was also determined that there was substantially less deposition of lipids in the liver of katha-fed rats. It was concluded that katha had hypocholesterolemic activity in this study, and that it helped prevent fatty degeneration of the liver (Chaudhari and Hatwalne 1973).

Hypoglycemic Activity

Acacia (Not Gum Arabic)

Wassel et al. (1992) studied the hypoglycemic activity of ethanolic extracts of the pod, leaf, stem, old stem, and flower of *Acacia farnesiana L. Willd* using groups of 11 alloxanized diabetic albino rats (weights = 150 to 200 g). To prevent the development of fatal hypoglycemia during the first 12 h after alloxan administration, a 25% glucose solution (5 to 10 ml) was subcutaneously injected at 2 to 3 h intervals. Extract from each plant part (dose = 30 or 50 mg/kg in polysorbate 80) was administered orally to a group of 11 rats, and blood samples were taken at 2 h post administration. Blood samples were collected

prior to treatment in order to estimate the normal blood glucose level of fasting rats.

The hypoglycemic activity of ethanolic extracts of *Acacia farnesiana* stem and pod was considerable following the administration of a 50 mg/kg dose. *Acacia farnesiana* stem and pod caused 21% and 36% reductions in the normal fasting blood sugar level, respectively (Wassel et al. 1992).

Effects on Smooth Muscle

Acacia (Not Gum Arabic)

Wassel et al. (1992) also studied the effect of ethanolic extracts of the pod, leaf, stem, old stem, and flower of *Acacia farnesiana L. Willd* on uterine motility. Rat uteri at various stages of the estrous cycle were suspended in 50-ml baths containing oxygenated Krebs solution; uteri were equilibrated in the solution for at least 90 min. Drugs were added to the water bath and were retained until the highest contraction was achieved.

Normal rhythmic contractions of the isolated uteri were first recorded using a T_2 isotonic transducer and two channel MD_2 oscillograph. Subsequently, the plant extracts (in polysorbate 80) were added to organ water baths at a dose of 50 or 75 mg/50 ml bath. The drug used to induce uterine contraction was then removed by washing the preparation with fresh Krebs solution.

Most of the *Acacia farnesiana* ethanolic extracts stimulated uterine muscular contraction during the estrous cycle and pregnancy. However, some of the extracts had a stimulatory effect on uterine contraction, followed by inhibition (i.e., leaf extract on non-estrus uteri and pod extract on pregnant uterus). The stem extract of *Acacia farnesiana* inhibited contraction of the pregnant uterus (Wassel et al. 1992).

Trivedi et al. (1986) evaluated the bronchodilator activity of *Acacia farnesiana* using the perfused, isolated guinea pig lung. The control guinea pig lung preparation was treated with saline. The unripe pods of *Acacia farnesiana* were collected and dried at room temperature. The glycosidal fraction of the ethyl alcohol extract of coarsely powdered Acacia pods was then isolated, and an aqueous solution of this fraction was tested.

Doses of 2, 5, and 10 μg of the aqueous solution increased outflow in the isolated lung perfusion preparation, indicating that the glycosidal fraction induced a smooth muscle relaxant effect. The same doses also increased outflow following histamine (10 μg)-induced contraction, and the bronchodilator effect was not blocked by propranolol (400 μg). These results suggested that the glycosidal fraction exerted a direct relaxant action on the bronchial muscles. The investigators noted that this effect is not mediated through β-adrenergic receptors.

The vasodilator activity of *Acacia farnesiana* was evaluated in vitro. The glycosidal fraction of the ethyl alcohol extract of coarsely powdered Acacia pods was isolated, and an aqueous solution of this fraction was tested. The hind limb of dogs was perfused through the femoral artery with oxygenated, defibrinated blood in Ringer's solution. Femoral venous outflow was recorded periodically. The control preparation was treated with normal saline.

The aqueous glycosidal fraction induced vasodilation at doses of 2, 5, and 10 μg (% increases in blood flow/min of 21.4, 20.86, and 24.3, respectively; $n = 5$). Vasodilation was not blocked following the addition of any of the following agents: chlorphenaramine maleate (20 μg), atropine (20 μg), or propranolol (400 μg). Study results indicated that the glycosidal fraction of *Acacia farnesiana* had a smooth muscle relaxant effect. The investigators noted that this effect was not mediated through cholinergic or H_1 receptors (Trivedi et al. 1986).

Anti-Inflammatory Activity

Acacia (Not Gum Arabic)

The anti-inflammatory activity of *Acacia farnesiana* was evaluated in vitro. The glycosidal fraction of the ethyl alcohol extract of coarsely powdered Acacia pods was isolated, and an aqueous solution of this fraction was tested. The effect of this fraction on chemically induced edema of the rat hind paw was evaluated according to the method of Winter et al. (1962). The glycosidal fraction inhibited carrageenin and formaldehyde induced inflammation of the rat hind paw in vivo (% inhibition of 38.2 and 26.26, respectively; $p < .001$, $n = 10$). It was concluded that this fraction has a promising anti-inflammatory effect (Trivedi et al. 1986).

Oxidative Phosphorylation

Gum Arabic

Bachmann et al. (1978) administered gum arabic twice daily to groups of four rats (weights = 100 to 110 g) at concentrations of 1%, 2%, and 10%, respectively, 5 days per week for 4 weeks. The test substance was suspended in distilled water and administered orally at a dose volume of 0.2 ml/100 g body weight; control rats were given equal volumes of distilled water. The actual doses of gum arabic administered were 2×20, 2×40, and 2×200 mg/kg/day. Groups of four rats were killed by cervical dislocation 16 h after administration of the last dose. Following maceration and homogenization, heart and liver mitochondria were isolated by differential centrifugation. Electron transfer reactions (oxygen consumption) and oxidative phosphorylation were measured polarographically. The hydroxylation of biphenyl was chosen as the assay system for measuring mixed function oxidases of hepatic cell endoplasmic reticulum.

Dose-dependent uncoupling of oxidative phosphorylation was the primary effect on cardiac and hepatic cell mitochondrial function. The damage to cardiac mitochondria progressed as dosing continued. However, hepatic cell mitochondrial function seemed to have gradually returned to normal during the fourth week of dosing.

At the highest administered dose (2×200 mg/kg/day) marked uncoupling of oxidative phosphorylation was observed in the heart and liver after 2 days of dosing. Partial recovery was reported for cardiac mitochondria after the first week of dosing; however, the same degree of uncoupling was noted up to the end of the experiment. Hepatic cell mitochondria were said to have recovered slowly as the experiment progressed. Gum arabic also

caused a progressive inhibition of the biphenylhydroxylase system in the hepatic microsomal fraction (Bachmann et al. 1978).

Lutz et al. (1978) considered these results and investigated whether comparable biochemical effects of gum arabic (USP grade) could also be demonstrated in vivo. The measurement of maximal aminopyrine demethylation as expired CO_2 was deemed a suitable approach for this investigation, which was conducted using female rats of the ZUR SIV-Z strain (weights = 152 to 180 g). Oral dosing with 10% (w/v) gum arabic had no effect on the in vivo demethylation of 4-dimethyl[^{14}C]-aminoantipyrine (Lutz et al. 1978).

Antimicrobial Activity

Acacia (Not Gum Arabic)

The antimicrobial activity of ethanolic extracts of plant organs from *Acacia farnesiana* was evaluated. Extracts were made from the following plant parts: the pod, leaf, stem, old stem, and flower. Bacteria and yeast were cultured and filter paper disks were impregnated with 10 μl of each extract. Each disk (one extract per disk) was then dried and placed on the surface of the inoculated agar medium, and cultures were incubated for 48 h and observed for zones of inhibition. All plant extracts were inhibitory to *Bacillus subtilis* and *Staphylococcus aureus.* Additionally, most of the extracts were inhibitory to *Sarcina lutea*, *Pseudomonas aeruginosa*, and *Escherichia coli*. The plant extracts had no effect on *Mycobacterium phlei* or *Candida albicans* (Wassel et al. 1992).

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Gum Arabic

In an acute oral toxicity study using rabbits (weights and strain not stated), an Acacia Gum LD_{50} of 80 g/kg was reported (Dangerous Properties of Industrial Materials Report 1981).

Acacia (Not Gum Arabic)

Letizia et al. (2000) conducted a study in which the acute oral toxicity of Acacia Farnesiana Extract (from flowers) was evaluated using ten rats (strain not stated). The test substance was administered at a dose of 5.0 g/kg, and animals were observed for 14 days. Necropsy was performed at the end of the observation period.

An LD_{50} of greater than 5.0 g/kg was reported. Signs observed in animals during the study included chromorhinorrhea in five or more animals and isolated instances of the following: tachypnea, chromodacryorrhea, ptosis, lethargy, piloerection, emaciation, ataxia, and respiratory noise. Necropsy findings for the only animal that died included abnormalities of the lungs, kidneys, liver, spleen, and gastrointestinal tract (Letizia et al. 2000).

The Societe Bertin (1987) reported an acute oral toxicity study in which Cire Essentielle Cassie (trade name for Acacia Farnesiana Flower Wax) was evaluated using groups of five rats (males and females) of the OFA Sprague-Dawley IOPS strain. Mean weights for male and female test animals were 219.60 g and 183.60 g, respectively. Control mean weights were 224.0 g (males) and 183.80 g (females). The animals were all approximately the same age (ages not stated). A single 10 ml/kg dose of the product was administered orally to each animal, and followed by a 14-day observation period. Control animals were dosed with corn oil (10 ml/kg). The animals were killed at the end of the observation period and necropsy performed.

Significant changes in general condition (weight changes included) or behavior between test and control animals were not observed. None of the animals died and no test substance-related organ lesions were observed. The test material was classified as innocuous at the dose administered (Societe Bertin 1987).

Biogir S.A. Conseil Recherche (1990a) also reported the acute oral toxicity of Cire Essentielle de fleurs de Mimosa (trade name for Acacia Dealbata Leaf Wax) in a suspension with paraffin oil using five male (178.3 $\pm$ 9.8 g) and five female (172.8 $\pm$ 5.9 g) rats of the OFA Sprague-Dawley strain (SPF). The animals were 2 months old. A single oral dose of 2 g/kg (10 ml/kg) of the product was administered to each animal by gavage, and dosing was followed by a 14-day observation period. Feeding resumed at 4 h post dosing. At the end of the observation period, the animals were killed and gross necropsy performed.

Weight gain was described as normal and no deaths were reported. Additionally, none of the animals had overt signs of central nervous system or neurovegetative system toxicity, and no lesions of organs examined were noted at necropsy. The minimal lethal dose was greater than 2 g/kg (Biogir S.A. Conseil Recherche 1990a).

Acute Dermal Toxicity

Acacia (Not Gum Arabic)

The acute dermal toxicity of Acacia Farnesiana Extract (from flowers) was evaluated using 10 rabbits (strain and weights not stated). A single dose of 5.0 g/kg was administered dermally to each animal, and observations were made over a period of 14 days. Gross necropsy was performed at the end of the observation period. Signs observed during the study were as follows: isolated instances of lethargy, diarrhea, ptosis, and nasal discharge (yellow). Gross observations at necropsy were normal for each animal. An LD_{50} of greater than 5.0 g/kg was reported (Letizia et al. 2000). Skin irritation reactions observed in this study are included in the section on Skin Irritation later in the report text.

Acute Intraperitoneal Toxicity

Gum Arabic

In a study using dogs (number and weights not stated), the intraperitoneal injection of 4.8 g/kg gum arabic did not induce toxicity. However, the same dose killed dehydrated dogs (highest no-effect level = 1.9 g/kg) (FASEB 1973).

Short-Term Oral Toxicity

Gum Arabic

Informatics Inc. (1972) reported a study in which diets containing Gum Arabic were fed to 133 guinea pigs. Except for one diet containing 20% gum arabic, all of the diets contained 15% gum arabic. The animals were fed for periods ranging from three to nine weeks. No toxic effects resulted from the administration of gum arabic.

Groups of rats (number and weights not stated) were fed 15% gum arabic in the diet for 62 days. A cathartic effect was noted. Weight gain, feed efficiency, hematological findings, and organ weights were normal (World Health Organization 1974).

Anderson et al. (1984) fed three groups of three male Albino Wistar rats (weights = 140 to 160 g) diets containing 1%, 4%, and 8% (w/w) gum arabic (Acacia Senegal Gum), respectively, daily for 28 days. A fourth group served as the negative control. At necropsy, hepatic and cardiac tissues were obtained for electron microscopy and microsomal P-450 assays.

No discernible ultrastructural differences were observed between the livers of test (all dietary groups) and control rats; particularly, the mitochondria were normal. Also, no discernible ultrastructural differences were found between the hearts of test (all dietary groups) and control rats. Particularly, both the appearance and concentration of the mitochondria and myofibrils were identical in this comparison. The results of assays of hepatic microsomal protein and cytochrome P-450 for each dietary group indicated that gum arabic did not cause inductive effects. The investigators noted that when induction by active agents (e.g., phenobarbitone) takes place, cytochrome P-450 values are increased by several-fold within a few days (Anderson et al. 1984).

Anderson et al. (1986) fed 10% (w/w) gum arabic (Acacia Senegal Gum) daily for 45 days to Wistar albino rats (99 to 120 g). The number of rats in the study was not stated. The rats were then killed by cervical dislocation while under ether anesthesia. Portions of the jejunum, ileum, and cecum were excised and the ultrastructure of each was evaluated using transmission electron microscopy.

No abnormalities in organelles were observed within cells of the jejunum, ileum, or cecum of rats fed gum arabic. Additionally, neither inclusions nor other pathological changes were detected. It was concluded that no significant ultrastructural differences occurred between experimental and control rats (Anderson et al. 1986).

Cook et al. (1992) evaluated the oral toxicity of gum arabic (Acacia species not stated) using 3-week-old Sprague-Dawley rats (16 males, 16 females). Three days before dosing, mean body weights were 122 g and 125 g for males and females, respectively. The animals were fed gum arabic (dose not stated) daily for 28 days and then killed by exsanguination. Blood samples were obtained for hematological examination and serum analysis the day before animals were killed. Microscopic examination of most organs was performed, which included examination of any tissues that appeared abnormal.

No treatment-related behavioral effects were noted. All values for serum chemistry parameters were within the normal limits for laboratory rats. Mean red blood cell volume values were said to have been within the normal range for Sprague-Dawley rats. No toxicologically significant lesions were noted at microscopic examination (Cook et al. 1992).

Short-Term Intravenous Toxicity

Gum Arabic

Acacia (Gum Arabic) was administered intravenously to three dogs (weights not stated) over a period of 76 days. The number of intravenous injections ranged from 32 to 35 over this period, and the range for the total cumulative dose was 15.7 to 47.7 g/kg. An enlarged liver was observed in the dog that received the greatest cumulative dose; death occurred four months after the last injection. The cause of death was not stated. The remaining two dogs remained in good condition. The results of biopsies performed on the two animals indicated that Acacia was present in the liver 26 months after the last injection (World Health Organization 1974).

In another study, gum arabic was administered intravenously to dogs (number and weights not stated) over a period ranging from 1 to 84 days. Doses ranged from 1 to 2 g/kg. Enlarged livers and swollen kidneys were the most characteristic changes. Similar doses were fatal when administered to two rabbits (weights not stated) (FASEB 1973).

Subchronic Oral Toxicity

Gum Arabic

Anderson et al. (1982) evaluated the subchronic oral toxicity of gum arabic (Acacia Senegal Gum) in two experiments using albino Wistar rats (24 to 28 days old). Body weights prior to initiation of the study were not included.

In the first experiment, groups of 15 male rats were fed gum arabic at concentrations of 0.91% (dietary level = 0.53 g/kg/day), 2.0% (1.08 g/kg/day), 4.3% (2.55 g/kg/day), and 8.6% (5.22 g/kg/day), respectively, for 13 weeks. Groups of 15 female rats were fed concentrations of 0.75% (0.5 g/kg/day), 1.7% (1.05 g/ kg/day), 3.7% (2.6 g/kg/day), and 7.5% (5.31/g/kg/day), respectively. Fifteen males and 15 females served as controls.

In the second experiment, 15 male rats were fed gum arabic at an average concentration of 18.6% (14 g/kg/day) for 13 weeks. Fifteen female rats were fed an average concentration of 18.1% (13.8 g/kg/day). The two control groups consisted of 15 males and 15 females, respectively. Urine and blood samples were obtained during the study. The animals were killed under anesthesia by cervical dislocation at the end of the treatment period and prepared for necropsy.

The results for the two experiments included the reported deaths of two control female rats. Growth rates were not reduced for male or female rats at dietary doses up to 5 g/kg/day (~8.5% gum arabic in diet). At a concentration of approximately 18% in the diet (14 g/kg/day), male rats had a reduced growth rate and

smaller final body weight ($p < .01$). The average weight gain for male rats was 78% of that of controls.

Following the ingestion of gum arabic, 5 g/kg/day, by male rats, kidney weights (absolute and relative to body weight) were reduced ($p < .05$). At the highest dietary doses tested (~18%, 14 g/kg/day), kidney weights for male and female rats were significantly reduced ($p < .01$). Liver weight was reduced in a dose-dependent manner in male rats; the difference between experimental and control groups was not significant at doses of gum arabic less than 5 g/kg/day. No significant differences were observed in urine volume or composition between control and test groups at any of the dietary concentrations of gum arabic tested.

Similarly, no significant hematological changes were observed between test and control groups. At microscopic examination, no alterations were found that were attributable to the ingestion of gum arabic. The only treatment-related alteration noted at necropsy was cecal enlargement in rats of the highest-dose groups (Anderson et al. 1982).

In another study, Anderson et al. (1984) fed four groups of five male albino Wistar rats (weights = 40 to 60 g) diets containing 0.5%, 1.5%, 2.5%, and 3.5% (*w*/*w*) gum arabic (Acacia Senegal Gum), respectively, daily for 91 days. A fifth group served as the negative control. At the end of the feeding period, the animals were killed by cervical dislocation for necropsy. Samples of liver and heart from each treatment group were obtained for transmission electron microscopy. Livers from the remaining rats (two per group) were used for assays of microsomal protein and cytochrome P-450.

Electron microscopic findings for cardiac muscle included no abnormality of myofilaments, no depletion of glycogen reserves, no abnormality of the intracytoplasmic mitochondria or endoplasmic reticulum, no excessive infiltration with lipid, and no evidence of interstitial infiltration. Additionally, no abnormalities were observed with respect to the size, chromatin content, or nucleoli of nuclei. Electron microscopic findings for the liver included no abnormalities in hepatocytes, Kupffer cells, or lining cells of the biliary passages. The mitochondria and nuclei were normal both in appearance and internal structure, and no abnormalities were observed in intracytoplasmic glycogen stores (Anderson et al. 1984).

Skin Irritation

Acacia (Not Gum Arabic)

In an acute dermal toxicity study, Acacia Farnesiana Extract (from flowers) was administered dermally (single dose of 5.0 g/kg) to 10 rabbits, after which animals were observed for 14 days. On day 1, moderate erythema and moderate edema were observed in all ten rabbits (Letizia et al. 2000).

Biogir S.A. Conseil Recherche (1990b) evaluated the skin irritation potential of Cire Essentielle de fleurs de Mimosa (trade name for Acacia Dealbata Leaf Wax) using six New Zealand albino rabbits. The undiluted product (volume = 0.5 ml on an occlusive patch) was applied to scarified skin (clipped free of hair) of the right flank of each animal. The left flank (nonscarified skin) of each animal served as the control. Each patch was secured with a hypoallergenic, microporous adhesive strip and an elastic band (fixed with adhesive tape) that was wrapped around the trunk. Patches were removed after 24 h of contact.

At 24 h and 72 h post application, reactions were scored according to the following grading scales: 0 (no erythema) to 4 (severe erythema [crimson red] with or without eschar [deep injuries] and lesions showing a serious cutaneous reaction such as a burn, a necrosis) and 0 (no edema) to 4 (severe edema [more than 1 mm thick and extending beyond the area of exposure] showing a serious cutaneous reaction such as a burn). Scores for erythema and edema (intact and scarified skin) were determined at 24 and 72 h post application. The scores (intact and scarified skin) obtained were added together and divided by 24 to calculate the primary cutaneous irritation index.

Cire Essentielle de fleurs de Mimosa (Acacia Dealbata Leaf Wax) was classified as a nonirritant (primary irritation index = 0.5) in New Zealand albino rabbits (Biogir S.A. Conseil Recherche 1990b).

Bertin Laboratories (1987) reported on a study in which the skin irritation potential of Cire Essentielle Cassie (Acacia Farnesiana Flower Wax) was evaluated using six New Zealand rabbits. The test substance (in pure form, 0.5 ml under occlusive pad) was applied to intact and scarified skin of the right and left flank, respectively, that had been clipped free of hair. A stretch bandage was then wound around the torso of each animal and secured with adhesive tape. Patches were removed at 24 h post application. Reactions were scored at 24 and 72 h post application according to the following grading scales: 0 (no erythema) to 4 (serious erythema [purple red] with slight scarring [deep lesions] and 0 (no edema) to 4 (serious edema [over 1 mm thick] with a surface area greater than 1 mm^2).

At 24 h, reactions at intact sites were described as somewhat pronounced erythema (2 rabbits [slight erythema, score = 1]; 1 rabbit [highly visible erythema, score = 2]). Very slight edema (score = 1, intact site) was also noted in the rabbit with highly visible erythema. Identical results were reported for scarified skin sites. At 72 h, reactions were observed in one rabbit; slight erythema and very slight edema were observed at intact and scarified sites. Cire Essentielle Cassie (Acacia Farnesiana Flower Wax) was classified as a slight skin irritant (primary cutaneous irritation index = 0.6) (Bertin Laboratories 1987).

Phototoxicity

Acacia (Not Gum Arabic)

The phototoxicity of a 20% solution of Acacia Farnesiana Extract (from flowers) in methanol was evaluated using six SKH:hairless mice. The test substance was applied to a 5-cm^2 area on the back of each animal. At 30 min post application, test sites were irradiated with UV light for 1 h. The light source consisted of a bank of six fluorescent, black light lamps positioned

at a distance of 35 cm, or an Atlas xenon lamp (model Rm 60 or 65 [wavelength: 280 to 320 nm] with a Schott WG320 filter) positioned at a distance of 1 m. Reactions were scored at 4, 24, 48, 72, and 96 h post exposure. No phototoxic effects were observed (Letizia et al. 2000).

Immunological Responses

Studies on immunological responses to gum arabic and Acacia solution/extract are summarized in Table 9.

Acacia (Not Gum Arabic)

Maytum and Magath (1932) reported a series of three experiments that evaluated the allergenicity of an Acacia solution (exact composition not stated). In the first experiment, six rabbits (12 weeks old) were injected intravenously with 50 cc Acacia, and this dose was repeated 5, 12, and 17 days later. At 4 weeks after the last injection, each rabbit was injected intravenously with 2 cc of Acacia.

The rabbits appeared normal during a 1-h observation period following this injection. On the same day, one of the rabbits was injected intravenously with 2 cc of a 50% egg white solution to determine whether exposure to a foreign protein would result in greater sensitivity to Acacia. Acacia (2 cc) was injected intravenously 3 weeks later, and then 3 weeks after this injection at a dose of 15 cc. No signs of anaphylaxis were observed in this animal (Maytum and Magath 1932).

In the second experiment, eight guinea pigs (weights = 300 g) were injected intraperitoneally with a dose of 10 cc, and this dose was repeated 5, 12, and 17 days later. At four weeks after the last dose, two of the animals were injected intravenously with 0.5 cc Acacia.

Typical anaphylactic signs (sneezing and coughing, scratching the nose, and dyspnea) were noted in both guinea pigs after approximately 30 s. The two animals died approximately 3 min after signs were first noted. Two other guinea pigs were injected intracardially with Acacia solution (0.5 cc; exact composition not stated), after which both had milder signs of anaphylaxis. One animal recovered, and the other died after 1 h. The remaining four guinea pigs each received an intraperitoneal injection of Acacia solution (0.5 cc). Mild reactions were noted in two of the animals, and no signs were reported for the remaining two.

A follow-up third experiment was performed to determine whether the guinea pig deaths reported were due to the intravenous method of test substance administration in the second experiment. Four guinea pigs were injected intravenously with 0.5 cc Acacia solution (exact composition not stated), and no deleterious effects were noted. Acacia solution (10 cc) was administered intraperitoneally to eight guinea pigs; four of the animals died within five days after injection.

Seven days later, intraperitoneal injections of Acacia solution (10 cc) were given to the four remaining guinea pigs (from second experiment) that were injected intraperitoneally, the four guinea pigs that were injected intravenously in the first experiment, and four new guinea pigs. Of the four new guinea pigs, two died from peritonitis within 4 days.

Seven days after intraperitoneal injection, the remaining 10 animals from the third experiment were injected intraperitoneally with 10 cc Acacia. Four of the 10 died of peritonitis on the next day. It was stated that Acacia was capable of inducing peritonitis (followed by death) only after intraperitoneal administration.

In total, these authors reported on the results of studies involving a total of 19 guinea pigs (8 guinea pigs from preceding experiment included) that include sensitization induced by Acacia solution (administered parenterally; exact composition not stated) and no anaphylactic signs developed in seven of the animals.

Mild and moderate anaphylactic signs developed in four and three guinea pigs, respectively, and severe signs were noted in two guinea pigs. Three of the 19 guinea pigs died. In addressing the results from the preceding experiments, the investigators noted that anaphylactic sensitivity to Acacia can develop under certain unusual conditions. It was also stated that no danger was associated with an initial dose of Acacia if the solution was properly prepared; however, subsequent doses administered after at least 3 weeks should be given cautiously because of the possibility of anaphylactic reactions (Maytum and Magath 1932).

Aronson and McMaster (1972) sensitized 12 guinea pigs (strain not stated; weights $\approx$ 300 g) via single intra-abdominal injections of 600 mg Acacia (6% solution, 10 ml; composition of solution and Acacia species not stated). The animals were challenged 1 month later with an intravenous injection of 60 mg of the sensitizing sample or other samples of Acacia.

The nonnecrotizing toxicity of Acacia extract was evaluated using germ-free and conventional guinea pigs of the Hartley strain. The ages of the germ-free animals tested were as follows: group A (12 animals, 8 days old), group B (9 animals, 3 weeks old), and group C (6 animals, 12 weeks old). The test substance (40 mg/ml) was suspended in phosphate buffer (pH 7.4, 0.1 M) and applied topically to the cornea of the right eye; phosphate buffer was applied to the cornea of the left eye. For both substances, one drop was applied every half hour for a total of seven applications.

The following three groups of conventional guinea pigs were also treated according to the same procedure: group 1 (six animals, 8 days old), group 2 (seven animals, 12 weeks old), and group 3 (two animals, 7 months old). All animals were killed 30 min after application of the last drop. Additionally, phosphate buffer was instilled into both eyes of two animals (killed when 8 days old), and the same was true for two other animals (killed when 3 weeks old). The eyes were enucleated immediately after all animals were killed. The animals were bled prior to killing, and serum samples were subsequently obtained for determination of antibody or y-globulin. At microscopic examination, a severe inflammatory response was observed in both germ-free and conventional 8-day-old guinea pigs.

TABLE 9
Immunological responses

Test substance	Animals tested	Test procedure	Results	Reference
Acacia solution	6 rabbits (12 weeks old)	Four i.v. injections (50 cc) on days 0, 5, 12, and 17, followed by single i.v. injection (2 cc) 4 weeks after fourth injection	No signs of anaphylaxis	Maytum and Magath 1932
Acacia solution	8 guinea pigs (weights = 300 g)	Four i.p. injections (10 cc) on days 0, 5, 12, and 17 followed by single i.v. injection (0.5 cc) 4 weeks after fourth injection	Anaphylactic signs (sneezing, coughing, dyspnea) in 8 animals; 2 deaths. Milder signs noted in 2 surviving animals injected intracardially (0.5 cc); 1 died. Mild signs also in 2 of remaining 4 survivors injected intraperitoneally (0.5 cc). In a follow-up experiment involving guinea pigs, it was concluded that Acacia was capable of inducing peritonitis (followed by death) regardless of the route of administration, i.p. or i.v.	Maytum and Magath 1932
Acacia solution	19 guinea pigs (8 guinea pigs in preceding study included)	Parenteral administration	No anaphylactic signs (10 animals); mild and fairly severe anaphylactic signs in 4 and 3 animals, respectively; extremely severe signs in 2 animals; 3 of 19 died	Maytum and Magath 1932
Anti-Gum Acacia rabbit serum	5 guinea pigs (weights = 300 to 450 g)	Passive sensitization with 2 ml of serum (i.p. injection), followed by i.v. dose of a homologous gum (1 mg)	3 animals died at 2 to 3 min post injection. The remaining 2 recovered from anaphylactic shock slowly	Partridge and Morgan 1942
7% Gum Acacia solution	Two groups of 10 guinea pigs (weights = 600 to 1000 g)	Injected subcutaneously (5 ml) repeatedly over 7-week period. After 2 weeks of dosing, animals injected with 1 ml *Brucella abortus* vaccine	No deleterious effects on antibody production resulted, as judged by the development of agglutinative and complement-fixing activity in the serum to *Brucella abortus*	Rice 1954a
7% Gum Acacia solution	4 rabbits (weight range = 1800 to 2650 g)	Injected subcutaneously (10 ml) repeatedly over 4-week period. Injected with *Brucella abortus* vaccine 4 days (2 ml) and 8 days (3 ml) later	No deleterious effects on antibody production resulted, as judged by the development of agglutinative and complement-fixing activity in the serum to *Brucella abortus*	Rice 1954a

(Continued on next page)

TABLE 9
Immunological responses *(Continued)*

Test substance	Animals tested	Test procedure	Results	Reference
7% Gum Acacia solution	Two groups of 10 guinea pigs	Group1: Injected subcutaneously (5 ml) repeatedly over 16-day period. Actively sensitized after seven doses and challenged in 3 weeks Group 2: Received 11 subcutaneous injections. Passively sensitized and challenged 48 h later	Group 1: One animal with signs of asphyxia; 8 animals with shock signs; 2 died Group 2: Typical respiratory signs developed; no deaths Both groups: No significant decline in serum-complement activity	Rice, 1954b
7% Gum Acacia solution	Two groups of 10 guinea pigs	Group1: Injected subcutaneously (5 ml) repeatedly over 16-day period. Actively sensitized after seven doses and challenged in 3 weeks Group 2: Received 11 subcutaneous injections. Passively sensitized and challenged 48 h later	Group 1: One animal with signs of asphyxia; 8 animals with shock signs; 2 died Group 2: Typical respiratory signs developed; no deaths Both groups: No significant decline in serum-complement activity	Rice 1954b
6% Acacia solution	12 guinea pigs (weights = 300 g)	Twelve animals sensitized via single intra-abdominal injections of 600 mg Acacia (6% solution, 10 ml). Challenged 1 month later with i.v. injection of solution or other samples of Acacia. Two additional guinea pigs tested subsequently with Acacia from different lot	Twelve animals with anaphylactic shock; 10 died. Two additional guinea pigs sensitized by intra-abdominal injection of 160 mg Acacia with Freund's adjuvant (2 ml of emulsion containing two parts 20% Acacia), followed by i.v. challenge with 60 mg Acacia 1 month later, died of anaphylactic shock	Silvette et al. 1955
Three grades of Gum Arabic (dissolved in 0.15 M NaCl at concentration of 4 mg/ml). One of the grades was derived from food grade gum arabic	Groups of 6 to 8 female CBA mice (6 weeks old)	Mice immunized by injection of the antigen (0.1 mg in 0.05 ml Freund's adjuvant) into footpad. Delayed-type hypersensitivity measured 21 days after primary immunization	Compared to controls, no significant increase in footpad thickness. Antigen-specific hypersensitivity reaction noted for all three grades of gum arabic	Strobel et al. 1982

Gum Arabic (dissolved in 0.15 M saline at concentration of 400 mg/ml)	Two groups of 8 female BDF1 [(C57BL/6] × DBA/2 F_1] mice (6 to 8 weeks old)	Initially dosed with Gum Arabic (80 mg) by intragastric administration. Mice then immunized by injection of 100 μg gum arabic in saline and complete Freund's adjuvant into hindpaw. Delayed hypersensitivity measured at 3 weeks post immunization	Compared to controls, footpad swelling significantly suppressed. Systemic immunological hyporesponsiveness (oral tolerance) developed in mice fed gum arabic	Strobel and Ferguson 1986
Five different samples of Gum Arabic (*Acacia senegal*)	5 groups of 6 to 8 male [(C57BL/6J] × DBA/2 F_1] (BDF_1) mice	Footpad swelling test. Unimmunized male mice injected intradermally with each sample	All but one sample induced footpad swelling at 24 h. Footpad swelling said to have been indicative of nonspecific irritant effect	Strobel et al. 1986
Five different samples of Gum Arabic (*Acacia senegal*), each emulsified in Freund's complete djuvant	5 groups of 30 to 40 [(C57BL/6J] × DBA/2 F_1] mice	Footpad swelling test. Initially, mice immunized with each sample (200 μg per sample) in left hind footpad. Presence of delayed-type hypersensitivity measured	All samples found to be immunogenic. Intradermal challenge after immunization caused significant increase in footpad thickness at 24 h	Strobel et al. 1986
Five different samples of gum arabic (*Acacia senegal*), each emulsified in Freund's complete adjuvant	5 groups of 30 to 40 [(C57BL/6J] × DBA/2 F_1] mice	Test for cross-reactivity. Blood samples obtained from mice in preceding experiment at 3 weeks post immunization. Antibodies assayed using enzyme-linked immunosorbent assay (ELISA)	Except for one sample, assay results indicated that antigens were shared between the samples tested	Strobel et al. 1986
Acacia Extract	Germ-free and conventional guinea pigs of Hartley strain	Acacia Extract (40 mg/ml) applied topically to the right eye	Microscopic examination results: Severe inflammatory response observed in germ-free and conventional guinea pigs (14 animals total, 8 days old). Minimal inflammatory response in germ-free and conventional guinea pigs (13 animals total, 12 weeks old). Inflammatory response most severe in conjunctiva	Aronson and McMaster 1972

The inflammatory response was described as minimal in 12-week-old germ-free and conventional guinea pigs. In the 7-month-old conventional animals, the responses were much more severe than that noted for 12-week-old germ-free animals. This comparison was made because 7-month-old germ-free animals were not available.

The inflammatory response to Acacia was most severe in the conjunctiva and the subconjunctival tissues were relatively free of inflammatory changes. Swelling of superficial epithelial cells of the central cornea and necrosis of a few of these cells were also observed. The severity of inflammatory responses was correlated with serum y-globulin concentrations. The extent of the inflammation induced by Acacia paralleled y-globulin concentrations in germ-free guinea pigs more closely than in conventional guinea pigs (Aronson and McMaster 1972).

Gum Arabic

Five guinea pigs (weights = 300 to 450 g) were passively sensitized with 2 ml of anti-Gum Acacia rabbit serum via intraperitoneal injection. At 24 to 36 h post injection, an intravenous dose of a homologous gum (1 mg) was administered to each animal, and the animals were observed for signs of anaphylaxis. Three guinea pigs died 2 to 3 min after intravenous administration, and the remaining two slowly recovered from shock during the following 2 to 3 h (Partridge and Morgan 1942).

Rice (1954a) evaluated the effect of Gum Acacia (species not stated) on complement and antibody production using two groups of 10 guinea pigs (strain not stated; weights = 600 to 1000 g). The animals were injected subcutaneously with gum arabic (7% solution, 5 ml) on alternate days prior to and during immunization; gum arabic was injected repeatedly over a period of seven weeks. After 2 weeks of dosing, the animals were bled and injected intraperitoneally with 1 ml of *Brucella abortus* vaccine. Three additional injections of this vaccine were made 4 days (2-ml injection), 8 days (3 ml), and 21 days (3 ml) later.

The guinea pigs were bled again one week after the third and fourth doses of vaccine, and all sera were titrated for hemolytic complement and for agglutinative and complement-fixing activity with *Brucella abortus* antigens. Surviving animals were retested for 6 weeks, bled again, injected with a fifth dose of vaccine, and bled for a fourth time 7 days later. Twenty guinea pigs of comparable weight were included in each of the control groups (immunized and non-immunized).

A sharp decline in complement titers was noted in both groups of guinea pigs injected with Gum Acacia. Following seven injections, only 2 of 18 surviving guinea pigs had complement titers over 1000 units per ml (minimum titer = 455). After 14 injections, one of the remaining animals had a titer that approached normal (minimum titer = 385). During the ensuing period, a rise in complement titer to over 1000 units per ml was noted for five guinea pigs and complement titers below 500 units were noted for eight guinea pigs; the reason for these changes in titer was undetermined. In addition to the reductions in complement titer noted in the two groups, antibody and total serum protein production were also reduced. It was determined that no deleterious effects on antibody production resulted, as judged by the development of agglutinative and complement-fixing activity in the sera to the bacterial antigen *Brucella abortus* (Rice 1954a).

Rice (1954a) also evaluated the effect of Gum Acacia (species not stated) on complement and antibody production using four rabbits (weight range = 1800 to 2650 g). This experiment is from the study summarized in the preceding paragraph. The rabbits were injected subcutaneously with a 7% solution of Gum Acacia (10 ml) every other day for 4 weeks. All rabbits were bled on the 15th day and immunized with 1 ml *Brucella abortus* vaccine. The vaccine was also injected 4 and 8 days later in 2-ml and 3-ml volumes, respectively. The rabbits were bled again seven days after the third dose of vaccine. Untreated rabbits (immunized) and nonimmunized rabbits served as controls.

In contrast to the effects noted in guinea pigs in the preceding study, Gum Acacia did not appreciably lower complement activity. The authors concluded that no deleterious effects on antibody production resulted, as judged by the development of agglutination and complement-fixing activity in the sera to the bacterial antigen *Brucella abortus* (Rice 1954a).

In another study, Rice (1954b) evaluated complement titers in guinea pigs (strain and weights not stated) that were either actively or passively sensitized to a 7% solution of Gum Acacia. Ten guinea pigs were injected subcutaneously with 16 doses (5 ml per dose) of a 7% Gum Acacia (species not stated) solution over a period of 16 days. The animals were actively sensitized after 7 doses, and the nine survivors were bled, challenged, and rebled in 3 weeks.

Signs of asphyxia were reported for one of the nine survivors; this animal survived for more than 3 h. The other guinea pigs became excited shortly after challenge, running around wildly and squealing (shock signs); two eventually died. An additional 10 guinea pigs that had received 11 injections of Gum Acacia solution were passively sensitized, bled, and challenged 48 h later. Typical respiratory signs developed; none of the animals died. No significant decline in serum-complement activity was detected in animals challenged shortly after passive sensitization or in actively sensitized Gum Acacia-treated guinea pigs; however, a decline in this activity was noted. Additionally, in both sensitized groups, initial excitement followed by fatigue and weakness were the most striking clinical signs (Rice 1954b).

Silvette et al. (1955) reported that anaphylactic shock resulted in each of the 12 guinea pigs sensitized via intra-abdominal injection of 160 mg Acacia with Freund's complete adjuvant (FCA) (2 ml of emulsion containing two parts 20% Acacia). Ten guinea pigs died. Two additional guinea pigs were sensitized via intra-abdominal injection of 160 mg Acacia with FCA (2 ml of emulsion containing two parts 20% Acacia). This Acacia sample was from another lot. The animals were challenged intravenously with 60 mg Acacia 1 month later. Typical anaphylactic death was reported for both guinea pigs.

The results of this experiment as well as additional experiments (rabbits and guinea pigs) in this study collectively indicated that four different lots of Gum Acacia were equally effective as immunizing, sensitizing, and anaphylactogenic and desensitizing antigens, based on the results of cross-precipitin tests and cross-anaphylaxis experiments (Silvette et al. 1955).

Antibodies directed against gum arabic (species not stated) have been isolated using affinity chromatography on AH-Sepharose 4B containing gum arabic ligands. These antibodies were induced in rabbits immunized with gum arabic in FCA. It was determined that the antibodies were anti-carbohydrate antibodies with specificity for certain carbohydrate units of the gum arabic. The results of chemical modification and inhibition experiments indicated that 4-α-L-arabinofuranosyl-D-glucuronic acid units of the polysaccharide were the major immunodeterminant groups (Pazur et al. 1986).

Blood group antigens have been demonstrated in gum arabic (species not stated). The following substances were identified using an agglutinin inhibition test of mild hydrolyzed gum arabic: B, C (of ABO blood group system) and H substances (of H blood group system) and Le^a ($Lewis^a$ antigen, in Lewis blood group system). The results of a revised latex agglutination technique indicated the presence of P and S (of MN blood group system) as well as the substances mentioned in the preceding statement. Elution processes, using sensitized and agglutinated latex or kaolin particles, resulted in the identification of B, H, and Le^a substances in gum arabic; the elution of anti-P and anti-S did not occur (Matsuzawa 1968).

Narita (1985) reported the isolation of high-titer anti-Gum Arabic sera obtained from rabbits injected with gum arabic (species not stated). The antisera had cross-reactivity with the $Lewis^a$ antigen (Le^a), as measured by both a single diffusion tube test and the Ouchterlony test (Narita 1985).

Strobel et al. (1982) evaluated the allergenicity of three grades of gum arabic using female CBA mice (6 weeks old; six to eight mice per group). The grades of gum arabic tested were as follows: (1) processed gum arabic recovered by spray-drying from a solution of commercial food grade gum arabic after filtration to remove sand, etc., and after heat treatment to effect pasteurization; (2) finely powdered natural gum arabic of poor commercial quality giving solutions of a dark red-brown color; (3) finely powdered natural gum arabic of very high quality, giving essentially colorless solutions.

The gum exudates were dissolved in 0.15 M NaCl at a concentration of 4 mg/ml by incubation at 37°C for 16 h. The resulting solution was sterilized by irradiation. The mice were immunized by injection of the antigen (0.1 mg in 0.05 ml of FCA) into the left hind footpad. At 21 days after primary immunization, delayed-type hypersensitivity was measured using a skin test. In this test, the antigen (0.1 mg dissolved in 0.15 M saline in volume of 0.05 ml) was injected intradermally into the plantar side of the right footpad of anesthetized mice. Using a micro caliper, footpad thickness was measured in triplicate immediately before intradermal injection and 24 h later. For controls, footpad swelling was measured before and after antigen injection into the footpad of nonimmunized mice, and before and after saline injection into the footpad of immunized mice. All mice were killed one week after the skin tests. The animals were bled and serum separated and decomplemented.

The intradermal injection of antigen into nonimmunized, control mice (four mice per antigen) did not induce significant footpad swelling at 24 h. Similarly, the intradermal injection of saline into immunized control mice did not cause a significant increase in footpad thickness. However, compared to the control, significant positive responses were noted in mice of the test groups ($p < .01$), indicating an antigen-specific hypersensitivity reaction for all three gum arabic specimens that were tested. A comparison of results for the three grades of gum arabic indicated that footpad swelling in mice immunized and tested with the dark, red-brown grade was significantly greater ($p < .005$) when compared to the colorless grade (Strobel et al. 1982).

Strobel and Ferguson (1986) studied the immunological activity of gum arabic (species not stated) using two groups of eight female BDF1 [(C57BL/6] $\times$ DBA/2)F_1] mice (6 to 8 weeks old). A finely powdered sample of gum arabic was dissolved in 0.15 M saline at a concentration of 400 mg/ml. Each of eight mice was then dosed with gum arabic (80 mg) by intragastric administration. Control mice were dosed with saline. At 7 days post dosing, the mice were immunized by injecting a saline solution of 100 μg gum arabic emulsified in an equal volume of FCA (total volume injected = 0.05 ml) into the left hind footpad.

Control mice were immunized with 0.15 M saline in FCA. Prior to and 3 weeks after immunization all mice were bled and decomplemented sera were tested for anti-Gum Arabic antibodies by a micro-ELISA (enzyme-linked immunosorbent assay) technique.

Delayed-type hypersensitivity was also measured (skin test) at 3 weeks post immunization. The mice were anesthetized and 0.1 mg gum arabic (in volume of 0.05 ml) was injected intradermally into the right footpad. Footpad thickness was measured in triplicate immediately before intradermal injection and 24 h later. As controls, footpad swelling was measured before and after gum arabic was injected into the footpad of saline/adjuvant-immunized animals, as well as before and after saline was injected into the footpad of mice immunized with gum arabic.

Footpad swelling was negligible in both control groups. Antibodies were not detected in the serum of mice that were bled before systemic immunization. Serum antibodies were identified in five of eight control (saline prefed) mice after systemic immunization. However, antibodies were not detected in the serum of mice that were prefed with gum arabic. Regarding delayed-type hypersensitivity, a similar pattern was noted. Positive skin tests were reported for all saline-prefed mice. However, footpad swelling in mice prefed with gum arabic was significantly suppressed. Test results indicated that systemic immunological hyporesponsiveness (oral tolerance) developed in mice that were fed gum arabic (Strobel and Ferguson 1986).

Strobel (1986) evaluated the immunogenicity, cross-reactivity, and nonspecific irritant properties of gum arabic (Acacia Senegal Gum) using male mice (6 to 8 weeks old) of the [(C57BL/6J × DBA/2F$_1$] (BDF$_1$) strain. Nonspecific irritant properties were assessed in the foot pad swelling test using control groups of nonimmunized mice. Immunogenicity was evaluated in an in vivo footpad swelling test, and cross-reactivity was assessed by secondary antibody response.

The following gum arabic samples (identified as samples A, B, C, D, and E) were tested in each experiment: (1) Sample A (sodium arabate) resulted from the neutralization of sample C with sodium hydroxide. (2) Sample B resulted from three successive precipitations of sample C from aqueous solution with acidified ethanol. (3) Sample C, gum arabic, was a water-soluble polysaccharide containing rhamnose, arabinose, glucuronic acid, and galactose. (4) Sample D was defined as powdered food grade natural gum arabic. (5) Sample E was obtained by exhaustive ethanolic extraction of sample D. In the nonspecific footpad swelling test, five groups (six to eight mice per group) of nonimmunized male mice were injected intradermally with the five samples, respectively.

Sample A did not induce significant swelling at 24 h; however, samples B, C, and D increased, but only slightly, nonspecific swelling ($p < .05$). Sample E induced the greatest extent of footpad swelling. These results (footpad swelling) were indicative of a nonspecific irritant effect.

In a second experiment, five groups (30 to 40 mice per group) of mice were immunized with the five gum arabic samples (200 μg per sample), respectively, in the left hind footpad. Each gum arabic sample was emulsified in FCA prior to immunization. Control mice (30 to 40 mice) were immunized with saline in FCA. At 21 days post immunization, the presence of delayed-type hypersensitivity (specific cell mediated immunity) was measured in the footpad swelling skin test.

All gum arabic samples were immunogenic in this test. In each case, intradermal challenge after immunization caused a significant increase in footpad thickness at 24 h. In the test for cross-reactivity, blood samples were obtained from mice that had been immunized and tested (footpad swelling test) 3 weeks after immunization. Antibodies were assayed by an ELISA.

Assay results indicated that antigens were shared between all of the samples, except for sample E. Mice immunized with sample A had significant reactions when tested with samples A, B, C, and D. The greatest nonspecific swelling was produced by samples B and C (Strobel et al. 1986).

GENOTOXICITY

Gum Arabic

Both in vitro and in vivo studies on the mutagenicity of gum arabic described as gum arabic, Acacia, or Gum Acacia are summarized in Table 10. Although a few positive results are described, most studies were negative for genotoxicity.

UV Damage Repair

Acacia (Not Gum Arabic)

Jain et al. (1987) evaluated the effect of *Acacia arabica* on UV-induced damage in the WP-2 strain of *Escherichia coli*. Cultures were irradiated with UV light (1.5 J/m^2/s) for 15 s, with intermittent stirring. The bark of *Acacia arabica* was extracted with methanol and the extract was added to cultures at a concentration of 5 mg/plate. The revertants and viable cells were counted after incubation for two days at a temperature of 37°C.

Compared to control cultures exposed to UV light (mean number of revertants per plate = 216), the mutagenic activity of UV light was reduced in cultures dosed with *Acacia arabica* extract. The mean number of revertants per plate in test cultures was 34. The survival for control and test cultures was 100% and 70.6%, respectively. The investigators stated that the decrease in UV-induced mutagenicity in the presence of Acacia could have been due to some enzymatic action that reverted the formation of pyrimidine dimers (Jain et al. 1987).

Effect on Genotoxicity of Other Agents

Gum Arabic

The effect of 3% gum arabic (solvent) on the mutagenicity of 4-nitroquinoline-*N*-oxide was evaluated using results from the bone marrow micronucleus assay. Based on an analysis of time-response and dose-response data on 4-nitro-quinoline-*N*-oxide, it was determined that the mutagenicity of this chemical was six times greater in gum arabic when compared to test results for the chemical in DMSO. When the mutagenicity of other chemicals, such as mitomycin C, was evaluated using different solvents, no solvent effect on mutagenicity was observed. The investigators concluded that no clear relationship existed between the solvent used and the mutagenicity observed (Katz et al. 1981).

Carcinogenicity

Gum Arabic

No evidence of carcinogenicity was noted in rats dosed intraperitoneally with gum arabic (1.75% or 7% in saline or water) three times per week for up to 15 weeks. Based on the data presented, it was difficult to ascertain the size of the dose administered. The doses administered were on the order of several hundred mg/kg. Also, no evidence of carcinogenicity was found in a similar study using mice (doses injected not stated) (FASEB 1973).

Gum arabic gruel was injected intramediastinally (single dose) into five (0.5 ml dose of test substance) and 10 (1 ml dose) guinea pigs. The animals (strain not specified) ranged in weight from 220 to 450 g and were 4 to 10 months old. Neoplasms were not observed in any of the guinea pigs either at necropsy or at microscopic examination of tissue. On the average, the animals survived from 1200 to 1490 days (Tlolka-Pluszczyk 1970).

Melnick et al. (1983) studied the carcinogenicity of gum arabic using 4-week-old F344 rats (50 males, 50 females) and

TABLE 10
In vitro and in vivo mutagenicity of Gum Arabic, as Gum Arabic, Acacia, and Gum Acacia

Test substance	Strains/cells/animals tested	Test procedure	Test results	References
		Gum Arabic		
Bacterial Cell Test Systems				
Gum Arabic	*Saccharomyces cerevisiae* D4	Host-mediated assay for mitotic recombination (Gabridge and Legator 1969); test concentration of 5% w/v if no lethal effects observed	Not mutagenic	Maxwell and Newell 1974
Gum Arabic	*Salmonella typhimurium* G-46 and TA-1530	Ames test (Ames 1971)	Not mutagenic	Maxwell and Newell 1974
Gum Arabic (in DMSO)	*Salmonella typhimurium* TA1535, TA1537, and TA1538 *Saccharomyces cerevisiae* D4	Plate and suspension assays with and without metabolic activation. Plate test concentrations up to 3.3%. Suspension assay concentrations up to 0.36%	Not mutagenic with or without metabolic activation	Litton Bionetics, Inc. 1975
Gum Arabic	*Saccharomyces cerevisiae* D3	Plate test (Brusick 1973)	Not mutagenic	Green 1977
Gum Arabic (in 0.067 M sodium phosphate buffer)	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, and TA 100 *E. coli* WP2 (uvrA)	*Salmonella*/microsome assay with and without metabolic activation; concentrations up to 10,000 μg/plate	Not toxic or mutagenic	SRI International 1980
Gum Arabic (in water)	*Bacillus subtilis* M 45 Rec^- and H 17 Rec^+	Spore rec-assay (with and without metabolic activation) for DNA-damaging activity	Not mutagenic	Ishizaki and Ueno 1987
Gum Arabic (in 0.067 M potassium or phosphate buffer)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538 *Escherichia coli* WP2	*Salmonella* strains tested in plate incorporation assay (Ames et al. 1975) with and without metabolic activation; doses up to 10 mg/plate. *E. coli* tested according to modification of plate incorporation assay at same doses	Not mutagenic with or without metabolic activation	Prival et al. 1991
Gum Arabic	*Salmonella typhimurium* TA100, TA1535, TA1537, TA97, and TA98	Modification of preincubation procedure by Haworth et al. (1983) with and without metabolic activation. Cultures incubated with 0.05 ml gum arabic	Not mutagenic with or without metabolic activation	Zeiger et al. 1992
Mammalian Cell Test Systems				
Gum Arabic	Diploid human embryonic lung (WI-38) cells	Cytogenetics assay; concentrations up to 1000 μg/ml culture if no cytotoxicity observed at this level. Anaphase analyses according to procedure of Nichols et al. (1971)	Response classified as "slight positive." No definite abnormal anaphase figures observed	Maxwell and Newell 1974

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TABLE 10
In vitro and in vivo mutagenicity of Gum Arabic, as Gum Arabic, Acacia, and Gum Acacia *(Continued)*

Test substance	Strains/cells/animals tested	Test procedure	Test results	References
Gum Arabic	WI-38 human embryonic lung cells	Test methodology not stated	Chromosomal aberrations induced in anaphase	Green 1977
Animal Test Systems				
Gum Arabic	Male albino rats (weights 200 g)	Acute and short-term in vivo cytogenetics assays. Doses up to maximum tolerated dose administered. Cytogenetic evaluations on bone marrow cells in metaphase	No significant positive response, but may have been a slight positive response. Further tests and detailed statistical evaluation needed to confirm this possibility	Maxwell and Newell 1974
Gum Arabic	Male and female Swiss mice (10 to 12 weeks old; weights = 25 to 30 g)	Dominant lethal test. Male mice dosed orally with 1% gum arabic prior to mating	No dominant lethal effect	Kar et al. 1984
Gum Arabic	NMRI mice (weights between 30 to 35 g)	Micronucleus test (bone marrow smears). Mice dosed i.p. with 3% gum arabic	Not genotoxic	Wild et al. 1985
Gum Arabic	Male NMRI mice (weights between 30 to 35 g)	Intrasanguineous host-mediated assay. *Salmonella typhimurium* strain TA 98 culture (0.1 ml) injected into tail vein. Intravenous injection followed by oral dose of 3% gum arabic	Not mutagenic to strain TA 98	Wild et al. 1985
	C57BL virgin female mice	Mouse coat color spot test (transplacental mutagenicity test). Gum Arabic (3%) injected i.p. after mating. Spots classified as relevant caused by mutations at heterozygous coat-color loci	Not mutagenic	
	C57BL mice	Mouse melanocyte test—Used to detect somatic mutations that affect the morphology of pigment cells. Pregnant females received i.p. injections of 3% gum arabic on 16th day after detection of vaginal plug	Not genotoxic	
Gum Arabic	Male and female Sprague-Dawley rats (males: 6 to 8 weeks old; females: 10 to 12 weeks old)	Dominant lethal test. Male rats fed concentrations up to 4% w/w gum arabic prior to mating. Number of live and dead implants counted 14 days after midweek of mating	Statistically significant dominant lethal effects in male rats	Sheu et al. 1986

	(SEC × C57BL)F1 and (C3H × C57BL)F1 female mice (10 to 12 weeks old)	Dominant lethal test. Male mice fed diets containing up to 20% gum arabic prior to mating	No evidence of dominant lethal effect	
	(101 × C3H)F1 male mice (8 weeks old)	Heritable translocation test. Male mice fed test diet containing 15% *w/w* gum arabic prior to mating	No reduction in average litter size. Number of translocation-carrying male progeny in test group was comparable to that of control group	
		Acacia		
Animal Test Systems				
Acacia (in water)	Male Swiss-Webster mice (6 weeks old; mean weights between 16 to 32 g)	Micronucleus test (bone marrow smears). Mice dosed with 2% Acacia in water	Not genotoxic	MacGregor et al. 1983
Acacia	Inbred female Chinese hamsters (*Cricetulus griseus*) (weight range, 26 to 32 g)	Assay for sister chromatid exchanges. Hamsters dosed i.p. or orally with 10% Acacia (dose volume = 10 ml/kg)	Mean number of sister chromatid exchanges not significantly different, compared to control hamsters dosed with 0.9% normal saline	Neal and Probst 1983
Gum Acacia	Male Swiss mice (6 to 8 weeks old)	Chromosomal aberrations and sperm-head morphology assays. Mice dosed with 5% Gum Acacia by gavage (volume per dose = 0.5 ml)	No statistically significant differences in frequency of chromosomal aberrations and incidence of sperm head abnormalities, compared to control (distilled water) group	Prasad et al. 1987
Gum Acacia	Male Swiss albino mice (8 weeks old)	Micronucleus test (bone marrow smears). Mice dosed orally with 5% Gum Acacia	The ratio of polychromatic erythrocytes to monochromatic erythrocytes (P/N ratio) was slightly higher, compared to mice dosed with water	Pentiah et al. 1989
Acacia	Male ICR mice (7 weeks old; weights between 28 and 32 g)	Micronucleus test (bone marrow smears). Mice dosed with 10% Acacia by gavage (volume per dose = 0.02 ml/g body weight	Not genotoxic	Parton et al. 1988
Acacia	Male ICR mice	Micronucleus test (bone marrow smears). Mice dosed with 10% Acacia by gavage (volume per dose = 20 ml/kg)	Not genotoxic	Parton et al. 1990

4- to 5-week-old B6C3F$_1$ mice (50 males, 50 females) in a 2-year chronic study. Both male and female rats were divided into high- and low-dose groups. Low-dose animals were fed gum arabic at a concentration of 25,000 ppm in the diet and high-dose animals were fed 50,000 ppm. Test diets were fed for 103 consecutive weeks, followed by 1 to 2 weeks of feeding of the basal diet. Control mice (50 males, 50 females) and rats (50 males, 50 females) were fed the basal diet only according to the same schedule. Moribund animals and animals that survived to the end of the study were killed using carbon dioxide and necropsied. Tissues were preserved for histopathologic evaluation.

Changes in mean body weight for male and female rats were comparable to those of the respective control groups throughout the study. Slight decreases in body weight (7% to 13%) were observed in female rats. Compared to controls, consistent differences in mean body weight were noted for female mice of the high dose group (50,000 ppm in diet). No significant differences were found in survival between experimental mice or rats when compared to the respective control groups.

Neoplasms were observed only in male rats, and were diagnosed as malignant lymphomas or leukemia/lymphoma. The incidences of malignant lymphomas for control, low-dose (25,000 ppm gum arabic), and high-dose (50,000 ppm gum arabic) experimental groups of male rats were as follows: 4/50 (low-dose), 1/50 (high-dose), 8/50 (concurrent controls), and 31/1066 (historical controls). Compared to the concurrent control group, a significant decrease ($p < .05$) in tumor incidence was observed in the high dose group, and this was the only statistically significant finding for this neoplasm.

The incidences of neoplasms classified as leukemia/lymphoma in control, low-dose (25,000 ppm gum arabic), and high-dose (50,000 ppm gum arabic) groups of male rats were: 19/50 (low-dose), 16/50 (high-dose), 18/50 (concurrent controls), and 238/1066 (historical controls). Compared to concurrent controls, no statistically significant differences were observed in the incidence of tumors of this type.

No significant changes were observed in the incidence of primary neoplasms in mice that were fed gum arabic in the diet at concentrations of 25,000 or 50,000 ppm. Based on the preceding results, the investigators concluded that gum arabic was not carcinogenic in F344 rats or B6C3F$_1$ mice of either sex (Melnick et al. 1983).

Cocarcinogenicity

Gum Arabic

Vogel and Zaldivar (1971) studied the cocarcinogenicity of Gum Acacia using male rats of the Buffalo strain (6 to 10 weeks old). Thirty-four rats were exposed to fission neutrons (single exposure of 300 to 364 rads; whole-body irradiation), followed by three intraperitoneal injections (0.5 ml per injection) of a 7% solution of Gum Acacia in 0.85% sodium chloride weekly for 23 weeks.

A second test group (30 rats) was irradiated after treatment with Gum Acacia according to the same procedure. Three groups of rats served as controls: one of the control groups (50 rats) was exposed to fission neutrons only. Two additional control groups consisted of 40 rats injected intraperitoneally with 7% Gum Acacia only (according to test group protocol) and an untreated control group of 79 rats.

No significant neoplasm incidence was present in the two control groups. However, the survival time for the 40 control rats injected with Gum Acacia (554.8 $\pm$ 39.4 days, $n = 30$) was significantly shortened when compared to untreated controls (669.2 $\pm$ 19.0 days, $n = 58$). Increases in hepatic, gastric, and intestinal neoplasms were noted in the first test group (34 rats; neutron exposure followed by Gum Acacia injections), when compared to the group of 50 rats exposed to fission neutrons only.

Except for gastric neoplasms, these differences in neoplasm incidence were considered small and probably not significant. It is important to note that no gastric neoplasms were observed in the 50 rats exposed to fission neutrons only, whereas, 20% of the 34 test rats had gastric cancers. No explanation for this difference was given.

Tissues of 28 of the 34 test rats in this group were subjected to complete histopathological analysis after necropsy. Similarly (compared to fission neutrons control group), no gastric neoplasms were noted in the group of 30 rats treated with Gum Acacia and then exposed to fission neutrons. The investigators stated that this finding could have been due to the small number of rats ($n = 14$, compared to $n = 28$ in other test group) subjected to complete histopathological examination after necropsy.

The authors stated that the data presented in this study suggest that Gum Acacia might be considered a "potentiator" for carcinogenesis (Vogel and Zaldivar 1971).

Gum arabic has been reported to increase the number of metastases in mice injected intraperitoneally with Ehrlich ascites carcinoma cells. The carcinoma cells were injected 6 or 24 h after the mice were injected intravenously with gum arabic. However, under some conditions, ascites tumor formation was inhibited (Osswald 1968).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Gum Arabic

Studies on the reproductive and developmental toxicity of gum arabic are summarized in Table 11 and discussed below.

The antifertility activity of Gum Acacia (1 ml in water) was evaluated using 10 female rats (strain and weights not stated). The test substance was administered by stomach tube daily for a period of 5 days after mating. After performing laparotomy on anesthetized dams, the number of fetuses was counted on the 10 day of pregnancy. The average number of implants per rat was 7.8. The percentage of rats with no implant was 0 (Sabir and Razdan 1970).

In a study by the Food and Drug Research Laboratories (1972), the teratogenicity of gum arabic was evaluated using six

TABLE 11
Reproductive and developmental toxicity studies

Test substance	Animals/cells tested	Test procedure	Test results	References
		Acacia		
10% aqueous Acacia solution	9 Little Dutch female rabbits (average weight between 2.1 kg)	After mating, 10% aqueous Acacia solution administered orally on day 0 and the following 6 days	Normal microscopic variations in blastocysts reported: minor trophoblastic vacuolation, trophoblastic degeneration granules, and trophoblastic knob formations	Schardein et al. 1965
Gum Acacia	10 female rats	Gum Acacia (1 ml in water) administered orally during 5-day period after mating	No antifertility activity. Average number of implants per rat = 7.8	Sabir and Razdan 1970
Gum Acacia	Two groups of 5 male albino Wistar rats (4 months old; weights between 180 to 200 g)	First group dosed orally (dose = 1 ml) daily for 24 days. Second group dosed orally (dose = 1 ml) for 48 days	No suppression of spermatogenesis	Akbarsha and Manivannan 1973
4% Gum Acacia	6 Haffkine albino rabbits (weights between 175 to 225 g)	Males dosed orally daily for 28 days and mated with untreated females for total of 12 weeks	No statistically significant difference in number of pregnant females. No antifertility effect in males	Yegnanarayan and Joglekar 1978
	Adult female rabbits (weights between 1 to 2 g)	Dosed orally with 4% Gum Acacia for two days	No inhibitory effect on ovulation	
	Female albino rats (weights between 150 to 200 g)	4% Gum Acacia administered orally to 10 females over period of two estrus cycles, followed by mating with males during proestrus phase of third estrus cycle (short-term experiment). 4% Gum Acacia administered orally to 6 females over period of 6 estrus cycles, followed by mating during proestrus stage of 7th estrus cycle	No significant differences in mating (number of females inseminated) between experimental and control groups. No significant changes in duration of estrus cycles after dosing	

(Continued on next page)

TABLE 11
Reproductive and developmental toxicity studies *(Continued)*

Test substance	Animals/cells tested	Test procedure	Test results	References
	10 female rats (weights between 150 to 200 g)	Females dosed orally with 4% gum arabic on days 1 to 7 of pregnancy	No statistically significant difference in average litter sizes between experimental and control groups, indicating that fetal resorption did not occur	
	10 female rats (weights between 150 to 200 g)	Females dosed orally with 4% gum arabic on days 10 to 16 of pregnancy	No statistically significant differences in number of pups delivered between experimental and control groups	
5% Gum Acacia	9 Syrian golden hamsters (8 weeks old; weights between 80 to 100 g)	Dosed orally with 5% Gum Acacia (dose volume = 0.1 ml/10 g body weight) daily for 54 days	All of the hamsters produced morphologically normal sperm	Waller et al. 1983
1% Gum Acacia	10 female Charles Foster rats (90 days old; weights between 200 ± 20 g)	Administered daily at dose of 50 mg/kg/day during the period of organogenesis	No gross or visceral defects	Sethi et al. 1989
		Gum Arabic		
1% aqueous suspension or mucilage prepared from gum arabic	NMRI mice	1% aqueous suspension or mucilage prepared from gum arabic injected intraperitoneally (single injection or series of 5 injections), subcutaneously (5 injections), and administered orally (5 times) between the 11th and 15th day of gestation	No lethal effects on fetuses	Frohberg et al. 1969
Gum Arabic	Adult female albino CD-1 outbred mice (4 groups). Most groups contained 22 to 23 mice	The four groups of mated mice received oral doses of 16, 75, 350, and 1600 mg/kg on days 6 through 15 of gestation	The number of abnormalities observed in soft or skeletal tissues of fetuses did not differ from the number occurring spontaneously in sham-treated controls	Food and Drug Research Laboratories 1972
	Groups of female rats, rabbits, and hamsters	Oral doses of 16, 75, 350, and 1600 mg/kg on gestation days 6 through 10 (hamsters) and 6 through 15 (rats). Oral doses of 8, 37, 173, and 800 mg/kg in corn oil on days 6 through 18 of gestation (rabbits)	The number of abnormalities observed in soft or skeletal tissues of fetuses did not differ from sham-treated controls	

Gum Arabic (Acacia Senegal Gum)	Groups of 4-week-old Osborne-Mendel (FDA strain) rats	Groups fed dietary concentrations up to 15% beginning at week 13 prior to mating	Gum Arabic not classified as a reproductive or developmental toxicant in rats	Collins et al. 1987
5% aqueous gum arabic solution	36 female Sprague-Dawley Crl:CDBR rats (~9 months; weights between 207 to 314 g)	Solution administered orally once daily (5 ml/kg/day) on days 6 through 17 of gestation	External, visceral, and skeletal malformations observed were unrelated to dosing with Acacia	Morseth and Ihara 1989a
5% aqueous gum arabic solution	30 male Sprague-Dawley Crl:CDBR male rats (6 weeks old; weights between 181.9 to 226.3 g) 30 female rats of same strain (10 weeks old; weights between 210.9 to 309.9 g)	Solution administered orally to females once daily (5 ml/kg/day) for 14 days prior to mating, throughout the mating period, and through day 19 of gestation or day 21 of lactation. Solution also administered to males prior to and during mating and until animals killed	No treatment-related abnormal estrous cycles. No external, skeletal, or soft tissue malformations	Morseth and Ihara 1989b
Gum Arabic	12 Sprague-Dawley rats (adult males)	Control rats fed 30% gum arabic in the diet for 82 days	No effect on spermatogenesis (all males were fertile)	Huynh et al. 2000

groups of mated adult female albino CD-1 outbred mice. Three of the test groups consisted of 22 to 23 mice per group and received doses of 16, 75, and 350 mg/kg, respectively, on days 6 through 15 of gestation. Doses were administered by oral intubation. The fourth test group of 31 mice was dosed with gum arabic (1600 mg/kg) according to the same procedure. Sham-treated mice (28) served as negative controls, and positive-control mice were dosed with aspirin (150 mg/kg). Mean body weights for the test groups ranged from 30 to 39.7 g and were 31.2 g and 31.8 g for negative and positive controls, respectively.

On day 17, all dams were placed under anesthesia and cesarean section was performed. The numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The urogenital tract of each dam was examined in detail for anatomical normality. Gross examinations for the presence of external congenital abnormalities were performed on all fetuses. Detailed visceral examinations employing 10× magnification were performed on one-third of the fetuses from each litter. The remaining two-thirds were examined for skeletal defects.

The administration of gum arabic to pregnant mice at doses up to 1600 mg/kg had no clearly discernible effect on nidation or maternal or fetal survival. The number of abnormalities observed in either soft or skeletal tissues of fetuses from test groups did not differ from the number occurring spontaneously in sham-treated controls.

As part of this study, groups of rats, rabbits, and hamsters were dosed with gum arabic according to the following modifications of the above test procedure: doses (indicated above) were administered to hamsters (gestation days 6 through 10), rats (gestation days 6 through 15), and rabbits (gestation days 6 through 18). Cesarean sections were performed earlier on hamsters (day 14) and later on rats (day 20). Positive-control rats and hamsters received a higher dose of aspirin (250 mg/kg). Rabbits were dosed with gum arabic in corn oil (8, 37, 173, and 800 mg/kg, respectively); cesarean sections were performed on day 29. Rabbits were injected with human chorionic gonadotropin (day 0) and artificially inseminated. Mean weights for the dams tested were as follows: 200 to 216 g (24 rats per group), 104.6 to 118.4 g (21 to 24 hamsters per group), and 2.01 to 2.43 kg (15 rabbits per group).

The administration of gum arabic, in corn oil, to pregnant rabbits at doses up to 37 mg/kg (highest dose tested = 800 mg/kg) had no clear effect on nidation or maternal or fetal survival. The number and types of abnormalities observed in fetal soft or skeletal tissues from this group did not differ from the number occurring spontaneously in the sham-treated controls. Of the four test groups of rabbits (15 dams per group), the number of survivors per dose group was reported as follows: 13 rabbits (8.0 mg/kg dose group), 15 rabbits (37.0 mg/kg), 12 rabbits (173.0 mg/kg), and 9 rabbits (800.0 mg/kg). In 173 and 800 mg/kg dose groups, maternal death was preceded by severe bloody diarrhea, urinary incontinence, and anorexia. At necropsy, hemorrhage in the mucosa of the small intestines was the only gross pathological finding (Food and Drug Research Laboratories 1972).

Akbarsha and Manivannan (1993) studied the reproductive toxicity of Gum Acacia using two groups of five male albino rats of the Wistar strain (4 months old; weights between 180 and 200 g). The test substance was administered orally (dose = 1 ml) to the first group daily for 24 days. The second group was dosed (dose = 1 ml) daily for 48 days. Rats in both groups were necropsied 24 h after the last dose.

The testis, epididymis (divided into caput and cauda), seminal vesicle, ventral prostate, and coagulating gland were excised, homogenized, and centrifuged. The supernatant was used for determination of total protein and acid phosphatase (ACPase) and alkaline phosphatase (ALPase) activities. Supernatant obtained from the testes was also used for the determination of glycogen and cholesterol, and lactate dehydrogenase (LDH) activity.

The authors stated that increased glycogen and LDH in the testis are both consequences of spermatogenic arrest, and that decreased ACPase and increased ALPase activities in the testis also reflect the suppression of spermatogenesis. They concluded that Gum Acacia did not suppress spermatogenesis in this study (Akbarsha and Manivannan 1993).

Huynh et al. (2000) used gum arabic as the vehicle control in a study evaluating the effect of triptolide (deterpene triepoxide) on spermatogenesis in adult male Sprague-Dawley rats (12 animals, 90 days old). Control males were fed 30% gum arabic in the diet daily for 82 days. Males in the test group were each fed triptolide at a daily dose of 100 μg/kg body weight. Male and female rats (two females per male) were housed together during the feeding period, after which pregnancy rates were determined. The presence of sperm in morning vaginal smears was used to determine whether or not mating was successful. Any male that impregnated at least one of the females was considered fertile. All 12 control males were fertile, whereas all males fed triptolide in the diet were sterile.

Collins et al. (1987) evaluated the teratogenicity of gum arabic (Acacia Senegal Gum) using groups of 4-week-old Osborne-Mendel (FDA strain) rats. Beginning at 13 weeks prior to mating, the rats were fed gum arabic at concentrations of 1%, 2%, 4%, 7.5%, or 15%, respectively. Another group of rats was fed a control diet. Control and test diets were also fed throughout mating and gestation. After mating was confirmed, females were placed in groups of 41 to 47. The dams were killed on day 20 of gestation.

One female rat (1% dietary group) died during the study. External observations of the dams were unremarkable. One female (7.5% dietary group) did have a cystic ovary and one had lung nodules (15% dietary group). Sporadic nonsignificant increases in body weight were observed in all experimental groups.

The percentage of pregnant females was approximately the same in all experimental groups and controls. Mean numbers of corpora lutea and implants per female were also similar to control values, and the average number of viable fetuses was similar in all groups. No effect was seen in any group with

respect to the mean number of viable males and females. Three litters were totally resorbed, one litter from the control, 1%, and 4% dietary groups. Gum arabic in the diet had no effect on the percentage of females with at least one resorption or with at least two resorptions. The numbers of early and late deaths, singly or combined (as average percentage of resorptions), were similar to control values.

The feeding of gum arabic had no effect on mean fetal body weights and crown-rump lengths. The ingestion of gum arabic also had no effect on the distribution of fetuses by sex. A significant decrease in mean female body weight in the 1% dietary group was noted; however, this observation was deemed a random occurrence. The significant increase in the length of females in the 4% and 7.5% dietary groups was not considered biologically significant.

The investigators stated that because of the large group of animals in this study, small variations in crown-rump length can result in significant effects. Similar numbers of runts were noted among male and female fetuses from all dietary groups, with the exception of no runts among male fetuses in the 1% and 15% dietary groups.

Regarding external variations in live fetuses, spina bifida and exencephaly were observed in two fetuses from the control group. No other terata were observed, and the external variations were distributed randomly. Similar numbers of fetuses with hemorrhages were observed in all dietary groups.

The mean numbers of sternebral variations per litter varied from 4.18 (4% gum arabic dietary group) to 5.09 (15% dietary group) in experimental groups, and the mean number of sternebral variations per litter in the control group was 5.21. The variations included reduced ossification and bipartite, missing, and malaligned sternebrae. No dose-related increases were found with respect to any of the observed sternebral deficiencies, and no significant differences were found between experimental and control groups. The significant decrease in the average number of fetuses with one or more sternebral variations per litter that was observed in the 4% and 7.5% dietary groups was considered a random occurrence. Thus, the ingestion of gum arabic did not affect the incidence of litters with fetuses with sternebral variations.

Skeletal ossification deficiencies were observed in bones other than sternebrae; however, no dose-related differences were observed between experimental and control groups with respect to any variation. Furthermore, no dose-related effect was found on the incidence of variations, fetuses with variations, or litters affected in any of the dietary groups.

Also, no dose-related effect was observed on the incidence of any type of soft-tissue variation. Most of the soft tissue variations involved the kidneys. Additionally, the incidence of soft tissue variations in fetuses from experimental and control groups was similar. The mean numbers of soft tissue variations per litter ranged from 0.30 (15% dietary group) to 0.82 (7.5% dietary group), and the mean was 0.76 per litter in the control group (Collins et al. 1987).

Schardein et al. (1965) administered a 10% aqueous *Acacia* solution by gavage to two groups of nine Little Dutch strain mated female rabbits (average weight = 2.1 kg) at doses of 1.26 and 1.5 ml/kg, respectively. Doses were administered on day 0 and the following 6 days (7 doses per female). Nine untreated rabbits served as negative controls. Blastocysts were removed from the uterine horns at 6.5 days of age, prepared as flat mounts, and then evaluated.

The number of fertile rabbits with blastocysts recovered (eight of nine rabbits) in the 1.26 and 1.5 ml/kg dose groups was the same as that noted for the untreated control group. The mean numbers of blastocysts per rabbit were as follows: untreated controls (5.3 ± 1.2), 1.26 ml/kg dose group (7.0 ± 1.7), and 1.5 ml/kg dose group (5.4 ± 2.2). Normal microscopic variations in blastocysts were reported for test and control groups. These variations included minor trophoblastic vacuolation, trophoblastic degeneration granules, and trophoblastic knob formations (Schardein et al. 1965).

Morseth and Ihara (1989a) studied the teratogenicity of a 5% solution of gum arabic (powder) in distilled water using 36 female Crl: CDBR rats (~9 months old) for which mating had been confirmed. Body weights on gestation day 0 ranged from 207 to 314 g. The solution was administered by gavage once daily (5 ml/kg/day) on gestation days 6 through 17. The dams were necropsied on day 20 of gestation. Fetuses were subjected to external (303 fetuses), visceral (102 fetuses), and skeletal (201 fetuses) examinations.

External variations were not observed in any of the fetuses evaluated; however, external malformations, brachygnathia and rudimentary/short tail, were observed in one fetus. Visceral variations included only two fetuses with increased renal pelvic cavitation. At skeletal evaluation, one fetus had brachygnathia, tail short/rudimentary, abnormal fusion of sternebrae, and vertebral anomaly with/without associated rib anomaly. The external, visceral, and skeletal malformations observed were unrelated to dosing with Acacia (Morseth and Ihara 1989a).

Morseth and Ihara (1989b) evaluated the effect of a 5% solution of gum arabic (powder) in distilled water on fertility and general reproductive performance using 30 male (6 weeks old; weights = 181.9 to 226.3 g) and 30 female (10 weeks old; weights = 210.9 to 309.9 g) Sprague-Dawley Crl: CDBR rats. The solution was administered (oral intubation) to male and female rats once daily (5 ml/kg/day) for 63 days prior to mating, throughout the mating period, and until the animals were killed. Male rats were killed after the females had littered. The oral dosing schedule for female rats was daily for 14 days prior to mating, throughout the mating period, and through gestation day 19 or day 21 of lactation. Fifteen female rats were killed on day 20 of gestation, and the remaining females were allowed to raise their neonates to day 22 postpartum.

No abnormal estrous cycles that were considered treatment-related were observed in any of the females. Twenty-nine of the 30 females became pregnant; the male fertility index was 97%. Mean viability and mean weaning indices were 96% and 98%,

respectively. No external, skeletal, or soft tissue malformations were observed (Morseth and Ihara 1989b).

The reproductive toxicity of 5% Gum Acacia was evaluated using nine male Syrian golden hamsters (8 weeks old; weights = 80 to 100 g). The males were mated with female Syrian golden hamsters in order to confirm fertility. Subsequently, the males were dosed (oral gavage) with 5% Gum Acacia (dose volume = 0.1 ml/10 g body weight) daily for 54 days. The animals were killed 3 days after the last dose. As determined by analysis of testis sections, spermatogenesis was reported for all hamsters. All of the hamsters produced morphologically normal sperm, which were also observed in the epididymis (Waller et al. 1983).

Yegnanarayan and Joglekar (1978) studied the antifertility effects of 4% Gum Acacia in a series of five experiments using male and female rats and female rabbits of the Haffkine strain.

In the first study, six male albino rats (weights = 175 to 225 g) were tested. The rats were dosed orally daily for 28 days using a rubber catheter. Beginning on the first day of feeding, males were mated (one male to two females) with females for 12 weeks. Females were replaced each week of feeding. Additional groups of females were mated with control males dosed with saline according to the same procedure. Vaginal smears were examined daily for the presence of spermatozoa. Pregnant females were surgically observed on the tenth day of pregnancy.

The number of inseminated females (73) was the same in experimental and control groups. The total number of pregnant females in experimental and control groups was 24 and 37, respectively, but this difference was not statistically significant.

In the second experiment, the effect of 4% Gum Acacia on the estrus cycle and mating was evaluated using fertile female albino rats (weights = 150 to 200 g). The experiment was divided into two phases. In the first phase (short-term treatment), 4% Gum Acacia was administered orally to 10 female rats over a period of two estrus cycles, beginning on the day of proestrus. The females were mated singly with males during the proestrus phase of the third estrus cycle. In the second phase (long-term treatment), 4% Gum Acacia was administered orally to six female rats over a period of six estrus cycles, beginning in the proestrus phase. Mating was allowed in the proestrus stage of the seventh estrus cycle. In both the first and second experimental phases, control females dosed with saline were mated with males according to the same procedures, respectively. Results for the first and second phases of this experiment indicated no significant differences in mating (number of females inseminated) between experimental and control groups. Additionally, for both phases, no significant changes were observed in the duration of estrus cycles after dosing.

The third experiment, for determining anti-implantation effects, involved 10 fertile rats (weight range from 150 to 200 g) that were mated in proestrus singly with fertile males. Females were dosed orally with 4% gum arabic on days 1 to 7 of pregnancy. The animals were allowed to deliver normally and litter sizes were recorded. Ten control females dosed with saline were mated according to the same procedure. No statistically significant differences were observed in average litter sizes between experimental and control groups, indicating that fetal resorption did not occur in litters of rats dosed with 4% gum arabic.

The fourth experiment was performed to determine any postimplantation effect of 4% gum arabic using ten fertile rats (weights = 150 to 200 g). Female rats were dosed orally with 4% gum arabic on days 10 to 16 and the number of pups delivered was determined. The rats were observed for vaginal bleeding, indicative of abortifacient activity during pregnancy. Control females were dosed with saline according to the same procedure. One of 10 experimental rats did not have a litter. All control females had litters. No statistically significant differences were observed in the number of pups delivered between experimental and control groups.

In the fifth experiment, the antiovulatory potential of 4% Gum Acacia was evaluated using adult female rabbits (number not stated; weights = 1 to 2 kg). The rabbits were dosed orally with 4% gum arabic for 2 days. Copper acetate (4 mg/kg) was then injected into the marginal ear vein in order to induce ovulation. At 48 h post injection, laparotomy was performed; fresh bleeding points on the ovaries were indicative of ovulation. Control rabbits were pretreated with saline according to the same procedure prior to the injection of copper acetate. After the injection of copper acetate, bleeding points on the ovaries were observed in all control and experimental rabbits. Therefore, the authors concluded that 4% Gum Acacia did not have an inhibitory effect on ovulation (Yegnanarayan and Joglekar 1978).

A 1% aqueous suspension or mucilage prepared from gum arabic had no lethal effects on fetuses of NMRI mice injected intraperitoneally (single injection or series of five injections), subcutaneously (five injections), or administered orally (five times) between the 11th and 15th day of gestation (Frohberg et al. 1969).

The embryotoxicity of 1% Gum Acacia was evaluated using ten Charles Foster rats (90 days old; weights = 200 ± 20 g). The test substance was administered daily at a dose of 50 mg/kg/day during the period of organogenesis. The fetuses were delivered by cesarean section on day 20 of gestation, fixed in Bouin's solution, and examined for visceral and skeletal defects. None of the fetuses had gross or visceral defects (Sethi et al. 1989).

CLINICAL ASSESSMENT OF SAFETY

Absorption, Distribution, and Excretion

Gum Arabic

The FASEB (1973) review stated that there was no evidence of the absorption of intact gum arabic found in a study using infants. Twenty-two infants, 1 to 15 months old, were fed gum arabic (15 to 20 g per day) in milk. No urinary excretion of pentose or significant excretion of gum arabic was observed in the stools.

In a nephrotic patient, 20% of the gum arabic injected intravenously over a period of 6 weeks was excreted in the urine.

Other studies involving patients with nephrosis indicated that intravenously injected Gum Acacia, or some product associated with it, accumulated in the liver and remained in the tissues for several months. Serious disturbances in hemoglobin, white blood cells, and serum proteins, all nonlethal effects, were noted (FASEB 1973).

Ross et al. (1984a) evaluated the excretion of gum arabic and its effect on glucose absorption and routine hematological and biochemical measurements in five healthy male volunteers (30 to 55 years old). All subjects were free of signs of gastrointestinal disease. The study was divided into two time periods, a 7-day control period that was followed by a 24-day treatment period. After an overnight fast, glucose (50 g in 200 ml H_20) was fed to each subject on the first day of the control period. During the 24-day treatment period, gum arabic (25 g in 125 ml 7% dextrose) was ingested daily by each subject. Urine was collected on 1 day of the control period and on 1 day during the 3rd week of the treatment period. Complete 5-day fecal collections were made on days 2 to 6 of the control period and on days 16 to 20 of the treatment period. Pooled stool slurry samples from the five subjects were centrifuged. A precipitate typical of gum arabic was not detected in fecal specimens collected before or after the administration of gum arabic.

The marked increases in breath hydrogen production noted after gum arabic ingestion were indicative of bacterial breakdown of gum arabic in the cecum and colon after 3 weeks of administration. Additional study results are summarized in the following paragraph.

No significant differences in the mean concentration of serum lipids (phospholipids and triglycerides) were noted before and after gum arabic ingestion. However, a significant decrease in serum cholesterol (0.39 mmol/L reduction; $p < .05$) was noted. Also, no statistically significant differences were observed between the mean blood glucose concentration (control) and the glucose concentration after the administration of gum arabic.

Similarly, no significant differences were found in the mean insulin concentration (before versus after gum arabic ingestion). Alanine aminotransferase and aspartate aminotransferase activities were significantly reduced ($p < .0025$; $p < .001$) after gum arabic ingestion; however, both mean values were within the normal limits for the population. Of the 13 biochemical measurements that were estimated in the plasma, these reductions in plasma enzyme concentrations represented the only noted significant changes (Ross et al. 1984a).

Short-Term Oral Toxicity

Gum Arabic

Five healthy male subjects (30 to 55 years old) ingested 25 g gum arabic (Acacia Senegal Gum) daily for 21 days. Toxic effects were not observed during the 21-day period; breath hydrogen concentrations increased only after chronic administration. The fact that gum arabic was not recovered from the feces suggest that it is degraded extensively in the human colon (Anderson 1986).

Short-Term Intravenous Toxicity

Acacia (Not Gum Arabic)

Acacia was administered to nine patients with nephrotic edema over periods up to 8 weeks. The test substance was administered intravenously, and total doses ranged from 80 to 325 g. No signs or symptoms of hepatic enlargement or any other complications were observed. Five of the patients excreted 5.5% to 38% of a single dose in the urine during periods ranging from 10 to 30 days, respectively (World Health Organization 1974).

Skin Irritation

Acacia (Not Gum Arabic)

The skin irritation potential of Acacia Farnesiana Extract (from flowers, 4.0% in petrolatum) was evaluated in a 48-h closed-patch test using 30 healthy male and female volunteers. Skin irritation was not observed (Letizia et al. 2000).

Shaligram and Vakil (1990) evaluated the skin irritation potential of Acacia Concinna Fruit Extract (2% in carageenan base [pH of 6 to 7] or 2% in a shampoo [pH of 7 to 8]) in a use test involving 30 normal subjects. The carageenan base and the shampoo, both without the fruit extract, served as controls. The application procedure was described as a routine half head (wet surface) application of Acacia Concinna Fruit Extract (in carrageenan base or in shampoo). The respective controls were applied to the other half of the head (wet surface). Application of test and control materials was followed by rinsing with warm water at 10 to 15 min post exposure. The scalp of each subject was evaluated for signs of irritation (erythema, edema, or any other reaction) at 24 and 48 h post application.

Neither Acacia Concinna Fruit Extract (2% in carrageenan or 2% in shampoo base) nor the controls induced skin irritation (Shaligram and Vakil 1990).

Skin Sensitization

Gum Arabic

Ivy Laboratories (2000) evaluated the skin sensitization potential of a mascara containing 8.0% Acacia Senegal in a maximization test using 28 healthy adult volunteers (males and females, 18 to 49 years old). Twenty-five subjects completed the study because three withdrew for reasons that were unrelated to the test procedure. During the induction phase, approximately 0.1 ml of 0.25% aqueous sodium lauryl sulfate (SLS) was applied (under an occlusive patch) to each subject. Patches were applied to the upper outer arm, volar forearm, or to the back for 24 h. After patch removal, 0.1 ml of the mascara was applied (under an occlusive patch) to the same site on each subject. Patches remained in place for 48 h, except for weekend applications in which the contact period was 72 h. Sites were observed for signs of irritation at the time of patch removal.

If skin irritation was not observed, an occlusive patch containing 0.25% aqueous SLS was applied to the same test site for 24 h. An occlusive patch containing the test substance was then applied to the same site for 48 h. The preceding patch application

TABLE 12
Case reports on Gum Arabic and other species of Acacia

Ingredient studied	Patients evaluated	Procedure/route of exposure	Results	Reference
Acacia	78-year-old male with hard nodular mass in right upper quadrant (shock symptoms reported)	Subcutaneous injection of two doses of the drug tyramin (0.06 g/dose). Second dose followed by i.v. dose of 6% Acacia in saline (500 cc)	Death accelerated by intravenous administration of Acacia solution	Lee 1922
Acacia	Male patient with pulmonary hemorrhage	Intravenous administration of 6% Acacia in saline (150 cc)	Patient's condition worsened immediately after injection, followed by death 2 h 20 min later	Lee 1922
Acacia	27-year-old female recovering from elephantiasis surgery	Intravenous administration of 6% Acacia solution (500 cc) and 500 cc of physiologic saline solution after initial surgery and after second operation 7 months later	No adverse effects after first infusion. Signs/symptoms noted after second infusion: nasal obstruction and lacrimation, followed by difficulty in breathing, coughing, and suggestion of laryngeal stridor. Symptoms disappeared rapidly after epinephrine administration	Maytum and Magath 1932
Acacia	15 kidney transplant patients. Itching/rash in 3 patients	Patients had been treated with prednisone and azathioprine for 10 months to 5 years. Prednisone tablets contained Acacia and tragacanth gums as adhesives. Itching/rash not observed after tablets withdrawn. Scratch tests performed	Scratch test results for 2 of 3 patients with reactions tested: Positive reactions to Acacia and tragacanth gums, respectively. Scratch test results negative in remaining transplant patients	Rubinger et al. 1978
Gum Arabic	65-year-old male with allergic reactions	Four allergic accidents experienced after drinking coffee. Gum arabic used to coat roasted coffee beans. Prick tests and human basophil degranulation tests performed	Dual sensitization to coffee and gum arabic	Moneret-Vautrin 1993
Gum Arabic	57-year-old male with chronic alveolitis	Chronic alveolitis due to repeated and prolonged inhalation of sweets containing gum arabic.	Progress satisfactory in terms of clinical status and lung function measurement after exposure discontinued	De Fenoyl et al. 1987

Acacia (crude and purified forms)	53-year-old plaster molder in candy factory with bronchial asthma	Bronchial asthma due to inhalation of dust from factory environment. Scratch and intradermal injection tests performed	Markedly positive reaction to crude Acacia. Purified Acacia more reactive; induced positive reactions when tested at concentrations as low as 1:5000 dilution in scratch and intradermal injection tests	Spielman and Baldwin 1933
Gum Arabic (extracted with sodium carbohydrate buffer)	50-year-old confectioner at candy factory with strong respiratory allergy to gum arabic	Skin prick and intracutaneous tests	No reaction to gum arabic (1:1000 dilution) in prick test. Intracutaneous test results: +++ (1:10,000 dilution), + (1:100,000 dilution), and (1:1,000,000 dilution). Evaluation of IgE antibody response indicated that patient's serum reacted strongly to gum arabic	Fötisch et al. 1998
Gum Arabic	53-year-old printer with asthma	Asthma due to exposure to offset spray containing gum arabic. Repeat cutaneous and intracutaneous tests performed	4+ reaction to gum arabic in repeat cutaneous and intracutaneous tests	Bohner et al. 1941
Gum Acacia	32 male printers with asthma	Exposure to spray (used in color-printing) containing Gum Acacia and isopropyl alcohol. Average duration of exposure = 4 to 8 years	Asthma developed after exposure to spray	Fowler 1952
Gum Arabic	12 employees of gum processing factory (office and mill workers)	Sensitization test performed	Seven of 12 workers had positive skin reactions to gum arabic. All 12 had respiratory symptoms that were of an allergic nature	Gelfand 1943
Gum Arabic (as supplied)	24-year-old printer with 3-month history of hand dermatitis	Exposure to gum arabic on the job. Patch tests (Finn chambers) performed	++ reaction to gum arabic	Freeman 1984
Wet clay containing 5 to 7% gum arabic	45-year-old female with rash on hands	Exposure to wet clay for 2 years on the job. Patch tests performed	+ reaction to 1% and 5% aqueous gum arabic. ++ reaction to 25% aqueous gum arabic	Ilchyshyn and Smith 1985
Gum Arabic	44-year-old lithoprinter with 2-year history of hand eczema	Exposure to gum arabic (used to coat printing plates) on the job. Eczema worsened after exposure to gum arabic. Patch testing of 10% aqueous gum arabic	Positive patch test reaction to 10% aqueous gum arabic	van Ketel 1984

sequence was repeated for a total of five induction exposures, after which a 10-day nontreatment period was observed. Prior to challenge patch application, a new site on the opposite arm, forearm, or side of the back was pretreated for 1 h with 5% aqueous SLS (0.1 ml under occlusive patch). A single challenge patch (occlusive patch) was then applied to the same site for 48 h. Reactions were scored at 1 and 24 h after patch removal according to the following scale: 0 (not sensitized) to 3 (strong sensitization [large vesiculobullous reaction]).

Sensitization reactions were not observed at 1 or 24 h after challenge patch removal. It was concluded that, under the conditions of this test, the mascara containing 8.0% Acacia Senegal did not possess a detectable contact-sensitizing potential, and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 2000).

Acacia (Not Gum Arabic)

Letizia et al. (2000) evaluated the sensitization potential of Acacia Farnesiana Extract (from flowers, 4% in petrolatum) in a maximization test using 30 healthy male and female volunteers. The test substance was applied, under occlusion, to the same site on both forearms of each subject throughout induction. The induction phase consisted of a total of five 48-h exposures (on alternate days).

Prior to application of the initial induction patch, the test site was pretreated with 5% aqueous SLS, under occlusion. The induction phase was followed by a 14-day nontreatment period, after which a challenge patch was applied (48 h) to new sites on each subject. Challenge patch applications were preceded by 30 min applications of 2% aqueous SLS, under occlusion, on the left side. Challenge sites on the right side were not pretreated. A fifth challenge site (petrolatum applied) served as the control.

It was concluded that none of the reactions observed could be classified as a significant skin irritation or allergic reaction (Letizia et al. 2000).

Case Reports

Gum Arabic

Gelfand (1949) reported allergic disorders in 10 subjects (7 males, 3 females; 11 to 55 years old) who had ingested various gum-containing foods. Gum arabic was among the gums present in each food ingested. Some of the allergic symptoms reported included bronchial asthma, generalized urticaria, and vasomotor rhinitis. Allergic symptoms were not observed upon removal of suspect gum-containing foods from the diet, and symptoms were reproduced when clinical trials were repeated.

Positive skin reactions (test procedure not stated) to gum arabic were observed in each of the 10 subjects. The results of serologic studies (sera from four subjects) indicated that gum arabic was the dominant gum antigen in two subjects and that tragacanth and karaya were the dominant gum antigens in the remaining two subjects. The serological studies included passive transfer tests in serial dilutions and neutralization studies. It was determined that gum arabic and other vegetable gums could cause allergic disorders by ingestion in sensitive subjects (Gelfand 1949).

Raghuprasad et al. (1980) reported cross-reactivity between Gum Acacia and gum tragacanth in a 24-year-old patient who developed sensitization to Quillaja bark (*Quillaja saponaria*) dust, which resulted in rhinitis and asthma. The CIR Expert Panel has previously evaluated the safety of Tragacanth Gum in cosmetics, and concluded that this ingredient is safe in the present practices of use and concentration (Elder 1987). Specific immunoglobulin E(IgE) to pulverized Quillaja bark, gum arabic, and gum tragacanth were measured according to a modification of the radioallergosorbent test (RAST). Each of the three antigens (20 mg/ml) was coupled directly to methyl cellulose disks that had been activated previously by cyanogen bromide dissolved in acetonitrile. Results were expressed as percent binding.

The amount of radioactivity bound by the patient's serum was compared with control sera from healthy, nonallergic volunteers (number not stated) not known to be exposed to Quillaja bark dust. The mean percent binding of IgE to Quillaja bark in patient sera was 22.4%, compared to 3.2% for the control. Compared to negligible binding in control sera, significant binding was reported for gum arabic (32.5% binding) and gum tragacanth (30.8% binding) (Raghuprasad et al. 1980).

Additional case reports on gum arabic and other species of *Acacia* are summarized in Table 12. Although two fatalities are reported, neither related to gum arabic and most case reports involve sensitization reactions.

SUMMARY

This safety assessment includes the following ingredients, derived from Acacia, that are listed in the *International Cosmetic Ingredient Dictionary and Handbook*: Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, Acacia Senegal Extract, Acacia Senegal Gum, and Acacia Senegal Gum Extract.

Gum arabic is another name for Acacia Senegal Gum. Gum arabic is generally recognized as safe for direct addition to food for human ingestion. Acacia Senegal Gum has been described as the major commercial Acacia gum. Gum arabic is produced when the Acacia tree is stressed by infection, poor nutrition, heat, or lack of moisture. The gum exudes through wounds in the bark that occur naturally or are purposely made to stimulate production.

Gum arabic is composed of D-galactose, L-rhamnose, L-arabinose, and D-glucuronic acid residues in an arrangement of a main chain of galactosyl units joined by β-D-(1 $\rightarrow$ 3) linkages and side chains or branched oligosaccharides linked to the main chain by β-D-(1 $\rightarrow$ 6) linkages. It has also been described as a complex mixture of calcium, magnesium, and potassium salts of arabic acid. Arabic acid is a complex of galactose, rhamnose, arabinose, and glucuronic acid.

Aflatoxin has been reported as an impurity in Acacia Catechu, but not in gum arabic. Acacia Gum (Acacia Senegal) did not contain detectable pesticide residues.

Qualitative information is available on the components that may be found in ingredients derived from various Acacia species and plant parts. This information indicates a few similarities and many differences in constituents. Quantitative or semiquantitative data were not available.

The principal UV absorbance of gum arabic occurred at wavelengths below 240 nm. At wavelengths above 240 nm, the UV absorbance was not significant.

Acacia Decurrens Extract and Acacia Farnesiana Extract are described as a cosmetic astringent, and Acacia Decurrens is also described as a skin-conditioning agent—occlusive, although none of these are reported to be in current use. Cosmetic functions of the other Acacia-derived ingredients included in this review are not described. Product formulation data submitted to the FDA indicated that Acacia was used in 22 cosmetic products—no information is available to further describe the species or plant part. Cosmetic use concentration data supplied by the cosmetics industry indicated maximum use concentrations of 9% in shampoos for Acacia Senegal Gum and 0.001% for Acacia Senegal Gum Extract, in bath soaps and detergents.

Recommended use concentrations of Acacia Concinna Fruit Extract are 1.0% to 2.0% for use in shampoos, hair packs, hair conditioners, and hair rinses, although no uses have been reported to FDA.

The weight gain for rats fed gum arabic at a dietary concentration of 16% was 75% of that reported for control rats. Approximately 80% of the gum arabic was absorbed. Results from other studies involving rats suggest that the metabolism of gum arabic is mediated by bacteria in the cecum.

Results of studies in which dogs and rabbits were injected intravenously with gum arabic indicated that gum arabic or some other product associated with it accumulated in the liver and remained in the tissues for several months. Nonlethal effects included disturbances in hemoglobin values, white blood cells, and serum proteins.

Based on absorption and metabolism studies an expert analysis determined that gum arabic is capable of being digested to simple sugars. It was also determined that conclusive evidence indicating that the intact gum arabic molecule is absorbed under normal conditions was lacking.

In an in vitro assay, dose-dependent uncoupling of oxidative phosphorylation was noted in groups of rats dosed orally with gum arabic up to 10% twice daily for 4 weeks, but comparable biochemical effects were not observed in vivo.

An acute oral LD_{50} of 8000 mg/kg was reported for Acacia Gum in rabbits. The acute oral LD_{50} for Acacia Farnesiana Extract (from flowers) in rabbits was >5.0 g/kg. A minimal lethal dose of >2 g/kg (10 ml/kg) for Acacia Dealbata Leaf Wax in a suspension with paraffin oil was reported in an acute oral toxicity study involving rats. None of the animals died, and no test substance-related lesions of organs examined were noted at necropsy. Similarly, in another study, no deaths or test substance-related, organ lesions were reported following the oral administration of Acacia Farnesiana Flower Wax at a dose of 10 ml/kg.

In an acute dermal toxicity study of Acacia Farnesiana Extract (from flowers) involving rabbits, an LD_{50} of >5.0 g/kg was reported.

Gum arabic did not cause any abnormal changes in serum chemistry parameters or induce toxicologically significant lesions in rats that received oral doses daily for 28 days. Gum arabic was also administered to rats in four other short-term oral toxicity studies. Collectively, test concentrations ranged from 1% to 20% and study durations ranged from 28 days to 9 weeks. No significant or discernible ultrastructural differences were found between tissues (heart, liver, small intestine) of control rats and test rats; hematological findings were normal. Gum arabic was nontoxic, even at the highest concentration tested.

One of three dogs injected intravenously (32 to 35 injections) with gum arabic over a period of 76 days died. The range for the total cumulative dose was 15.7 to 47.7 g/kg, and death occurred at the highest dose (47.7 g/kg). An enlarged liver was observed in the animal that died, and the cause of death was not determined. Enlarged livers and swollen kidneys were also observed in dogs that received doses ranging from 1 to 2 g/kg.

In a subchronic (13 weeks) oral toxicity study on Acacia Senegal Gum, the only treatment-related alteration noted in rats at necropsy was cecal enlargement in animals of the highest dose (14 g/kg/day) groups.

Electron microscopic findings for samples of livers and kidneys from groups of five rats fed diets containing 0.5% to 3.5% w/w Acacia Senegal Gum daily for 91 days were negative. Mitochondria and nuclei were ultrastructurally normal in appearance and internal structure.

The administration of a single dermal dose of Acacia Farnesiana Extract (from flowers, 5.0 g/kg) to rabbits induced moderate erythema and edema. Undiluted Acacia Dealbata Leaf Wax was classified as a non-irritant after application, under occlusive patches, to scarified skin of albino rabbits for 24 h. Undiluted Acacia Farnesiana Flower Wax was classified as a slight irritant when tested according to a similar procedure.

A 20.0% solution of Acacia Farnesiana Extract in methanol (from flowers) did not induce phototoxicity in SKH:hairless mice.

Anaphylactic signs in guinea pigs injected intraperitoneally (mild challenge reactions) or intravenously (strong challenge reactions) with Acacia solution have been reported. No signs of anaphylaxis were observed in rabbits injected intravenously (no challenge reaction) with Acacia solution. In rabbits and guinea pigs injected with 7% Gum Acacia solution, no deleterious effects on antibody production resulted.

Mouse footpad swelling test results indicated a significant increase in footpad thickness (compared to controls) in mice immunized by injection of gum arabic in saline and Freund's adjuvant. Antigen-specific hypersensitivity reactions were noted. In a similar test, footpad swelling was significantly suppressed

(compared to controls) in mice dosed orally with gum arabic and then immunized by injection of gum arabic in saline and Freund's adjuvant. In another test, intradermal challenge after immunization of mice with Acacia Senegal Gum caused a significant increase in footpad thickness.

Gum arabic was not mutagenic in numerous in vitro mutagenicity tests using *Salmonella typhimurium, Saccharomyces cerevisiae,* and *Bacillus subtilis* bacterial strains. In an in vitro cytogenetics assay, though results were classified as slightly positive, gum arabic did not induce definite abnormal anaphase figures in diploid human embryonic lung (WI-38) fibroblasts. The mutagenicity of gum arabic was also evaluated in numerous in vivo assays, the results of which were mostly negative.

Statistically significant positive results were noted in one of the three dominant lethal tests (rat assay, but not in two mouse assays) that were performed. Further testing in the mouse heritable translocation test yielded negative results. In acute and short-term in vivo cytogenetics assays (rats), though no significant positive responses were observed, there may have been a slight positive response. It was stated that further tests and a detailed statistical evaluation are needed in order to confirm this possibility. There were no statistically significant findings in mouse chromosomal aberrations and sperm-head morphology assays. Negative results were also reported in micronucleus tests (mouse bone marrow smears) and other in vivo assays.

No evidence of carcinogenicity was observed in rats dosed intraperitoneally with gum arabic (1.75% or 7.0% in saline or water) three times per week for up to 15 weeks. In another study, tumors were not observed in guinea pigs injected intramediastinally with 0.1 ml of a gruel of gum arabic (single dose).

The carcinogenicity of gum arabic was also evaluated using 4-week-old F344 and 4- to 5-week-old $B6C3F_1$ mice. Low-dose animals were fed gum arabic at a concentration of 25 g/kg in the diet and high-dose animals were fed 50 g/kg for 103 weeks. Neoplasms were observed only in male rats, and were diagnosed as malignant lymphomas or leukemia-lymphoma. Compared to controls, no significant increases were observed in the incidence of either type of neoplasm at either of the two test concentrations; gum arabic was classified as noncarcinogenic in rats and mice.

Oral administration of gum arabic (1 ml) did not cause antifertility effects in female rats or the suppression of spermatogenesis in male rats. Gum arabic was not teratogenic when administered orally to mice at doses up to 1600 mg/kg. Oral doses of gum arabic up to 1600 mg/kg also were not teratogenic in rats and hamsters, and oral doses up to 800 mg/kg were not teratogenic in rabbits.

No effects on fertility or ovulation (4% gum arabic), or any abnormal variations in blastocysts (10% gum arabic) were found in rabbits. Gum arabic, at a concentration of 15%, failed to induce teratogenicity or other reproductive effects in female rats. Gum arabic (5%) also did not cause abnormal sperm development in hamsters. Embryotoxicity was not noted in mice injected intraperitoneally with a 1% aqueous suspension or mucilage prepared from gum arabic.

No evidence of absorption of intact gum arabic was found in 22 infants fed gum arabic in milk. In a patient with nephrosis, 20% of the gum arabic injected intravenously was excreted in the urine over a period of 6 weeks. Gum arabic was not detected in feces specimens collected from five male volunteers before or after administration of the gum.

Toxic effects were not observed in five male subjects who ingested 25 g of gum arabic daily for 21 days.

In a 48-h closed patch test, Acacia Farnesiana Extract (from flowers, 4.0% in petrolatum) did not induce skin irritation in any of the 30 subjects tested. In an "in-use test," skin irritation was not observed in any of the 30 subjects tested with Acacia Concinna Fruit Extract (2% in natural base [such as carageenan] and a routine shampoo base). The test substance remained in contact with the scalp for 10 to 15 min, and skin irritation was evaluated immediately after application and 24 and 48 h later.

The skin sensitization potential of a mascara containing 8.0% Acacia Senegal was evaluated in the maximization test using 28 healthy adult volunteers. It was concluded that, under the conditions of this test, the mascara containing 8.0% Acacia Senegal did not possess a detectable contact-sensitizing potential, and, hence, is not likely to cause contact sensitivity reactions under normal use conditions.

The results of a study involving ten subjects who had ingested various gum-containing foods, indicated that gum arabic could cause allergic disorders in sensitive subjects. Analyses of sera from 4 of the 10 subjects indicated that gum arabic was the dominant gum antigen in two subjects. Cross-reactivity between gum arabic and gum tragacanth was reported for a 24-year-old patient who developed sensitization to Quillaja bark (*Quillaja saponaria*) dust, which led to rhinitis and asthma.

Neither significant skin irritation nor allergic reactions to 4% Acacia Farnesiana Extract (from flowers) in petrolatum were observed in a maximization test (30 subjects).

A number of case reports of gum arabic allergenicity have been identified in the published literature.

DISCUSSION

Extensive safety test data are available on gum arabic that demonstrate its safety in a wide variety of applications, including cosmetic use. Based on the available information, the Panel concluded that Acacia Senegal Gum is equivalent to gum arabic and should be considered safe as used in cosmetics. It also appears that gums from other species are not the same as Acacia Senegal Gum. It follows that the safety test data on gum arabic can be used to support the safety of Acacia Senegal Gum and not gum from other Acacia species. Because Acacia Senegal Gum Extract is derived from Acacia Senegal Gum, the Panel considered that Acacia Senegal Gum Extract would present no additional safety issues.

The Panel recognized the potential for allergic responses to gum arabic. However, because of negative results for all 25 subjects in a human maximization study (mascara containing 8%

Acacia Senegal) and the expected slow rate of dermal absorption of gum arabic due to its large molecular size and water solubility, the Panel determined that it is not likely that normal use of gum arabic in a cosmetic product would result in sensitization.

The Panel is concerned that the available data suggesting the absence of pesticide residues in Acacia plants harvested wild are limited. The Panel advised the industry that the total polychlorinated biphenyl (PCB)/pesticide contamination of any plant-derived cosmetic ingredient should be limited to not more than 40 ppm, with not more than 10 ppm for any specific residue. The Panel also advised that limits were appropriate for the following impurities: arsenic (3 mg/kg maximum), heavy metals (0.002% maximum), and lead (5 mg/kg maximum).

The limited safety test data on Acacia Farnesiana Extract and on Acacia Concinna Fruit Extract were not sufficient to assess the safety of these ingredients in cosmetics.

The Panel found no information that adequately characterized the composition of fruit, leaf or other extracts, leaf wax, flower wax, or gum from Acacia species other than *A. senegal*. Therefore, the Panel could not extrapolate the available data on gum arabic to support the safety of Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, and Acacia Senegal Extract. The Panel concluded that available data are insufficient to support the safety of these Acacia-derived ingredients.

The additional data needed for these ingredients include

1. concentration of use in cosmetics;
2. identify the chemical composition; if they are sufficiently different from those of Acacia Senegal Gum, then the following data would be needed:
   a. UV absorption spectrum; if there is significant absorbance in the UVA or UVB range, then phototoxicity and photosensitization studies may be needed;
   b. with the exception of Acacia Farnesiana Extract and Acacia Concinna Fruit Extract, sensitization and irritation data are needed;
   c. two genotoxicity assays, one in a mammalian system; if positive, then a 2-year dermal carcinogenicity study using National Toxicology Program (NTP) methods may be needed;
   d. dermal absorption data; if there is any evidence of significant dermal absorption, then reproductive and developmental toxicity data may be needed.

CONCLUSION

Based on the available animal and clinical data included in this report, the CIR Expert Panel concluded that Acacia Senegal Gum and Acacia Senegal Gum Extract are safe as used in cosmetic products. The Panel also concluded that the available data are insufficient to support the safety of the following ingredients in cosmetic products: Acacia Catechu Gum, Acacia Concinna Fruit Extract, Acacia Dealbata Leaf Extract, Acacia Dealbata Leaf Wax, Acacia Decurrens Extract, Acacia Farnesiana Extract, Acacia Farnesiana Flower Wax, Acacia Farnesiana Gum, and Acacia Senegal Extract.

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