Toxicological profile for

Maltodextrin

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

(2R,3S,4R,5R)-2,3,4,5,6-Pentahydroxyhexanal (BPDB, 2023)

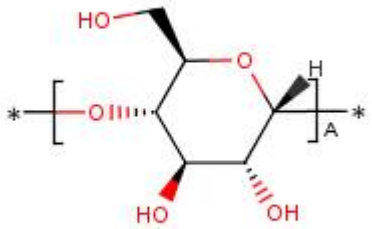
1.2. Synonyms

Corn Sugar (Dextrose); Corn sugar; D(+)-Glucose; D-Glucose; D-Glucose, anhydrous; D-Glucose; dextrose, glucolin, glucose; D-glucosa; Dextropur; Dextrose; Dextrose, anhydrous; Dextrosol; Maldex 15; Maltodextrin; Maltodextrina; Maltodextrins; Maxim Energy Gel; NSC 406891; Sirup; Staleydex 111; Staleydex 333; Sugar, grape; Tabfine 097(HS); Vadex; Dextrose (ToxInfo)

1.3. Molecular formula

$(C_{12}H_{20}O_{11})n$ (BPDB, 2023); (C6H10n+2O5n+1) (EFSA, 2023)

1.4. Structural Formula



1.5. Molecular weight (g/mol)

Variable (polymeric); (240)n (BPDB, 2023); Variable (range 504-3,258 g/mol) (EFSA, 2023)

1.6. CAS registration number

9050-36-6 [Two other CAS numbers are listed in ToxInfo].

1.7. Properties

1.7.1. Melting point

(°C): Decomposes before melting(BPDB, 2023); not relevant (autoignition occurs at 420°C) (EFSA, 2011)

1.7.2. Boiling point

(°C): Not relevant (autoignition occurs at 420°C) (EFSA, 2011); Decomposes before boiling (BPDB, 2023)

1.7.3. Solubility

No solubility limits identified, but one paper notes the use of a solution containing 67 g maltodextrin per 100 ml water (Viinamaki et al., 1989); >600 g/L at 20°C (EFSA, 2011); 600g/L (BPDB, 2023)

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

(°C): 287 (BPDB,2023)

1.7.6. Flammability limits (vol/vol%)

No data available to us at this time.

1.7.7. (Auto)ignition temperature

(°C): 420 (EFSA, 2011)

1.7.8. Decomposition temperature

(°C): No data available to us at this time.

1.7.9. Stability

Avoid reaction with oxidizing agents; non-corrosive; explosive under certain conditions (BPDB, 2023)

1.7.10. Vapor pressure

“Assumed negligible at 20°C” (EFSA, 2011)

1.7.11. log Kow

assumed <3 (EFSA, 2011)

2. General information

2.1. Exposure

Cosmetics: Yes (Cosing)

Food: No evidence

Environment: No evidence

Pharmaceuticals: Yes (Martindale, 1999)

Maltodextrin, a source of carbohydrate, is often used in oral dietary supplements and tube feeding.

Used as a pharmaceutical excipient.

As taken from Martindale, 1999

Maltodextrins are a group of oligosaccharides, which are being increasingly used as a source of carbohydrate in many commercially available foods and drinks. This study investigated the effect of

three different maltodextrins on the pH of dental plaque, in vivo, in 10 adult volunteers using the plaque harvesting method. The three maltodextrins tested in this study were DE=5.5, 14.0 and 18.5 (DE=dextrose equivalents), made up as 10% solutions. Also, three commercially available maltodextrin containing children's drinks were evaluated for their acidogenicity. 10% sucrose and 10% sorbitol solutions were used as positive and negative controls, respectively. The minimum pH achieved for DE=5.5, 14.0 and 18.5 was 5.83+/-0.30, 5.67+/-0.24 and 5.71+/-0.29, respectively, and were significantly higher as compared with that for 10% sucrose (5.33+/-0.17). The area under the curve was the least for DE=5.5 (12.03+/-4.64), followed by DE=18.5 (13.13+/-8.87) and DE=14.0 (17.35+/-6.43), but were all significantly smaller as compared with 10% sucrose (24.50+/-8.64). The minimum pH achieved for the infant drinks was 6.01+/-0.24, 5.99+/-0.28 and 5.8+/-0.19 for the Lemon Barley and Camomile Herbal baby drink, Mixed Citrus and Hibiscus baby drink, and Infant Milk, respectively. It was concluded that though maltodextrins appeared to be significantly less acidogenic than 10% sucrose, they can lead to a substantial drop in plaque pH and may, therefore, have a potential to cause demineralisation of enamel.

As taken from Al-Khatib GR et al. 2001. J. Dent. 29(6), 409-14. PubMed, available at https://pubmed.ncbi.nlm.nih.gov/11520589/

“The objective of the study was to examine the cariogenic potentials of maltodextrins and glucose syrups (two glucose polymers derived from starch) using a range of techniques in vitro and in laboratory animals. The experimental methods used were: (1) measurement of acid production from glucose syrups and maltodextrins by human dental plaque micro-organisms; (2) evaluation of the role salivary alpha-amylase in degrading oligosaccharides (degree of polymerisation > 3) in the glucose polymers, estimating the products by HPLC; (3) assessment of the fermentability of trioses relative to maltose; (4) measurement of dental caries levels in three large-scale studies in laboratory rats fed on diets containing the glucose polymers. It was found that acid production from the glucose polymers increased as their higher saccharide content fell. Salivary alpha-amylase rapidly degraded the oligosaccharides (degree of polymerisation > 3), mainly to maltose and maltotriose. In the presence of oral micro-organisms, maltotriose took longer to ferment than maltose, but by the end of a 2 h period the total amount of acid produced was the same from both. Incorporated into the diets in solid form, the glucose syrups and maltodextrins were associated with unexpectedly high levels of dental caries. In conclusion, the findings were unforeseen in the light of earlier data that a glucose syrup was less cariogenic than sucrose.”

As taken from Grenby TH & Mistry M. 2000. Br. J. Nutr. 84(4), 565-74. PubMed, available at https://pubmed.ncbi.nlm.nih.gov/11103228/

“One hundred reconstituted milk-based infant formulae (IMF) representative of 10 leading brands available in many European Economic Community countries were examined for Bacillus cereus and for the presence of diarrheal enterotoxin. Sixty-three reconstituted IMF supported growth of the organism after 14 h at 25°C, and in 4 of these, which contained maltodextrin, enterotoxin was detected. Reconstituted IMF (and basal synthetic media) supplemented with \ 0.1% maltodextrin supported both growth of B. cereus and diarrheal toxin production when incubated for 14 h or more at 25°C.”

As taken from ROWAN NJ & ANDERSON JG. 1997. APPLIED AND ENVIRONMENTAL MICROBIOLOGY 63(3). 1182-1184. PubMed, available at https://pubmed.ncbi.nlm.nih.gov/9055435/

Maltodextrin (CAS RN 9050-36-6) is used as an absorbent, anticaking agent, binder, bulking agent, coating agent, cryoprotectant, delivery system, diluent, filler, skin-conditioning agent, stabilizing agent, suspending agent – nonsurfactant, thickening agent and viscosity increasing agent in non-medicinal natural health products.

As taken from Health Canada, 2021INCI Name	MALTODEXTRIN
Description	Maltodextrin

CAS #	9050-36-6
EC #	232-940-4
Cosmetics Regulation provisions	
Functions	ABSORBENT BINDING EMULSION STABILISING FILM FORMING HAIR CONDITIONING SKIN CONDITIONING
SCCS opinions	
Identified INGREDIENTS or substances e.g.	

As taken from CosIngMaltodextrin is listed as an ingredient (at given concentrations, where specified) in personal care (0-10%), “old” pet care, inside the home and auto products by the CPID.

”Active ingredient in the EU for use as an insecticide on non-edible plants, soft fruit, cane fruit, bush fruit, brassicae, and top fruit; [ExPub: EFSA - PRAPer Conclusion] Used as a flavoring agent, anticaking agent, humectant, nutritional supplement, nutritive sweetener, solvent, stabilizer or thickener, surface-active agent, and texturizer for foods; [FDA]”

As taken from Haz-Map, 2020

2.2. Combustion products

No data available to us at this time.

2.3. Ingredient(s) from which it originates

“A glucose polymer prepared by the partial hydrolysis of starch.”

As taken from Martindale, 1999

3. Status in legislation and other official guidance

States approving use in tobacco: Unknown

Food use approved in:

EU: Unknown

USA: Maltodextrin is included on the US FDA’s list of Substances Added to Food (formerly EAFUS) as an anticaking agent or free-flow agent, flavoring agent or adjuvant, humectant, nutrient supplement, nutritive sweetener, solvent or vehicle, stabilizer or thickener, surface-active agent and texturizer and is covered under US CFR Title 21, Part 184 Direct Food Substances Affirmed As Generally Recognized As Safe, Subpart B - Listing of Specific Substances Affirmed as GRAS, Section 184.1444 – Maltodextrin (US FDA, 2024a).

ADI/TDI: No ADI identified.

Codex Alim.: Not listed

C of E no.: Not listed

FEMA no.: Not listed

TLV/OEL: Not listed

Cosmetics(UK): Not listed in Schedule 1

Maltodextrin is listed as a fragrance ingredient by IFRA.

Maltodextrin is listed on the US EPA InertFinder Database as approved for food and non-food use pesticide products. Maltodextrin is not registered under REACH (ECHA).

Maltodextrin is not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2024).

EC Regulation 1107/2009 (repealing 91/414):

EC Regulation 1107/2009 Status	Approved
Dossier rapporteur/co-rapporteur	UK
Date EC 1107/2009 inclusion expires	30/09/2026
EU Candidate for substitution (CfS)	No
Listed in EU database	Yes

As taken from BPDB, 2023.

Maltodextrin (CAS RN 9050-36-6) is included on the US EPA's list of Safer Chemical Ingredients (US EPA, 2024).

Maltodextrin (CAS RN 9050-36-6) is listed on the US EPA Toxic Substances Control Act (TSCA) inventory, and also on the US EPA 2024 CDR (Chemical Data Reporting) Regulation and 2024 CDR Full Exempt list.

The TSCA inventory, and 2024 CDR and 2024 CDR Full Exempt lists.

Maltodextrin is classified as a natural health product (NHP) under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations (Health Canada, 2021).

Maltodextrin is included on the US FDA's list of inactive ingredients for approved drug products. It is permitted for use as an ingredient in various products, at the following maximum potencies per unit dose and maximum daily exposures (MDE):

Inactive Ingredient	**Route**	**Dosage Form**	**CAS Number**	**UNII**	**Maximum Potency per unit dose**	**Maximum Daily Exposure (MDE)**
MALTODEXTRIN	ORAL	CAPSULE	9050366	7CVR7L4A2D		200mg
MALTODEXTRIN	ORAL	FILM, SOLUBLE	9050366	7CVR7L4A2D	3.2mg	
MALTODEXTRIN	ORAL	GRANULE, FOR SUSPENSION	9050366	7CVR7L4A2D		952mg
MALTODEXTRIN	ORAL	LOZENGE	9050366	7CVR7L4A2D		175mg
MALTODEXTRIN	ORAL	PASTE	9050366	7CVR7L4A2D		1050mg
MALTODEXTRIN	ORAL	POWDER, FOR SUSPENSION	9050366	7CVR7L4A2D		8000mg
MALTODEXTRIN	ORAL	SOLUTION	9050366	7CVR7L4A2D		1451mg

MALTODEXTRIN	ORAL	SUSPENSION	9050366	7CVR7L4A2D		6040mg
MALTODEXTRIN	ORAL	TABLET	9050366	7CVR7L4A2D		80mg
MALTODEXTRIN	ORAL	TABLET, CHEWABLE	9050366	7CVR7L4A2D	292mg	
MALTODEXTRIN	ORAL	TABLET, COATED	9050366	7CVR7L4A2D	5.6mg	
MALTODEXTRIN	ORAL	TABLET, EFFERVESCENT	9050366	7CVR7L4A2D		14404mg
MALTODEXTRIN	ORAL	TABLET, EXTENDED RELEASE	9050366	7CVR7L4A2D		3239mg
MALTODEXTRIN	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	9050366	7CVR7L4A2D	NA	
MALTODEXTRIN	ORAL	TABLET, ORALLY DISINTEGRATING	9050366	7CVR7L4A2D		12mg

As taken from US FDA, 2024b

Maltodextrin (CAS RN 9050-36-6) “poses no unreasonable risk to human health based on Tier I assessment under the NICNAS IMAP assessment framework” and has been “identified as low concern to human health by application of expert validated rules under the NICNAS targeted tier I approach” (AICIS, 2017).

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

“PURPOSE: To compare the effects of high (HMW) versus low molecular weight (LMW) glucose polymer solutions on the pattern of substrate oxidation during exercise. METHODS: Eight cyclists (VO(2max): 63 +/- 8 mL.kg(-1).min(-1)) performed three 150-min cycling trials at 64 +/- 5% VO(2max) while ingesting 11.25% HMW (500-750 kg.mol(-1), 21 mOsm.kg(-1)) or LMW (8 kg.mol(-1), 110 mOsm.kg(-1)) solutions providing 1.8 g of carbohydrate per minute, or plain water. Substrate oxidation was determined using stable-isotope methods and indirect calorimetry.RESULTS: Exogenous carbohydrate oxidation rate was not affected by carbohydrate molecular weight (P = 0.89, peak rate: 0.93 x// 1.37 g.min(-1)). There was no effect of carbohydrate molecular weight on endogenous carbohydrate or fat oxidation rates (P = 0.30), plasma free fatty acid (P = 0.14), lactate (P = 0.38), or glucose concentrations (P = 0.98), nor were there any serious gastrointestinal complaints reported for either of the two solutions during exercise.

CONCLUSIONS: Despite previous reports of faster gastric emptying and glycogen resynthesis suggesting enhanced glucose delivery, a markedly hypotonic HMW glucose polymer solution had no effect on exogenous and endogenous substrate oxidation rates during exercise, relative to a LMW glucose polymer solution. These data are consistent with there being no effect of carbohydrate structure or solution osmolality or viscosity on exogenous glucose oxidation and that ingested glucose polymers can only be oxidized on average up to 1.0 g.min during exercise.”

As taken from Rowlands DS et al. 2005Med. Sci. Sports Exerc. 37(9), 1510-6. PubMed, available at https://pubmed.ncbi.nlm.nih.gov/16177602/

“It is accepted that maltodextrin is rapidly metabolised to glucose following ingestion. No further investigation is considered necessary.” As taken from EFSA, 2023

4.2. Absorption, distribution and excretion

“Hydrogenated resistant maltodextrin (H-RMD) is a dietary fiber whose energy value has not previously been reported. We evaluated the energy value of H-RMD. We conducted an in vitro digestion test, in vivo blood glucose measurement after ingestion, in vitro fermentability test, excretion test by rats and indirect calorimetry combined with breath hydrogen measurement for humans. H-RMD was hydrolyzed in vitro in a very small amount by human salivary amylase and by the rat small intestinal mucosal enzyme. Ingestion of H-RMD did not increase the blood glucose level of human subjects. An examination of in vitro fermentability suggested that H-RMD was fermented by several enterobacteria. Oral administration of H-RMD showed a saccharide excretion ratio of 42% by rats. A combination of indirect calorimetry and breath hydrogen measurement evaluated the metabolizable energy of H-RMD as 1.1 kcal/g in humans. We concluded from these results that H-RMD was not digested or absorbed in the upper gastrointestinal tract and was fermented in the colon to produce short-chain fatty acids which provided a lower amount of energy than that of resistant maltodextrin.” As taken from Tagami H et al. 2012. Biosci. Biotechnol. Biochem. 76(10), 1828-1834. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/23047091

“Maltodextrin is rapidly broken down to glucose following ingestion” (EFSA, 2011).

4.3. Interactions

“To determine whether combined ingestion of maltodextrin and fructose during 150 min of cycling exercise would lead to exogenous carbohydrate oxidation rates higher than 1.1 g.min.

METHODS: Eight trained cyclists VO2max: 64.1 +/- 3.1 mL.kg.min) performed three exercise trials in a random order. Each trial consisted of 150 min cycling at 55% maximum power output (64.2+/-3.5% VO2max) while subjects received a solution providing either 1.8 g.min of maltodextrin (MD), 1.2 g.min of maltodextrin + 0.6 g.min of fructose (MD+F), or plain water. To quantify exogenous carbohydrate oxidation, corn-derived MD and F were used, which have a high natural abundance of C.

RESULTS: Peak exogenous carbohydrate oxidation (last 30 min of exercise) rates were approximately 40% higher with combined MD+F ingestion compared with MD only ingestion (1.50+/-0.07 and 1.06+/-0.08 g.min, respectively, $P<0.05$). Furthermore, the average exogenous carbohydrate oxidation rate during the last 90 min of exercise was higher with combined MD+F ingestion compared with MD alone (1.38+/-0.06 and 0.96+/-0.07 g.min, respectively, $P<0.05$).

CONCLUSIONS: The present study demonstrates that with ingestion of large amounts of maltodextrin and fructose during cycling exercise, exogenous carbohydrate oxidation can reach peak values of approximately 1.5 g.min, and this is markedly higher than oxidation rates from ingesting maltodextrin alone.”

As taken from Wallis GA et al. 2005. Med. Sci. Sports Exerc. 37(3), 426-32. PubMed, available at https://pubmed.ncbi.nlm.nih.gov/15741841/

5. Toxicity

5.1. Single dose toxicity

“Maltoxdextrin is concluded to not pose a short-term toxicity hazard due to the fact that it is rapidly metabolised with metabolites being a standard energy source. Maltodextrin is not toxic and its status as a permitted food additive with no toxicological concerns is concluded to preclude the need for any additional short-term toxicity studies”

As taken from EFSA, 2011.

“Several acute toxicity studies were performed with the product ‘Hugtite’ (50% w/w aqueous solution) and did not provide evidence of acute toxic properties. However, it is noted that ‘Hugtite’ has not been demonstrated to be equivalent to the representative plant protection product ‘Eradicoat’.”

As taken from EFSA, 2013.

"One acute oral toxicity study has been performed. The study was carried out with Hugtite, a 50% w/w solution derived from potato starch, not maize starch, but this was considered acceptable. The study followed OECD 401 (1981) and no deviations were noted.

Hugtite was found to be of low acute oral toxicity, with no mortalities, no clinical signs and no abnormalities at necropsy in any animals. Bodyweight gain was also normal. The oral LD50 of Hugtite was found to be in excess of 2,000 mg/kg bw."

"One acute dermal toxicity study has been performed. The study was carried out with Hugtite, a 50% w/w solution derived from potato starch, not maize starch, but this was considered acceptable. The study followed OECD 402 (1981) and no deviations were noted.

Hugtite was found to be of low acute dermal toxicity, with no mortalities, no clinical signs and no abnormalities at necropsy in any animals. Bodyweight gain was also normal. The dermal LD50 of Hugtite was found to be in excess of 2,000 mg/kg bw."

"One acute inhalation toxicity study has been performed. The study was carried out with Hugtite, a 50% w/w solution derived from potato starch, not maize starch, but this was considered acceptable. The study followed OECD 403 (1981) and no deviations were noted.

Hugtite was found to be of low acute inhalation toxicity, with no mortalities and no abnormalities at necropsy in any animals when dosed with 5.16 mg/L and having achieved an inhalable fraction (% <4 µm) of 68.2%. Some minor observations of wet fur and staining around the snout and/or eyes were made during or after exposure, but all had resolved one day after dosing. Bodyweight gain was also normal. The inhalation LC50 of Hugtite was found to be in excess of 5.16 mg/L."

As taken from EFSA, 2023

“A series of safety assessments were performed on hydrogenated resistant maltodextrin prepared by converting the reducing terminal glucose of resistant maltodextrin into sorbitol. ..... Acute .... oral toxicity studies in rats showed no death was observed in any groups, including the group receiving the highest single dose of 10 g/kg body weight ..... Mucous or watery stools were observed in the hydrogenated resistant maltodextrin treatment group on the acute study, which were transient and were associated with the osmotic pressure caused by intake of the high concentrations. ..... These results indicated that the no observed adverse effect level (NOAEL) of hydrogenated resistant maltodextrin was 10 g/kg body weight or more on the acute oral toxicity study ..... in rats. Further study performed in healthy adult humans showed that the acute no-effect level of hydrogenated resistant maltodextrin for diarrhea was 0.8 g/kg body weight for men and more than 1.0 g/kg body weight for women. The results of the current safety assessment studies suggest that hydrogenated resistant maltodextrin is safe for human consumption.” As taken from Yoshikawa Y et al. 2013. J. Toxicol. Sci. 38, 459-470. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/23665944

“The objective of the present study was to determine the maximum dose of resistant maltodextrin (Fibersol)-2, a non-viscous water-soluble dietary fiber), that does not induce transitory diarrhea. Ten healthy adult subjects (5 men and 5 women) ingested Fibersol-2 at increasing dose levels of 0.7,

0.8, 0.9, 1.0, and 1.1 g/kg body weight (bw). Each administration was separated from the previous dose by an interval of 1 wk. The highest dose level that did not cause diarrhea in any subject was regarded as the maximum non-effective level for a single dose. The results showed that no subject of either sex experienced diarrhea at dose levels of 0.7, 0.8, 0.9, or 1.0 g/kg bw. At the highest dose level of 1.1 g/kg bw, no female subject experienced diarrhea, whereas 1 male subject developed diarrhea with muddy stools 2 h after ingestion of the test substance. Consequently, the maximum non-effective level for a single dose of the resistant maltodextrin Fibersol-2 is 1.0 g/kg bw for men and >1.1 g/kg bw for women. Gastrointestinal symptoms were gurgling sounds in 4 subjects (7 events) and flatus in 5 subjects (9 events), although no association with dose level was observed. These symptoms were mild and transient and resolved without treatment." As taken from Kishimoto Y et al. 2013. J. Nutr. Sci. Vitaminol. (Tokyo) 59(4), 352-7. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24064737

5.2. Repeated dose toxicity

"Maltodextrin is concluded to not pose a long-term toxicity or carcinogenicity hazard due to the fact that it is rapidly metabolised with metabolites being a standard energy source. Maltodextrin is not toxic and its status as a permitted food additive with no toxicological concerns is concluded to preclude the need for any additional long-term toxicity or carcinogenicity studies."

As taken from EFSA, 2011.

"A series of safety assessments were performed on hydrogenated resistant maltodextrin prepared by converting the reducing terminal glucose of resistant maltodextrin into sorbitol. .... 90-day subchronic oral toxicity studies in rats showed no death was observed in any groups, including the group receiving the highest ..... dose of 5 g/kg body weight per day for 90 days. ..... Subchronic study showed dose-dependent increases in the weights of cecum alone, cecal contents alone, and cecum with cecal contents as well as hypertrophy of the cecal mucosal epithelium, which are considered to be common physiological responses after intake of indigestible carbohydrates. These results indicated that the no observed adverse effect level (NOAEL) of hydrogenated resistant maltodextrin was ..... 5.0 g/kg body weight/day or more on the 90-day subchronic repeated oral toxicity study in rats. ..... The results of the current safety assessment studies suggest that hydrogenated resistant maltodextrin is safe for human consumption." As taken from Yoshikawa Y et al. 2013. J. Toxicol. Sci. 38, 459-470. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/23665944

"Resistant maltodextrin (RM) is a novel soluble, nonviscous dietary fiber. Its metabolizable energy (ME) and net energy (NE) values derived from nutrient balance studies are unknown, as is the effect of RM on fecal microbiota. A randomized, placebo-controlled, double-blind crossover study was conducted (n = 14 men) to determine the ME and NE of RM and its influence on fecal excretion of macronutrients and microbiota. Participants were assigned to a sequence consisting of 3 treatment periods [24 d each: 0 g/d RM + 50 g/d maltodextrin and 2 amounts of dietary RM (25 g/d RM + 25 g of maltodextrin/d and 50 g/d RM + 0 g/d maltodextrin)] and were provided all the foods they were to consume to maintain their body weight. After an adaptation period, excreta were collected during a 7-d period. After the collection period, 24-h energy expenditure was measured. Fluorescence in situ hybridization, quantitative polymerase chain reaction, and 454 titanium technology-based 16S rRNA sequencing were used to analyze fecal microbiota composition. Fecal amounts of energy (544, 662, 737 kJ/d), nitrogen (1.5, 1.8, 2.1 g/d), RM (0.3, 0.6, 1.2 g/d), and total carbohydrate (11.1, 14.2, 16.2 g/d) increased with increasing dose (0, 25, 50 g) of RM ($P < 0.0001$). Fat excretion did not differ among treatments. The ME value of RM was 8.2 and 10.4 kJ/g, and the NE value of RM was -8.2 and 2.0 kJ/g for the 25 and 50 g/d RM doses, respectively. Both doses of RM increased fecal wet weight (118, 148, 161 g/d; $P < 0.0001$) and fecal dry weight (26.5, 32.0, 35.8 g/d; $P < 0.0001$) compared with the maltodextrin placebo. Total counts of fecal bacteria increased by 12% for the 25 g/d RM dose ($P = 0.17$) and 18% for the 50 g/d RM dose ($P = 0.019$). RM intake was associated with statistically significant increases ($P < 0.001$) in various operational

taxonomic units matching closest to ruminococcus, eubacterium, lachnospiraceae, bacteroides, holdemania, and faecalibacterium, implicating RM in their growth in the gut. Our findings provide empirical data important for food labeling regulations related to the energy value of RM and suggest that RM increases fecal bulk by enhancing the excretion of nitrogen and carbohydrate and the growth of specific microbial populations." As taken from Baer DJ et al. 2014. J. Nutr. 144(7), 1023-9. PubMed, 2015 available at http://www.ncbi.nlm.nih.gov/pubmed/24744316

"In the context of the well-documented metabolic and behavioural effects of supplementing rats' diets with access to a sucrose solution, the aim of this study was to compare the impact of 10% sucrose with that of an isoenergetic (10.4%) solution of hydrolysed starch, maltodextrin. This polysaccharide is metabolised at least as rapidly as sucrose and is also very palatable to rats, but does not contain fructose. Each of three experiments contained three groups: one given a sucrose solution, one given a maltodextrin solution and a control group maintained on standard chow and water alone. In Experiment 1 the sucrose and maltodextrin groups were given their supplementary drinks for 2 h each day, while in Experiments 2 and 3 these groups had 24-h access to their supplements. Ad libitum access to maltodextrin produced at least as rapid weight gain as sucrose and in Experiment 2 retroperitoneal fat mass was greater in the two carbohydrate groups than in the control group. Moreover, in Experiment 3, impaired performance on a location recognition task was also found in both carbohydrate groups after only 17 days on the diets. These results indicate that the harmful effects of excess sucrose consumption can also be produced by another rapidly absorbed carbohydrate that does not contain fructose." As taken from Kendig MD et al. 2014. Appetite 77, 1-12. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24582585

"Many studies have utilized a variety of methods to induce obesity in rodents, but they often received inconsistent results. The present study intended to use resistant maltodextrin (RMD) as a means to investigate the variations in its efficacy on body fat accumulation under the influence of four high-fat (HF) models of 23% or 40% total fat, comprising soybean oil, lard, and/or condensed milk. Results indicated that integrating condensed milk into the diets could help increase diet intake, boost energy intake, increase weight gain, and enhance fat formation. Supplementation of RMD (2.07 g/kg) notably reduced total body fat levels in three HF models, with the exception of a condensed-milk-added 40%-fat diet that may have misrepresented the functions of RMD. The uses of the 23% HF diets, with and without milk, and the milk-free 40% HF diet were therefore recommended as suitable models for antiobesity evaluations of RMD, or other fiber-rich products." As taken from Chu HF et al. 2014. J. Agric. Food Chem. 62(1), 192-7. PubMed, 2015 available at http://www.ncbi.nlm.nih.gov/pubmed/24313233

"Glucagon-like peptide-1 (GLP-1), which is produced and released from enteroendocrine L cells, plays pivotal roles in postprandial glycaemia. The ingestion of resistant maltodextrin (RMD), a water-soluble non-digestible saccharide, improves the glycaemic response. In the present study, we examined whether the continuous feeding of RMD to rats affected GLP-1 levels and glycaemic control. Male Sprague-Dawley rats (6 weeks of age) were fed an American Institute of Nutrition (AIN)-93G-based diet containing either cellulose (5 %) as a control, RMD (2·5 or 5 %), or fructo-oligosaccharides (FOS, 2·5 or 5 %) for 7 weeks. During the test period, an intraperitoneal glucose tolerance test (IPGTT) was performed after 6 weeks. Fasting GLP-1 levels were significantly higher in the 5 % RMD group than in the control group after 6 weeks. The IPGTT results showed that the glycaemic response was lower in the 5 % RMD group than in the control group. Lower caecal pH, higher caecal tissue and content weights were observed in the RMD and FOS groups. Proglucagon mRNA levels were increased in the caecum and colon of both RMD and FOS groups, whereas caecal GLP-1 content was increased in the 5 % RMD group. In addition, a 1 h RMD exposure induced GLP-1 secretion in an enteroendocrine L-cell model, and single oral administration of RMD increased plasma GLP-1 levels in conscious rats. The present study demonstrates that continuous ingestion of RMD increased GLP-1 secretion and production in normal rats, which could be stimulated by its direct and indirect (enhanced gut fermentation) effects on GLP-1-producing cells, and contribute to improving glucose tolerance." As taken from Hira T et al. 2015. Br. J. Nutr. 114(1), 34-42. PubMed, 2016 available at: http://www.ncbi.nlm.nih.gov/pubmed/25671387

“Commercial pigs display an innate attraction for sweet taste compounds. However, the impact of long-term availability to supplementary carbohydrate solutions on their general feeding behavior has not been examined. In this work we assess the effect of 12-days exposure to 16% sucrose and 16% maltodextrin solutions on the feed intake and growth performance of piglets, and on their preference and appetence for sweet or protein solutions. The innate preference of piglets was assessed by an initial choice test between 2% sucrose and 2% animal plasma solutions for a period of three minutes. Piglets showed higher intake and preference for 2% sucrose than for 2% animal plasma. In Experiment 1, piglets were then free-offered a 16% sucrose solution as a supplement to the diet, showing a higher intake of it than water and a reduction in feed intake and weight gain. A similar situation occurred during the last days of free-exposure to a 16% maltodextrin solution in Experiment 2. The choice test between 2% sucrose and 2% animal plasma solution was repeated after the exposure to the concentrated solutions. In both experiments, a reduction in the initial preference for 2% sucrose was observed. Similarly, piglets that had previous access to the 16% sucrose and 16% maltodextrin solutions showed a decrease in the appetence for 2% sucrose in comparison with that for 2% animal plasma, as measured by a one-pan test at the end of the experiments. It is concluded that long-term exposure to concentrated sucrose and maltodextrin solutions reduces feed intake and growth in weanling piglets, and also reverses their innate preference and appetence for dilute sweet over protein solutions.” As taken from Guzmán-Pino SA et al. 2015. Physiol. Behav. 141, 85-91. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25582514

5.3. Reproduction toxicity

“Maltodextrin is concluded to not pose a reproductive toxicity hazard due to the fact that it is rapidly metabolised with metabolites being a standard energy source. Maltodextrin is not toxic and its status as a permitted food additive with no toxicological concerns is concluded to preclude the need for any additional reproductive toxicity studies.”

As taken from EFSA, 2011.

Species	**Test conditions**	**Effects**	**Reference**
Rat (25 males and 25 females per group)	Parent (F0) animals fed 9% (w/w) maltodextrin (about 4.5 g/kg bw/day) for 3 weeks prior to mating. Offspring (F1) fed similarly for 13 weeks.	No effect on an extensive range of reproductive endpoints or on offspring development.	Becci et al., 1983
Rat (5-10 pregnant females per group)	Females fed a liquid diet containing maltose-dextrin "throughout pregnancy" [concentration not stated, but the dose level provided 35% of calories and would, therefore, have been high]. Offspring tested for shock-induced aggression at an undisclosed age. Study only reported in limited detail.	Pregnancy was longer in maltodextrin-treated rats than in controls. No effects on birth weight, pup growth or survival. No effect on aggression response in offspring	Means et al., 1984
A number of studies cited in Toxline used maltodextrin as an isocaloric control substance when investigating (in mice and rats) the effects of maternal ethanol consumption on offspring, suggesting that maltodextrin has no significant ability to adversely affect reproduction and development.			

"This study investigated the effect of resistant maltodextrin (RMD) on reproduction in streptozotocin (STZ)-nicotinamide-induced type 2 diabetic male rats. Forty male rats were induced with diabetes by a single intraperitoneal injection of STZ (50 mg kg(-1)) and nicotinamide (100 mg kg(-1)). Five groups were analysed in total: normal, diabetic rats without RMD, diabetic rats with RMD 1.2 g per 100 g diet (1×), with RMD 2.4 g per 100 g (2×), and with RMD 6.0 g per 100 g (5×). The groups of diabetic rats with the RMD supplement, compared to those without supplement, showed improved

plasma glucose control, attenuated insulin resistance and recovery of testosterone level and spermatogenesis stage. The STZ-nicotinamide-induced diabetes mellitus (DM) caused a significant reduction in serum testosterone, testis androgen receptor (AR), steroidogenic acute regulatory protein (StAR) and 3β-hydroxysteroid dehydrogenase (3β-HSD) protein, but a statistical recovery in each of these was observed in the 5× group. TUNEL-positive cells were observed in the diabetic without RMD group, and RMD treatment reduced apoptotic germ cells. The expression of Bax/Bcl2 was induced in the diabetic group and also significantly reduced in the 5× group. Dietary RMD may improve metabolic control in STZ-nicotinamide-induced diabetic rats and attenuate hyperglycaemia-related impaired male reproduction and testicular function." As taken from Liu CY et al. 2016. Andrologia 48(4), 363-73. PubMed, 2017 available at: https://www.ncbi.nlm.nih.gov/pubmed/26190442

5.4. Mutagenicity

“Maltodextrin is not considered to be genotoxic and is a permitted food additive. No genotoxicity studies are considered necessary.”

As taken from EFSA, 2011.

“A series of safety assessments were performed on hydrogenated resistant maltodextrin prepared by converting the reducing terminal glucose of resistant maltodextrin into sorbitol. The reverse mutation assay did not show mutagenicity. ..... The results of the current safety assessment studies suggest that hydrogenated resistant maltodextrin is safe for human consumption.” As taken from Yoshikawa Y et al. 2013. J. Toxicol. Sci. 38, 459-470. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/23665944

5.5. Cytotoxicity

“Resistant maltodextrin Fibersol-2 is a soluble and fermentable dietary fiber that is Generally Recognized As Safe (GRAS) in the United States. We tested whether Fibersol-2 contains anti-tumor activity. Human colorectal cancer cell line, HCT116, and its isogenic cells were treated with FIbersol-2. Tumor growth and tumorigenesis were studied in vitro and in vivo. Apoptotic pathway and generation of reactive oxygen species (ROS) were investigated. We discovered that Fibersol-2 significantly inhibits tumor growth of HCT116 cells by inducing apoptosis. Fibersol-2 strongly induces mitochondrial ROS and Bax-dependent cleavage of caspase 3 and 9, which is shown by isogenic HCT116 variants. Fibersol-2 induces phosphorylation of Akt, mTOR in parental HCT116 cells, but not in HCT116 deficient for Bax or p53. It prevents growth of tumor xenograft without any apparent signs of toxicity in vivo. These results identify Fibersol-2 as a mechanism-based dietary supplement agent that could prevent colorectal cancer development.” As taken from So EY et al. 2015. Cancer Biol. Ther. 16(3), 460-5. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25692338

“Purpose: Dissolvable microneedle arrays (MNAs) can be used to realize enhanced transdermal and intradermal drug delivery. Dissolvable MNAs are fabricated from biocompatible and water-soluble base polymers, and the biocargo to be delivered is integrated with the base polymer when forming the MNAs. The base polymer is selected to provide mechanical strength, desired dissolution characteristics, and compatibility with the biocargo. However, to satisfy regulatory requirements and be utilized in clinical applications, cytotoxicity of the base polymers should also be thoroughly characterized. This study systematically investigated the cytotoxicity of several

important carbohydrate-based base polymers used for production of MNAs, including carboxymethyl cellulose (CMC), maltodextrin (MD), trehalose (Treh), glucose (Gluc), and hyaluronic acid (HA). Methods: Each material was evaluated using in vitro cell-culture methods on relevant mouse and human cells, including MPEK-BL6 mouse keratinocytes, NIH-3T3 mouse fibroblasts, HaCaT human keratinocytes, and NHDF human fibroblasts. A common laboratory cell line, human embryonic kidney cells HEK-293, was also used to allow comparisons to various cytotoxicity studies in the literature. Dissolvable MNA materials were evaluated at concentrations ranging from 3 mg/mL to 80 mg/mL. Results: Qualitative and quantitative analyses of cytotoxicity were performed using optical microscopy, confocal fluorescence microscopy, and flow cytometry-based assays for cell morphology, viability, necrosis and apoptosis. Results from different methods consistently demonstrated negligible in vitro cytotoxicity of carboxymethyl cellulose, maltodextrin, trehalose and hyaluronic acid. Glucose was observed to be toxic to cells at concentrations higher than 50 mg/mL. Conclusions: It is concluded that CMC, MD, Treh, HA, and glucose (at low concentrations) do not pose challenges in terms of cytotoxicity, and thus, are good candidates as MNA materials for creating clinically-relevant and well-tolerated biodissolvable MNAs.“ As taken from Yalcintas EP et al. 2020. Pharm. Res. 37(3), 33. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31942659/

5.6. Carcinogenicity

“Maltodextrin is concluded to not pose a long-term toxicity or carcinogenicity hazard due to the fact that it is rapidly metabolised with metabolites being a standard energy source. Maltodextrin is not toxic and its status as a permitted food additive with no toxicological concerns is concluded to preclude the need for any additional long-term toxicity or carcinogenicity studies.”

As taken from EFSA, 2011.

“Non-digestible carbohydrates (NDC(4)) have been used as a low-calorie sweetener and prebiotics that stimulate the growth of certain intestinal bacteria that support healthy colon conditions. In this study, we examined the dietary effect of commercially available NDCs on estrogen receptor positive (ER+) human breast cancer. We conducted a feeding study of fructooligosaccharides (FOSs), Fibersol 2 (F2; digestion resistant maltodextrin), Hi-Maize (HM; high amylose cornstarch), and Frutafit (FF; a range of powdered inulins) (5% in diet, w/w) to evaluate their effects on the growth of ER(+) human breast cancer (MCF-7) tumors in the presence of 17β-estradiol (E(2)) using an athymic xenograft model. F2, HM, and FOSs supplementation significantly reduced E(2)-stimulated MCF-7 tumor growth by inhibiting cellular proliferation (Ki-67) and increasing apoptosis (M30) in tumors. F2, HM, and FOSs treatments also lowered serum E(2) level and reduced uterine weight compared to the control diet. NDCs treatments downregulated relative mRNA expression of the E(2)-responsive gene markers pS2, bcl2, bcl-xL, and cyclin D1 in MCF-7 tumors. In conclusion, the NDC intake may have a protective effect against ER(+) tumors by inhibiting cellular proliferation and increasing apoptosis.” As taken from Kondegowda NG et al. 2011. Nutr. Cancer 63(1), 55-64. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/21170812

“Resistant maltodextrin Fibersol-2 is a soluble and fermentable dietary fiber that is Generally Recognized As Safe (GRAS) in the United States. We tested whether Fibersol-2 contains anti-tumor activity. Human colorectal cancer cell line, HCT116, and its isogenic cells were treated with FIbersol-2. Tumor growth and tumorigenesis were studied in vitro and in vivo. Apoptotic pathway and generation of reactive oxygen species (ROS) were investigated. We discovered that Fibersol-2 significantly inhibits tumor growth of HCT116 cells by inducing apoptosis. Fibersol-2 strongly induces mitochondrial ROS and Bax-dependent cleavage of caspase 3 and 9, which is shown by isogenic HCT116 variants. Fibersol-2 induces phosphorylation of Akt, mTOR in parental HCT116 cells, but not in HCT116 deficient for Bax or p53. It prevents growth of tumor xenograft without any apparent signs of toxicity in vivo. These results identify Fibersol-2 as a mechanism-based dietary supplement agent that could prevent colorectal cancer development.” As taken from So EY et al.

2015. Cancer Biol. Ther. 16(3), 460-5. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25692338

"The consumption of dietary fibers has been implicated with a lowered risk of human colorectal cancer. Proposed mechanisms involve alterations in the stool consistency, transit time, and formation of short-chain fatty acid by dietary fiber fermentation, and the reorganization of gut microbiota. Here we show that Fibersol-2, a digest-resistant maltodextrin, not only inhibits proliferation of colorectal SW480 cancer cell lines by increasing reactive oxygen species (ROS), but decreases the numbers of the adenoma count in Multiple Intestinal Neoplasia (MIN) mice carrying a mutation in the Adenomatous Polyposis Coli gene by 84 d of age. These observations provide direct evidence that Fibersol-2 intrinsically contains anti-cancer activity, independent of the intestinal metabolism and any potential interactions with the microbiota." As taken from Sancho SC et al. 2016. Cancer Biol. Ther. 17(6), 657-63. PubMed, 2017 available at: https://www.ncbi.nlm.nih.gov/pubmed/27143108

5.7. Irritation/immunotoxicity

Chronic inhalation of maltodextrin “at 4%” [it is unclear what this means; for solids, inhalation concentrations are usually expressed as mg/m3] was reported to have induced minimal, reversible irritation of the larynx, a finding considered by the investigator to be a "background finding of no consequence to man" [no further details given in the citing source] (Baldrick, 2000a).

Not irritating, based on a study with ‘Hugtite’, a 50% w/w aqueous solution (EFSA, 2011, 2013).

“One skin irritation study has been performed. The study was carried out with Hugtite, a 50% w/w solution derived from potato starch, not maize starch, but this was considered acceptable. The study followed OECD 404 (1981) and no deviations were noted.

In the study, very slight erythema was noted in one male at one hour post treatment and in one female at the 24 hour observation. All treated sites had resolved by 48 hours. No other effects were seen. Overall mean skin irritation scores according to Draize scheme were 0.1 for erythema and 0 for oedema.”

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Skin Irritation OECD 404 (1981) Acceptable	Rabbit, New Zealand White, 2 females 1 male	Hugtite (50% w/w maltodextrin)	0.5ml undiluted, 4h	Observations made at 1, 24, 48 and 72 h Mean scores from 24, 48, 72 h: Erythema: 0, 0.3, 0 Oedema: 0, 0, 0 Reversibility: all resolved by 48 h observation	Walker, D.J (1991b)

“No study on eye irritation has been performed. The technical material might be irritating as a dust cloud, however this would be down to physical irritation and not due to any intrinsic chemical properties of the material.”

“No study on skin sensitisation has been performed. Maltodextrin is not considered to be a skin sensitiser however alpha amylase, which is a known sensitiser, is involved in the method of manufacture. Five batch data was provided and demonstrated that alpha-amylase is virtually absent in the technical material and is below level which triggers classification.” As taken from EFSA, 2023

A respiratory tract irritant and skin sensitizer.

As taken from BPDB, 2023.

“Resistant maltodextrin (RMD) is a soluble dietary fibre that exerts several physiological functions as a result of its microbial degradation and changes in the intestinal environment. It has been reported that RMD enhanced immunoglobulin A (IgA) secretion, which protects the mucosa from foreign substances. However, the effect of RMD on excessive immunity has yet to be investigated. In this study, we aimed to investigate the effect of RMD on excessive immune responses such as food allergy. OVA23-3 mice were fed an AIN-76-based diet containing 20% egg-white protein with or without RMD. While RMD was shown to contribute to an increase in goblet cells, RMD did not change the overall inflammatory status when ingested with the egg-white diet. RMD suppressed IL-4 and IL-10 production from splenocytes but not cells from mesenteric lymph nodes. RMD also downregulated the serum levels of OVA-specific Th1- and Th2-related antibodies, which were elevated in the food-allergic condition. RMD significantly increased the total amount of short-chain fatty acids, especially acetate and propionate, in the caecum of OVA23-3 mice fed the egg-white diet. Our study demonstrated that dietary RMD modulates systemic rather than intestinal antigen-specific immune responses in the food-allergic condition of OVA23-3 mice. Although the relevant mechanism has yet to be investigated, RMD shows potential for alleviating food allergy through adjustment of systemic immunity.” As taken from Miyazato S et al. 2019. Biosci. Microbiota Food Health 38(3), 89-95. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/31384520

“Purpose: Many studies have been published on the beneficial effects of oral carbohydrate solutions (OCS) administered prior to surgery. However, the risk of pulmonary aspiration cannot be excluded in all patients undergoing anesthesia. But, there are few studies on the safety of OCS at lung aspiration. Methods: Experiments were conducted with mice (Nine- to ten-week-old male BALB/c mice weighted 23-26 g). Lung aspiration was performed by intratracheal administration of OCS and its major constituents, fructose and maltodextrin. Bronchoalveolar lavage fluid (BALF) was collected 3 and 24 h after lung aspiration. The level of Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and macrophage inflammatory protein-2 (MIP-2) were measured in BALF. The total white blood cell, neutrophil counts, wet to dry ratio and histological examination were performed in BALF and lung tissue, respectively, at 24 h after aspiration. Results: The OCS increased the level of TNF-α, IL-6 and MIP-2 at 3 h and the neutrophil count at 24 h in BALFs, compared to a phosphate-buffered saline (PBS) group. The increase in IL-6 level induced by OCS was maintained for 24 h. The OCS also increased the number of white blood cells and the percentage of neutrophils in BALFs. Compared to fructose, maltodextrin significantly increased the production of MIP-2 in BALFs. OCS and maltodextrin also increased neutrophil recruitment in lung tissue. Conclusion: Aspiration of OCS may cause inflammation of the lungs. The preoperative use of OCS may require caution under specific clinical conditions, such as patients at risk of lung aspiration.” As taken from Kim J et al. 2021. J. Anesth. 35(1), 86-92. PubMed, 2021 available at https://pubmed.ncbi.nlm.nih.gov/33221959/

5.8. All other relevant types of toxicity

“Resistant maltodextrin is a non-viscous dietary fiber that is fermentable in the colon by colonic bacteria. The objective of this review is to summarize the studies of resistant maltodextrin and its effect on metabolic profile, such as blood glucose, lipid profile, and body weight. Several studies support the idea that resistant maltodextrin may improve blood glucose, insulin sensitivity, lipid profile, and obesity. However, the use of resistant maltodextrin should be limited to minimize the

adverse effect on the gastrointestinal system. This review provides information regarding the benefits of resistant maltodextrin on metabolic health as well as its proposed mechanism to enhance the knowledge of this novel fiber. Key teaching points Resistant maltodextrin is a novel non-viscous dietary fiber classified as resistant starch type V that is produced by debranching of the starch structure. Resistant maltodextrin is fermentable in the colon and thus produces short-chain fatty acid. Resistant maltodextrin helps to maintain blood and lipid profiles as well as promote satiety and reducing food intake. High intake of resistant maltodextrin may cause gastrointestinal discomfort due to the gas production and increased osmotic pressure." As taken from Astina J and Sapwarobol S et al. 2019. J. Am. Coll. Nutr. 38(4), 380-385. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/30351215

"The glycemic response produced by a food depends on both the glycemic index of the food itself, and on how the body reacts to the food as it is consumed and digested, in turn dependent on sensory cues. Research suggests that taste stimulation can induce the cephalic phase insulin response before food has reached the digestion, priming the body for an incoming glucose load. This glycemic response can consequently affect the amount of food consumed in a subsequent meal. The aim of this study was to investigate the effects on satiety of four preloads that differed in caloric content and sensory properties, in a small group of female and male participants (n = 10). Water, sucrose, sucralose, and maltodextrin were used to represent 4 different conditions of the preload, with or without energy, and with or without sweet taste. Individual plasma glucose concentrations were sampled at baseline, 45 min after consuming the preload, and after consuming an ad-libitum test meal. Hunger, fullness, desire to eat, and thoughts of food feeling were assessed every 15 min using visual analog scales. Results in male participants when comparing two solutions of equal caloric content, maltodextrin and sucrose, showed that plasma glucose concentration spiked in the absence of taste input ($p = 0.011$). Maltodextrin, while providing calories does not have the sweet taste that can serve to trigger cephalic phase insulin release to attenuate an incoming glucose load, and was accompanied by significantly greater change in feelings of satiety than with the other preloads. Despite the difference in postprandial blood glucose, the energy consumed in the test meal across the treatments was not significantly different in either males or females. Results highlight the importance of taste in stimulating the body for the efficient and effective glucose homeostasis." As taken from Sae Iab T and Dando R. 2020. Foods 9(11), 1578. PubMed, 2021 available at https://pubmed.ncbi.nlm.nih.gov/33143284/

"The first of the four intestinal studies was an in-vivo study in mice, who were given drinking water containing 5% maltodextrin (MDX) and then challenged with dextran sulfate sodium or indomethacin. In parallel, mice fed a MDX-enriched diet were given the endoplasmic reticulum (ER) stress inhibitor tauroursodeoxycholic acid (TUDCA). In-vitro analysis was also performed where murine intestinal crypts and the human mucus-secreting HT29-methotrexate treated cell line were stimulated with MDX in the presence or absence of TUDCA or a p38 MAP kinase inhibitor. The study showed that MDX exacerbated intestinal inflammation in both the in-vivo mouse models and the in-vitro experiments, and when challenged with dextran sulfate sodium or indomethacin, developed severe colitis. Analysis of the mechanisms underlying the detrimental effect of MDX showed up regulation of inositol requiring protein 1b, a sensor of ER stress, in goblet cells, and a reduction of mucin-2 expression, with no significant change in mucosa associated microbiota. The findings suggest a role for MDX in colitis but as the exposure to mice was considerably higher than what could be expected from use as a plant protection product (PPP), the study does not contribute to or trigger any classifications." As taken from EFSA, 2023

6. Functional effects on

6.1. Broncho/pulmonary system

No data available to us at this time.

6.2. Cardiovascular system

“The replacement of dietary carbohydrates with proteins can lower blood pressure (BP), but the mechanisms remain unclear. This randomized, double-blind, parallel-group study aimed to compare 12-h postprandial sympathetic and hemodynamic responses after high-protein (HP) meals and high-carbohydrate (HC) meals. Fifty-two men and women with untreated elevated BP were tested on d 1 and after 4 wk of supplementation [3 × 20 g protein (HP) or maltodextrin (HC) per day]. No between-group differences were found in postprandial plasma norepinephrine on d 1 and at wk 4. On d 1, postprandial mean arterial pressure (MAP) decreased more in the HC group than in the HP group ($P = 0.002$). This difference was not present at 4 wk, because the postprandial decline in MAP tended to become larger in the HP group after 4 wk of supplementation ($P = 0.07$). On both test days, postprandial total peripheral resistance tended to decrease more in the HC group ($P < 0.08$). After 4 wk of supplementation, cardiac output tended to increase more in the HC group ($P = 0.08$). In conclusion, ingestion of an HP diet induced a smaller decrease in BP on d 1 than did ingestion of an HC diet. This difference disappeared after 4 wk due to a more pronounced decrease in BP in the HP group after 4 wk than on d 1. These findings cannot explain the BP-lowering effect ascribed to dietary proteins.” As taken from Teunissen-Beekman KF et al. 2013. J. Nutr. 143(4), 424-9. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23325917

“Postprandial hypotension (PPH) is under-recognised, but common, particularly in the elderly, and is of clear clinical importance due to both the independent association between PPH and an increase in mortality and lack of effective management for this condition. Following health concerns surrounding excessive consumption of sugar, there has been a trend in the use of low- or non-nutritive sweeteners as an alternative. Due to the lack of literature in this area, we conducted a systematic search to identify studies relevant to the effects of different types of sweeteners on postprandial blood pressure (BP). The BP response to ingestion of sweeteners is generally unaffected in healthy young subjects, however in elderly subjects, glucose induces the greatest decrease in postprandial BP, while the response to sucrose is less pronounced. The limited studies investigating other nutritive and non-nutritive sweeteners have demonstrated minimal or no effect on postprandial BP. Dietary modification by replacing high nutritive sweeteners (glucose, fructose, and sucrose) with low nutritive (d-xylose, xylitol, erythritol, maltose, maltodextrin, and tagatose) and non-nutritive sweeteners may be a simple and effective management strategy for PPH.” As taken from Pham H et al. 2019. Nutrients 11(8), E1717. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/31349678

The essential data is based on a fully blinded experimental design and reveals that a single spike of increased blood D-glucose, but not of inert L-glucose, is sufficient to dramatically increase the platelet-rich thrombotic response to laser-induced focal perturbation to a vein. This suggests that the susceptibility to vascular thrombo-inflammation is heightened by transient hyperglycemia, even at levels of blood glucose, e.g., 1 g/kg D-glc dosage, that are below the fasting glucose diabetic threshold in mice. The results of the current study, combined with past in vitro studies, supports a hypothesis that hyperglycemia, whether it is chronic or transient, facilitates platelet thrombus formation in response to vascular tissue disruption. As taken from Shaked I et. Al. 2024. J Cereb Blood Flow Metab. Available at; https://pubmed.ncbi.nlm.nih.gov/37737093/

6.3. Nervous system

“Maltodextrin is concluded to not pose a neurotoxicity hazard due to the fact that it is rapidly metabolised with metabolites being a standard energy source. Maltodextrin is not toxic and its status as a permitted food additive with no toxicological concerns is concluded to preclude the need for any additional neurotoxicity studies.”

As taken from EFSA, 2011.

No effects on brain levels of serotonin or 5-hydroxyindoleacetic acid were ascribed to maltodextrin in a study where monkeys were given mixtures of tryptophan and maltodextrin in the diet for 13 weeks. Increasing dietary trypotophan was associated with increases in these markers in certain areas of the brain (Leathwood & Fernstrom, 1990).

BACKGROUND: There has been a dramatic escalation in sugar intake in the last few decades, most strikingly observed in the adolescent population. Sugar overconsumption has been associated with several adverse health consequences, including obesity and diabetes. Very little is known, however, about the impact of sugar overconsumption on mental health in general, and on reward-related behavioral disorders in particular. This study examined in rats the effects of unlimited access to sucrose during adolescence on the motivation for natural and pharmacological rewards in adulthood.

METHODOLOGY/PRINCIPAL FINDINGS: Adolescent rats had free access to 5% sucrose or water from postnatal day 30 to 46. The control group had access to water only. In adulthood, rats were tested for self-administration of saccharin (sweet), maltodextrin (non-sweet), and cocaine (a potent drug of abuse) using fixed- and progressive-ratio schedules, and a concentration-response curve for each substance. Adult rats, exposed or not exposed to sucrose, were tested for saccharin self-administration later in life to verify the specificity of adolescence for the sugar effects. Sugar overconsumption during adolescence, but not during adulthood, reduced the subsequent motivation for saccharin and maltodextrin, but not cocaine. This selective decrease in motivation is more likely due to changes in brain reward processing than changes in gustatory perception.

CONCLUSIONS/SIGNIFICANCE: Sugar overconsumption induces a developmental stage-specific chronic depression in reward processing that may contribute to an increase in the vulnerability to reward-related psychiatric disorders.

Vendruscolo et al. Sugar overconsumption during adolescence selectively alters motivation and reward function in adult rats. PLoS One. 2010 Feb 19;5(2):e9296. As taken from PubMed, 2011, http://www.ncbi.nlm.nih.gov/pubmed/20174565

“In the context of the well-documented metabolic and behavioural effects of supplementing rats' diets with access to a sucrose solution, the aim of this study was to compare the impact of 10% sucrose with that of an isoenergetic (10.4%) solution of hydrolysed starch, maltodextrin. This polysaccharide is metabolised at least as rapidly as sucrose and is also very palatable to rats, but does not contain fructose. Each of three experiments contained three groups: one given a sucrose solution, one given a maltodextrin solution and a control group maintained on standard chow and water alone. In Experiment 1 the sucrose and maltodextrin groups were given their supplementary drinks for 2 h each day, while in Experiments 2 and 3 these groups had 24-h access to their supplements. Ad libitum access to maltodextrin produced at least as rapid weight gain as sucrose and in Experiment 2 retroperitoneal fat mass was greater in the two carbohydrate groups than in the control group. Moreover, in Experiment 3, impaired performance on a location recognition task was also found in both carbohydrate groups after only 17 days on the diets. These results indicate that the harmful effects of excess sucrose consumption can also be produced by another rapidly absorbed carbohydrate that does not contain fructose.” As taken from Kendig MD et al. 2014. Appetite 77, 1-12. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24582585

“Caffeine (CAF) and maltodextrin (MALT) mouth rinses (MR) improve exercise performance. The current experiment aims to determine the effect of CAF and MALT MR on cognitive performance and brain activity. Ten healthy male subjects (age 27 ± 3 yr) completed three experimental trials. Each trial included four Stroop tasks: two familiarization tasks, and one task before and one task after an MR period. The reaction time (in milliseconds) and accuracy (percent) of simple, congruent, and incongruent stimuli were assessed. Electroencephalography was applied throughout the experiment to record brain activity. The amplitudes and latencies of the P300 were determined during the Stroop tasks before and after the MR period. Subjects received MR with CAF (0.3 g/25 ml), MALT (1.6 g/25 ml), or placebo (PLAC) in a randomized, double-blind, crossover

design. During MR, the brain imaging technique standardized low-resolution brain electromagnetic tomography was applied. Magnitude-based inferences showed that CAF MR is likely trivial (63.5%) and likely beneficial (36.4%) compared with PLAC MR, and compared with MALT MR likely beneficial to reaction time on incongruent stimuli (61.6%). Additionally, both the orbitofrontal and dorsolateral prefrontal cortex were activated only during CAF MR, potentially explaining the likely beneficial effect on reaction times. MALT MR increased brain activity only within the orbitofrontal cortex. However, this brain activation did not alter the reaction time. Furthermore, no significant differences in the accuracy of stimuli responses were observed between conditions. In conclusion, only CAF MR exerted a likely beneficial effect on reaction time due to the subsequent activation of both the orbitofrontal and dorsolateral prefrontal cortexes." As taken from De Pauw K et al. 2015. J. Appl. Physiol. (1985). 118(6), 776-82. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25614603

"The fifth supplementary study was an in-vivo mice study which conducted three experiments to assess whether maltodextrin can produce similar metabolic and cognitive effects to those of sucrose in the rat. Mice received 10.4% Maltodextrin, 10% Sucrose or 0% carbohydrate (control) in drinking water for short-term, unrestricted exposures or for long-term, unrestricted/restricted exposure, and then metabolic and/or cognitive measures were taken. Metabolic measures were fasting blood glucose, insulin and leptin and cognitive measures were either the Morris Water Maze Test or a Hippocampus-Dependent Spatial And Memory Test. In Experiment 3, where mice received unrestricted access to drinking solutions for 18 and were measured with the Hippocampus-Dependent Spatial And Memory Test, the ability of the Maltodextrin and Sucrose groups to recognise that an object was in a new location was near chance, while the Control group continued to perform at a high level, all ps < 0.001. In the ther experiments, the results indicated that, just like sucrose, excessive intakes of a maltodextrin solution can produce faster weight gain and larger retroperitoneal fat pads than control mice. Again, the direct dietary exposure is considerably higher than expected PPP exposure, so the findings of the study do not contribute to or trigger any classifications.

It was shown that consumption of either 10% sucrose or maltodextrin solution for less than 3 weeks can impair performance on a hippocampus-dependent short-term location recognition task, but not a similar object recognition task. In the opinion of the RMS, this finding alone is not substantive enough to be toxicologically relevant for this evaluation of maltodextrin." As taken from EFSA, 2023

6.4. Other organ systems, dependent on the properties of the substance

"In the latter half of the 20th century, societal and technological changes led to a shift in the composition of the American diet to include a greater proportion of processed, pre-packaged foods high in fat and carbohydrates, and low in dietary fiber (a "Western diet"). Over the same time period, there have been parallel increases in Salmonella gastroenteritis cases and a broad range of chronic inflammatory diseases associated with intestinal dysbiosis. Several polysaccharide food additives are linked to bacterially-driven intestinal inflammation and may contribute to the pathogenic effects of a Western diet. Therefore, we examined the effect of a ubiquitous polysaccharide food additive, maltodextrin (MDX), on clearance of the enteric pathogen Salmonella using both in vitro and in vivo infection models. When examined in vitro, murine bone marrow-derived macrophages exposed to MDX had altered vesicular trafficking, suppressed NAPDH oxidase expression, and reduced recruitment of NADPH oxidase to Salmonella-containing vesicles, which resulted in persistence of Salmonella in enlarged Rab7+ late endosomal vesicles. In vivo, mice consuming MDX-supplemented water had a breakdown of the anti-microbial mucous layer separating gut bacteria from the intestinal epithelium surface. Additionally, oral infection of these mice with Salmonella resulted in increased cecal bacterial loads and enrichment of lamina propria cells harboring large Rab7+ vesicles. These findings indicate that consumption of processed foods containing the polysaccharide MDX contributes to suppression of intestinal anti-microbial defense mechanisms and may be an environmental priming factor for the development of chronic

inflammatory disease." As taken from Nickerson KP et al. 2014. PLoS One 9(7), e101789. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25000398

"Inflammatory bowel disease (IBD) is a complex, multi-factorial disease thought to arise from an inappropriate immune response to commensal bacteria in a genetically susceptible person that results in chronic, cyclical, intestinal inflammation. Dietary and environmental factors are implicated in the initiation and perpetuation of IBD; however, a singular causative agent has not been identified. As of now, the role of environmental priming or triggers in IBD onset and pathogenesis are not well understood, but these factors appear to synergize with other disease susceptibility factors. In previous work, we determined that the polysaccharide dietary additive, maltodextrin (MDX), impairs cellular anti-bacterial responses and suppresses intestinal anti-microbial defense mechanisms. In this addendum, we review potential mechanisms for dietary deregulation of intestinal homeostasis, postulate how dietary and genetic risk factors may combine to result in disease pathogenesis, and discuss these ideas in the context of recent findings related to dietary interventions for IBD." As taken from Nickerson KP et al. 2015. Gut Microbes 6(1), 78-83. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25738413

"This 24-mo randomized, double-blind, controlled trial aimed to examine whether supplementation with a natural marine-derived multi-mineral supplement rich in calcium (Ca) taken alone and in conjunction with short-chain fructo-oligosaccharide (scFOSs) has a beneficial effect on bone mineral density (BMD) and bone turnover markers (BTMs) in postmenopausal women. A total of 300 non-osteoporotic postmenopausal women were randomly assigned to daily supplements of 800 mg of Ca, 800 mg of Ca with 3.6 g of scFOS (CaFOS), or 9 g of maltodextrin. BMD was measured before and after intervention along with BTMs, which were also measured at 12 mo. Intention-to-treat ANCOVA identified that the change in BMD in the Ca and CaFOS groups did not differ from that in the maltodextrin group. Secondary analysis of changes to BTMs over time identified a greater decline in osteocalcin and C-telopeptide of type I collagen (CTX) in the Ca group compared with the maltodextrin group at 12 mo. A greater decline in CTX was observed at 12 mo and a greater decline in osteocalcin was observed at 24 mo in the CaFOS group compared with the maltodextrin group. In exploratory subanalyses of each treatment group against the maltodextrin group, women classified with osteopenia and taking CaFOS had a smaller decline in total-body ($P = 0.03$) and spinal ($P = 0.03$) BMD compared with the maltodextrin group, although this effect was restricted to those with higher total-body and mean spinal BMD at baseline, respectively. Although the change in BMD observed did not differ between the groups, the greater decline in BTMs in the Ca and CaFOS groups compared with the maltodextrin group suggests a more favorable bone health profile after supplementation with Ca and CaFOS. Supplementation with CaFOS slowed the rate of total-body and spinal bone loss in postmenopausal women with osteopenia-an effect that warrants additional investigation." As taken from Slevin MM et al. 2014. J. Nutr. 144(3), 297-304. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24453130

"Glucagon-like peptide-1 (GLP-1), which is produced and released from enteroendocrine L cells, plays pivotal roles in postprandial glycaemia. The ingestion of resistant maltodextrin (RMD), a water-soluble non-digestible saccharide, improves the glycaemic response. In the present study, we examined whether the continuous feeding of RMD to rats affected GLP-1 levels and glycaemic control. Male Sprague-Dawley rats (6 weeks of age) were fed an American Institute of Nutrition (AIN)-93G-based diet containing either cellulose (5 %) as a control, RMD (2.5 or 5 %), or fructo-oligosaccharides (FOS, 2.5 or 5 %) for 7 weeks. During the test period, an intraperitoneal glucose tolerance test (IPGTT) was performed after 6 weeks. Fasting GLP-1 levels were significantly higher in the 5 % RMD group than in the control group after 6 weeks. The IPGTT results showed that the glycaemic response was lower in the 5 % RMD group than in the control group. Lower caecal pH, higher caecal tissue and content weights were observed in the RMD and FOS groups. Proglucagon mRNA levels were increased in the caecum and colon of both RMD and FOS groups, whereas caecal GLP-1 content was increased in the 5 % RMD group. In addition, a 1 h RMD exposure induced GLP-1 secretion in an enteroendocrine L-cell model, and single oral administration of RMD increased plasma GLP-1 levels in conscious rats. The present study demonstrates that continuous

ingestion of RMD increased GLP-1 secretion and production in normal rats, which could be stimulated by its direct and indirect (enhanced gut fermentation) effects on GLP-1-producing cells, and contribute to improving glucose tolerance." As taken from Hira et al. 2015. Br J Nutr 114(1), 34-42. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/25671387

"Adenosine triphosphate is a critical neurotransmitter in the gustatory response to the 5 primary tastes in mice. Genetic deletion of the purinergic P2X2/P2X3 receptor greatly reduces the neural and behavioral response to prototypical primary taste stimuli. In this study, we examined the behavioral response of P2X double knockout mice to maltodextrin and fat stimuli, which appear to activate additional taste channels. P2X double knockout and wild-type mice were given 24-h choice tests (vs. water) with ascending concentrations of Polycose and Intralipid. In Experiment 1, naive double knockout mice, unlike wild-type mice, were indifferent to dilute (0.5-4%) Polycose solutions but preferred concentrated (8-32%) Polycose to water. In a retest, the Polycose-experienced double knockout mice, like wild-type mice, preferred all Polycose concentrations. In Experiment 2, naive double knockout mice, unlike wild-type mice, were indifferent to dilute (0.313-2.5%) Intralipid emulsions but preferred concentrated (5-20%) Intralipid to water. In a retest, the fat-experienced double knockout mice, like wild-type mice, strongly preferred 0.313-5% Intralipid to water. These results indicate that the inherent preferences of mice for maltodextrin and fat are dependent upon adenosine triphosphate taste cell signaling. With experience, however, P2X double knockout mice develop strong preferences for the nontaste flavor qualities of maltodextrin and fat conditioned by the postoral actions of these nutrients." As taken from Sclafani and Ackroff 2014. Chem Senses. 39(6), 507-514. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/24833134

"Increased protein intake versus maltodextrin intake for 4 weeks lowers blood pressure. Concerns exist that high-protein diets reduce renal function. Effects of acute and 4-week protein intake versus maltodextrin intake on renal acid load, glomerular filtration rate and related parameters were compared in this study. Seventy-nine overweight individuals with untreated elevated blood pressure and normal kidney function were randomized to consume a mix of protein isolates (60 g/day) or maltodextrin (60 g/day) for 4 weeks in energy balance. Twenty-four-hour urinary potential renal acid load (uPRAL) was compared between groups. A subgroup (maltodextrin N = 27, protein mix N = 25) participated in extra test days investigating fasting levels and postprandial effects of meals supplemented with a moderate protein- or maltodextrin-load on glomerular filtration rate, effective renal plasma flow, plasma renin, aldosterone, pH, and bicarbonate. uPRAL was significantly higher in the protein group after 4 weeks ($P \leq 0.001$). Postprandial filtration fraction decreased further after the protein-supplemented breakfast than after the maltodextrin-supplemented breakfast after 4 weeks of supplementation ($P \leq 0.001$). Fasting and postprandial levels of glomerular filtration rate, effective renal plasma flow, renin, aldosterone, angiotensin-converting enzyme, pH and bicarbonate did not differ between groups. In conclusion, 4 weeks on an increased protein diet (25% of energy intake) increased renal acid load, but did not affect renal function. Postprandial changes, except for filtration fraction, also did not differ between groups. These data suggest that a moderate increase in protein intake by consumption of a protein mix for 4 weeks causes no (undesirable) effects on kidney function in overweight and obese individuals with normal kidney function." As taken from Teunissen-Beekman KF et al. 2016. Physiol. Rep. 4(5), e12687. PubMed, 2017 available at: https://www.ncbi.nlm.nih.gov/pubmed/26997623

"BACKGROUND/OBJECTIVES: The pathogenesis of enteritis after abdominal radiotherapy (RT) is unknown, although changes in fecal microbiota may be involved. Prebiotics stimulate the proliferation of Lactobacillus spp and Bifidobacterium spp, and this may have positive effects on the intestinal mucosa during abdominal RT. SUBJECTS/METHODS: We performed a randomized, double-blind, placebo-controlled trial involving patients with gynecological cancer who received abdominal RT after surgery. Patients were randomized to receive prebiotics or placebo. The prebiotic group received a mixture of fiber (50 inulin and 50% fructo-oligosaccharide), and the placebo group received 6 g of maltodextrin twice daily from 1 week before to 3 weeks after RT. The number of bowel movements and stool consistency was recorded daily. Diarrhea was evaluated according to the Common Toxicity Criteria of the National Cancer Institute. Stool consistency was

assessed using the 7-point Bristol scale. Patients' quality-of-life was evaluated at baseline and at completion of RT using the EORTC-QLQ-C30 (European Organization for Research and Treatment of Cancer quality-of-life Questionnaire C30) test. RESULTS: Thirty-eight women with a mean age of 60.3±11.8 years participated in the study. Both groups (prebiotic (n=20) and placebo (n=18)) were comparable in their baseline characteristics. The number of bowel movements per month increased in both groups during RT. The number of bowel movements per day increased in both groups. The number of days with watery stool (Bristol score 7) was lower in the prebiotic group (3.3±4.4 to 2.2±1.6) than in the placebo group (P=0.08). With respect to quality-of-life, the symptoms with the highest score in the placebo group were insomnia at baseline and diarrhea toward the end of the treatment. In the prebiotic group, insomnia was the symptom with the highest score at both assessments, although the differences were not statistically significant. CONCLUSIONS: Prebiotics can improve the consistency of stools in gynecologic cancer patients on RT. This finding could have important implications in the quality-of-life of these patients during treatment." As taken from Garcia-Peris P et al. 2016. Eur. J. Clin. Nutr. 70(2), 170-4. PubMed, 2017 available at: https://www.ncbi.nlm.nih.gov/pubmed/26603881

“BACKGROUND & AIMS: Food additives, such as emulsifiers, stabilizers, or bulking agents, are present in the Western diet and their consumption is increasing. However, little is known about their potential effects on intestinal homeostasis. In this study we examined the effect of some of these food additives on gut inflammation. METHODS: Mice were given drinking water containing maltodextrin (MDX), propylene glycol, or animal gelatin, and then challenged with dextran sulfate sodium or indomethacin. In parallel, mice fed a MDX-enriched diet were given the endoplasmic reticulum (ER) stress inhibitor tauroursodeoxycholic acid (TUDCA). Transcriptomic analysis, real-time polymerase chain reaction, mucin-2 expression, phosphorylated p38 mitogen-activated protein (MAP) kinase quantification, and H&E staining was performed on colonic tissues. Mucosa-associated microbiota composition was characterized by 16S ribosomal RNA sequencing. For the in vitro experiments, murine intestinal crypts and the human mucus-secreting HT29-methotrexate treated cell line were stimulated with MDX in the presence or absence of TUDCA or a p38 MAP kinase inhibitor. RESULTS: Diets enriched in MDX, but not propylene glycol or animal gelatin, exacerbated intestinal inflammation in both models. Analysis of the mechanisms underlying the detrimental effect of MDX showed up-regulation of inositol requiring protein 1β, a sensor of ER stress, in goblet cells, and a reduction of mucin-2 expression with no significant change in mucosa-associated microbiota. Stimulation of murine intestinal crypts and HT29-methotrexate treated cell line cells with MDX induced inositol requiring protein 1β via a p38 MAP kinase-dependent mechanism. Treatment of mice with TUDCA prevented mucin-2 depletion and attenuated colitis in MDX-fed mice. CONCLUSIONS: MDX increases ER stress in gut epithelial cells with the downstream effect of reducing mucus production and enhancing colitis susceptibility.” As taken from Laudisi F et al. 2019a. Cell. Mol. Gastroenterol. Hepatol, 7(2), 457-473. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/30765332

“Dietary fiber stimulates the growth of potentially beneficial bacteria (eg, bifidobacteria), yet most Americans do not meet daily fiber recommendations. Resistant maltodextrin (RMD), a fermentable functional fiber, may help individuals meet total fiber recommendations and potentially increase bifidobacteria. It was hypothesized that fecal bifidobacteria counts/ng fecal DNA would increase after adding 25 g RMD to inadequate fiber diets of healthy adults. In this double-blind, controlled crossover study, 51 participants (26.3 ± 6.8 years, mean ± SD) were randomized to consume 0, 15, and 25 g RMD daily for 3 weeks followed by a 2-week washout. Participants collected all stools for 2 days at weeks 0 and 3 of each intervention for stool wet weight (WW) measurements and fecal bifidobacteria counts. Weekly 24-hour dietary recalls assessed total fiber intake. Only 25 g RMD resulted in a change (final minus baseline) in bifidobacteria that was significant compared with 0 g (0.17 ± 0.09 vs -0.17 ± 0.09 log10[counts], respectively, mean ± SEM, P = .008). Stool WW increased only with 25 g (150 ± 11 vs baseline 121±11 g/d; P = .011). Mean daily total fiber intake (including RMD) was significantly higher (both P< .001) with 15 g (17.8 ± 0.6 g/1000 kcal or 4184 kJ) and 25 g (25.3 ± 1.1 g/1000 kcal) compared with 0 g RMD (8.4±0.4 g/1000 kcal). Mean daily

total fiber intakes exceeded recommendations (14 g/1000 kcal) with 15 and 25 g of RMD, and 25 g RMD increased fecal bifidobacteria counts and stool WW, suggesting health benefits from increasing total fiber intake." As taken from Burns AM et al. 2018. Nutr. Res. 60, 33-42. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/30527258

"In physiological conditions, the gut is heavily infiltrated with various subsets of inflammatory cells, whose activity is tightly controlled by counter-regulatory mechanisms. Defects in such mechanisms can favour the development of chronic intestinal disorders, such as Crohn's disease (CD) and ulcerative colitis (UC), the principal forms of inflammatory bowel diseases (IBD) in humans, as well as systemic disorders. Over the last years, the frequency of intestinal and systemic immune-inflammatory disorders has increased in previously low incidence areas, likely due to the Westernization of lifestyles, including dietary habits. The Western diet is characterized by high consumption of proteins, saturated fats and sweets, as well as by a broad use of food additives (e.g., emulsifiers, bulking agents), which are used to preserve and enhance food quality. Accumulating evidence suggests that food additives can perturb gut homeostasis, thereby contributing to promote tissue-damaging inflammatory responses. For instance, mice given the emulsifiers carboxymethylcellulose and polysorbate 80 develop dysbiosis with overgrowth of mucus-degrading bacteria. Such an effect triggers colitis in animals deficient in either interleukin-10, a cytokine exerting anti-inflammatory and regulatory functions, or Toll-like receptor 5, a receptor recognizing the bacterial flagellin. Similarly, the polysaccharide maltodextrin induces endoplasmic reticulum stress in intestinal goblet cells, thereby impairing mucus release and increasing host susceptibility to colitis. In this review, we report and discuss the current knowledge about the impact of food additives on gut homeostasis and their potential contribution to the development of inflammatory disorders." As taken from Laudisi F et al. 2019b. Nutrients 11(10), 2334. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31581570/

This study aims to assess the renoprotective effect of hydration with dextrose water (DW) 5% versus normal saline (N/S) 0.9% against methotrexate (MTX) induced nephrotoxicity. Materials and methods: This experimental animal study has been conducted on 36 Wistar rats (200-250 g) categorized into six groups, including male (n = 6) and female (n = 6) rats receiving sodium chloride 0.9% saline plus MTX, DW 5% plus MTX, or MTX alone. By the fifth day after the MTX injection, biochemical indexes were measured. The rats were also sacrificed and renal specimens were evaluated microscopically to determine kidney tissue damage (KTD). Results: The groups were not significantly different with regard to blood urea nitrogen (BUN) (P = 0.5), creatinine (Cr) (P = 0.24), kidney weight (P = 0.34), and urine flow (UF) (P = 0.5), while KTD score was remarkably less in the hydrated groups (P < 0.001). Weight loss in DW-treated rats was significantly more than N/S-treated ones, and creatinine clearance (CrCl) and urine load (UL) of Cr were statistically similar between males and females in the control group, but significantly lower among the DW5% treated males. Conclusion: Based on the findings of this study, hydration with N/S was superior to DW5% for the prevention from HDMTX-induced nephrotoxicity. As taken from Hasanpour Z et. Al. 2024. Adv Biomed Res. Available at: https://pubmed.ncbi.nlm.nih.gov/38525397/

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

This ingredient was considered as part of an overall safety assessment of ingredients added to tobacco in the manufacture of cigarettes. An expert panel of toxicologists reviewed the open literature and internal toxicology data of 5 tobacco companies to evaluate a composite list of ingredients used in the manufacture of cigarettes. The conclusion of this report was that these ingredients did not increase the inherent biological activity of tobacco cigarettes, and are considered to be acceptable under conditions of intended use (Doull et al., 1994 & 1998).

Tobacco smoke condensates from cigarettes containing Maltodextrin and an additive free, reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the condensate was not changed by the addition of Maltodextrin. Table below provides tested level(s) and specific endpoint(s).

Endpoint	Tested level (ppm)	Reference
Smoke chemistry	41,000	Gaworski et al., 2011 & Coggins et al., 2011
	1300	JTI KB Study Report(s)
In vitro genotoxicity	41,000	Gaworski et al., 2011 & Coggins et al., 2011
In vitro cytotoxicity	41,000	Gaworski et al., 2011 & Coggins et al., 2011
Inhalation study	816	Gaworski et al., 1998
	41,000	Gaworski et al., 2011 & Coggins et al., 2011
Skin painting	816	Gaworski et al., 1999

9. Heated/vapor emissions toxicity

Aerosol from heated tobacco stick(s) containing Maltodextrin was tested in aerosol chemistry and a battery of in vitro test(s). Under the test conditions and within the sensitivity and specificity of the bioassay(s), the activity of the total particulate matter (TPM) and/or gas vapor phase (GVP) were not increased by the addition of this ingredient when compared to TPM and/or GVP from reference combustible cigarettes. The table below provides the highest tested level(s) and specific endpoint(s):

Endpoint	Tested level (mg/stick)	Reference
Aerosol chemistry	1.46	Labstat International Inc. (2020a) Labstat International Inc. (2021a) JTI Heated Tobacco Stick Study Report(s)
In vitro genotoxicity	1.46	Labstat International Inc. (2020b) Labstat International Inc. (2021b) JTI Heated Tobacco Stick Study Report(s)
In vitro cytotoxicity	1.46	Labstat International Inc. (2020b) Labstat International Inc. (2021b) JTI Heated Tobacco Stick Study Report(s)

10. Ecotoxicity

10.1. Environmental fate

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that maltodextrin is of uncertain persistence in the environment.

Data accessed June 2017 on the OECD website“No studies on the route and rate of degradation of maltodextrin in the environment have been submitted; instead the applicant made reference to

published information. Microbial degradation is the major route of transformation of polysaccharides in the environment. In the case of maltodextrin, which has relatively few glucose units, it is cleaved by glycoside hydrolase enzymes which act on α-1,4-glycosidic bonds, breaking the molecule up into simple sugars (glucose). These degradation products are considered of no toxicological concern, in fact they are natural energy sources.

Initial soil PEC (Predicted Environmental Concentration) values for maltodextrin were provided considering a single annual application at a maximum rate of 33.7 kg a.s./ha with 0% crop interception. Although there are no specific data relating to the abiotic hydrolysis, it is assumed that maltodextrin will be subject to enzymatic hydrolysis and subsequently degraded into oligosaccharides and monosaccharides of no toxicological concern. Worst case initial PEC in surface water were calculated for a single application of 33.7 kg a.s./ha based on a drift value of 2.77% at 1 m for field crops, assuming no degradation, and a standard water body (length 100m, width 1 m and depth 30 cm).

It is acknowledged that maltodextrin used as a plant protection product has no pesticidal activity once in the soil and water column, however it has been requested to be approved as an insecticide and it is an organic compound. Therefore, based on Council Directive 98/83/EC7, an assessment of groundwater exposure is required for comparison to the parametric legal drinking water limit (0.1 µg/L) that is applied as a decision making criterion for product approval. This has been identified as a data gap.

Estimation of degradation by photo-oxidation in air using the air-model calculation according to Atkinson (AOP v1.92) gives a DT50 at 25°C (12h day) of 0.132 days indicating that long-range transport of maltodextrin through the atmosphere is not expected”

As taken from EFSA, 2013.

10.2. Aquatic toxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that maltodextrin is not inherently toxic to aquatic organisms and is of low ecotoxicological concern.

Data accessed June 2017 on the OECD website“With the exception of acute laboratory studies on honeybees, no ecotoxicological data have been submitted for either maltodextrin or the formulated product ‘Eradicoat’.”

“A risk assessment to aquatic organisms was provided on the basis of the lowest publicly available endpoint. However, the non-species related TER was considered insufficient and the proposed approach that maltodextrin could not cause adverse effects on aquatic organisms due to the physical mode of action, was not supported by data. Therefore, further data were requested during the peer review to address the risk to aquatic organisms. On the basis of the additional information (including aQSAR analysis) provided in the Addendum I to the DAR (United Kingdom, 2012), a low risk was concluded to aquatic organisms.”

As taken from EFSA, 2013.

“The aim of the present study was to determine the potential long-term metabolic effects of early nutritional programming on carbohydrate utilisation in adult zebrafish (Danio rerio). High-carbohydrate diets were fed to fish during four ontogenetic stages: from the first-feeding stage to the end of the yolk-sac larval stage; from the first-feeding stage to 2 d after yolk-sac exhaustion; after yolk-sac exhaustion for 3 or 5 d. The carbohydrate stimuli significantly increased the body weight of the first-feeding groups in the short term. The expression of genes was differentially regulated by the early dietary intervention. The high-carbohydrate diets resulted in decreased plasma glucose levels in the adult fish. The mRNA levels and enzyme activities of glucokinase, pyruvate kinase, α-amylase and sodium-dependent glucose co-transporter 1 were up-regulated in the first-feeding groups. There was no significant change in the mRNA levels of glucose-6-

phosphatase (G6Pase) in any experimental group, and the activity of G6Pase enzyme in the FF-5 (first feeding to 2 d after yolk-sac exhaustion) group was significantly different from that of the other groups. The expression of phosphoenolpyruvate carboxykinase gene in all the groups was significantly decreased. In the examined early programming range, growth performance was not affected. Taken together, data reported herein indicate that the period ranging from the polyculture to the external feeding stage is an important window for potential modification of the long-term physiological functions. In conclusion, the present study demonstrates that it is possible to permanently modify carbohydrate digestion, transport and metabolism of adult zebrafish through early nutritional programming." As taken from Fang L et al. 2014. Br. J. Nutr. 111(5), 808-18. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24112146?dopt=AbstractPlus

10.3. Sediment toxicity

No data available to us at this time.

10.4. Terrestrial toxicity

"With the exception of acute laboratory studies on honeybees, no ecotoxicological data have been submitted for either maltodextrin or the formulated product 'Eradicoat'.

Considering that maltodextrin is a naturally formed polysaccharide, the risk to birds and mammals was considered low."

"A high first tier risk was indicated for honeybees i.e. HQs above the trigger, although this was likely to be due to the relatively high application rates compared with the maximum doses tested. No higher tier data were available to further address the risk for the representative uses by taking into account the mode of action. Therefore, a data gap is identified and a high risk to bees cannot be excluded (critical area of concern).

A high risk to non-target arthropods which come into direct contact with the product could not be excluded. It was argued that due to drying and likely degradation between applications, only a shortterm (physical) effect is expected and recovery might occur within an ecologically relevant period.

However, no data were submitted to support such a weight of evidence approach and therefore a data gap is identified.

The risk to earthworms, soil macro- and microorganisms, non-target plants and sewage treatment plants was considered low"

As taken from EFSA, 2013.

Pesticide type	Insecticide, Other
Other constituent type	Binding agent, Carrier
Substance group	Polysaccharide
Substance origin	Natural
Mode of action	Mode of action is purely physical, substance coats and dries on target pest blocking the spiracles and leading to death by suffocation. Also has entrapment properties.

Birds (unknown species) – acute LD_{50} > 2500 mg/kg.

Honeybees – acute 48 hr LD_{50} > 200 n++-íg/bee.

Earthworms (unknown species) – acute 14 day LD_{50} > 500 mg/kg.

As taken from PPDB, 2015.

10.5. All other relevant types of ecotoxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that maltodextrin is of uncertain bioaccumulative potential in the environment.

Data accessed June 2017 on the OECD website

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Safety Assessment of Polysaccharide Gums as Used in Cosmetics

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The 2015 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (the Panel) reviewed the safety of 106 ingredients, which function as viscosity increasing agents in cosmetic products. The Panel reviewed relevant animal and human data on these ingredients. The Panel concluded that most of the polysaccharide gums are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment, but that the available data are insufficient to make a determination that hydrolyzed carrageenan is safe under the intended conditions of use in cosmetics. The Panel was concerned about the presence of alkylating and other agents that are used to modify polysaccharide gums in cosmetics. Industry should use good manufacturing practices to limit impurities.

INTRODUCTION

The safety of 106 polysaccharide gums (see Tables 1 and 2) as used in cosmetics is reviewed in this safety assessment. The polysaccharide gums are each naturally derived materials that comprise polysaccharides obtained from plants or algae. Based on the different chemical structures that are associated with polysaccharide gums, these ingredients can be subdivided into categories such as modified, unmodified, linear, branched, and cyclic. Regardless of how they are structured, all of the "moieties" that comprise the molecular structures of these ingredients are polymers composed of monosaccharides.

Although these ingredients could be categorized in multiple ways, all of these ingredients fall into two predominate categories, modified and unmodified. The ingredients in the Modified subgroup have been further subdivided into Linear, Branched, Cyclic, and Unknown Structural Configuration. The ingredients in the Unmodified subgroup have been subdivided into Linear Polysaccharides and Their Salts, Branched - Unmodified, Cyclic, and Unknown Structural Configuration.

Based on chemical similarities, relevant data on the following are included for use in evaluating the safety of ingredients in this review: wheat bran extract (contains ~ 80% arabinoxylan oligopeptides) - for use in the safety assessment of arabinoxylan (branched - unmodified subgroup); pectin-derived acidic oligosaccharides (mixture of linear oligomers and small polymers of galacturonic acid) - for safety assessment of pectin (branched - unmodified subgroup), which consists chiefly of partially methoxylated polygalacturonic acids; and carboxymethyl inulin - for safety assessment of sodium carboxymethyl inulin (branched - modified subgroup). Many of the polysaccharide gums reviewed in this safety assessment function as viscosity increasing agents in cosmetic products.[1] Other functions are listed in Table 2.

As a group, polysaccharide gums comprise polymers of simple saccharide monomers. Their substantial molecular sizes suggest that skin penetration of these ingredients would be unlikely. Thus, these ingredients are unlikely to have significant systemic accessibility and any major decomposition products are likely to be simple saccharides.

In addition, the Panel has issued "safe as used" conclusions for the following cosmetic ingredients which are structurally similar to some of the ingredients reviewed in this safety assessment: galactomannans,[2] microbial polysaccharide gums,[3] astragalus gummifer gum,[4,5] aloe barbadensis leaf polysaccharides,[6] oryza sativa (rice) starch,[7] zea mays (corn) starch,[8] acacia senegal gum,[9] glyceryl alginate,[10] hyaluronic acid,[11] and triticum vulgare (wheat) starch.[12,13]

CHEMISTRY

Definition and Structure

Polysaccharide nomenclature follows the general principles of established organic and carbohydrate nomenclature. Polysaccharide (glycan) is the name given to a macromolecule consisting of a large number of monosaccharide (glycose) residues joined to each other by glycosidic linkages (Figure 1). The term poly(glycose) is not a synonym for polysaccharide (glycan), because it refers to macromolecules composed of glycose residues joined to each other by non-glycosidic linkages. Polysaccharides may be linear, branched, or cyclic. Definitions, structures, and functions of the polysaccharide gums reviewed in this safety assessment, as used in cosmetics and defined in the *International Cosmetic Ingredients Dictionary and Handbook*, are presented in Tables 1 and 2.[1]

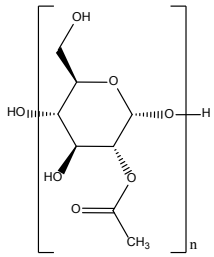


Figure 1. Starch Acetate – an example of a polysaccharide gum

The polysaccharide gums are each naturally derived materials that comprise polysaccharides obtained from plants or algae. Their substantial molecular sizes suggest that skin penetration of these ingredients would be unlikely. While, for the sake of clarity and organization, these ingredients can be subdivided into categories such as linear, branched, cylic, modified, and unmodified, these moieties represent a family of structurally similar polymeric materials, composed of simple saccharide monomers. So, in intended cosmetic application, these ingredients are unlikely to have significant systemic accessibility and any major decomposition products are likely to be simple saccharides, albeit chemically modified ones in some instances (*vide supra*).

Physical and Chemical Properties

Physical and chemical properties of polysaccharide gums are presented in Table 3. These gums have high molecular weights, and many are insoluble in water.

Method of Manufacture

Methods of manufacture of polysaccharide gums are presented in Table 3. The manufacturing processes for hydrolyzed furcellaran and starch hydroxypropyltrimonium chloride are presented in the following sections.

Linear – Modified

Hydrolyzed Furcellaran

The manufacturing process for hydrolyzed furcellaran is presented in Figure 2 below.

Fresh Seaweed
(Furcellaria lumbricalis)
↓
Drying
Extraction (water 90˚C)
Filtration
Sedimentation
Drying
↓
Furcellarane Powder
(Sulfated Polysaccharide)
↓
Depolymerization by sub-critical CO_2
(105˚C, 250 bar) with water (2%)
↓
Hydrolyzed Furcellaran
(Depolymerized Sulfated
Polysaccharide; MW: 200 kDa
on average)

→

Solubilization of Phenoxyethanol in Water
↓
Heating until 70˚C under shaking
↓
Cooling at room temperature
↓
Water
Phenoxyethanol
Hydrolyzed Furcellaran
Sea salt

←

Spray Dried Sea Water
Concentrate

Figure 2. Manufacturing Process for Hydrolyzed Furcellaran.[14]

Branched – Modified

Starch Hydroxypropyltrimonium Chloride

The manufacturing process for starch hydroxypropyltrimonium chloride is presented in Figure 3 below.

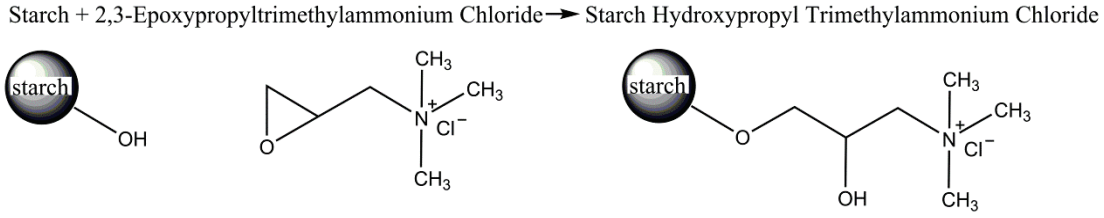


Figure 3. Reaction to form cationic starch ether.[15]

Composition/Impurities

Composition and impurities data on polysaccharide gums are presented in Table 4. Composition/properties data on two hydrolyzed starch products are presented in Table 5.

USE

Cosmetic

Many of the ingredients reviewed in this safety assessment function as viscosity increasing agents in cosmetic products, and the complete list of polysaccharide gum functions in cosmetic products is presented in Table 2.[1] According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), and the results from a survey of ingredient use concentrations conducted by the Personal Care Products Council (Council) in 2013, 58 of these polysaccharide gums are being used in cosmetic products and maltodextrin has the highest reported use frequency.[16,17,18,19]

The Council survey data also indicate that polysaccharide gums are being used in rinse-off cosmetic products at maximum ingredient use concentrations up to 50% (i.e., for algin in paste masks and mud packs), and in leave-on cosmetic products at maximum ingredient use concentrations up to 45.7% (i.e., for corn starch modified in tonics, dressings, and other hair grooming aids).[16,18] Frequency of use/use concentration data for polysaccharide gums are summarized in Table 6.

Cosmetic products containing polysaccharide gums may be applied to the skin and hair or, incidentally, may come in contact with the eyes (maximum ingredient use concentration in these products = 30%) and mucous membranes (maximum ingredient use concentration in these products = 32%). Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Polysaccharide gums are used at concentrations up to 9.5% (avena sativa (oat) starch) in cosmetic products that are sprayed, which also includes use in a pump hair spray at a maximum concentration of 0.45% (corn starch modified), and at concentrations up to 45.7% (corn starch modified) in cosmetic products that possibly are sprayed. Ingredient use in underarm aerosol deodorant sprays is being reported at maximum use concentrations ranging from 0.001% (algin) to 2.5% (cyclodextrin). Hydroxypropyl cyclodextrin is being used in underarm pump deodorant sprays at a maximum use concentration of 0.34%. Additionally, polysaccharide gums are used in powders at concentrations up to 33% (tapioca starch). Because polysaccharide gums are used in products that are sprayed, they could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm, compared with pump sprays.[20,21,22,23] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[20,21] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aero-

dynamic equivalent diameters in the range considered to be respirable.[21] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Non-cosmetic

According to the FDA, the following polysaccharide gums are approved direct food additives affirmed as generally recognized as safe (GRAS):[24,25] agar, alginic acid, ammonium alginate, amylose (i.e., high-amylose corn starch is GRAS), calcium alginate, pectin, potassium alginate, dextrin, maltodextrin, solanum tuberosum (potato) starch, solanum tuberosum (potato) starch, starch acetate, tapioca starch, hydroxypropyl starch, propylene glycol alginate, carrageenan, ghatti gum, and sterculia urens gum.

Linear Polysaccharides and Their Salts

Algin

The viscosity of blood substitutes is among the important determinants in restoring microcirculation.[26] Sodium alginate (algin) is frequently mentioned as a viscosity modifier in the development of blood substitutes.

Alginates

Alginate dressings are among the types of absorbent dressings that are used to treat exuding wounds.[27]

Carrageenan

κ-Carrageenan (thickening agent) stabilizes milk proteins and is widely used in dairy products.[28]

At the June 2014 meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Committee concluded that the use of carrageenan in infant formula or formula for special medical purposes at concentrations up to 1000 mg/L is not of concern.[29] Furthermore, the Committee recognized that there is variability in medical conditions among infants requiring formulas for special medical purposes that contain the higher levels of carrageenan, and noted that these infants would normally be under medical supervision. A summary of the discussion on which the Committee's conclusion is based is summarized in the Repeated Dose Toxicity-Oral section of this report.

Inulin

Inulin is a prebiotic, meaning a non-digestible food ingredient that selectively stimulates the growth and/or activity of one or several bacterial species in the colon.[30]

Branched - Unmodified

Ghatti Gum

Ghatti gum (thickening agent) is used to stabilize table syrup emulsions, as a glaze in candy products, and as a component of chewing gum, cough drops, and candy lozenges.[28]

Sterculia Urens Gum

Sterculia urens gum has the following uses in food: formulation aid, stabilizer and thickener, and emulsifier and emulsifier salt.[31] World Health Organization (WHO) reports affirming the safety of karaya gum as a food additive are available.[32,33]

Cyclic

Cyclodextrin

Cyclodextrins have been used to solubilize drugs in aqueous vehicles as guest-host complexes.[34]

TOXICOKINETICS

Non-Human

Linear Polysaccharides and Their Salts

Carrageenan

Carrageenan is not degraded or absorbed in the gastrointestinal tracts of rodents, dogs, and non-human primates.[35]

Branched - Unmodified

Sterculia Urens Gum

A toxicokinetic study on sterculia urens gum was performed using 2 groups of 4 male Sprague-Dawley rats of the CD strain. One group was fed a pelleted diet containing 5% sterculia urens gum for 24 h, and the control group was fed a similar laboratory pelleted diet without the gum. Urine and feces were collected and weighed after 24 h, 48 h, and 72 h. The polysaccharide of sterculia urens gum is composed essentially of rhamnose, galactose and galacturonic acid. Fecal polysaccharide was calculated as sterculia urens gum polysaccharide after correction for background levels of rhamnose, galactose, and galacturonic acid in the control feces. The quantity and monosaccharide composition of the fecal polysaccharide were compared with the dose and original composition of the gum polysaccharide. Aggregated polysaccharide estimated over the 72-h collection period ranged from 81% to 108%, with a mean value of 95% of that consumed. Thus, 95% of the gum ingested was excreted in the feces.[36]

Cyclic

Cyclodextrin

The absorption of orally administered ^{14}C-β-cyclodextrin, in methylcellulose solution, was studied using 4 Wistar R x Long Evans F_1 male rats.[37] Two rats received an oral dose of 36.7 mg/kg, and the other 2 rats received 36.9 mg/kg. The average dose volume was 1.5 ml. The maximum radioactivity of the blood derived from ^{14}C-β-cyclodextrin occurred between the 4th and 11th hour after exposure, and the maximum radioactivity in different experiments ranged from 5% to 17% of the total administered radioactivity. Radioactivity excreted in the urine ranged from 4.2% to 4.8% of the total radioactivity administered. No specific accumulation of ^{14}C-β-cyclodextrin in organs was found after dosing. The large intestine contained 10% to 15% of the ^{14}C-β-cyclodextrin radioactivity at 24 h post-dosing.

In another experiment, a female CFY rat received an oral dose of 313 mg/kg ^{14}C-β-cyclodextrin (homogenized in dextran solution, volume = 2.5 ml). In the 8th hour after dosing, no more than 3 to 50 ppm β-cyclodextrin was detectable in the blood. In a third experiment, a female CFY rat was dosed orally with 36.1 mg/kg ^{14}C-β-cyclodextrin (homogenized in 1 ml dextran solution), and another rat was dosed orally with 313.5 mg/kg ^{14}C-β-cyclodextrin (homogenized in 2.5 ml dextran solution). Three female CFY rats also received an oral dose of 1.88 mg/kg chromatographically purified ^{14}C-β-cyclodextrin (homogenized in 1.5 ml dextran solution). The radioactivity peak was detected in the exhaled air between the 4th to 6th or the 6th to 8th hour, depending on the dose. The total radioactivity exhaled by ^{14}C-β-cyclodextrin-treated rats in 24 h represented 55% to 64% of the administered ^{14}C-β-cyclodextrin. The authors suggested, based on the results of this study, that the rate-determining step in β-cyclodextrin absorption is the enzymatic hydrolysis of β-cyclodextrin to yield linear dextrins, which are rapidly hydrolyzed to maltose and glucose.[37]

Human

Branched - Unmodified

Starch Acetate

The pharmacokinetics of starch acetate (acetyl starch) and hydroxyethyl starch was studied using 2 groups of 16 surgical patients (18 to 70 years old).[38] Patients in one group were initially infused intravenously (i.v.) with 15 mL/kg of a 6% acetyl starch solution, and then up to a maximal dosing volume of 1,000 mL/kg, over a 30-minute period. The other group was infused with a 6% hydroxyethyl starch solution (same dosing volume) according to the same procedure. When compared to hydroxyethyl starch, rapid and nearly complete enzymatic degradation to acetic acid and glucose (and to products that can be excreted renally) was reported for acetyl starch.

Sterculia Urens Gum

Five male volunteers were involved in a study in which 24-h urine samples were collected prior to, and following, the ingestion of 10 g karaya gum for 15 days.[39] Total gum intake was 10-fold greater than the approved average daily intake (ADI) of 0-12.5 mg/kg body weight. The detection limit for rhamnose in the urine was 0.2 µg; however, rhamnose was not detected in any of the urine specimens. The authors noted that if 1% of the rhamnose in 10 g karaya gum appeared in the 24-h urine specimens, it would have been detected. Furthermore, the results of this study confirmed that dietary gum karaya is neither digested nor degraded by enteric bacteria, and is not absorbed to any significant extent in the digestive tract.

Tapioca Starch

Ten men (29 to 41 years old) participated in an oral exposure study.[40] Blood was collected after a 12-h fast. Tapioca starch (30 g) containing 0.1 g aspartame was dissolved in 150 L of water, and the solution or dispersion remained for 3 minutes in boiling water. Subjects then drank the solution 1 to 2 min later. Three tolerance tests were performed, using a crossover design, over three days. Tapioca starch produced a large, rapid increase in plasma glucose concentration, which peaked in 30 minutes and then decreased toward the basal value.

Percutaneous Absorption

Cyclic - Modified

Hydroxypropyl Cyclodextrin

The percutaneous absorption of 2% ^{14}C-2-hydroxypropyl-β-cyclodextrin *in vivo* was studied using 3 to 5 female hairless mice.[41] The test material (100 µL on occlusive patch) was applied to dorsal skin (2 cm^2) for 24 h. Radioactivity in the patches, in the stratum corneum (collected by tape stripping), and in the epidermis and cutis of the skin (obtained by peeling off the treated portion) was measured using a scintillation counter. The percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin through intact skin was extremely low, i.e., ~ 0.02% of the amount applied to the skin. The absorption rate of ^{14}C-2-hydroxypropyl-β-cyclodextrin through skin from which the stratum corneum had been removed by tape stripping was approximately 24% of the amount applied to the skin. The latter finding suggests that the stratum corneum may act as a barrier to the percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin. Thus, the results of this study clearly demonstrate that 2-hydroxypropyl-β-cyclodextrin has low permeability through hairless mouse skin.

TOXICOLOGICAL STUDIES

A toxicity profile of β-cyclodextrin (a cyclic polysaccharide gum) is available from the WHO.[42] The toxicity profile of cyclodextrins can differ depending on the route of administration. For example, β-cyclodextrin administered orally induces limited toxicity.[43,44] In both rats and dogs, β-cyclodextrin is considered to be non-toxic at a daily dose less than 600 mg/kg body weight or at 3% or less in the diet.[45] However, if β-cyclodextrin is administered at higher doses in animals via a subcutaneous (s.c.) route, it will cause a decrease in body weight gain, a decrease in liver weight, and nephrotoxicity, with an increase in kidney weight, proximal tubular nephrosis and cellular vacuolation.[45,46] In another study (rats), s.c. administration of β-cyclodextrin (≥ 450 mg/kg) induced similar changes in kidney proximal tubules.[47] Acute and repeated dose toxicity studies on polysaccharide gums (according to type of exposure) are summarized in Tables 7 and Table 8, respectively. The following acute toxicity studies (according to type of exposure) on polysaccharide gums are summarized in Table 7: inhalation, oral, dermal,

intravenous, intrapleural, and transbronchial. Oral and dermal repeated dose toxicity studies on polysaccharide gums are summarized in Table 8.

Cytotoxicity

Linear Polysaccharides and Their Salts

Calcium Alginate

In a cytotoxicity assay, calcium alginate fibers were introduced into human embryonic kidney cells and human fibroblasts.[48] A total of nine experimental groups were prepared according to the following weights of calcium alginate fibers: 0.005, 0.01, 0.02, 0.03, 0.04, 0.05, 0.08, 0.10, and 0.15 g. Next, 1-cm lengths of fibers were cut and sterilized with UV irradiation prior to their addition to the cells. The cells were in their exponential growth phase, and were incubated for 48 h. Calcium alginate fibers were not cytotoxic.

Allergenicity/Immune System Effects

Non-Human

Linear Polysaccharides and Their Salts

Polianthes Tuberosa Polysaccharide

The potential for a modulatory effect on the murine self-defense system by an acidic polysaccharide (ANK-102) produced by *Polianthes tuberosa* cells in liquid culture was examined.[49] The pretreatment (intraperitoneal [i.p.] injection) of C3H/HeN mice with ANK-102 (2 mg in 0.2 ml solution) deteriorated murine survival against lethal infection with *Listeria monocytogenes***,** an intracellular gram positive bacterium eliminated mainly by macrophages through the T-cell mediated immune response. Pretreatment with ANK-102 resulted in the accumulation of Mac 1 and Mac 2 positive cells in the peritoneal cavity of the infected animals and the reduction of Thy 1.2 expression on the surface of the thymocytes. ANK-102 was classified as an immunosuppressive polysaccharide.

Potassium Carrageenan

Male Sprague-Dawley rats (8 animals, 7 weeks old) were injected i.p. with potassium carrageenan (50 mg in 5 ml PBS).[50] The control group received a single injection of PBS (0.5 ml). At 3 weeks post-injection, serum levels of IgM, IgG and slow α_1- and slow α_2-globulins were measured using quantitative radial immunodiffusion (IgG) or immunoelectrophoresis (IgM and slow α-globulins). There was a significant elevation in levels of IgM and slow α_1 globulin that was maximal on day 4; levels returned to normal by day 14. Slow α_2-globulin was detectable within 24 h, reached a peak at day 2, and, in most animals, was no longer measurable by day 14. Levels of IgG were not affected by potassium carrageenan injection.

Branched - Unmodified

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

The allergenicity of karaya gum was studied in adult male and female guinea pigs (number not stated).[51] Karaya gum (1 g/kg) was dissolved in normal saline to make a 3% solution, which was injected i.p. The gum was also administered orally (1 g/animal daily) for 3 months, or mixed with food (single feeding of 5 g/animal). Egg albumen served as the control in each experiment. Animals that received single i.p. injections or single oral doses were killed at intervals within a range of 4 to 12 weeks after the attempted sensitization. Animals dosed orally daily for 3 months were killed either on the day after the last dose or after an interval of 6 weeks after the last dose. Isolated pieces of small intestine from treated males and females, seminal vesicles from males, and the uterus of females were suspended in an organ bath and exposed to karaya gum or egg albumen for 10 minutes. The organs of

animals exposed *in vivo* to karaya gum where challenged first with egg albumen and, later, with karaya gum, and *vice versa*. Study results indicated that allergic sensitivity did not develop in guinea pigs dosed orally (single or repeated doses) or i.p. Injection of albumen resulted in marked allergic sensitization.

An animal model was used to investigate the immunogenicity of karaya gum (*Sterculia* spp.).[52] Groups of [(C57BL/6J x DBA/2)F_1] (BDF_1) mice were intradermally immunized with the gum in Freund's complete adjuvant. Serum antibody levels were measured using an enzyme-linked immunosorbent assay (ELISA), and delayed hypersensitivity responses assayed by a footpad swelling test. Karaya gum elicited systemic immune responses after immunization. Further processing reduced immunogenicity, although there was no evidence that systemic immunity to complex polysaccharide antigen responses could be completely abolished by processing or purification. Karaya gum caused considerable footpad swelling when injected intradermally.

Human

Branched - Modified

Propylene Glycol Alginate

Following a 7-day control period, 5 male volunteers consumed propylene glycol alginate at a dose of 175 mg/kg body weight for 7 days.[53] This regimen was followed by dosing with 200 mg/kg body weight for an additional 16 days. No allergic responses were reported by, nor observed in, any of the volunteers.

In Vitro

Linear Polysaccharides and Their Salts

Potassium Alginate

The acute tissue reactions to potassium alginate, locally applied to a microvascular bed, were studied using the vital microscopic hamster cheek-pouch model and correlative histology.[54] This experimental model permitted the study of microvascular permeability, blood flow, vessel diameters and leucocyte adhesion to vessel walls intravitally, and leucocyte migration and mast cell degranulation histologically. Deionized water alone and potassium alginate with flavor and color mixed in saline was found to cause severe microvascular alterations, while potassium alginate, without flavor and color, mixed in saline and applied to the microvasculature resulted in a minor inflammatory reaction

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity data on polysaccharide gums are summarized in Table 9. Except for a dose-dependent increase (40-600 mg/kg) in the incidence of missing skeletal sternebrae in rabbits dosed orally with *kappa/lambda*- carrageenan, the results for polysaccharide gums in reproductive and developmental toxicity studies were essentially negative.

GENOTOXICITY

Genotoxicity data (bacterial and mammalian) on polysaccharide gums are summarized in Table 10. In bacterial assays, the following were not genotoxic either with or without metabolic activation: arabinoxylan, carboxymethyl inulin, carrageenan, ghatti gum, glucomannan, and pectin-derived acidic oligosaccharides. In mammalian assays with and without metabolic activation, wheat bran extract, carboxymethyl inulin, carrageenan, ghatti gum, and glucomannan were not genotoxic. However, results for pectin-derived acidic oligosaccharides in mammalian assays were either equivocal or it was classified as clastogenic, only at highly cytotoxic concentrations. Sterculia urens gum was not genotoxic in cytogenetic assays (*in vitro* and *in vivo*) or in the *in vivo* dominant lethal gene test.

CARCINOGENICITY

Studies relating to the carcinogenicity of polysaccharide gums are summarized in Table 11. Agar (50,000 ppm in diet) was not carcinogenic in rats, and up to 25% sodium alginate in the diet was not carcinogenic in mice. Results relating to the carcinogenic potential of carrageenan were mixed. Carrageenan (25% in the diet) was not carcinogenic in mice, but 15% carrageenan in the diet enhanced the colon tumor incidence in azoxymethane (AOM)- and N-nitrosomethylurea (NMU)-treated rats. In the aberrant crypt focus (ACF) assay, 10% carrageenan in the diet did not initiate colon tumors, 0.25% carrageenan reduced the number of ACF, and 2.5% carrageenan promoted the growth of ACF in rats. In another study, carrageenan (up to 5% in the diet) did not possess promoting activity for colorectal carcinogenesis in rats. It should also be noted that 5% carrageenan in the diet increased colonic cell proliferation in rats, but that it was concluded that this response was probably adaptive, and would not contribute to the increased risk of colon neoplasia in rats. There was no evidence of carcinogenicity in mice fed 55% starch acetate or in rats fed 5% cyclodextrin in the diet. Pectin (2.5% in diet) caused mucosal hyperplasia of the small intestine of rats. Degraded carrageenan, which may or may not be similar to the cosmetic ingredient hydrolyzed carrageenan, caused colon cancer in rats at dietary concentrations of 5% and 10%, but not 1%, in rats. Degraded carrageenan (also known as poligeenan) results from a manufacturing process of seaweed that involves intentional extensive acid hydrolysis, resulting in sulfated galactose polymers with an average molecular weight of approximately 15,000 Da.[35]

Inulin (15 g in basal diet) inhibited the growth of 2 tumor cell lines that were implanted in mice, and the dietary intake of 4.8% arabinoxylan reduced the occurrence of preneiplastic lesions in rats. Glucomannan (10% in the diet) inhibited the development of spontaneous liver tumors in mice.

IRRITATION AND SENSITIZATION

Dermal Irritation and Sensitization

Skin irritation and sensitization studies on polysaccharide gums are summarized in Table12. The results of animal and human tests indicate that these gums can be mild skin irritants, but are non-sensitizers.

Phototoxicity

Branched - Modified

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

The phototoxicity of a sodium hydrolyzed potato starch dodecenylsuccinate was evaluated using the *in vitro* neutral red uptake phototoxicity assay.[55] The trade name material (in Hanks' balanced salt solution) was evaluated at concentrations ranging from 68.1 to 1,000 µg/ml in BALB/3T3 clone A31 mouse embryo fibroblast cultures. Chlorpromazine served as the positive control. Following incubation, cultures were irradiated for 50 minutes with 1.7 mW/cm^2 UVA to achieve an irradiated dose of 5 J/m^2. A positive result was defined as a photo-irritant factor (PIF) > 5. The PIF was defined as the EC_{50} without solar simulated light (SSL)/ EC_{50} with SSL. The test material was not considered to have phototoxicity potential (PIF = 0.8). A PIF of 27.9 was reported for the chlorpromazine positive control.

Clinical Trial

Linear Polysaccharides and Their Salts

Calcium Alginate

Fourteen patients (7 males) with spina bifida were treated for pressure sores. Each patient had calcium alginate dressings applied for 4 to 6 weeks.[56] The mean number of dressings removed per week was 3.5 ± 2.1. Good tolerance to treatment was reported for each patient. It was also noted that no severe side effects were recorded during the trial.

Case Reports

Linear Polysaccharides and Their Salts

Calcium Alginate

A 50-year-old woman was referred for treatment after the discovery of adenoid cystic carcinoma in an excised left submandibular gland.[57] Treatment involved clearing the left submandibular fossa, and selective neck dissections. After removal of the clot (submandibular hematoma), a calcium alginate fiber pack was left in place to control the bleeding. After an extended period, the pack was reported to have stimulated a foreign body reaction which, on a computed tomogram, mimicked a recurrence of the tumor.

Alginate

A 52-year-old general practitioner injected 0.1 ml of an alginate solution into the deep dermis of her left arm.[58] Ten days later, she observed a small pink nodule at the injection site; a bluish papule was observed at 3 months post-injection. A biopsy was performed 2 months after injection. At histopathological examination, a granulomatous reaction involving the deep dermis and the subcutaneous fat was observed. The papule regressed, having resolved completely at 5 months post-injection.

Four of 10 patients injected with an aesthetic injectable resorbable filler consisting of purified alginate (extracted from crusted brown algae), into tear troughs and⁄or dorsa of the hands, developed severe granulomatous reactions within months after injections.[59] The 40% incidence of this disfiguring effect was considered high.

Sodium Carrageenan

Within minutes of receiving a barium enema solution that contained sodium carrageenan, a 26-year-old female had an anaphylactic reaction associated with the following signs/symptoms:[60] abdominal cramps, mild generalized pruritus, generalized urticaria, hypotension, transient loss of consciousness, chest tightness, wheezing, and cyanosis. A skin prick test for a component of the barium enema solution, 0.4% weight/volume sodium carrageenan, were positive (i.e., an 8 mm wheal diameter with surrounding flare). This is the only component of the barium enema solution that yielded a positive reaction.

Ocular Irritation

Non-Human

Linear Polysaccharides and Their Salts

Algin

The ocular irritation potential of algin (2%) was studied in 3 experiments using rabbits (number not stated).[61] Instillation of the test substance was followed by scoring after 1 h, 24 h, 2 days, 3 days, 4 days, and 7 days. Corneal opacity and ulceration or granulation were evaluated. Ocular irritation was graded on a scale of 0 to 110, and an ocular irritation index (OII) was calculated. It was noted that a compound does not provoke any significant injury to the mucous membrane of the eye when no opacity of the cornea occurs and when the ocular irritation index is less than 15. OII values of 3.00, 9.17, and 5.50 were reported in the 3 experiments, respectively. Pathological lesions of the ocular mucosa were not observed.

Carrageenan

Food grade *iota*-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units) was not irritating to unrinsed eyes of rabbits and was minimally irritating to rinsed eyes.[62]

Branched – Modified

Calcium Starch Isododecenylsuccinate and Corn Starch Modified

A material described as structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn starch modified was evaluated for ocular irritation potential in a study involving 6 New Zealand White rabbits.[63,64,65] The OECD 405 test protocol was used. The powder (0.1 ml) was placed in one eye of each animal. Iritis was observed in 2 rabbits, and reactions had cleared by day 1. Conjunctival irritation was observed in 6 rabbits, and reactions had cleared by day 3. There was no evidence of corneal opacity or abnormal systemic signs during the observation period. The test material was classified as a minimal ocular irritant.

Corn Starch Modified

Corn starch modified, dry powder form, was placed in one eye of each of 6 New Zealand White rabbits (5 males, 1 female).[66] Iritis was observed in 1 of 6 rabbits, and the reaction had cleared by 24 h post-administration. Mild conjunctival irritation was observed in all 6 rabbits, and reactions had cleared by 48 h post-administration. There was no evidence of corneal opacity or abnormal physical signs in any of the animals tested. The test substance was classified as minimally irritating to the eye.

Dextrin Myristate

The ocular irritation potential of dextrin myristate was studied using 6 New Zealand white rabbits. The test concentration and protocol were not stated. Ocular irritation was not observed.[67]

Dextrin Palmitate

In an ocular irritation study involving 3 New Zealand white rabbits per test substance, dextrin palmitate (concentration and test protocol not stated) did not cause reactions in the cornea or iris. Slight conjunctival redness was observed in one rabbit at 1 h post-instillation, but had resolved after 24 h.[68,69]

Potato Starch Modified

A 16.8% aqueous suspension of potato starch modified was evaluated in an ocular irritation study involving 3 rabbits (strain not stated), according to the OECD 405 test guideline. Conjunctival irritation/edema was observed in the 3 rabbits, and all reactions had cleared in 2 rabbits by 24 h post-instillation. In the remaining rabbit, slight swelling of the conjunctivae remained at 24 h, and the reaction had cleared by 48 h post-instillation. It was concluded that the potato starch modified suspension was slightly irritating to the eyes of rabbits.

The ocular irritation potential of potato starch modified (28-1808) was evaluated according to the OECD 405 protocol using 3 New Zealand White rabbits.[70] An 18.5% solids solution of the test substance (0.1 ml) was instilled into one eye of each animal, and reactions were scored for up to 72 h post-instillation. Abnormal physical signs were not observed during the observation period. Conjunctival irritation was observed in all animals, having cleared by 48 h. Neither corneal opacity nor iritis was observed during the study. Potato starch modified (28-1808) was classified as a minimal ocular irritant.

Stearoyl Inulin

The ocular irritation potential of steraroyl inulin (test concentrations and protocol not stated) was evaluated in two tests, each using 6 Japanese white rabbits. The test substance was classified as practically non-irritating.[71,72]

In Vitro

Linear - Modified

Hydrolyzed Furcellaran

The ocular irritation potential of a trade name mixture containing 1.35% furcellaran powder and 1% phenoxyethanol was evaluated in a cytotoxicity assay involving cultured fibroblasts (source not stated). The method of diffusion on agarose gel was used. The product (pure) was applied to cultures during a 24-h period, and was classified as slightly toxic. This finding was interpreted as almost non-irritating to slightly irritating to the eyes.[73] The ocular irritation potential of another trade name mixture containing 1.35% furcellaran powder, 0.1% potassium sorbate, and 0.05% citric acid was evaluated according to the same procedure, and the same results were reported.[73]

Maltodextrin

The ocular irritation potential of maltodextrin was evaluated using the *in vitro* bovine corneal opacity and permeability assay.[74] In this assay, plastic cassettes mimicking eye structure are used as holders for excised corneas. The posterior chamber was filled with cell support media, and the anterior chamber was filled with an eye gel containing 2.45% maltodextrin. After a 10-minute period, opacity was measured by passing visible light from an opacitometer through the cornea and on to the surface of a light sensor. It was noted that a clear cornea unchanged by the test substance would allow light to pass through and be detected by the sensor. Opaque corneas would produce light scattering (Tyndall effect) and reduced detection that is proportional to the degree of ocular damage. Also, following exposure, fluorescein was added to the anterior chamber of the cassette. The amount of dye passing through the cornea and into the posterior chamber is a measure of corneal permeability, and an increase in corneal permeability is indicative of corneal damage. Based on the results of this study, the eye gel was classified as a non-irritant. The positive control, 5% benzalkonium chloride, was classified as a severe irritant.

In addition, the EPI-Ocular® skin model assay was used to evaluate the ocular irritation potential of an eye gel containing 2.45% maltodextrin.[75] In this assay, the degree of ocular irritation is based on the amount of cytotoxicity observed in tissues exposed to the test substance. Cytotoxicity is measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye. The end point established in this assay is the time required for the test substance to reduce tissue viability by 50% (ET_{50}). An $ET_{50} > 4$ h (non-irritant) was reported for the eye gel. The positive control, Triton X-100, was classified as a mild irritant ($ET_{50} = 28.8$ minutes).

Branched – Modified

Hydroxypropyltrimonium Hydrolyzed Corn Starch

The ocular irritation potential of hydroxypropyltrimonium hydrolyzed corn starch was evaluated using the hen's egg test – utilizing the chorioallantoic membrane (HET-CAM).[76] Fertile White leghorn eggs were used. The chorioallantoic membrane (CAM) of the chick embryo responds to injury with a complete inflammatory reaction that is comparable to that induced in the rabbit ocular irritation test. The test substance (0.3 ml) was administered to the CAM at concentrations of 5%, 10%, and 15%. Results indicated that hydroxypropyltrimonium hydrolyzed corn starch would have practically no irritation potential *in vivo*. It was noted that the CAM results at 5%, 10%, and 15% are equivalent to Draize test results for the test substance at concentrations of 10%, 20%, and 30%.

Mucous Membrane Irritation and Sensitization

Non-Human

Branched - Unmodified

Glucomannan

Konjac flour was evaluated in the following study, but the composition of konjac flour is not stated. However, according to one source, every 100 g of konjac flour contains the following:[77] glucomannan (79.37 mg), protein (1.64 g), fat (0.004 g), phosphorus (57 mg), iron (4.06 mg), zinc (123 mg), manganese (0.2 mg), chromium (0.25 mg), and copper (0.08 mg). Prior to initiation of the study, a sensory irritation study on konjac flour (primary polysaccharide component is glucomannan) was performed using ND4 Swiss Webster mice (number not stated).[78] Sensory irritation was evaluated by monitoring the decrease in respiratory rate during 30 minutes of exposure to

konjac flour. The concentration of konjac flour that caused a 50% decrease in the respiratory rate (RD_{50}) was 110 mg/m^3.

A study was performed to investigate whether exposure to food grade konjac flour could produce respiratory hypersensitivity.[78] The composition of the sample tested was in agreement with *Food Chemical Codex* specifications of <8% protein, >75% carbohydrate, and <5% ash. Groups of male Hartley guinea pigs were randomly assigned to the following 4 groups (whole-body exposure in chambers): negative control (4 animals, air-exposed), positive control (4 animals, trimellitic anhydride [TMA] exposure), and konjac flour exposure group (8 animals). Test animals were exposed to konjac flour on days 1-5 of the study (42 minutes/induction exposure), and challenged (35 minutes/challenge exposure) on days 19, 26, and 40. The mean (± S.D.) konjac flour concentration during induction exposure was 111 ± 8.3 mg/m^3, and the mean exposure concentration during the challenge phase ranged from 50 to 68 mg/m^3. The days of exposure (induction and challenge) for positive control animals exposed to TMA aerosol were identical to those for the test group. The target exposure concentrationof TMA was 94 mg/m^3 for induction and challenge. Negative control animals were exposed to room air on days 1-5, but were challenged with konjac flour (target concentration = 114 mg/m^3) only on day 40 to avoid the possibility of repeated challenges resulting in sensitization.

The criteria used to define respiratory tract sensitization (increase in respiratory rate of 36% and change in respiratory waveform) were achieved in 25% of the animals during each challenge in the konjac flour exposure group. Additionally, a few animals responded with slightly lower increases in respiratory frequency and a change in waveform that were suggestive of a slight pulmonary hypersensitivity response.[78] According to a more recent publication, the purified antigen from konjac flour is named Ag40D-2 (acidic protein; ~ 24,000 daltons), suggesting that the respiratory sensitizer in konjac flour is actually a protein, rather than glucomannan.[79]

Cyclic - Modified

Methyl Cyclodextrin

The acute histological effects of methylated β-cyclodextrin on the epithelium of the nasal cavity has been investigated in rats using light microscopy.[80] After a single nasal administration of 2% randomly methylated β-cyclodextrin, only minor changes were observed in the appearance of the cilia and the apical cell membranes, and small amounts of mucus were excreted into the nasal cavity. These effects were similar to those noted for control animals dosed with physiological saline (0.9% NaCl). Using confocal laser scanning microscopy, no changes in nasal epithelial cell morphology were observed after a single intranasal administration of 2% randomly methylated β-cyclodextrin, whereas 1 % sodium taurodihydrofusidate resulted in swelling of the cells and substantial mucus extrusion.

Human

Branched - Unmodified

Glucomannan

The inhalation of konjac dust in factories producing konnyaku, a popular food in Japan made from konjac tubers, has been reported to produce allergic bronchial asthma (known as konnyaku asthma) in sensitized individuals.[81] Furtherhmore, bronchial asthma that was likely triggered by the inhalation of Maiko powder has been associated with residents near a konjac milling plant in Japan.[79] Konjac root is dried and ground into powder in the process of manufacturing the food known as konjac. Maiko is a fine konjac root powder that is blown by air pressure to obtain konjac powder for commercial use.

EPIDEMIOLOGY

Linear Polysaccharides and Their Salts

Carrageenan, Agar, and Alginate

An epidemiology study was performed to examine the hypothesis that the increasing incidence of mammary carcinoma in the United States in the twentieth century may be related to the consumption of carrageenan and possibly other water-soluble polymers.[82] A time-trend analysis using age-adjusted incidence data and consumption data from established sources was used to test this hypothesis. Statistical analysis, using Pearson and Spearman correlation coefficients, was performed to identify associations between water-soluble polymer consumption and cancer incidence. Lag periods of 10, 15, 20, 25, 30, and 35 years were introduced to consider a latent effect between intake and the occurrence of breast cancer.

At least 4 values for consumption and corresponding incidence were required for inclusion in the correlation analysis. Consumption data on the polysaccharide gums studied were reported as pounds/person/year. These water-soluble polymer utilization data, obtained from several libraries throughout the United States, were predominantly from published data compiled as research for the food industry. For carrageenan, 80% of total consumption was identified as food consumption, and the remainder was attributed to products such as toothpaste, deodorants, room deodorizers, etc. Food consumption data on other gums were as follows: sterculia urens gum (< 10%), agar (50%), alginates (60%), and pectin (80 to 95%). Incidence data for breast cancer were obtained from published sources and were presented as the age-adjusted incidence data per 100,000 population using the 1970 census data.

The following positive correlations between gum consumption and the incidence of mammary carcinoma were found. For carrageenan, positive correlations (statistically significant) were found at 25 years ($r = 0.88$; $P = 0.048$) and 30 years ($r = 0.96$; $P = 0.042$). The Spearman correlation coefficient for carrageenan at 30 years was also statistically significant ($r = 1.0$; $P < 0.0001$). Statistically significant positive correlations were also reported for alginate (at 30-year lag period) and agar (at 10- and 25-year lag periods). The Spearman correlation coefficient was significant for pectin at at 30 years. Sterculia urens gum did not demonstrate any statistically significant correlations. This analysis demonstrated that polysaccharide gum consumption correlated positively with increased incidence of breast carcinoma.

Branched - Unmodified

Pectin and Sterculia Urens Gum

Epidemiology data on pectin and sterculia urens gum are included in the preceding study on carrageenan, agar and alginate.[82]

MISCELLANEOUS STUDIES

Endocrine Function and Vitamin D Absorption

Branched - Unmodified

Glucomannan

A double-blind trial on the efficacy of glucomannan in the treatment of pediatric obesity was performed.[83] The study involved 60 children under the age of 15 (mean age: 11.2 years; mean overweight: 46%). Thirty children received 1 g of glucomannan twice daily for two months, and the other 30 children received a placebo according to the same schedule. Clinical side effects were evaluated in both groups by measuring indicators of intestinal absorption, lipid metabolism, and thyroid and adrenocortical function. When the 2 groups were compared, there were no significant differences in intestinal absorption, thyroid or adrenocortical function, or clinical symptoms. However differences in lipid metabolism were significant. The treated group had decreased α-lipoprotein and increased pre-β-lipoprotein and triglyceride. The authors suggested that the metabolic alteration observed may have been due to a primary decrease in α-lipoprotein, most likely because of inadequate water intake. It was noted that these study results question the efficacy of glucomannan in the treatment of childhood obesity.

Antifungal Activity

Linear Polysaccharides and Their Salts

Calcium Alginate

The antifungal properties of calcium alginate fiber were studied using *Candida albicans*.[48] Fungal inhibitory rates were measured using the plate-count method, following the shake-flask test. Additionally, an inhibition-zone test and observation by scanning electron microscopy were performed. The inhibitory rate of calcium alginate fibers was 49.1%, and was classified as weak when compared to zinc alginate (92.2% inhibitory rate). The inhibitory rate was calculated using the following equation: Inhibitory rate = [(A – B)/A] x 100%. A was defined as the number of fungal colony on blank control plates. B was defined as the number of fungal colony on test plates.

Muscle Inflammation

Linear Polysaccharides and Their Salts

Carrageenan

Local muscle inflammation was induced by injecting carrageenan (10 mg/kg) into the right tibialis anterior muscle in 22 healthy ARC mice (6 weeks old).[84] The contralateral muscle was injected with sterile isotonic saline, and the muscles were removed after 24 h for measurement of contractile function and cytokine concentration. Carrageenan significantly reduced maximum specific force, decreased the maximum rate of force development, altered the force-frequency relationship, and increased intramuscular levels of pro-inflammatory cytokines and chemokines. These results indicate that injected carrageenan directly affects contractile function and causes skeletal muscle weakness.

Anti-inflammatory/Antioxidant Activity

Linear Polysaccharides and Their Salts

Alginic Acid

Alginic acid, isolated from brown algae (*Sargassum wightii*), was evaluated in a study involving groups of 6 arthritic adult male Sprague-Dawley rats.[85] The oral dosing of alginic acid (100 mg/kg) in arthritic rats reduced paw edema and the activities of enzymes such as cyclooxygenase, lipoxygenase and myeloperoxidase. Reduction in the level of C-reactive protein, ceruloplasmin, and rheumatoid factor were also observed in arthritic rats treated with alginic acid. Additionally, reduced lipid peroxidation and enhanced activities of antioxidant enzymes were reported, which suggest the antioxidant potential of the compound. Histopathological analysis indicated that alginic acid treatment reduced paw edema and inflammatory infiltration in arthritic rats. Overall, study results suggest that alginic acid isolated from *Sargassum wightii* exhibits potent anti-inflammatory and antioxidant activity.

SUMMARY

The polysaccharide gums are naturally derived materials that comprise polysaccharides obtained from plants or algae. As a group, they comprise polymers of simple saccharide monomers. Based on the different chemical structures that are associated with polysaccharide gums, these ingredients can be subdivided into categories such as modified, unmodified, linear, branched, and cyclic. Many of the polysaccharide gums reviewed in this safety assessment function as viscosity increasing agents in cosmetic products. According to information supplied to the FDA by industry as part of the VCRP and results from a Council survey of ingredient use concentrations, 59 polysaccharide gums are being used in cosmetic products.

The Council survey data also indicate that polysaccharide gums are being used in cosmetics at maximum ingredient use concentrations up to 50% (i.e., for algin in paste masks and mud packs). Polysaccharide gums are used at concentrations up to 9.5% (avena sativa (oat) starch) in cosmetic products that are sprayed, which also includes use in a pump hair spray at a maximum concentration of 0.45% (corn starch modified), and at concentrations up to 45.7% (corn starch modified) in cosmetic products that possibly are sprayed. Additionally, polysaccharide gums are used in cosmetic products (powders) at concentrations up to 33% (tapioca starch). Because polysaccharide gums are used in products that are sprayed, they could possibly be inhaled.

Maltodextrin, the most frequently used cosmetic ingredient reviewed in this safety assessment, is prepared as a white powder or concentrated solution by partial hydrolysis of corn starch, potato starch, or rice starch. It is an approved direct food additive affirmed as GRAS by the FDA. The following other polysaccharide gums reviewed in this safety assessment have also been classified as GRAS direct food additives: agar, alginic acid, ammonium alginate, amylose (i.e., high amylose corn starch is GRAS), calcium alginate, pectin, potassium alginate, dextrin, solanum tuberosum (potato) starch, starch acetate, tapioca starch, hydroxypropyl starch, propylene glycol alginate, ghatti gum, and sterculia urens gum.

In 2014, the JECFA concluded that the use of carrageenan in infant formula or formula for special medical purposes at concentrations up to 1,000 mg/L is not of concern.

Data on native carrageenans extracted from different types of algae indicate that different types of carrageenan have reasonable stability to heating at 75°C down to pH 4, and that the rate of depolymerization increases dramatically as the pH decreases from 4 to 3. These data indicate the susceptibility of carrageenan to acid hydrolysis under certain conditions.

The results of a percutaneous absorption study involving hairless mouse skin indicate that 2-hydroxypropyl-β-cyclodextrin had extremely low permeability, approximately 0.02% of the amount applied to the skin.

In studies involving rats, there was no specific accumulation of orally administered cyclodextrin in organs, and it was rapidly hydrolyzed to maltose and glucose. In another study, 95% of ingested sterculia urens gum was excreted in the feces of rats. Carrageenan was not degraded or absorbed from the gastrointestinal tract of rodents, dogs, and non-human primates, and rapid and nearly complete enzymatic degradation of starch acetate was reported. Dietary sterculia urens gum was neither digested nor degraded by enteric bacteria in humans, which is similar to what was observed in rats. In a human oral feeding study on tapioca starch, a rapid increase in plasma glucose was observed after dosing.

An LC_{50} > 0.0015 mg/l was reported for glucomannan in an acute inhalation toxicity study involving rats. The transbronchial injection of 0.75% carrageenan (in physiological saline) induced pneumonia in rabbits.

Acute oral dosing of rats with sterculia urens gum at a dose of 10 g/kg body weight did not cause death, and the same was true for rats dosed with 5,000 mg/kg potato starch modified, 5,000 mg/kg calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified), 2,000 mg/kg corn starch modified, 2,000 mg/kg dextrin palmitate, 2,000 mg/kg dextrin myristate, or 2,000 mg/kg stearoyl inulin. Acute oral LD_{50} values of > 2,800 mg/kg body weight (mice) and > 5,000 mg/kg body weight (rats) have been reported for glucomannan.

In acute dermal toxicity studies on corn starch modified, potato starch modified, dextrin myristate, and dextrin palmitate, an LD_{50} of > 2,000 mg/kg (rats) was reported. The same results were reported for glucomannan in an acute dermal toxicity study involving rabbits.

Repeated dose oral toxicity studies on the following were performed: algin (25% in diet, mice) starch acetate (55% in diet, mice), arabinoxylan (~ 80% arabinoxylan oligopeptides in wheat bran extract [extract test concentrations up to 7.5% in diet], rats), inulin (7.5% in diet, rats), carboxymethyl inulin (31.1% aqueous at doses up to 1,000 mg/kg/day, rats), carrageenan (up to 5% in diet [rats]; up to 25% in diet [mice]; up to 500 mg/kg/day [monkeys]), cyclodextrin (up to 50,000 ppm in diet [rats]; up to 20% in diet [dogs]), ghatti gum (up to 5% in diet, rats), glucomannan (up to 8% in diet, rats), pectin (up to 10% pectin-derived acid oligosaccharides in diet, rats),

solanum tuberosum (potato) starch (up to 10% in diet, rats), and sterculia urens gum (5 g/kg/day, rats; 7% in diet, rats). Sodium alginate was nephrotoxic in mice, but results for starch acetate were of little, if any, toxicological significance. The NOAEL for wheat bran extract in rats was 4.4 g/kg/day, the highest dose administered; there were no remarkable findings in control rats dosed with inulin. There were no toxicologically significant findings in rats dosed with carboxymethyl inulin, and the same was true for ghatti gum. The liver and kidney were identified as target organs for toxicity in rats dosed with β-cyclodextrin, but there was no evidence of systemic toxicity in dogs. There were no treatment-related effects in dogs dosed with γ-cyclodextrin. Treatment-related histopathological changes in the urinary bladder were observed in rats fed pectin-derived acidic oligosaccharides in the diet. No adverse effects were observed in rats dosed repeatedly with sterculia urens gum. Transient fatty degeneration, with focal necrosis of the liver was observed in rats fed glucomannan in the diet.

Repeated oral feeding of humans with propylene glycol alginate (up to 200 mg/kg/day) or sterculia urens gum (10.5 g in diet/day) did not cause toxicity.

Systemic toxicity was not observed in guinea pigs that received repeated dermal applications of 31.1% aqueous carboxymethyl inulin, or in rats dosed dermally (2 g/kg body weight/day) with potato starch modified.

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

Pathological lesions of the ocular mucosa were not observed after 2% algin was instilled into the eyes of rabbits. Carrageenan was non-irritating to the unrinsed eyes of rabbits, but was minimally irritating to rinsed eyes. Ocular irritation was not observed in rabbits tested with dextrin myristate, dextrin palmitate, or stearoyl inulin. An eye gel containing 2.45% maltodextrin was classified as a non-irritant in the *in vitro* bovine corneal opacity and permeability assay, and in the *in vitro* EPI-Ocular® assay. Corn starch modified and calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified) were minimally irritating to the eyes of rabbits. Potato starch modified and a 16.8% aqueous suspension of potato starch modified were slightly irritating to the eyes of rabbits. Hydroxypropyltrimonium hydrolyzed corn starch had practically no irritation potential at concentrations of 5%, 10%, and 15% in the *in vitro* HET-CAM ocular irritation assay. Mixtures containing 1.35% hydrolyzed furcellaran were classified as slightly toxic in a cytotoxicity assay involving cultured fibroblasts, and this finding was classified as almost non-irritating to slightly irritating to the eyes.

In a primary skin irritation study, results were negative for 2% algin in rabbits. In a cumulative skin irritation study involving rabbits, the results observed at macroscopic or microscopic examination indicated that 2% algin did not induce a severe reaction. Potato starch modified (10% solids aqueous solution) caused minimal to slight acanthosis in rabbits, and a 50% slurry of calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified) was mildly irritating to the skin of rabbits. At a dose of 2,000 mg/kg in an acute dermal toxicity study, corn starch modified (30% solids in distilled water) was classified as a mild skin irritant in rabbits.

Skin irritation was not observed in albino guinea pigs patch-tested with 100% carboxymethyl inulin. Erythema and edema were observed in an acute dermal toxicity study involving rats dosed with 2 g/kg potato starch modified; all reactions cleared by 72 h. Neither erythema nor edema was observed in rats that received repeated dermal applications of the same dose of potato starch modified. Dextrin palmitate or dextrin myristate did not cause skin irritation in rabbits or skin sensitization in guinea pigs evaluated in the maximization test. A trade name mixture containing 1.35% hydrolyzed furcellaran was classified as non-irritating to the skin of human subjects. A trade name mixture containing 0.6% hydrolyzed furcellaran was classified as non-irritating and non-sensitizing when applied to the skin of human subjects.

In the guinea pig maximization test, corn starch modified (20% solution) and 31.1% aqueous carboxymethyl inulin did not induce sensitization. In the Buehler test for skin sensitization, potato starch modified (18.5% aqueous suspension) caused faint erythema during induction, but there was no evidence of sensitization in animals tested. Also, in the Buehler test, a paste of 50% calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified) was not a

sensitizer in guinea pigs. ι-Carrageenan and konjac flour (glucomannan is primary polysaccharide component; the antigen is an acidic protein [AG40D-2]) were also non-sensitizing to the skin of guinea pigs.

Corn starch modified (7.5%) did not induce cumulative skin irritation in 26 subjects or skin sensitization in 113 subjects tested. A 50% w/v slurry or 50% solids slurry of calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified) was classified as a probable mild irritant in a 21 day cumulative skin irritation study involving 23 human subjects.

Algae exopolysaccharides (1%) did not cause skin irritation or sensitization in an HRIPT involving 50 subjects. An eye gel containing 2.45% maltodextrin did not induce allergic contact dermatitis in an HRIPT involving 103 subjects. Results were negative for skin irritation and allergic contact dermatitis in 12 male subjects patch-tested with 20% aqueous sodium alginate. Negative results for skin sensitization were also reported for 227 subjects in a human RIPT on a cleanser containing 10 wt% sodium hydrolyzed potato starch dodecenylsuccinate. Neither skin irritation nor sensitization was observed in the following HRIPT's: 54 subjects tested with a rinse-off facial product containing 42.69% dextrin, 51 subjects tested with a leave-on facial product containing 0.3% dextrin myristate, and 47 subjects tested with hydroxypropyltrimonium hydrolyzed corn starch (15%).

Allergenicity was not associated with the oral dosing of human subjects with propylene glycol alginate, and dermal application of a calcium alginate dressing to patients did not cause any side effects that were classified as severe.

Sodium hydrolyzed potato starch dodecenylsuccinate was evaluated for phototoxicity at concentrations ranging from 68.1 to 1,000 µg/ml in the *in vitro* neutral red uptake phototoxicity assay (BALB/3T3 clone A31 mouse embryo fibroblast cultures). The test material was not considered to have phototoxicity potential.

The concentration of konjac flour that caused a 50% decrease in respiratory rate (RD_{50}) in mice in a sensory irritation evaluation was 110 mg/m^3. In a subsequent study, the criteria used to define respiratory tract sensitization (increase in respiratory rate of 36% and change in respiratory waveform) were achieved in 25% of the 8 guinea pigs challenged with konjac flour (mean exposure concentration range = 50 to 68 mg/m^3). The inhalation of konjac dust in factories producing konnyaku, a popular food in Japan made from konjac tubers, has been reported to produce allergic bronchial asthma in sensitized individuals.

In studies evaluating effects on the immune system, an acidic polysaccharide produced by *Polianthes tuberosa* cells was classified as an immunosuppressive polysaccharide. The injection (i.p.) of potassium carrageenan into rats resulted in significant elevation of serum IgM, but not IgG.

In pregnant mice that received doses of kappa/lambda-carrageenan (from *C. crispus*, sodium or calcium salt) at oral doses up to 900 mg/kg/day during gestation, there was a dose-dependent decrease in the number of live pups and in pup weight. Skeletal maturation was also retarded. In another study in which pregnant mice received oral doses of the same test substance (sodium or calcium salt) at doses up to 600 mg/kg/day during gestation, there was a dose-dependent increase in the incidence of missing skeletal sternebrae. However, feeding with the test substance (calcium salt) at dietary concentrations up to 5% prior to mating in a three-generation feeding study, no specific external, skeletal, or soft-tissue anomaly could be correlated with dosage. In a study in which calcium carrageenan was fed at dietary concentrations up to 1.8% prior to mating, during breeding, and throughout gestation, lactation, and post-weaning, there were no differences between test and negative control groups regarding length of gestation, litter size, or sex distribution.

The oral dosing of pregnant hamsters with doses of kappa/lambda-carrageenan (from *C. crispus*, sodium or calcium salt) up to 600 mg/kg/day during gestation resulted in some evidence of a dose-dependent delay in skeletal maturation. In a similar study in which hamsters received oral doses of the test substance (sodium or calcium salt) up to 200 mg/kg/day during gestation, there were no dose-related teratogenic or fetotoxic effects. When pregnant rabbits were dosed orally with the test substance (sodium or calcium salt) at doses up to 600 mg/kg/day during gestation, the numbers of skeletal or soft tissue abmormalities did not differ from those of controls.

Neither reproductive nor developmental toxicity was observed in rat dietary feeding studies on cyclodextrin (up to 20%), and pectin-derived acidic oligosaccharides (10%). Sterculia urens gum was not teratogenic when

administered in a corn oil suspension to rats (doses up to 900 mg/kg/day) rabbits (doses up to 635 mg/kg/day) or mice (doses up to 170 mg/kg/day) during gestation. Cyclodextrin also did not cause reproductive or developmental toxicity in rabbits when administered at dietary concentrations up to 20%, and the same was true when pregnant cats were fed 2% glucomannan in the diet during gestation.

In bacterial assays, the following were not genotoxic either with or without metabolic activation: arabinoxylan, carboxymethyl inulin, carrageenan, corn starch modified, ghatti gum, glucomannan, a trade name mixture containing 0.6% hydrolyzed furcellaran, pectin-derived acidic oligosaccharides, calcium starch isododecenylsuccinate (considered structurally similar to sodium hydrolyzed potato starch dodecenylsuccinate and corn-starch modified), and a sodium hydrolyzed potato starch dodecenylsuccinate tradename material. In mammalian assays with and without metabolic activation, wheat bran extract, carboxymethyl inulin, carrageenan, ghatti gum, and glucomannan were not genotoxic. However, results for pectin-derived acidic oligosaccharides in mammalian assays were either equivocal or it was classified as clastogenic. Sterculia urens gum was not genotoxic in cytogenetic assays (*in vitro* and *in vivo*) or in the *in vivo* dominant lethal gene test.

Agar, isolated from Pterocladia, was not carcinogenic in F344 rats or $B6C3F_1$ mice that received concentrations of 25,000 ppm or 50,000 ppm in the diet. Neither algin (25% in diet) nor starch acetate (55% in diet) was found to be carcinogenic in an oral feeding study involving mice. When fed in the diet to rats, carrageenan (up to 25% in diet), and cyclodextrin (up to 675 mg/kg/day), also were not carcinogenic. Carrageenan (up to 5% in diet) was not carcinogenic when fed to hamsters. In a co-carcinogenicity study, carrageenan (15% in the diet) enhanced the incidence of colon tumors in female Fischer 344 rats injected with azoxymethane or *N*-nitrosomethylurea.

Colorectal tumors were found in Sprague-Dawley rats fed 5% or 10% degraded carrageenan, but not 1% degraded carrageenan, in the diet for up to 24 months. Colorectal tumors were also observed in Sprague-Dawley rats that received 5% degraded carrageenan in drinking water for 15 months, and in Sprague-Daweley rats dosed with 1 g/kg or 5 g/kg degraded carrageenan by gastric intubation for 15 months. Fischer 344 rats that received 10% degraded carrageenan in the diet for up to 9 months also had colorectal tumors.

The feeding of rats with an inulin-enriched diet (10% in diet) resulted in the promotion of adenoma growth. Mucosal hyperplasia in the small intestine was observed in rats fed 2.5% pectin in the diet. In another feeding study, 5% methoxylated pectin in the diet increased the multiplicity of colon tumors in rats injected with DMH. In another co-carcinogenicity study, carrageenan (15% in the diet) enhanced the incidence of colon tumors in female Fischer 344 rats injected with azoxymethane or *N*-nitrosomethylurea.

Anticarcinogenic effects have been associated with arabinoxylan and inulin in studies involving rats, with glucomannan in mice, and with konjac flour in rats. The antitumor/anticarcinogenic activity of wheat bran arabinoxylan in mice and arabinoxylan-oligosaccharides in rats has also been reported.

In an epidemiology study, a positive correlation between polysaccharide gum consumption and the incidence of mammary carcinoma was found for carrageenan, alginate, agar, and pectin, but not for sterculia urens gum.

DISCUSSION

The polysaccharide gums comprise polysaccharides obtained from plants or algae. Based on the different chemical structures of polysaccharide gums, these ingredients can be subdivided into categories such as modified, unmodified, linear, branched, and cyclic. Regardless of how they are categorized, the molecular structures of these ingredients are polymers composed of monosaccharides. Based on chemical similarities, relevant data have been included on analogous polysaccharide ingredients. Therein, inference may be appropriate from one ingredient to the next and from one ingredient to one subgroup of polysaccahrides, of which that ingredient or analog is a member.

The substantial molecular sizes of many of these polysaccharides suggest that skin penetration would be unlikely. Specifically, the percutaneous absorption of ^{14}C-2-hydroxypropyl-β-cyclodextrin through intact hairless mouse skin was extremely low, i.e., approximately 0.02% of the amount applied to the skin. Thus, during cosmetic use, these ingredients are unlikely to have significant systemic bioavailability.

The use concentration data provided indicate that algin is being used in cosmetics at concentrations up to 50% (in mud packs). The Expert Panel acknowledged the absence of skin irritation and sensitization data on algin at this concentration, but noted that results were negative when carboxymethyl inulin was tested at concentrations up to 100% in a skin irritation study involving guinea pigs, and the absence of clinically relevant reactions to polysaccharide gums in dermatologic practice. The Panel is aware of severe granulomatous reactions in patients injected intradermally with an aesthetic injectable filler consisting of purified alginate; however, it was determined that these findings are not relevant to the use of alginates as cosmetic ingredients. Furthermore, systemic toxicity is not a concern in relation to repeated exposure to polysaccharide gums during cosmetic use, considering the absence of gross or microscopic changes in monkeys dosed orally/fed carrageenan in the diet for 7.5 years.

Genotoxicity data for pectin-derived acidic oligosaccharides in mammalian assays were equivocal, but some were classified as clastogenic. However, the Panel noted that clastogenicity was observed only at highly cytotoxic concentrations. The Panel reviewed data indicating that degraded carrageenan (also known as poligeenan) in the diet induced colorectal tumors in rats. Degraded carrageenan used in those studies was produced by acid hydrolysis of a certain type of seaweed. In light of this information and the colon carcinogenicity data, the Panel expressed concern about the use of hydrolyzed carrageenan as a cosmetic ingredient, in the absence of data demonstrating that hydrolyzed carrageenan is chemically dissimilar to poligeenan and does not share its carcinogenic properties. Thus, the Panel determined that method of manufacture and impurities data are needed to determine the safety of hydrolyzed carrageenan in cosmetic products.

Polysaccharide gums are used at concentrations up to 9.5% (avena sativa (oat) starch) in perfumes, at a maximum concentration of 0.45% (corn starch modified) in pump hair sprays, and at concentrations up to 33% (tapioca starch) in powders. The available data indicate that food grade konjac flour (primary polysaccharide component is glucomannan) induced sensory irritation of the respiratory tract in mice and respiratory tract sensitization in guinea pigs. Furthermore, the inhalation of konjac dust in factories in Japan has produced allergic bronchial asthma in sensitized individuals. Additional research suggested that the purified antigen AG40D-2 (acidic protein) was responsible for the respiratory sensitization observed, and that this effect was not attributed to glucomannan. Transbronchial injection of 0.75% carrageenan (in physiological saline) induced pneumonia, followed by emphysema, in rabbits. In consideration of these data, the Panel discussed the potential for incidental inhalation exposures to polysaccharide gums in products that are sprayed or in powder form and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone and ingredient use, incidental inhalation would not lead to local respiratory effects or systemic effects.

The Panel expressed concern about pesticide residues and heavy metals that may be present in ingredients txhat are derived from plants. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities. The Panel also agreed that the same suggestion is applicable to alkylating and other agents (e.g., haloethylaminopropionic acid; 3-(dodecenyl)-2,5-furandione; and 2,3-epoxypropyltrimethylammonium chloride) that are used to modify polysaccharide gums.

CONCLUSION

The CIR Expert Panel concluded that the following 105 ingredients are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment, and that the available data are insufficient for determining the safety of hydrolyzed carrageenan in cosmetic products.

Linear Polysaccharides and Their Salts

Agar	Alginic Acid	Astragalus Gummifer Gum
Agarose	Ammonium Alginate*	Calcium Alginate
Algin	Amylose*	Calcium Carrageenan*

Carrageenan
Magnesium Alginate*
Mannan
Polianthes Tuberosa Polysaccharide
Potassium Alginate
Potassium Carrageenan*
Sodium Carrageenan
TEA-Alginate*

Linear -Modified

Amylodextrin
Hydrolyzed Furcellaran*
Maltodextrin
Sodium Algin Sulfate*

Branched -Unmodified

Amylopectin*
Aphanothece Sacrum Polysaccharide*
Arabinoxylan*
Avena Sativa (Oat) Starch
Cichorium Intybus (Chicory) Root Oligosaccharides
Galactoarabinan
Ghatti Gum*
Glucomannan
Inulin
Pectin
Phaseolus Angularis Seed Starch*
Phaseolus Radiatus Seed Starch*
Pisum Sativum (Pea) Starch*
Pueraria Lobata Starch
Solanum Tuberosum (Potato) Starch
Starch Acetate
Sterculia Urens Gum
Tamarindus Indica Seed Gum
Tapioca Starch
Triticum Vulgare(Wheat) Starch
Xyloglucan*

Branched - Modified

Calcium Starch Isododecenylsuccinate*
Calcium Starch Octenylsuccinate*
Corn Starch Modified
Dextrin
Dextrin Behenate*
Dextrin Isostearate*
Dextrin Laurate*
Dextrin Myristate
Dextrin Palmitate
Dextrin Palmitate/Ethylhexanoate
Dextrin Stearate*
Glyceryl Alginate
Glyceryl Dimaltodextrin*
Glyceryl Starch
Hydrolyzed Pectin
Hydroxypropyltrimonium Hydrolyzed Corn Starch
Hydroxypropyltrimonium Hydrolyzed Wheat Starch
Hydroxypropyl Oxidized Starch*
Hydroxypropyl Starch
Hydroxypropyltrimonium Maltodextrin Crosspolymer
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch
Palmitoyl Inulin*
Potassium Dextrin Octenylsuccinate*
Potassium Undecylenoyl Alginate*
Potassium Undecylenoyl Carrageenan*
Potato Starch Modified
Propylene Glycol Alginate
Sodium Carboxymethyl Inulin*
Sodium Carboxymethyl Starch
Sodium Dextrin
Sodium Hydrolyzed Potato Starch Octenylsuccinate*
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate
Sodium Hydroxypropyl Oxidized Starch Succinate*
Sodium Oxidized Starch Acetate/Succinate
Sodium Starch Octenylsuccinate
Sodium/TEA-Undecylenoyl Carrageenan*
Sodium/TEA-Undecylenoyl Alginate*
Starch Acetate/Adipate*
Starch Diethylaminoethyl Ether
Starch Hydroxypropyltrimonium Chloride
Starch Laurate*
Starch Tallowate*
Stearoyl Inulin
Tapioca Starch Crosspolymer*
TEA-Dextrin Octenylsuccinate*
Undecylenoyl Inulin*

Cyclic

Cyclodextrin

Cyclotetraglucose*

Cyclic - Modified

Hydroxyethyl Cyclodextrin
Hydroxypropyl Cyclodextrin
Cyclodextrin Hydroxypropyltrimonium Chloride*
Cyclodextrin Laurate
Methyl Cyclodextrin

Unknown Structural Configuration

Algae Exopolysaccharides*
Cassia Angustifolia Seed Polysaccharide*
Prunus Persica (Peach) Gum*

Unknown Structural Configuration - Modified

Hydrogenated Potato Starch*
Hydrogenated Starch Hydrolysate
Hydrolyzed Corn Starch Hydroxyethyl Ether*
Hydrolyzed Corn Starch Octenylsuccinate
Hydrolyzed Soy Starch*
Hydrolyzed Starch
Hydrolyzed Triticum Spelta Starch*
Hydrolyzed Wheat Starch

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

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

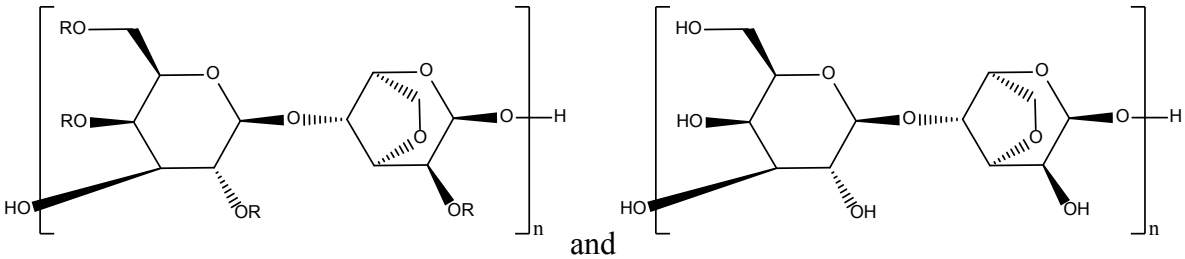
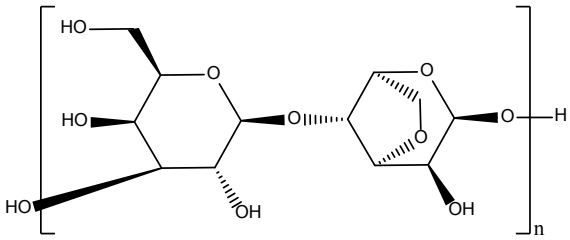
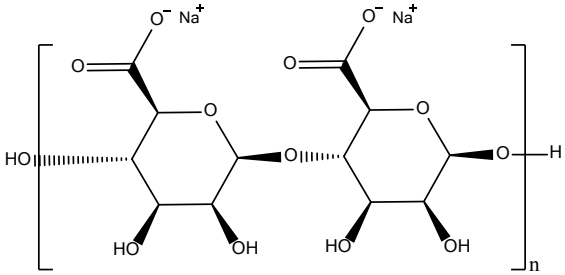
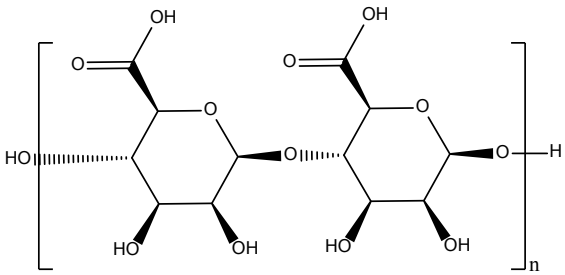
Ingredient CAS No.	Definition	Formula/structure
Linear polysaccahrides and their salts		
Agar 9002-18-0	Agar is the dried, hydrophilic, colloidal polygalactoside derived from various Gelidium species or closely related red alga. *Agar is typically a mixture of agarose and agaropectin.*[86]	 and wherein R is hydrogen, sulfate, or pyruvate
Agarose 9012-36-6	Agarose is the polysaccharide extracted from the red seaweed Gracilaria.	
Algin 9005-38-3	Algin is the sodium salt of Alginic Acid. *Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.* Other source: Algin is a linear polymer of anhydro-β-D-mannuronic acid. The main structural feature of this molecule is a chain of 1,4-linked-β-D-mannuronic acid residues.[87]	
Alginic Acid 9005-32-7	Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae. *Alginic acid is a polysaccharide comprised of 1,4-linked-β -D-mannuronic and α-L-guluronic acids.*[88]	

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

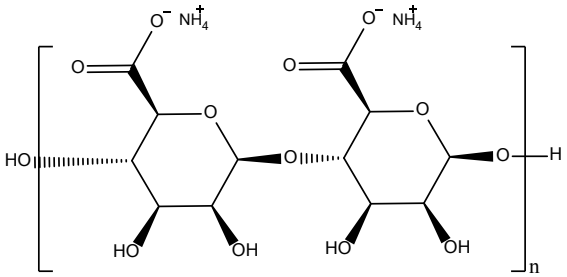
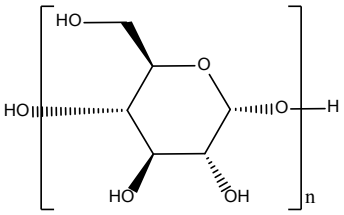
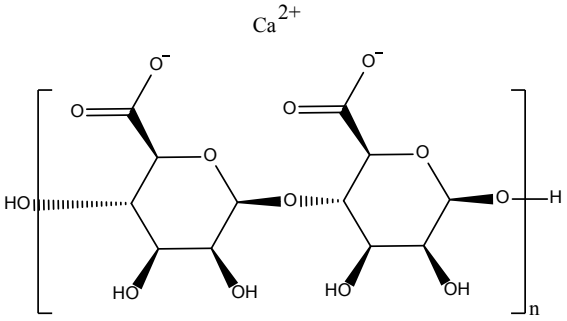
Ingredient CAS No.	Definition	Formula/structure
Ammonium Alginate 9005-34-9	Ammonium Alginate is the ammonium salt of Alginic Acid. *Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.* Other sources: Alginate, a term that refers to salts and derivatives of alginic acid, is a gelling polysaccharide and a structural component extracted from marine brown algae (*Phaeophyceae*), in which it is present in the cell wall as water-insoluble salts.[89] Alginates are polymers composed of β-1,4-D-mannuronic acid (M) and α-1,4-L-guluronic acid (G). Alginates have been determined to be true block copolymers, organized in homopolymeric blocks consisting of either mannuronate or guluronate, or mixed in heteropolymeric MG-block structures. Alginate, the monovalent salt form of alginic acid, is a non-repeating copolymer that contains two uronic acid monomers, 1,4- linked-β-D-mannuronic and α-L-guluronic acid.[90] These residues exist in linear polysaccharide chains that can dimerize to form hydrogels at room temperature in the presence of divalent ions such as calcium.	
Amylose 9005-82-7	Amylose is the carbohydrate stored by plants that consists of a linear (1→4)-(structure)-D-glucan polymer. Other source: Starch is composed of two polysaccharides, amylose and amylopectin.[91] Amylose is a complex α-glucan. It is an essentially linear polymer made up of α(1-4)-linked glucopyranose units.	
Astragalus Gummifer Gum	Astragalus Gummifer Gum is a dried resinous exudate obtained from Astragalus gummifer. It *is a complex polysaccharide composed of D-galacturonic acid, D-galactose, D-xylose, and L-arabinose, with associated calcium, and potassium cations.*	
Calcium Alginate 9005-35-0	Calcium Alginate is the calcium salt of Alginic Acid. *Alginic Acid is the carbohydrate obtained by the alkaline extraction of various species of brown seaweed, Phaeophyceae.*	
Calcium Carrageenan 9049-05-2	Calcium Carrageenan is the calcium salt of Carrageenan.	
Carrageenan 9000-07-1	Carrageenan is the plant material obtained from various members of the *Gigartinaceae* or *Solieriaceae* families of the red seaweed, *Rhodophyceae*. Other sources: Carrageenan is a high-molecular-weight sulfated polygalactan derived from several species of red seaweeds of the class *Rhodophyceae*.[35] Native carrageenan is defined as a hydrocolloid isolated from red algae (seaweed) and consisting mainly of varying amounts (depending on the processing methods) of the ammonium, calcium, magnesium, potassium or sodium salts of sulfate esters of galactose and 3,6-anhydrogalactose copolymers (the two hexose units are alternately linked α-1,3 and β-1,4 in the polymer).[92] A product called 'degraded carrageenan' has been produced from extracts of *Eucheuma spinosum* seaweed by treatment with dilute hydrochloric acid. The most common forms of carrageenan are designated as kappa-, iota-, and lambda carrageenans.[93] Kappa carrageenan is mostly the alternating polymer of D-galactose-4-sulfate and 3,6-anhydro-D-galactose. Iota carrageenan is similar, but with the 3,6-anhydro-D-galactose sulfated at the 2-hydroxyl. Between kappa and iota carrageenan, there is a continuum of intermediate compositions that differ only in the degree of sulfation at the 2-OH. Lambda carrageenan has alternating monomeric units composed mostly of D-galactose-2-sulfate (1,3- linked) and D-galactose-2,6-disulfate (1,4-linked).	

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

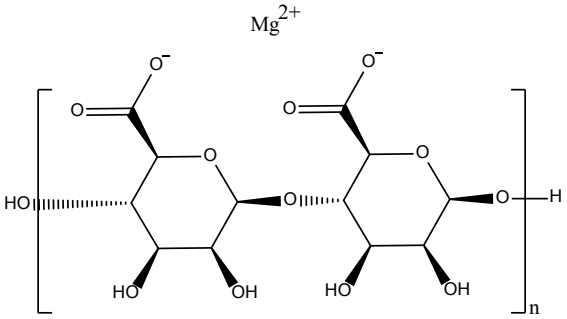
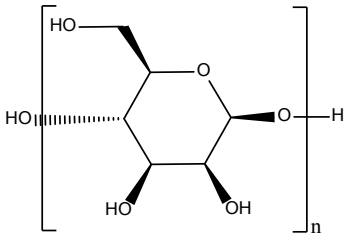
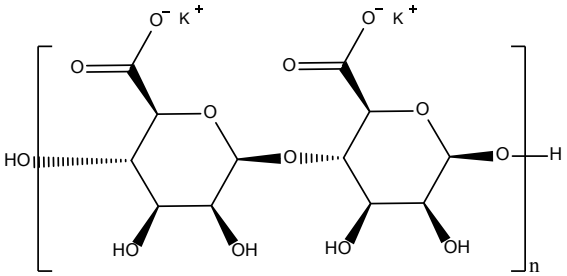
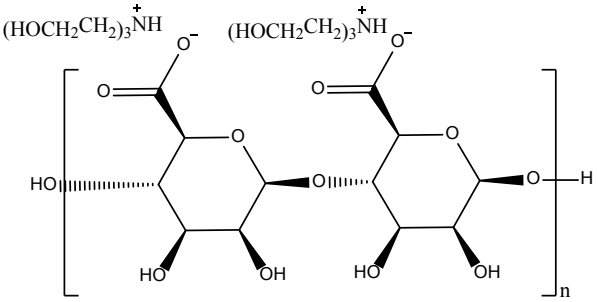
Ingredient CAS No.	Definition	Formula/structure
Magnesium Alginate 37251-44-8	Magnesium Alginate is the magnesium salt of Alginic Acid.	
Mannan 9036-88-8 51395-96-1	Mannan is a natural polysaccharide consisting of a polymer of Mannose.	
Polianthes Tuberosa Polysaccharide	Polianthes Tuberosa Polysaccharide is the polysaccharide fraction produced by the cultured cells of *Polianthes tuberosa.*	
Potassium Alginate 9005-36-1	Potassium Alginate is the potassium salt of Alginic Acid.	
Potassium Carrageenan 64366-24-1	Potassium Carrageenan is the potassium salt of Carrageenan.	
Sodium Carrageenan 60616-95-7 9061-82-9	Sodium Carrageenan is the sodium salt of Carrageenan.	
TEA-Alginate	TEA-Alginate is the triethanolamine salt of Alginic Acid.	

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

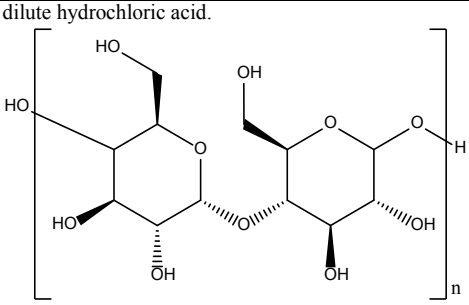
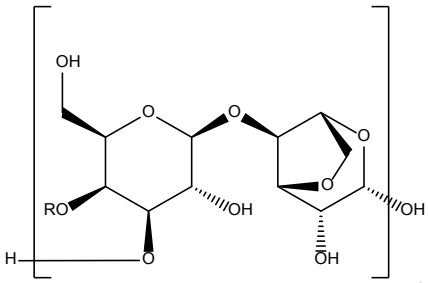
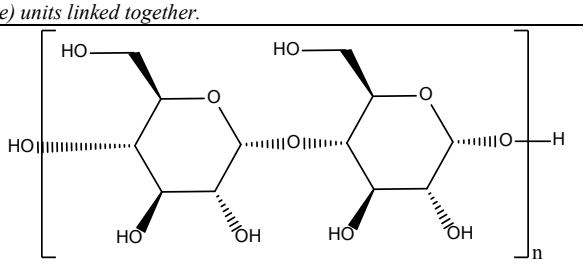
Ingredient CAS No.	Definition	Formula/structure
Linear - modified		
Amylodextrin 9005-84-9	Amylodextrin is the product obtained by treating potato or corn starch with dilute hydrochloric acid.	
Hydrolyzed Carrageenan 53973-98-1	Hydrolyzed Carrageenan is the hydrolysate of Carrageenan derived by acid, enzyme or other method of hydrolysis.	
Hydrolyzed Furcellaran 73297-69-5	Hydrolyzed Furcellaran is the hydrolysate of furcellaran derived by acid, enzyme or other method of hydrolysis. *Furcellaran is composed of D-galactose, 3,6-anhydro-D-galactose and D-galactose- 4-sulfate.* Other source: Information relating to the algal source of hydrolyzed furcellaran indicates that this ingredient is a carrageenan (Kappa type) that is obtained from red algae, *Furcellaria lumbricallis*.[73]	 where R is hydrogen or SO_3^{2-}
Maltodextrin 9050-36-6	Maltodextrin is the saccharide material obtained by hydrolysis of starch. *Maltodextrin is a linear-chain oligosaccharide of glucose, usually obtained from starch by partial, enzymatic treatment.*[94] *The term "maltodextrin" can be applied to any starch hydrolysis product that contains fewer than 20 dextrose (glucose) units linked together.*	
Sodium Algin Sulfate 9010-06-4	Sodium Algin Sulfate is the sulfate ester of Algin.	

Table 1. Names, CAS Registry Numbers, Definitions and Idealized Structures of the Polysaccharide Gums.[1]
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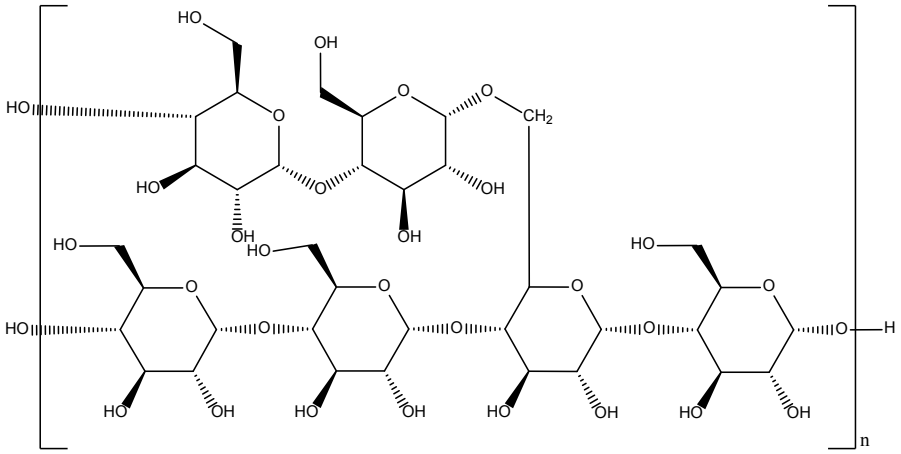
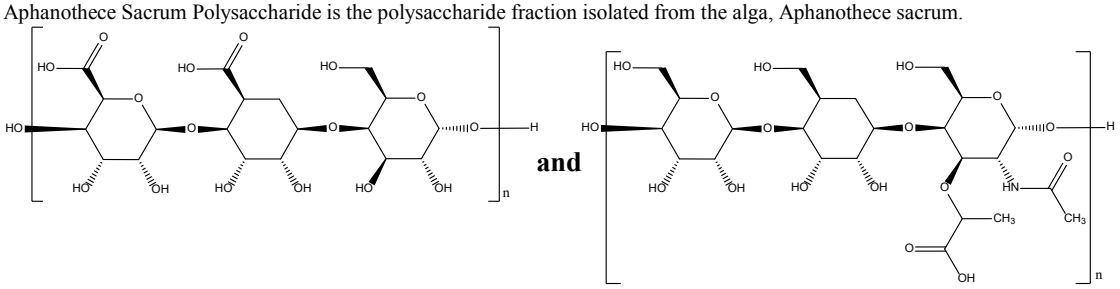
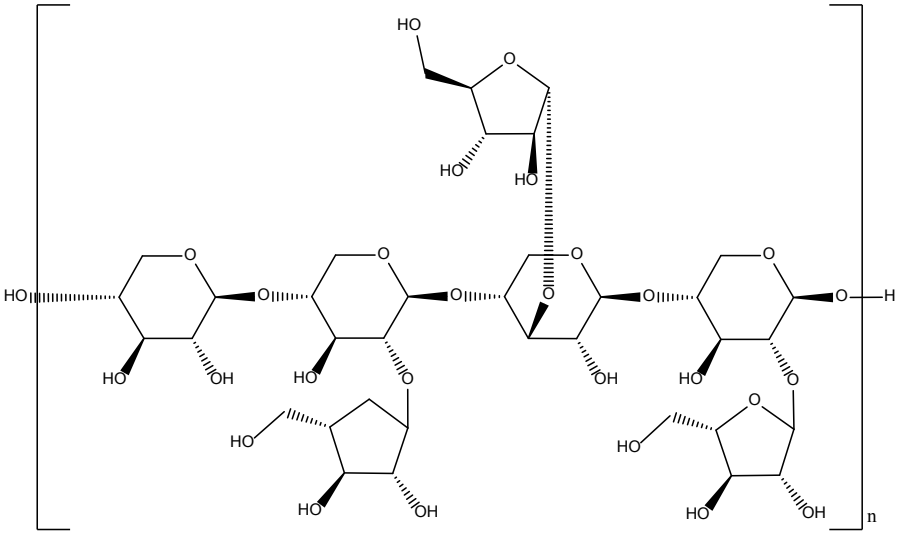
Ingredient CAS No.	Definition	Formula/structure
Branched-unmodified		
Amylopectin 9037-22-3	Amylopectin is the branched chain polysaccharide portion of starch. Other sources: Amylopectin is a complex α-glucan.[91] It is a highly branched polysaccharide composed of segments of linear α(1→4)-linked glucopyranose units joined at branching points via α(1→6) glycosidic linkages to give a structure that resembles a dendrimer. Amylopectin consists of numerous short chains of α(1→4)-linked D-glucopyranosyl residues with a chain length of approximately 6 to 35 units.[95] The chains are α(1→6)-linked into clusters defined as groups of chains, in which the internal chain length between the branches is less than 9 residues.	
Aphanothece Sacrum Polysaccharide	Aphanothece Sacrum Polysaccharide is the polysaccharide fraction isolated from the alga, Aphanothece sacrum.	
Arabinoxylan 9040-27-1	Arabinoxylan is a polysaccharide composed of a xylose backbone with arabinose side chains. Other sources: Arabinoxylan is a non-starch polysaccharide, and is also described as a pentosan.[96] It can also be sub-categorized as water-extractable arabinoxylan and water-unextractable arabinoxylan. Arabinoxylans consist of D-xylopyranosyl residues, connected together by *β*-(1/4) glycosidic bonds.[97,98] Moreover, acetic acid, hydroxycinnamic acids, ferulic acid, and p-coumaric acid are linked with xylose residues in arabinoxylan.[99,100] The attached moieties are partly or wholly lost when arabinoxylan is extracted from cereal or cereal subfractions using alkaline extraction.[96,101,102]	

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

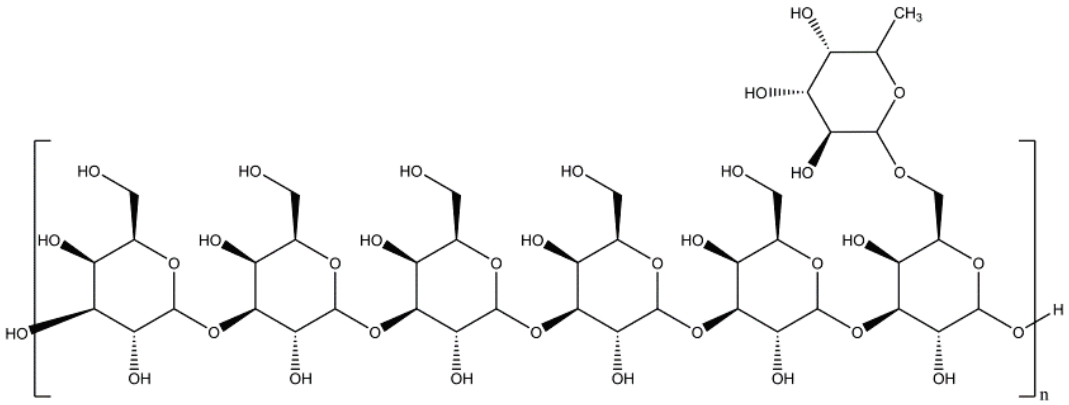
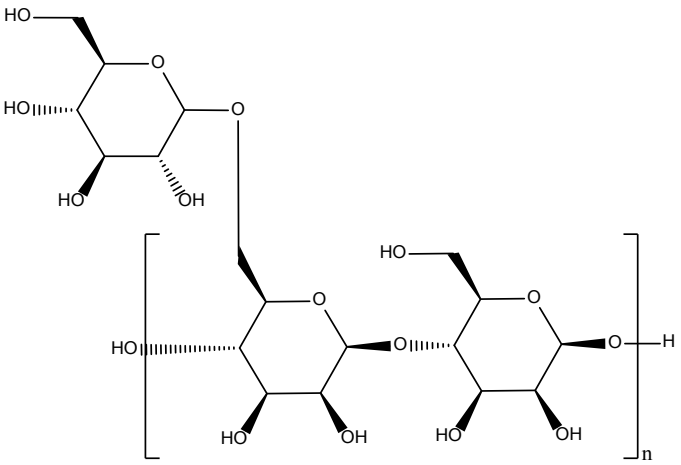
Ingredient CAS No.	Definition	Formula/structure
Avena Sativa (Oat) Starch 9005-25-8 (generic)	Avena Sativa (Oat) Starch is a starch obtained from oats, Avena sativa.	
Cichorium Intybus (Chicory) Root Oligosaccharides	Cichorium Intybus (Chicory) Root Oligosaccharides is the carbohydrate fraction isolated from the roots of Chicorium intybus.	
Galactoarabinan 9036-66-2	Galactoarabinan is the polysaccharide obtained from the extraction of one or more species of the larch tree, *Larix*. The structure of galactoarabinan is:[103]	
Ghatti Gum 9000-28-6	Ghatti Gum is the dried, gummy exudate obtained from the stems and bark of *Anogeissus latifolia*. Other sources: Ghatti gum has been defined as the dried exudate of *Anogeissus latifolia*.[28] Degradation studies have shown that ghatti gum is a polysaccharide that consists of a backbone of galactose units to which other sugars are attached.[104] The side chains can consist of arabinose residues and aldobiuronic acids.	
Glucomannan 37220-17-0 11078-31-2 76081-94-2	Glucomannan is the polymer of mannose containing side chains of glucose. Other sources: Glucomannan (a.k.a. konjac flour or konjac mannan) is a β-D-(1→4)-linked linear copolymer of glucose and mannose substituted with *O*-acetate every 9-19 sugar units.[105] It is derived from the tubers of *Amorphophallus* konjac. Due to the ß-glycosidic linkages between the glucose and mannose building blocks (β-1→4 linkages in the main chain and β-1→3 linkages at the branch points), glucomannan is commonly regarded as a non-digestible polysaccharide. Additionally, glucomannan contains acetyl groups, approximately one acetyl group per 19 sugar residues.[106]	

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

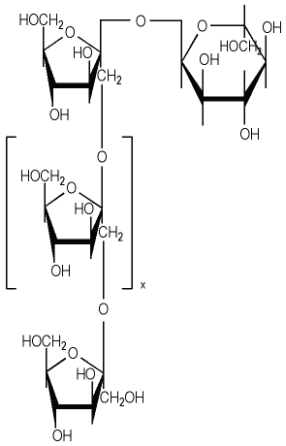
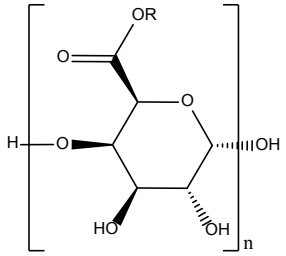
Ingredient CAS No.	Definition	Formula/structure
Inulin 9005-80-5	Inulin is the polysaccharide that conforms to the formula below. Other sources: Inulin has been identified as a fructan, a general term that is used to refer to naturally occurring plant oligo- and polysaccharides.[107] The term refers to any carbohydrate (linear or branched) in which one or more fructosyl-fructose links constitute the majority of the glycosidic bonds. Within the inulin-type fructans are two general groups of materials, inulin and its subsets, including oligofructose and fructooligosaccharides (FOS). FOS always terminate with a glucose molecule. Oligofructose most often contains only fructose molecules, but may end with a glucose molecule. Inulin is a polydisperse carbohydrate consisting mainly of β(2→1) fructosyl-fructose links and contains both GF_n and F_m compounds. The *n* or *m* represents the number of fructose units (F) linked to each other, which can vary from 2 to 70 with one terminal glucose (G). The terms oligofructose and FOS refer to inulin-type fructans with a maximum average degree of polymerization (DP) less than 10. Additionally, total hydrolysis of inulin yields fructose and glucose.[107]	
Pectin 9000-69-5	Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.	 where R is hydrogen or methyl
Phaseolus Angularis Seed Starch	Phaseolus Angularis Seed Starch is a starch obtained from the bean, *Phaseolus angularis.*	
Phaseolus Radiatus Seed Starch	Phaseolus Radiatus Seed Starch is the starch obtained from the seeds of the bean, *Phaseolus radiatus.*	
Pisum Sativum (Pea) Starch	Pisum Sativum (Pea) Starch is a starch obtained from *Pisum sativum.*	
Pueraria Lobata Starch 9005-25-8 (generic)	Pueraria Lobata Starch is the starch obtained from the roots of *Pueraria lobota.*	
Solanum Tuberosum (Potato) Starch 9005-25-8 (generic)	Solanum Tuberosum (Potato) Starch is a polysaccharide obtained from the potato, *Solanum tuberosum.*	

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

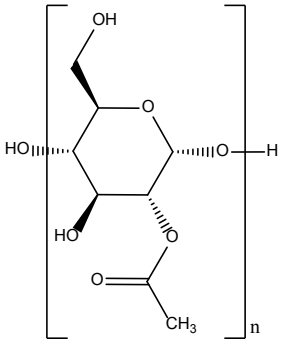
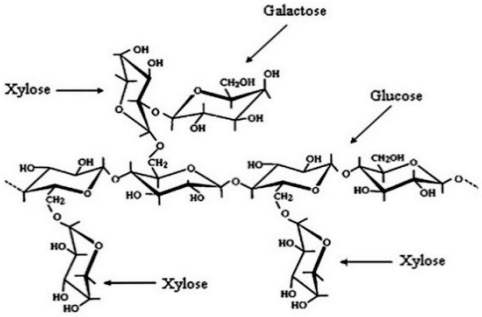
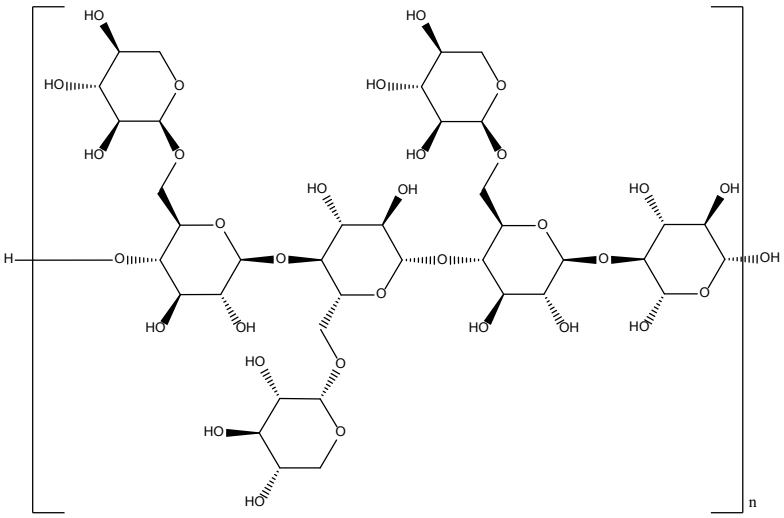
Ingredient CAS No.	Definition	Formula/structure
Starch Acetate 9045-28-7	Starch Acetate is the product obtained by the reaction of acetic acid with starch.	
Sterculia Urens Gum 9000-36-6 [VCRP name: Karaya Gum]	Sterculia Urens Gum is a dried exudate from the tree, *Sterculia urens.* Other source: Sterculia urens gum (a.k.a. karaya gum), the dried exudate of *Sterculia wens* Roxb. and other *Sterculia* spp. (fam. *Sterculiaceae),* is a complex, partially acetylated polysaccharide with a very high molecular weight.[39] Karaya gum is composed of the sugars galactose, rhamnose, and galacturonic acid.	
Tamarindus Indica Seed Gum 39386-78-2	Tamarindus Indica Seed Gum is the gum obtained from the seeds of *Tamarindus indica.*	
Tapioca Starch 9005-25-8	Tapioca Starch is the starch obtained from the roots of *Manihot esculenta.* It consists primarily of amylose and amylopectin.	
Triticum Vulgare (Wheat) Starch 9005-25-8 (generic)	Triticum Vulgare (Wheat) Starch is a starch obtained from wheat, *Triticum vulgare.*	
Xyloglucan 37294-28-3	Xyloglucan is an oligosaccharide containing a 1,4-β-glucan backbone with 1,6-α-xylosyl residues attached to the 6-position of β-glucosyl residues. Other source: The xyloglucan derived from tamarind seeds is composed of a (1-4)-β-glucan backbone chain, which has (1-6)-α-D-xylose branches that are partially substituted with (1-2)-β-D-galactoxylose.[108]	
***Branched – modified* (i.e., added sidechains are larger than acetate)**		
Calcium Starch Isododecenylsuccinate 194810-88-3	Calcium Starch Isododecenylsuccinate is the calcium salt of the product formed by the reaction of starch with isododecenylsuccinic anhydride.	

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

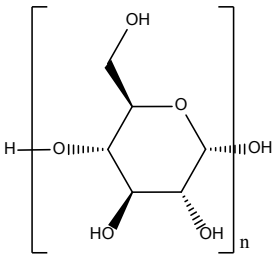
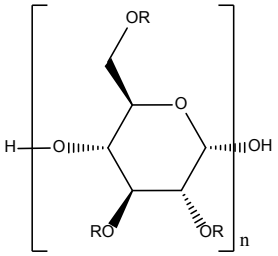
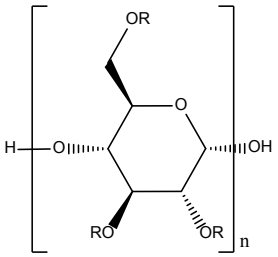
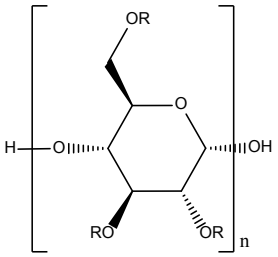
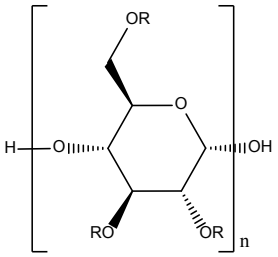
Ingredient CAS No.	Definition	Formula/structure
Calcium Starch Octenylsuccinate	Calcium Starch Octenylsuccinate is the calcium salt of the reaction product of octenylsuccinic anhydride with Zea Mays (Corn) Starch.	
Corn Starch Modified	Corn Starch Modified is the calcium salt of the ester formed from the reaction of 3-(dodecenyl)dihydro-2,5-furandione and corn starch in which the degree of substitution per glucose unit is less than 0.1.	
Dextrin 9004-53-9	Dextrin is a gum produced by the incomplete hydrolysis of starch.	
Dextrin Behenate 112444-74-3	Dextrin Behenate is the ester of Dextrin and Behenic Acid.	 wherein R is the residue of behenic acid
Dextrin Isostearate	Dextrin Isostearate is the ester of Dextrin and Isostearic Acid.	 wherein R is the residue of isostearic acid
Dextrin Laurate 79748-56-4	Dextrin Laurate is the ester of Dextrin and Lauric Acid.	 wherein R is the residue of lauric acid
Dextrin Myristate 93792-77-9	Dextrin Myristate is the ester of Dextrin and Myristic Acid.	 wherein R is the residue of myristic acid

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

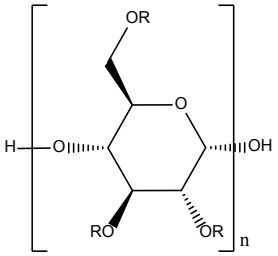
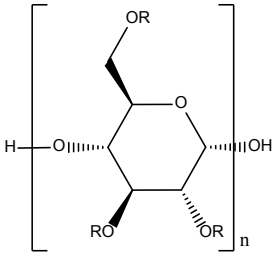
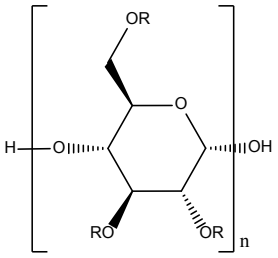
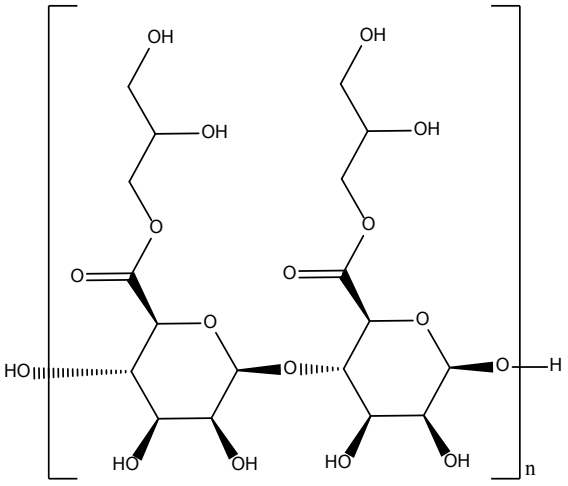
Ingredient CAS No.	Definition	Formula/structure
Dextrin Palmitate 83271-10-7	Dextrin Palmitate is the palmitic acid ester of Dextrin.	 wherein R is the residue of palmitic acid
Dextrin Palmitate/Ethylhexanoate 183387-52-2	Dextrin Palmitate/Ethylhexanoate is the mixed ester of Dextrin with palmitic and ethylhexanoic acids.	 wherein R is the residue of palmitic or ethylhexanoic acid
Dextrin Stearate 37307-33-8	Dextrin Stearate is the ester of Dextrin and Stearic Acid.	 wherein R is the residue of stearic acid
Glyceryl Alginate	Glyceryl Alginate is the ester of glycerin and Alginic Acid.	
Glyceryl Dimaltodextrin	Glyceryl Dimaltodextrin is the reaction product of Glycerin and Maltodextrin.	
Glyceryl Starch	Glyceryl Starch is a partially crosslinked corn starch.	

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

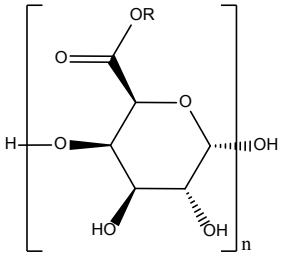
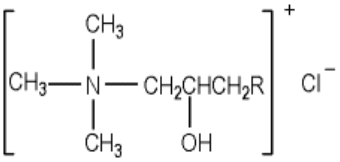
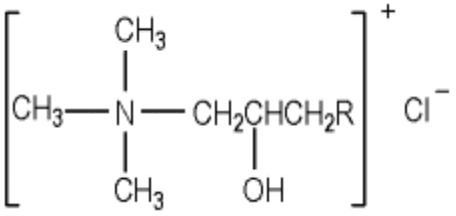
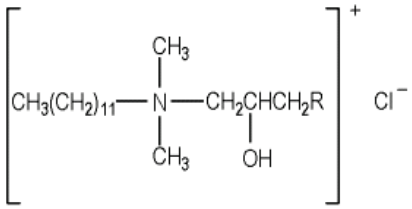
Ingredient CAS No.	Definition	Formula/structure
Hydrolyzed Pectin	Hydrolyzed Pectin is the hydrolysate of Pectin derived by acid, enzyme or other method of hydrolysis. *Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.*	 where R is hydrogen or methyl
Hydroxypropyltrimonium Hydrolyzed Corn Starch	Hydroxypropyltrimonium Hydrolyzed Corn Starch is the quaternary ammonium salt that conforms generally to the formula:	 where R represents the hydrolyzed corn starch moiety.
Hydroxypropyltrimonium Hydrolyzed Wheat Starch	Hydroxypropyltrimonium Hydrolyzed Wheat Starch is the quaternary ammonium salt that conforms generally to the formula:	 where R represents the hydrolyzed wheat starch moiety.
Hydroxypropyl Oxidized Starch	Hydroxypropyl Oxidized Starch is the reaction product of oxygen and Hydroxypropyl Starch.	
Hydroxypropyl Starch 68584-86-1 9049-76-7	Hydroxypropyl Starch is a propylene glycol ether of starch.	
Hydroxypropyltrimonium Maltodextrin Crosspolymer	Hydroxypropyltrimonium Maltodextrin Crosspolymer is a crosslinked polymeric quaternary ammonium salt prepared by the reaction of maltodextrin and glycidyltrimethylammonium chloride with epichlorohydrin.	
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch	Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch is the quaternary ammonium chloride that conforms generally to the formula:	 where R represents the hydrolyzed wheat starch moiety.

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

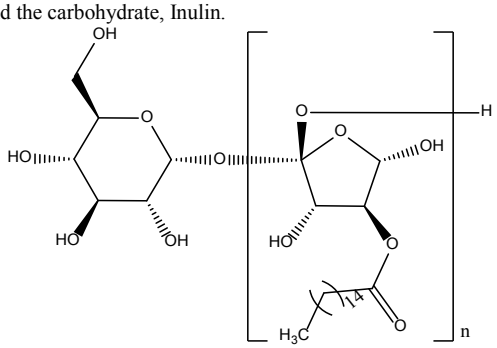
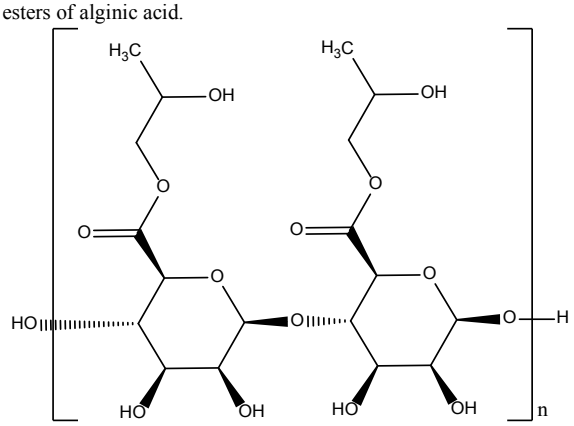
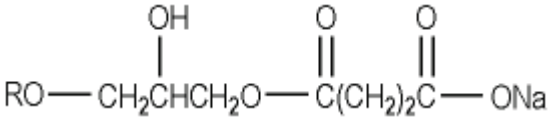
Ingredient CAS No.	Definition	Formula/structure
Palmitoyl Inulin	Palmitoyl Inulin is the condensation product of palmitic acid chloride and the carbohydrate, Inulin.	
Potassium Dextrin Octenylsuccinate	Potassium Dextrin Octenylsuccinate is the potassium salt of the reaction product of octenylsuccinic anhydride with Dextrin.	
Potassium Undecylenoyl Alginate	Potassium Undecylenoyl Alginate is the potassium salt of the condensation product of undecylenic acid chloride and Alginic Acid.	
Potassium Undecylenoyl Carrageenan	Potassium Undecylenoyl Carrageenan is the potassium salt of the condensation product of undecylenic acid chloride and Carrageenan.	
Potato Starch Modified	Potato Starch Modified is the ether formed from the reaction of haloethylaminodipropionic acid and potato starch in which the degree of substitution per glucose unit is less than 0.1.	
Propylene Glycol Alginate 9005-37-2	Propylene Glycol Alginate is a mixture of the propylene glycol esters of alginic acid.	
Sodium Carboxymethyl Inulin 430439-54-6	Sodium Carboxymethyl Inulin is the sodium salt of the product obtained by the reaction of chloroacetic acid with Inulin.	
Sodium Carboxymethyl Starch 9063-38-1	Sodium Carboxymethyl Starch is the sodium salt of a carboxymethyl derivative of starch.	
Sodium Dextrin Octenylsuccinate	Sodium Dextrin Octenylsuccinate is the sodium salt of the reaction product of octenylsuccinic anhydride with Dextrin.	
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate	Sodium Hydrolyzed Potato Starch Dodecenylsuccinate is the sodium salt of the product obtained by the reaction of dextrin with dodecenylsuccinic anhydride.	
Sodium Hydroxypropyl Oxidized Starch Succinate	Sodium Hydroxypropyl Oxidized Starch Succinate is the organic compound that conforms to the formula:	 where R represents the oxidized starch moiety.
Sodium Oxidized Starch Acetate/Succinate	Sodium Oxidized Starch Acetate/Succinate is the sodium salt of product of the esterification of oxidized starch with acetic acid and succinic acid anhydrides.	

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

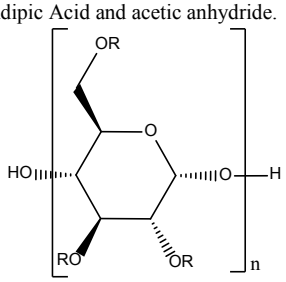
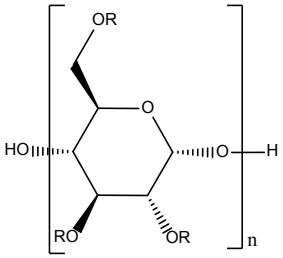
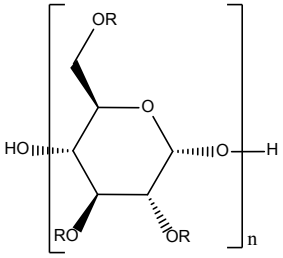
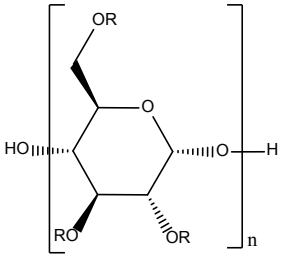
Ingredient CAS No.	Definition	Formula/structure
Sodium Starch Octenylsuccinate 52906-93-1 66829-29-6 70714-61-3	Sodium Starch Octenylsuccinate is the sodium salt of the reaction product of octenylsuccinic anhydride with Zea Mays (Corn) Starch.	
Sodium/TEA-Undecylenoyl Alginate	Sodium/TEA-Undecylenoyl Alginate is the mixed sodium and triethanolamine salt of the condensation product of undecylenic acid chloride and Alginic Acid.	
Sodium/TEA-Undecylenoyl Carrageenan	Sodium/TEA-Undecylenoyl Carrageenan is the mixed sodium and triethanolamine salt of the condensation product of undecylenic acid chloride and Carrageenan.	
Starch Acetate/Adipate 63798-35-6	Starch Acetate/Adipate is the product obtained by the reaction of Zea Mays (Corn) Starch with Adipic Acid and acetic anhydride.	 where R is adipate or acetate
Starch Diethylaminoethyl Ether 9041-94-5	Starch Diethylaminoethyl Ether is the product obtained by conversion of some hydroxyl groups in starch to diethylaminoethyl ether groups.	 where R is hydrogen or constitutes, with the attached oxygen, diethylaminoethyl ether
Starch Hydroxypropyltrimonium Chloride 56780-58-6	Starch Hydroxypropyltrimonium Chloride is the quaternary ammonium compound formed by the reaction of starch with 2,3-epoxypropyltrimethylammonium chloride. Other source: One of the starch hydroxypropyltrimonium chloride trade name materials is defiuned as an aqueous solution of a naturally derived cationic polysaccharide produced from food grade potato starch.[109]	 where R is hydrogen or constitutes, with the attached oxygen, hydroxypropyltrimonium
Starch Laurate	Starch Laurate is the product obtained by the reaction of lauric acid with starch.	 where R is hydrogen or laurate

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

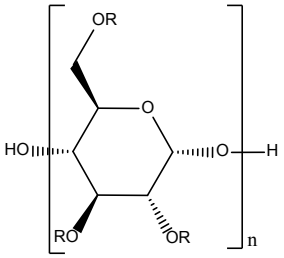
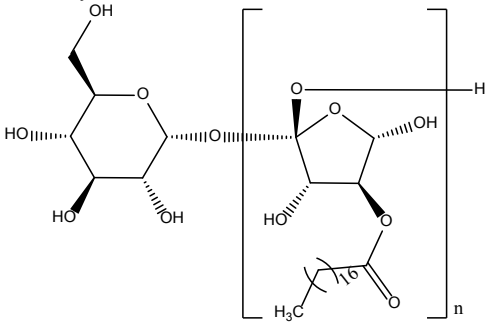
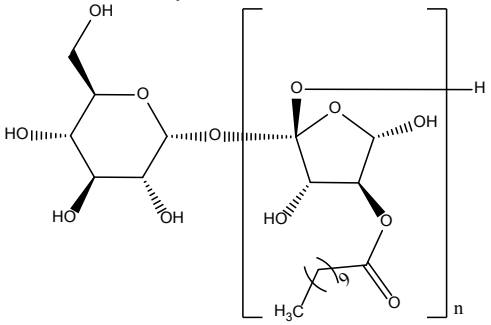
Ingredient CAS No.	Definition	Formula/structure
Starch Tallowate	Starch Tallowate is the ester of starch with the fatty acids derived from Tallow.	 where R is hydrogen or the residue of a fatty acid from tallow
Stearoyl Inulin	Stearoyl Inulin is the condensation product of stearic acid chloride with the carbohydrate, Inulin.	
Tapioca Starch Crosspolymer	Tapioca Starch Crosspolymer is Tapioca Starch crosslinked with epichlorohydrin.	
TEA-Dextrin Octenylsuccinate	TEA-Dextrin Octenylsuccinate is the triethanolamine salt of the reaction product of octenylsuccinic anhydride with Dextrin.	
Undecylenoyl Inulin	Undecylenoyl Inulin is the condensation product of undecylenic acid chloride with the carbohydrate, Inulin.	

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

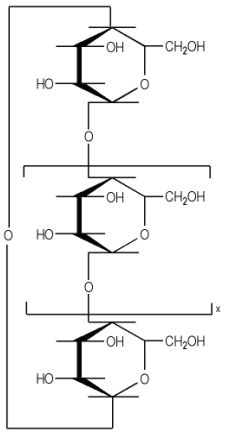
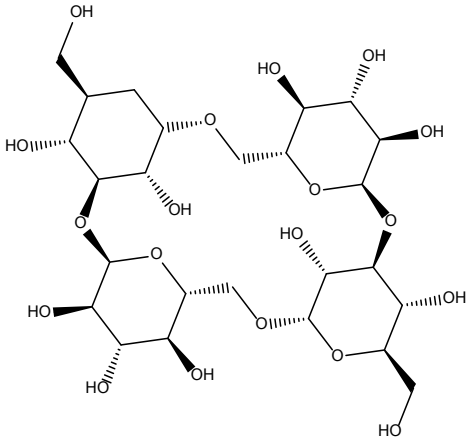
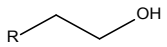
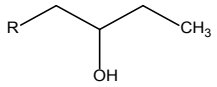
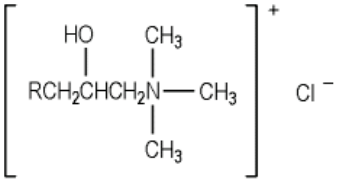
Ingredient CAS No.	Definition	Formula/structure
Cyclic		
Cyclodextrin 12619-70-4 7585-39-9	Cyclodextrin is a cyclic polysaccharide comprised of six to eight glucopyranose units. It conforms to the formula below: Other sources: Cyclodextrins are cyclic amylose-derived oligomers composed of a varying number of α-1-4-linked glucose units.[110] Cyclodextrins contain 6, 7, or 8 glucose units. β-Cyclodextrin is a carbohydrate consisting of seven glucose units.[111]	 where x may have values from 4 to 6.
Cyclotetraglucose 159640-28-5	Cyclotetraglucose is a cyclic polysaccharide comprised of four Glucose units.	
Cyclic - modified		
Hydroxyethyl Cyclodextrin	Hydroxyethyl Cyclodextrin is the hydroxyethyl ether of Cyclodextrin.	 where R represents the Cyclodextrin polymer.
Hydroxypropyl Cyclodextrin 128446-33-3 128446-35-5	Hydroxypropyl Cyclodextrin is a propylene glycol ether of Cyclodextrin.	 where R represents the Cyclodextrin polymer.
Cyclodextrin Hydroxypropyltrimonium Chloride	Cyclodextrin Hydroxypropyltrimonium Chloride is the organic compound that conforms to the formula:	 where R represents the Cyclodextrin polymer.

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

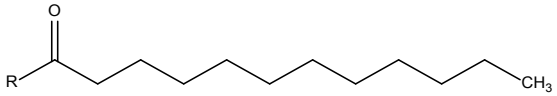
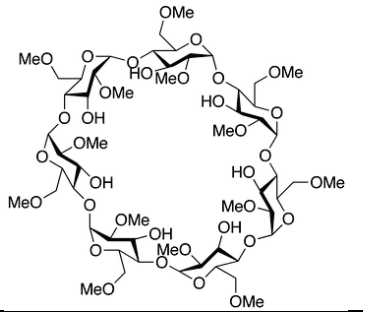
Ingredient CAS No.	Definition	Formula/structure
Cyclodextrin Laurate	Cyclodextrin Laurate is the product obtained by the reaction of Cyclodextrin and lauric acid chloride.	 where R represents the Cyclodextrin polymer.
Methyl Cyclodextrin 128446-36-6	Methyl Cyclodextrin is the product obtained by the methylation of Cyclodextrin.	
Unknown structural configuration		
Algae Exopolysaccharides	Algae Exopolysaccharides (Retired) are exopolysaccharides released by the fermentation of various species of microalgae of the divisions, Rhodophyta and Chlorophyta. The INCI Name, Algae Exopolysaccharides, originally published in 2010, was designated with a retired status in 2015. For an interim period of time, trade name assignments formerly published with the INCI Name Algae Exopolysaccharides will be retained in the retired monograph, and also published with the new name assignment based on the current genus and species name for the specific alga. For further information, consult the Introduction, Retired INCI Names.	
Cassia Angustifolia Seed Polysaccharide	Cassia Angustifolia Seed Polysaccharide is the polysaccharide fraction derived from the seed of Cassia angustifolia. Other source: Cassia angustofolia seed polysaccharide has been defined as a water-soluble galactomannan, consisting of D-galactose and D-mannose in the molar ratio of 3:2, isolated from the seeds of *Cassia angustifolia*.[112]	
Prunus Persica (Peach) Gum	Prunus Persica (Peach) Gum is the dried, gummy exudate obtained from *Prunus persica*.	
Unknown structural configuration - modified		
Hydrogenated Potato Starch 68412-29-3 (generic)	Hydrogenated Potato Starch is the end product of the controlled hydrogenation of Solanum Tuberosum (Potato) Starch.	
Hydrogenated Starch Hydrolysate 68425-17-2	Hydrogenated Starch Hydrolysate is the end-product of the controlled hydrogenation of hydrolyzed starch.	
Hydrolyzed Corn Starch Hydroxyethyl Ether	Hydrolyzed Corn Starch Hydroxyethyl Ether is the hydroxyethyl ether of Hydrolyzed Corn Starch.	
Hydrolyzed Corn Starch Octenylsuccinate 125109-81-1	Hydrolyzed Corn Starch Octenylsuccinate is the reaction product of octenylsuccinic anhydride with Hydrolyzed Corn Starch.	
Hydrolyzed Soy Starch 68412-29-3 (generic)	Hydrolyzed Soy Starch is the hydrolysate of soy starch derived by acid, enzyme or other method of hydrolysis.	
Hydrolyzed Starch 34612-38-9 68412-29-3 (generic)	Hydrolyzed Starch is the hydrolysate of starch obtained from *Ipomoea batatas, Manihot esculenta, Solanum tuberosum* or *Zea mays* by acid enzyme or other method of hydrolysis.	
Hydrolyzed Triticum Spelta Starch	Hydrolyzed Triticum Spelta Starch is the hydrolysate of the starch obtained from the grain, *Triticum spelta* derived by acid, enzyme or other method of hydrolysis.	
Hydrolyzed Wheat Starch 68412-29-3 (generic)	Hydrolyzed Wheat Starch is the hydrolysate of wheat starch derived by acid, enzyme or other method of hydrolysis.	

Table 2. Ingredient Functions in Cosmetic Products.[1]

Linear polysaccahrides and their salts	
Agar	Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Agarose	Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Algin	Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Alginic Acid	Binders; Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Aqueous
Ammonium Alginate	Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Amylose	Skin-Conditioning Agents - Humectant
Astragalus Gummifer Gum	Adhesives; Binders; Emulsion Stabilizers; Film Formers; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Calcium Alginate	Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Calcium Carageenan	Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Carrageenan	Binders; Fragrance Ingredients; Hair Conditioning Agents; Viscosity Increasing Agents - Aqueous
Magnesium Alginate	Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Mannan	Film Formers; Viscosity Increasing Agents - Aqueous
Polianthes Tuberosa Polysaccharide	Skin-Conditioning Agents - Miscellaneous
Potassium Alginate	Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Potassium Carrageenan	Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Sodium Carrageenan	Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
TEA-Alginate	Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Linear - modified	
Amylodextrin	Absorbents; Bulking Agents
Hydrolyzed Carrageenan	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Furcellaran	Skin Protectants
Maltodextrin	Absorbents; Binders; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Film Formers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Sodium Algin Sulfate	Skin-Conditioning Agents - Humectant
Branched – unmodified	
Amylopectin	Binders; Viscosity Increasing Agents - Aqueous
Aphanothece Sacrum Polysaccharide	Absorbents; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous
Arabinoxylan	Film Formers
Avena Sativa (Oat) Starch	Absorbents
Cassia Angustifolia Seed Polysaccharide	Skin-Conditioning Agents - Emollient
Cichorium Intybus (Chicory) Root Oligosaccharides	Skin-Conditioning Agents - Miscellaneous
Galactoarabinan	Film Formers; Fragrance Ingredients
Ghatti Gum	Binders; Emulsion Stabilizers; Surfactants - Emulsifying Agents; Viscosity Increasing Agents - Aqueous
Glucomannan	Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Inulin	Skin-Conditioning Agents - Humectant
Pectin	Binders; Emulsion Stabilizers; Oral Health Care Drugs; Viscosity Increasing Agents - Aqueous
Phaseolus Angularis Seed Starch	Absorbents
Phaseolus Radiatus Seed Starch	Abrasives; Bulking Agents
Pisum Sativum (Pea) Starch	Absorbents; Opacifying Agents; Slip Modifiers

Table 2. Ingredient Functions in Cosmetic Products.[1]

Pueraria Lobata Starch	Absorbents; Opacifying Agents; Slip Modifiers
Solanum Tuberosum (Potato) Starch	Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous
Starch Acetate	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient
Sterculia Urens Gum	Adhesives; Binders; Emulsion Stabilizers; Fragrance Ingredients; Hair Fixatives; Viscosity Increasing Agents - Aqueous
Tamarindus Indica Seed Gum	Adhesives; Emulsion Stabilizers; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Tapioca Starch	Viscosity Increasing Agents - Aqueous
Triticum Vulgare (Wheat) Starch	Abrasives; Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous
Xyloglucan	Humectants
Branched – modified **(i.e., added sidechains are larger than acetate)**	
Calcium Starch Isododecenylsuccinate	Absorbents; Skin-Conditioning Agents - Emollient
Calcium Starch Octenylsuccinate	Absorbents; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Corn Starch Modified	Absorbents; Film Formers; Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Nonaqueous
Dextrin	Absorbents; Binders; Bulking Agents; Viscosity Increasing Agents - Aqueous
Dextrin Behenate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Isostearate	Skin-Conditioning Agents - Miscellaneous
Dextrin Laurate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Myristate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Palmitate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Palmitate/Ethylhexanoate	Anticaking Agents; Surfactants - Emulsifying Agents
Dextrin Stearate	Anticaking Agents; Surfactants - Emulsifying Agents
Glyceryl Alginate	Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Aqueous
Glyceryl Dimaltodextrin	Humectants; Skin-Conditioning Agents - Humectant
Glyceryl Starch	Absorbents; Binders
Hydrolyzed Pectin	Skin-Conditioning Agents - Miscellaneous
Hydroxypropyltrimonium Hydrolyzed Corn Starch	Antistatic Agents; Film Formers; Hair Conditioning Agents; Hair Fixatives; Hair-Waving/Straightening Agents
Hydroxypropyltrimonium Hydrolyzed Wheat Starch	Antistatic Agents; Hair Conditioning Agents
Hydroxypropyl Oxidized Starch	Film Formers
Hydroxypropyl Starch	Dispersing Agents - Nonsurfactant; Viscosity Increasing Agents - Aqueous
Hydroxypropyltrimonium Maltodextrin Crosspolymer	Dispersing Agents - Nonsurfactant
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch	Antistatic Agents; Hair Conditioning Agents
Palmitoyl Inulin	Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Potassium Dextrin Octenylsuccinate	Emulsion Stabilizers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Potassium Undecylenoyl Alginate	Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Potassium Undecylenoyl Carrageenan	Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Potato Starch Modified	Viscosity Increasing Agents - Aqueous
Propylene Glycol Alginate	Binders; Fragrance Ingredients; Viscosity Increasing Agents - Aqueous
Sodium Carboxymethyl Inulin	Chelating Agents; Viscosity Increasing Agents - Aqueous
Sodium Carboxymethyl Starch	Binders; Emulsion Stabilizers; Film Formers; Viscosity Increasing Agents - Aqueous

Table 2. Ingredient Functions in Cosmetic Products.[1]

Sodium Dextrin Octenylsuccinate	Emulsion Stabilizers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate	Surfactants – Foam Boosters
Sodium Hydroxypropyl Oxidized Starch Succinate	Film Formers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Miscellaneous
Sodium Oxidized Starch Acetate/Succinate	Film Formers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Miscellaneous
Sodium Starch Octenylsuccinate	Absorbents; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous
Sodium/TEA-Undecylenoyl Alginate	Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Sodium/TEA-Undecylenoyl Carrageenan	Emulsion Stabilizers; Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Starch Acetate/Adipate	Viscosity Increasing Agents - Aqueous
Starch Diethylaminoethyl Ether	Film Formers; Skin-Conditioning Agents - Miscellaneous
Starch Hydroxypropyltrimonium Chloride	Antistatic Agents; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Hair Conditioning Agents; Viscosity Increasing Agents - Aqueous
Starch Laurate	Abrasives
Starch Tallowate	Skin-Conditioning Agents - Emollient
Stearoyl Inulin	Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Tapioca Starch Crosspolymer	Absorbents; Binders
TEA-Dextrin Octenylsuccinate	Emulsion Stabilizers; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
Undecylenoyl Inulin	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
Cyclic	
Cyclodextrin	Absorbents; Chelating Agents
Cyclotetraglucose	Binders; Bulking Agents; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Cyclic - modified	
Hydroxyethyl Cyclodextrin	Skin-Conditioning Agents - Miscellaneous
Hydroxypropyl Cyclodextrin	Chelating Agents; Emulsion Stabilizers
Cyclodextrin Hydroxypropyltrimonium Chloride	Film Formers; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Cyclodextrin Laurate	Film Formers; Skin Protectants; Skin-Conditioning Agents - Humectant
Methyl Cyclodextrin	Chelating Agents
Unknown structural configuration	
Algae Exopolysaccharides	Film Formers; Skin Protectants; Skin-Conditioning Agents - Humectant; Slip Modifiers
Prunus Persica (Peach) Gum	Viscosity Increasing Agents - Aqueous
Unknown structural configuration - modified	
Hydrogenated Potato Starch	Viscosity Increasing Agents - Aqueous
Hydrogenated Starch Hydrolysate	Film Formers; Humectants; Oral Care Agents; Skin-Conditioning Agents - Humectant
Hydrolyzed Corn Starch Hydroxyethyl Ether	Emulsion Stabilizers; Humectants; Skin-Conditioning Agents - Humectant; Viscosity Increasing Agents - Aqueous
Hydrolyzed Corn Starch Octenylsuccinate	Absorbents; Binders; Film Formers
Hydrolyzed Soy Starch	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Starch	Humectants; Skin Protectants; Skin-Conditioning Agents - Humectant
Hydrolyzed Triticum Spelta Starch	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Wheat Starch	Skin-Conditioning Agents - Humectant

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Linear Polysaccharides and Their Salts

Carrageenan

Average Molecular Weight: > 100,000 Da.[35] **Molecular Weight Range:** 196,000–257,000 Da.[113]

Stability: Data on carrageenans (in their sodium ion form without co-gelling cations) included κ-carrageenan from *Euchema cottoni*i, ι-carrageenan from *Eucheuma spinosoum*, a κ/λ mixture extracted from Chondrus crispus, and a κ/λ hybrid carrageenan from *Gigartina radula*. Reasonable stability to heating at 75˚C down to pH 4, and the rate of depolymerization increases dramatically as the pH decreases from 4 to 3. ι-Carrageenan is the most stable form, while κ-carrageenan has the greatest susceptibility to acid hydrolysis. The carrageenans from *Gigartina radula* and *Chondrus crispus* have intermediate stability.[114]

Carrageenan in the presence of co-gelling cations is much more stable than carrageenan in sodium ion form at 37˚C. However, at higher temperatures, the carrageenan is in the random coil state and is more susceptible to acid degradation. Studies of the stability of κ-carrageenan in the presence of potassium ions have shown that acid-catalyzed hydrolysis occurs at temperatures between 55˚C and 95˚C. Degradation was described as a first-order random hydrolysis process. A 25% reduction in molecular weight was produced at pH 3 after 1.4 h at 50˚C, and after only 28 seconds at 90˚C. At pH 4, a similar reduction in molecular weight was recorded after 8 h at 50˚C and after 15 minutes at 90˚C.[114]

Inulin

Method of Manufacture: Extraction from the roots of *Cichorium intybus*.[115]

Linear - Modified

Amylodextrin

Method of Manufacture: Prepared from waxy maize by enzymatic hydrolysis with pullulanase.[116]

Hydrolyzed Furcellaran

Method of Manufacture: The polymer furcellaran (a carrageenan [Kappa type]) obtained from *Furcellaria lumbricallis* is depolymerized by sub-critical CO_2 with a low percentage of water, and the product is an opalescent liquid **(See Figure 2)**.[73]

Maltodextrin

Method of Manufacture: Prepared as a white powder or concentrated solution by partial hydrolysis of corn starch, potato starch, or rice starch with suitable acids and enzymes.[117]

Branched - Unmodified

Arabinoxylan

Molecular Weight: 65 to 66 kDa (obtained by sedimentation),[118] 800 - 5000 kDa (obtained by gel filtration),[119] and 70 - 1,000 kDa (obtained by gel filtration).[120]

Cichorium Intybus (Chicory) Root Oligosaccharides

Method of Manufacture: Extraction from the roots of Cichorium intybus.[115]

Ghatti Gum

Molecular Weight: ≈ 8.94 x 10^7 Da.[121]

Glucomannan

Average Molecular Weight: 1,000,000 Da; between 200,000 and 2,000,000 Da (commercial samples).[122]

Form: biphasic liquid crystal phase in water at 7 weight% concentration; becomes completely anisotropic at >10 weight%.[106]

Decomposition: Begins to decompose at approximately 250˚C; decomposition is complete at 350˚C.[122]

Method of Manufacture: Obtained by a dry milling process of thin tuber (*Amorphophallus konjac*) slices.[105] Can also be obtained from monocot storage organs other than tubers, such as leaves, bulbs, roots, or seeds.[122] Glucomannan is found in specific large-sized idioblast cells located in the protoplast, and raphide crystal bundles of oxalic acid are enveloped in the polysaccharide. During processing, focus is placed on eliminating the protein membrane of these cells and removing the needle-shaped oxalic acid crystals by sieving, to give residual levels of approximately 0.2% for crude powder and lower for refined grades.[122]

Branched - Modified

Carboxymethyl Inulin

Method of Manufacture: Synthesized by reacting inulin with the sodium salt of monochloroacetic acid in the presence of sodium hydroxide.[123]

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Corn Starch Modified

Method of Manufacture: aqueous corn starch slurry reaction with 3-(dodecenyl) dihydro-2,5-furandione.[66,124]

Dextrin

Method of Manufacture: Dilute acid (e.g. HNO3) is added to native starch, and the starch is pre-dried. Next, pre-dried-starch is roasted at a temperature between 110°C and 150°C until the color of the starch changes to what is described as appropriate whiteness.[125] Another production method begins with the suspension of starch in water and adjustment of the pH to between 6 and 8. An enzyme (e.g., liquefying-type amylase) is added to the slurry, which is liquefied at 80°C and 90°C. Starch syrup is degraded to an appropriate viscosity, and the enzyme is made inactive. The syrup is purified by diatomite, active-carbon, ion-exchange resin and then dried.[125]

Dextrin Myristate

Form: Powder or particles.[67]

Color: White to pale yellow.[67]

Odor: Odorless or characteristic.[67]

Melting Point/Freezing Point: 50 ~ 150˚C.[67]

Flash Point: 210˚C.[67]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[67]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[126]

Dextrin Isostearate

Form: Soft solid.[127]

Color: Colorless to pale yellow.[127]

Odor: Odorless or characteristic.[127]

Melting Point/Freezing Point: 60 ~ 70°C.[127]

Flash Point: > 200°C.[127]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[127]

Method of Manufacture: The method of manufacture for dextrin isostearate begins with an esterification reaction involving 3-methylpyridine (beta-picoline) and n-heptane, followed by percolation, washing (methanol), drying, and filtration.[128]

Dextrin Palmitate

Form: Powder or particles.[68,69]

Color: White to pale yellow.[68,69]

Odor: Odorless or characteristic.[68,69]

Melting Point/Freezing Point: 50 ~ 130˚C; 100 ~ 130˚C.[68,69]

Flash Point: 200 ~ 250˚C.[68,69]

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[68,69]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[126]

Dextrin Palmitate/Ethylhexanoate

Form: Powder or particles.[129]

Color: White to pale yellow.[129]

Odor: Odorless or characteristic.[129]

Melting Onset Temperature: 120°C.[129]

Flash Point: 216°C.[129]

Dextrin Palmitate/Ethylhexanoate

Solubility: Insoluble in water, methanol, and ethanol; soluble in xylene, benzene, chloroform, and carbon tetrachloride.[129]

Method of Manufacture: An esterification reaction involving 3-methylpyridine (beta-picoline) and dimethylformamide (DMF) is followed by percolation, washing (methanol and water), centrifugation, drying, riddle, and use of magnets. Riddle is defined as a screening or sieving process that removes large particulate material. Magnets are used to remove metal particles.[126]

Glyceryl Dimaltodextrin

Method of Manufacture: Production of maltodextrins involves the obtention of products consisting of D-glucose units that are linked primarily by α(1→4) bonds and having dextrose equivalents less than 20.[130]

Hydroxypropyl Starch

Method of Manufacture: Sodium sulfate (Na2SO4) and sodium hydroxide (NaOH) are dissolved in water, and starch and propylene oxide are added, and heated to 38°C to 42°C. After the reaction is finished, the slurry is neutralized by acid (H2SO4). The starch is then dewatered, washed, and dried. The slurry of hydroxyl-propyl starch may also be degraded by an enzyme (e.g., liquefying-type amylase), purified by diatomite and active-carbon, and then dried.[125]

Potato Starch Modified

Method of Manufacture: An aqueous potato starch slurry is reacted with haloethylaminopropionic acid. This reaction is followed by washing, filtration, and drying.[70]

Sodium Dextrin Octenylsuccinate

Method of Manufacture: Method 1: The slurry of sodium starch octenylsuccinate is degraded by an enzyme (e.g., liquefying-type amylase), purified by diatomite and active-carbon, and dried. The dried starch film is crushed into a fine powder. **Method 2:** Dextrin solution and octenylsuccinic anhydride are esterified, whereby the pH value is adjusted between 7 and 8 with alkaline (triethanolamine; sodium hydroxide solution, potassium hydroxide solution). The sodium dextrin octenylsuccinate manufactured according to this method is sold as a liquid. **Method 3:** Dextrin solution and octenylsuccinic anhydride are esterified, whereby the pH value is adjusted between 7 and 8 with sodium hydroxide solution. The solution is then dried.[125]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

Solubility: Soluble in water (149.5 - 158.2 g/l).[131]

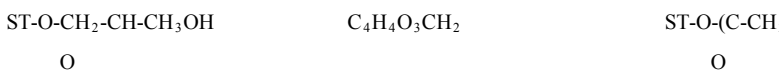
Method of Manufacture: Reaction of a hydrolyzed starch with dodecenylsuccinic anhydride.[132]

Sodium Hydroxypropyl Oxidized Starch Succinate

Method of Manufacture: Native starch (CAS No. 9005-25-8) and oxidized starch (CAS No. 065996-62-5) can be modified by reacting starch with etherifying and/or esterifying reagents in the presence of an alkaline catalyst.[15,133]

Reaction to form 2-hydroxypropyl, oxidized starch succinate

Starch 2-Hydroxypropyl Ether, Oxidized + Succinic Anhydride → Starch, 2-Hydroxypropyl, Oxidized, Succinic Acid Ester



Sodium Starch Octenylsuccinate

Method of Manufacture: Starch is suspended in water, and octenylsuccinic anhydride is added. The slurry is heated to approximately 40°C, and the pH value is adjusted between 6 and 9 with dilute sodium hydroxide solution. The pH value of the solution is stable between 7 and 8, and the slurry is neutralized by acid (H2SO4). The starch is then dewatered, washed, and dried. Sodium starch octenylsuccinate may also be suspended in water and dried. The dried starch film is crushed into a find powder.[125]

Starch Hydroxypropyltrimonium Chloride

Molecular Weight: 2,000,000 Da.[109]

Table 3. Properties and Method of Manufacture of Polysaccharide Gums

Starch Hydroxypropyltrimonium Chloride

Form: Clear to slightly hazy liquid (clear in 1:5 water solution).[109]

Dry Substance (%) 31-33.[109]

Color, Gardner: ≤ 2.5.[109]

Odor: Very mild; slightly sweet.[109]

pH @ 20°C: 3.5-4.5.[109]

Method of Manufacture: The starting materials for the production of starch hydroxypropyltrimonium chloride are: oxidized starch and the cationic reagent 3-chloro-2-hydroxypropyltrimethylammonium chloride (CAS No. 3327-22-8).[133] The reaction to form cationic starch ether appears below:[133]

Starch + 2,3-Epoxypropyltrimethylammonium Chloride → Starch Hydroxypropyl Trimethylammonium Chloride

ST-OH CH_2-CH-CH_2-$N^+(CH_3)_3$ Cl ST-O-CH_2-CH-$CH_2N^+(CH_3)_3$-Cl

According to another source, starch hydroxypropyltrimonium chloride is produced by an aqueous starch slurry reaction with 2,3-epoxypropyltrimethylammonium chloride in the presence of isopropanol. This reaction is followed by washing with isopropanol/water, and the material is then filtered and dried.[134]

Stearoyl Inulin

Form: Powder or particles.[71,72]

Color: White to pale yellow.[71,72]

Odor: Odorless or characteristic.[71,72]

Melting Onset Temperature: 64˚C; 68.2˚C.[71,72]

Flash Point: 210˚C; 214˚C.[71,72]

Solubility: Insoluble in water, methanol, and ethanol.[71,72]

Cyclic

Cyclodextrin

Solubility: Low aqueous solubility (1.85 g/100mL, β-Cyclodextrin).[135]

Unknown Structural Configuration

Algae Exopolysaccharides

Method of Manufacture: Microalgae is grown in fermenters under conditions that promote the production of the exopolysaccharide, which is secreted by the microalgae. The exopolysaccharides are removed from the cells via filtration or centrifugation, followed by precipitation with alcohol. The exopolysaccharide is then dried and ground to a fine powder. The supplier of this information stated that the CAS number for the ingredient produced (algae exopolysaccharides) is 1122611-69-1, and that the empirical formula for this ingredient is (C27H44O27S)n. Additionally, it was noted that this is the CAS number for D-galactopyranose.[136]

Cassia Angustifolia Seed Polysaccharide

Average Molecular Weight: 9.66 x 10^4 Da.[137]

Unknown Structural Configuration - Modified

Hydrolyzed Starch

Method of Manufacture: Raw Material (Starch) →Starch slurry→Liquefaction by thermostable α-amylase→Saccharification by isoamylase (to debranch starch amylose) and exomaltotetraohydrolase (to produce maltotetraose)→Heat treatment (inactivation of enzymes)→Filtration→Concentration→Decoloration→Filtration→Storage →Filling and weighing→Hydrolyzed starch.[138,139]

Table 4. Composition/Impurities Data on Polysaccharide Gums

Linear Polysaccharides and Their Salts

Algin

After exhaustive methylation of alginic acid, reduction to the corresponding mannoside derivative, and hydrolysis, chromatographic separation indicated that the hydrolyzate contained 88% 2,3-dimethylmannose, 4.5% monomethylmannose, 1% 2,3,4-trimethylmannose, and 6% dimethylglucose.[87]

Carrageenan

The low-molecular-weight forms of carrageenan are <5% of the total composition of the commercial product.[35]

Twenty-nine samples of food-grade refined carrageenan were analyzed using high-performance liquid gel permeation chromatography. Each sample had no obvious peak of poligeenan (which is defined as degraded carrageenan, detection limit ≈ 5%).[140] Poligeenan is produced by a different manufacturing process of seaweed that involves intentional extensive acid hydrolysis, resulting in sulfated galactose polymers with a weight average molecular weight of ~ 15,000 Da.[35] Furthermore**,** according to another source, the molecular weight of poligeenan is in the range of 10,000 to 20,000 Da.[141]

Inulin

According to the *Food Chemicals Codex*, inulin should contain no more than the following: 1 mg/kg lead, 0.2% ash, and 15% (combined) of monosaccharides (as fructose and glucose) and disaccharides (as sucrose), calculated on the dried basis.[115]

Linear - Modified

Hydrolyzed Furcellaran (Mixtures).[73,142]

Mixture 1: Components: hydrolyzed furcellaran (0.6%), concentrate of sea water (0.05%), phenoxyethanol (1%), and water (98.35%). **Impurities:** contains heavy metals at a concentration < the limit of quantification, except for Cr (4.74 mg/kg), Ni (1.93 mg/kg), Pb (0.23 mg/kg), Co (0.17 mg/kg), and As (0.11 mg/kg); contains iodine at a concentration < the limit of quantification (i.e., 1 ppm; contains polychlorobiphenyl (PCB) at a concentration < the limit of quantification (i.e., 2 µg/kg) and research pesticides at a concentration < the limit of quantification (i.e., 10 ng/g).

Mixture 2: Components: hydrolyzed furcellaran (1.35%), phenoxyethanol (1%), and water (97.65%)

Mixture 3: Components: hydrolyzed furcellaran (1.90%), citric acid (0.05%), potassium sorbate (0.10%), and water 97.95%). **Impurities:** contains heavy metals at a concentration < the limit of quantification, except for Cr (0.162 mg/kg) and Pb (0.08 mg/kg); contains iodine at a concentration < the limit of quantification (i.e., 9 ppm); contains PCB at a concentration < the limit of quantification (i.e.,10 µg/kg) and research pesticides at a concentration < the limit of quantification (i.e., 10 ng/g).

Maltodextrin

According to the *Food Chemicals Codex*, maltodextrin should contain no more than the following: 0.5 mg/kg lead, 0.0025% sulfur dioxide, 1% maltodextrins produced from high-amylose starches, and 0.5% all other types of maltodextrins.[115]

Branched - Unmodified

Arabinoxylan

Arabinoxylans are complex, as the side branches of the main chain arabinose and xylose units contain small amounts of xylopyranose, galactopyranose, and *α*-D-glucuronic acid or 4-*O*-methyl-*α*-D-glucuronic acid.[143]

Glucomannan

Konjac flour consists of the following: carbohydrates (as water-soluble fiber, ~75% of glucomannan composition), protein (2-8%), fat (<1%), ash (3-5%), and moisture (<15%).[105]

Sterculia Urens Gum

Commercial sterculia urens gum contains 19%-21% of rhamnose and similar proportions of galactose and galacturonic acid.[36] Nitrogen content (probably non-protein in nature) of 0.07% has also been reported.[51]

Branched - Modified

Dextrin Myristate

Dextrin myristate contains: dextrin myristate (> 95%); moisture, based on loss of drying (< 1%); myristic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detection limit).[144]

Dextrin Palmitate

Dextrin palmitate contains: dextrin palmitate (> 95%); moisture, based on loss on drying (< 1%); palmitic acid (< 5%); 3-methylpyridine (beta-picoline) (< 300 ppm; < 1,000 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detection limit).[145,146]

Dextrin Palmitate/Ethylhexanoate

Dextrin Palmitate/Ethylhexanoate contains: dextrin palmitate/ethylhexanoate (> 95%); moisture, based on loss on drying (< 3%); palmitic acid and 2-ethylhexanoic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm).[147]

Table 4. Composition/Impurities Data on Polysaccharide Gums

Dextrin Isostearate

Dextrin isostearate contains: dextrin isostearate (> 95%); isostearic acid (< 5%); 3-methylpyridine (beta-picoline) (< 300 ppm); heptane (< 200 ppm); and methanol (< 5 ppm, detection limit).[148]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate

Impurities: antimony (7.53 mg/kg), arsenic (< 2 mg/kg), barium (0.271 mg/kg), cadmium (< 0.2 mg/kg), chromium (< 0.25 mg/kg), cobalt (< 1.5 mg/kg), copper (<0.25 mg/kg), lead (< 1.5 mg/kg), nickel (< 1 mg/kg), selenium (< 4.86 mg/kg), zinc (1.49 mg/kg), and mercury (< 0.1 mg/kg).[149]

Starch Hydroxypropyltrimonium Chloride

Starch hydroxypropyltrimonium chloride consists of approximately 30% solids, and is preserved with food grade sodium benzoate.[109]

Impurities/residuals data: diol levels (< 2%), enol levels (< 1.5%), and quaternizing agent (< 0.1%).[134]

Stearoyl Inulin

Stearoyl inulin contains: stearoyl inulin (> 95%); moisture, based on loss on drying (< 1%); stearic acid (< 5%); 3-Methylpyridine (beta-picoline) (< 300 ppm); DMF (< 5 ppm, detection limit); and methanol (< 5 ppm, detection limit).[150]

Unknown Structural Configuration

Cassia Angustifolia Seed Polysaccharide
The purified seed galactomannan contains mannose:galactose in a ratio of 2.90:1.[137]

Unknown Structural Configuration – Modified

Hydrolyzed Starch

Composition/Properties data on two hydrolyzed starch products are available **(See Table 5)**.[138,139]

Table 5. Composition/Properties Data on Two Hydrolyzed Starch (unknown structural configuration – modified) Products.[138,139]

Product 1	Product 2
G1 (glucose): 2% (not more than 5% for the specification)	G1 (glucose): 2.5% (not more than 5% for the specification)
G2 (maltose): 7%	G2 (maltose): 6%
G3 (maltotriose)*: 10%	G3 (maltotriose)*: 9.5%
G4 (maltotetraose)**: 53% (not less than 50% for the specification)	G4 (maltotetraose)**: 74% (not less than 70% for the specification)
G5 (maltopentaose)***: 2%	G5 (maltopentaose)***: 0.5%
≥ G6****: 26%	≥ G6****: 8%
Loss on drying (water content): ≈ 25% (solids specification: not less than 74%)	Loss on drying (water content): ≈ 28% (solids specification: not less than 72%)
Residue on ignition: ≤ 0.05%	Residue on ignition: ≤ 0.05%
Heavy metals (as lead): ≤ 5 ppm	Heavy metals (as lead): ≤ 5 ppm
Arsenic (as As_2O_3): ≤ 2 ppm	Arsenic (as As_2O_3): ≤ 2 ppm

**O*-α-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucose (maltotriose)

***O*-α-glucopyranosyl-[(1→4)-*O*-α-D-glucopyranosyl]$_2$-(1→4)-D-glucose (maltotetraose)

****O*-α-glucopyranosyl-[(1→4)-*O*-α-D-glucopyranosyl]$_3$-(1→4)-D-glucose (maltopentaose)

*****O*-α-glucopyranosyl-[(1→4)-*O*-α-D-glucopyranosyl]$_n$-(1→4)-D-glucose (n ≥ 4)

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18,19]

	Maltodextrin		**Glucomannan**		**Agar**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	542	0.00001-4	NR	0.3-17	67	0.002-1
Duration of Use						
Leave-On	327	0.00001-3	NR	NR	49	0.002-1
Rinse off	188	0.00006-3	NR	0.3-17	17	0.0043-0.015
Diluted for (bath) Use	27	0.22-4	NR	NR	1	NR
Exposure Type						
Eye Area	42	0.001-2.5	NR	17	3	1
Incidental Ingestion	13	0.00075-0.6	NR	NR	NR	NR
Incidental Inhalation- Sprays	189	0.00012-0.38	NR	NR	24	0.0075-1*
Incidental Inhalation- Powders	178	0.005-1	NR	NR	25	0.0075**
Dermal Contact	377	0.00001-4	NR	0.3-17	64	0.002-1
Deodorant (underarm)	NR	0.0045-0.12	NR	NR	NR	NR
Hair - Non-Coloring	80	0.00012-2	NR	NR	3	1
Hair-Coloring	65	0.0001-0.0033	NR	NR	NR	NR
Nail	NR	0.0015-3	NR	NR	NR	NR
Mucous Membrane	80	4	NR	NR	5	NR
Baby Products	2	NR	NR	NR	NR	NR
	Agarose		**Algin**		**Alginic Acid**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	10	0.2-0.7	326	0.001-50	13	NR
Duration of Use						
Leave-On	10	0.2-0.7	194	0.001-18	12	NR
Rinse off	NR	NR	131	0.01-50	1	NR
Diluted for (bath) Use	NR	NR	1	0.1	NR	NR
Exposure Type						
Eye Area	NR	NR	40	0.025-0.75	3	NR
Incidental Ingestion	NR	NR	NR	1.1	NR	NR
Incidental Inhalation- Sprays	1	NR	111	0.001-0.025	6	NR
Incidental Inhalation- Powders	1	NR	119	0.025	6	NR
Dermal Contact	10	0.2-0.7	315	0.001-50	13	NR
Deodorant (underarm)	9	0.7	NR	0.001	NR	NR
Hair - Non-Coloring	NR	NR	3	0.001-0.05	NR	NR
Hair-Coloring	NR	NR	1	1.3	NR	NR
Nail	NR	NR	1	0.002	NR	NR
Mucous Membrane	NR	NR	3	0.01-1.1	NR	NR
Baby Products	NR	NR	4	NR	1	NR
	Amylodextrin		**Astragalus Gummifer Gum**		**Avena Sativa (Oat) Starch**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	2	0.00004	7	NR	5	0.1-9.5
Duration of Use						
Leave-On	2	NR	5	NR	3	0.1-9.5
Rinse off	NR	0.00004	2	NR	2	3.6
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	1	NR	3	NR	2	0.1-9.5
Incidental Inhalation- Powders	1	NR	3	NR	3	0.1
Dermal Contact	2	NR	4	NR	5	0.1-9.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.00004	2	NR	NR	NR
Hair-Coloring	NR	NR	1	NR	NR	3.6
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Calcium Alginate		Carrageenan		Cassia Angustifolia Seed Polysaccharide	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	9	0.01-3	249	0.003-15.7	36	0.002-0.75
Duration of Use						
Leave-On	9	0.01-3	181	0.003-15.7	35	0.002
Rinse off	NR	0.01	63	0.003-3.7	1	0.025-0.75
Diluted for (bath) Use	NR	NR	5	0.1-3	NR	NR
Exposure Type						
Eye Area	NR	NR	18	0.2-3.7	3	NR
Incidental Ingestion	NR	NR	25	1-1.1	3	0.002
Incidental Inhalation- Sprays	2	0.016-1	118	0.03-15.7*	15	0.0025*-0.075*
Incidental Inhalation- Powders	3	0.4-3	11	NR	21	0.0025**-0.025**
Dermal Contact	9	0.01-3	206	0.003-3.7	33	0.0025-0.025
Deodorant (underarm)	NR	0.016-1	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	14	0.003-15.7	NR	0.025-0.75
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	2	NR	NR	NR
Mucous Membrane	NR	NR	35	0.1-3	3	0.002
Baby Products	NR	NR	1	NR	NR	NR
	Cichorium Intybus (Chicory) Root Oligosaccharides		**Corn Starch Modified**		**Cyclodextrin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	2	NR	86	0.0062-45.7	128	0.000025-4
Duration of Use						
Leave-On	2	NR	75	0.12-45.7	101	0.000025-4
Rinse off	NR	NR	10	0.0062-3	26	0.0042-1.6
Diluted for (bath) Use	NR	NR	1	9	1	NR
Exposure Type						
Eye Area	NR	NR	7	0.9-8	19	0.05-0.25
Incidental Ingestion	NR	NR	2	0.4	2	0.1
Incidental Inhalation- Sprays	2	NR	48	0.45-45.7*	69	0.08-2.5
Incidental Inhalation- Powders	2	NR	33	0.44**-15	59	0.2
Dermal Contact	2	NR	59	0.0062-15	118	0.0005-4
Deodorant (underarm)	NR	NR	NR	0.12	NR	2.5-4
Hair - Non-Coloring	NR	NR	17	0.45-45.7	5	0.000025-1.6
Hair-Coloring	NR	NR	4	NR	3	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	6	0.0062-9	4	0.1-0.73
Baby Products	NR	NR	2	NR	NR	NR
	Cyclodextrin Laurate		**Dextrin**		**Dextrin Myristate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	5	0.0035	177	0.000008-43	NR	0.05-19
Duration of Use						
Leave-On	5	0.0035	159	0.000008-30	NR	0.094-19
Rinse off	NR	NR	18	0.001-43	NR	0.05-7
Diluted for (bath) Use	NR	NR	NR	5	NR	NR
Exposure Type						
Eye Area	2	NR	21	0.000008-30	NR	0.094-19
Incidental Ingestion	NR	NR	1	0.008	NR	7-15
Incidental Inhalation- Sprays	3	NR	95	0.00037-2.8	NR	0.099-18
Incidental Inhalation- Powders	3	0.0035**	96	0.0044-2.8	NR	0.3**-16**
Dermal Contact	5	0.0035	168	0.000008-43	NR	0.05-19
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	2	0.00026-0.001	NR	0.099-1
Hair-Coloring	NR	NR	2	NR	NR	NR
Nail	NR	NR	4	0.2	NR	NR
Mucous Membrane	NR	NR	3	0.008-5	NR	7-15
Baby Products	NR	NR	NR	NR	NR	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Dextrin Palmitate		**Dextrin Palmitate/Ethylhexanoate**		**Dextrin Palmitate/Stearate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	77	0.0001-16.8	4	NR	NR	0.1-18
Duration of Use						
Leave-On	71	0.0001-16.8	4	NR	NR	0.1-18
Rinse off	6	0.0002-0.0097	NR	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	13	0.0001-2	NR	NR	NR	0.3-18
Incidental Ingestion	37	0.1-16.8	2	NR	NR	4.5-5
Incidental Inhalation- Sprays	5	NR	1	NR	NR	NR
Incidental Inhalation- Powders	5	0.1-0.5**	1	0.1-3**	NR	0.1-3**
Dermal Contact	33	0.0001-13	2	NR	NR	0.1-10
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.025	NR	NR	NR	NR
Mucous Membrane	38	0.1-16.8	2	NR	NR	4.5-5
Baby Products	NR	NR	NR	NR	NR	NR
	Galactoarabinan		**Glyceryl Alginate**		**Glyceryl Starch**	
	# of Uses	# of Uses	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	97	NR	NR	0.5	1	4
Duration of Use						
Leave-On	73	NR	NR	0.5	NR	4
Rinse off	24	NR	NR	NR	1	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	21	NR	NR	NR	NR	NR
Incidental Ingestion	2	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	21	NR	NR	NR	NR	NR
Incidental Inhalation- Powders	21	NR	NR	0.5**	NR	4**
Dermal Contact	76	NR	NR	0.5	1	4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	5	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Hydrogenated Starch Hydrolysate		**Hydrolyzed Corn Starch Octenylsuccinate**		**Hydrolyzed Pectin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	60	0.00007-3.8	13	0.06-0.67	14	NR
Duration of Use						
Leave-On	41	0.00007-0.75	11	0.06	12	NR
Rinse off	19	0.13-3.8	2	0.18-0.67	2	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	0.00007-0.5	NR	NR	1	NR
Incidental Ingestion	1	0.065-3.8	NR	NR	NR	NR
Incidental Inhalation- Sprays	33	3.8*	7	NR	10	NR
Incidental Inhalation- Powders	29	0.0007**-0.54**	7	NR	10	NR
Dermal Contact	49	0.00007-0.75	13	0.06-0.67	14	NR
Deodorant (underarm)	NR	NR	3	NR	NR	NR
Hair - Non-Coloring	10	0.13	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.065-3.8	NR	0.67	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Hydrolyzed Starch		**Hydrolyzed Wheat Starch**		**Hydroxyethyl Cyclodextrin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	NR	0.000013-0.00046	274	0.000003-0.31	NR	1.2
Duration of Use						
Leave-On	NR	0.00046	118	0.00005-0.31	NR	1.2
Rinse off	NR	0.000013	156	0.000003-0.25	NR	NR
Diluted for (bath) Use	NR	NR	4	0.000003	NR	NR
Exposure Type						
Eye Area	NR	NR	6	0.03-0.038	NR	1.2
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	0.00046*	66	0.00005-0.02	NR	NR
Incidental Inhalation- Powders	NR	NR	6	0.0002**-0.06**	NR	NR
Dermal Contact	NR	NR	58	0.000003-0.06	NR	1.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.00046	186	0.000003-0.31	NR	NR
Hair-Coloring	NR	0.000013	26	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	47	0.000003-0.003	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Hydroxypropyl Cyclodextrin		**Hydroxypropyltrimonium Hydrolyzed Corn Starch**		**Hydroxypropyltrimonium Hydrolyzed Wheat Starch**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%
Totals/Conc. Range	53	0.00001-2	11	0.19-0.65	8	NR
Duration of Use						
Leave-On	52	0.00001-2	3	0.24-0.65	NR	NR
Rinse off	1	0.02-0.1	8	0.19-0.43	8	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	13	0.02-1.3	NR	0.65	NR	NR
Incidental Ingestion	NR	0.75	NR	NR	NR	NR
Incidental Inhalation- Sprays	33	0.34-1	3	0.24*	NR	NR
Incidental Inhalation- Powders	29	0.1-2	NR	NR	NR	NR
Dermal Contact	50	0.00001-2	NR	0.65	8	NR
Deodorant (underarm)	1	0.34-2	NR	NR	NR	NR
Hair - Non-Coloring	2	1	11	0.19-0.43	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.02	NR	NR	NR	NR
Mucous Membrane	NR	0.75	NR	NR	8	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Hydroxypropyl Starch		**Hydroxypropyltrimonium Maltodextrin Crosspolymer**		**Inulin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	9	0.25-8.2	NR	0.00045	41	0.0005-3
Duration of Use						
Leave-On	8	0.25-8.2	NR	0.00045	14	0.0005-3
Rinse off	1	0.5-6	NR	NR	27	0.25
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	NR	NR	NR	1	0.0005
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	6	0.25-0.88	NR	NR	8	NR
Incidental Inhalation- Powders	NR	8.2**	NR	NR	9	0.0008**-2.5**
Dermal Contact	3	0.5-8.2	NR	0.00045	22	0.0005-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	6	0.25-1.4	NR	NR	18	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.5	NR	NR	4	0.25
Baby Products	NR	NR	NR	NR	1	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Laurdimonium Hydroxypropyl Hydrolyzed Wheat Starch		**Mannan**		**Methyl Cyclodextrin**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	6	0.017	19	0.01-0.25	20	4-5
Duration of Use						
Leave-On	NR	NR	16	0.01-0.25	20	4-5
Rinse off	6	0.017	3	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	11	NR	10	5
Incidental Inhalation- Powders	NR	NR	11	0.01**	NR	NR
Dermal Contact	6	0.017	17	0.01-0.25	19	4-5
Deodorant (underarm)	NR	NR	NR	NR	3	NR
Hair - Non-Coloring	NR	NR	2	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	6	0.017	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Pectin		**Polianthes Tuberosa Polysaccharide**		**Potassium Alginate**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	87	0.0001-9	2	0.001-0.1	37	1
Duration of Use						
Leave-On	33	0.001-0.05	2	0.001-1	1	1
Rinse off	54	0.0001-9	NR	NR	36	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	4	NR	NR	NR	NR	NR
Incidental Ingestion	NR	0.09-9	NR	NR	NR	NR
Incidental Inhalation- Sprays	25	0.05	2	0.001-0.1*	1	NR
Incidental Inhalation- Powders	17	NR	2	0.001-0.05**	1	NR
Dermal Contact	57	0.05	2	0.001-0.1	37	1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	30	0.0001-0.05	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	0.09-9	NR	NR	NR	NR
Baby Products	1	NR	NR	NR	NR	NR
	Potato Starch Modified		**Propylene Glycol Alginate**		**Pueraria Lobata Starch**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	61	0.3-1.3	16	0.00001-0.15	NR	3.6
Duration of Use						
Leave-On	40	0.3-1.3	16	0.00001-0.15	NR	NR
Rinse off	21	1.3	NR	NR	NR	3.6
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	2	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	9	1.3*	9	0.005-0.03*	NR	NR
Incidental Inhalation- Powders	5	0.3**	9	0.00001**-0.15**	NR	NR
Dermal Contact	11	0.3-1.3	15	0.00001-0.15	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	49	1.3	1	0.005-0.03	NR	NR
Hair-Coloring	1	NR	NR	NR	NR	3.6
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Sodium Carboxymethyl Starch		Sodium Carrageenan		Sodium Hydrolyzed Potato Starch Dodecenylsuccinate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	11	0.05-4.7	3	NR	2	NR
Duration of Use						
Leave-On	3	1.9-4.7	1	NR	NR	NR
Rinse off	8	0.05-2.5	2	NR	2	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	4.7	NR	NR	NR	NR
Incidental Ingestion	NR	NR	2	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	1	NR	NR	NR
Incidental Inhalation- Powders	NR	NR	1	NR	NR	NR
Dermal Contact	2	0.05-4.7	1	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	1.9	NR	NR	2	NR
Hair-Coloring	8	2.5	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Sodium Oxidized Starch Acetate/Succinate		**Sodium Starch Octenylsuccinate**		**Solanum Tuberosum (Potato Starch)**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	7	0.05	35	0.0001-0.26	4	3.4-3.6
Duration of Use						
Leave-On	1	0.05	22	0.0001-0.26	2	NR
Rinse off	5	NR	13	0.0023-0.026	2	3.4-3.6
Diluted for (bath) Use	1	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	1	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.026	NR	NR
Incidental Inhalation- Sprays	1	0.05	16	0.048-0.05	1	NR
Incidental Inhalation- Powders	1	NR	15	NR	1	NR
Dermal Contact	3	NR	21	0.048-0.26	3	NR
Deodorant (underarm)	NR	0.05	4	0.048	NR	NR
Hair - Non-Coloring	4	NR	12	0.0001-0.05	1	3.4
Hair-Coloring	NR	NR	1	NR	NR	3.6
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	1	0.026	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Starch Acetate		**Starch Diethylaminoethyl Ether**		**Starch Hydroxypropyltrimonium Chloride**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	11	2	1	NR	18	0.002-1.2
Duration of Use						
Leave-On	1	NR	NR	NR	1	0.02-1.2
Rinse off	10	2	1	NR	17	0.002-0.39
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	NR	NR	1	0.05-1.2*
Incidental Inhalation- Powders	NR	NR	NR	NR	NR	0.02**
Dermal Contact	NR	NR	1	NR	2	0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	11	2	NR	NR	16	0.002-1.2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	NR	2	NR
Baby Products	NR	NR	NR	NR	2	NR

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[16,17,18]

	Stearoyl Inulin		Sterculia Urens Gum		Tamarindus Indica Seed Gum	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	9	0.44-4.8	NR	0.2-0.7	NR	0.01-0.3
Duration of Use						
Leave-On	9	0.44-4.8	NR	0.2-0.7	NR	0.05-0.3
Rinse off	NR	NR	NR	NR	NR	0.01-0.25
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	7	0.44-4.8	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Powders	NR	NR	NR	NR	NR	0.3**
Dermal Contact	9	0.44-4.8	NR	0.7	NR	0.01-0.3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	0.25
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	0.2	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Tapioca Starch		**Triticum Vulgare (Wheat) Starch**			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Totals/Conc. Range	154	0.45-33	27	0.01-6		
Duration of Use						
Leave-On	124	0.5-33	17	0.01-6		
Rinse off	28	0.45-15	9	0.03-3.6		
Diluted for (bath) Use	2	0.86-32	1	NR		
Exposure Type						
Eye Area	13	NR	5	NR		
Incidental Ingestion	NR	NR	2	0.01		
Incidental Inhalation- Sprays	76	1-15*	1	NR		
Incidental Inhalation- Powders	84	3.7-33	9	NR		
Dermal Contact	115	0.5-33	24	0.03-6		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	18	0.45-15	1	NR		
Hair-Coloring	8	3.6	NR	3.6		
Nail	NR	NR	NR	NR		
Mucous Membrane	4	0.86-32	6	0.01		
Baby Products	1	NR	NR	NR		

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for (Bath)Use Product Uses.
*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
**It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
***Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 7. Acute Toxicity Studies on Polysaccharide Gums

Inhalation

Branched - Unmodified

Glucomannan (in konjac flour): An acute inhalation toxicity study on glucomannan was performed using male and female rats (number and strain not stated). An LC50 of > 0.0015 mg/l was reported.[151]

Oral

Branched - Unmodified

Glucomannan: Male and female mice (number and strain not stated). LD_{50} > 2,800 mg/kg body weight. No abnormalities with respect to the following: appearance, behavior, body weight changes, occult blood in the urine and feces, or macroscopic findings.[152]

Glucomannan (in konjac flour): Male and female rats (number and strain not stated. LD_{50} > 5,000 mg/kg body weight.[151]

Sterculia Urens Gum: Vehicle: corn oil. 5 fasted male Sprague-Dawley rats. LD_{50} > 10,000 mg/kg body weight. Transient depression, but no other toxic effects.[153]

Branched - Modified

Calcium Starch Isododecenylsuccinate: Material structurally similar to this gum tested. 5 male and 5 female Wistar albino rats. OECD Guideline 401 test protocol. Dosing followed by 14-day observation period. No abnormal systemic signs. LD_{50} > 5,000 mg/kg body weight.[63,64,154]

Corn Starch Modified: Vehicle: distilled water. 5 male and 5 female Wistar albino rats. Organisation for Economic Co-operation and Development (OECD) 401 protocol. 14-day observation period. Alopecia in one animal. LD_{50} > 2,000 mg/kg body weight.[66]

Dextrin Myristate: Rats (number and strain not stated). LD_{50} > 2,000 mg/kg body weight.[67]

Dextrin Palmitate: Rats (number and strain not stated). LD_{50} > 2,000 mg/kg body weight.[68,69]

Potato Starch Modified: 30% aqueous solution. Albino rats (5 males, 5 females). OECD 401 protocol. 14-day observation period. Soft stool (1 female); and no other signs. Body weight changes at necropsy normal. LD_{50} > 5,000 mg/kg body weight.[70,155]

Stearoyl Inulin: Rats (number and strain not stated). Protocol not stated. LD_{50} > 2,000 mg/kg body weight.[71,72]

Dermal

Branched - Unmodified

Glucomannan (in konjac flour): Male and female rabbits (number and strain not stated). Protocol not stated. LD_{50} > 2,000 mg/kg body weight.[151]

Branched - Modified

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs (4 weeks old). Maximization test. No mortality occurred and no clinical signs of systemic toxicity. Body weights and weight gains similar in treated and control groups.[156]

Corn Starch Modified: Corn starch modified (Amaze® [28-1890]) in distilled water (30% solids). 5 male and 5 female New Zealand White rabbits. OECD 402 protocol. 14-day observation period. Nine of 10 rabbits survived. LD_{50} > 2,000 mg/kg body weight.[66]

Dextrin Myristate: Rats (number and strain not stated). Occlusive dressing technique (details not included). LD_{50} > 2,000 mg/kg body weight.[67]

Dextrin Palmitate: Rats (number and strain not stated). Occlusive dressing technique (details not included). LD_{50} > 2,000 mg/kg body weight.[68,69]

Potato Starch Modified: 10 rats (strain not specified). OECD 402 test guideline. LD_{50} > 2,000 mg/kg body weight.[155]

Potato Starch Modified: 18.5% solids aqueous solution. 10 New Zealand White rabbits (5 males and 5 females). Semi-occlusive patch application. Dose per cm^2 was not stated. Very slight to slight erythema/edema at application sites (all animals); reactions had cleared by 72 h. Signs of local irritation may have been due to mechanical trauma. LD_{50} > 2,000 mg/kg body weight.[70]

Intravenous

Linear Polysaccharides and Their Salts

Carrageenan and Potassium Carrageenan: ι-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units) or potassium carrageenan (2 mg in phosphate-buffered saline [PBS]). Groups of 5 female MF1 mice. i.v. injection (lateral tail vein). Controls injected with PBS (0.3 ml). Animals killed at 1 h and 24 h post-injection, and tissues prepared for microscopic examination. Carrageenan persisted for at least 6 months in livers and kidneys. Within 24 h of i.v. injection, damage to liver Küpffer cells and changes in the microcirculation characteristic of disseminated intravascular coagulation (DIC) in the liver and kidney observed. No adverse effects in hepatocytes, but chronic renal damage observed. ι-carrageenan less toxic to liver and kidney, compared to the potassium carrageenan (less pure, compared to ι-carrageenan).[157]

Carrageenan and Potassium Carrageenan: ι-carrageenan or potassium carrageenan in saline (0.5 ml or 1 ml i.v. injection). Groups of 9 to 15 female CAF_1 mice (Balb/c x A/He). 7- or 14-day observation period. Treatment with either compound induced anemia, granulocytosis, and early profound thrombocytopenia. Treatment with ι-carrageenan caused an early lymphocytosis, and both compounds induced lymphopenia by 18 h post-treatment. Treatment with either compound was associated with an early moderate reduction in the number of nucleated cells and granulocyte/macrophage colony-forming cells per femur. Each compound induced splenomegaly, and ι-carrageenan-treated mice developed hypoplasia of the thymus by 18 h post-injection. Sustained increase in numbers of colony-forming cells in spleen after treatment with each compound.[158]

Table 7. Acute Toxicity Studies on Polysaccharide Gums

Intrapleural

Linear Polysaccharides and Their Salts

Carrageenan: Groups of 6 adult female Balb/c mice (6 to 7 weeks old). One group received single intrapleural injection of 0.1 ml sterile saline (0.9% NaCl) and λ-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units; 1% in solvent [not stated]), which induced pleurisy. Another group each received single intrapleural injection of 1% λ-carrageenan (0.1 ml) only. Animals were killed, and lung tissue samples obtained for microscopic examination at 4 h and 24 h post-injection. Dense inflammation with lobar lung pneumonia and thickened alveolar septum (with occasionally obliterated alveoli) were observed.[159]

Carrageenan: Injection of 2% λ-carrageenan in saline (200 mg/kg) into pleural cavity. Groups of 10 mice. Dosing caused pleurisy, characterized by marked accumulation of fluid and the migration of leukocytes to the site of inflammation in lung.[160]

Transbronchial

Linear Polysaccharides and Their Salts

Carrageenan: Transbronchial injection of 0.75% carrageenan in physiological saline. 27 male albino rabbits. Surviving animals were killed according to the following schedule: 2 at 24 h; 3 each at 3 days, 1 and 2 weeks, and 1 month; 5 at 2 months; and 8 at 4 months. Pneumonia, followed by emphysema in the insulted lung, observed. Of the 8 animals injected with carrageenan and killed at 4 months, 3 were deemed inappropriate for morphometry because of developing fibrosis, abscesses and/or emphysematous bullae in the lungs. Thus, the lungs (mild to severe erythema observed) of the remaining 5 animals injected with carrageenan and of the 5 control rabbits killed at 4 months were prepared for morphometric analysis. Scattered infiltration of polymorphonuclear leukocytes throughout the affected lobe, subsequently replaced by accumulation of carrageenan-laden macrophages; changes lasted for 1 to 2 months. Enlargement of alveoli and alveolar ducts observed at 2 weeks to 2 months post-injection, and pulmonary emphysema observed at 4 months. The lobes not injected with carrageenan had normal appearance throughout study.[161]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Oral - Non-Human

Linear Polysaccharides and Their Salts

Algin: 25% Sodium alginate (also known as algin) in diet. Mice (75 males and 75 females). Feeding with sodium alginate in the diet for 89 weeks. At week 87, half of the surviving male and female mice in each test group placed on control diet (containing 55% pregelatinized potato starch). During feeding period, dietary levels of test substances gradually increased until diets contained (by weight) 25% sodium alginate. All survivors killed during weeks 89 to 92. Sodium alginate caused increased water consumption, distinct caecal and colonic enlargement, and a slightly increased incidence of intratubular nephrosis. Sodium alginate was nephrotoxic, causing increased kidney weights, distension of the renal calyx and high incidence of dilated distal tubules.[162]

Carrageenan: 25,000 ppm or 50,000 ppm kappa carrageenan. Groups of Fischer 344 rats (20/sex/group). Feeding in diet for 90 days. Clinical signs limited to soft feces in high dose rats, and to a lesser extent, in low dose rats. No treatment-related effects on body weights, urinalysis, hematology or clinical chemistry parameters, or on organ weights or ophthalmic, macroscopic or microscopic findings. Gastrointestinal tract appeared normal in detailed histopathological evaluation. NOAEL = 50,000 ppm (mean calculated test material consumption of 3394 ± 706 mg/kg/day in males and 3867 ± 647 mg/kg/day in females).[113]

Carrageenan: kappa/lambda-carrageenan (from *C. crispus* or *G. mamillosa)* at concentrations of 0, 0.1, 5, 15, or 25%. Five male and five female mice of 2 unidentified strains. Lifetime dietary feeding had no adverse effect. Same test material and dietary concentrations. Five male and 5 female rats of 2 unidentified strains. Lifetime dietary feeding. Evidence of hepatic cirrhosis, only at the 25% concentration, with no effect on mortality.[62]

Carrageenan: Extracts of kappa-carrageenan (from *Hypnea musciformis* or *Irideae crispata)* at concentration of 1% or 5%. Groups of 15 male and female Sprague-Dawley rats. Feeding in diet for 1 year. Weight loss ($p = 0.05$) in all treatment groups, compared to control (alphacel) group. Livers of rats fed 1% concentration normal at gross and microscopic examination. Livers from rats given 5% kappa-carrageenan from *H. musciformis* normal at gross and microscopic examination, except for nodules in 2 of 12 livers. Gross examination of livers from rats fed 5% kappa-carrageenan (from *I. crispata*) showed decreased size, rough surface, and vascularization in 10/13 rats, probably treatment-related. Microscopically, these livers were normal, except for focal necrosis in 1 of 10 livers. No evidence of storage of carrageenan-like material (metachromatic) in liver cells of any of the treated rats, and no fibrillar material observed using electron microscopy. No changes observed in stools of rats receiving 1% of either carrageenan. Loose stools in female rats given 5% kappa-carrageenan from *I. crispata* and in males given either carrageenan at 5% concentrations. Blood found sporadically in stools, but frequency was not significant.[62]

Carrageenan: kappa/lambda-carrageenan. Groups of 19 male and 21 female rhesus monkeys. Feeding (gavage) with 0, 50, 200, or 500 mg/kg body weight (6 days/week for five years, and dietary feeding for an additional 2.5 years. Random distribution of loose stools, chronic intestinal disorders, poor appetite, and emaciation. Stool consistency decreased in dose-related trend over entire 7.5 years of the study; findings of fecal occult blood increased in similar fashion. Mean survival time similar in all groups; no gross or microscopic changes in tissues examined. Sporadic differences in body weight observed randomly. Females had significant body-weight depression (not dose-related) in last 2.5 years of study. No consistent, statistically significant changes in hematological or clinical chemical values, absolute organ weights, or organ-to-body weight ratios after 7.5 years of feeding. Cytochemical and ultrastructural observations revealed no storage of carrageenan-like material in livers, obtained at biopsy or in other organs obtained at necropsy; no dose-related gross or microscopic changes in other tissues.[62]

Inulin: 7.5% inulin. 20 Wistar rats of the Crl:(WI)BR strain (10 males, 10 females). Daily dietary feeding for 13 weeks. No remarkable microscopic or macroscopic findings.[163]

Branched - Unmodified

Arabinoxylan: Wheat bran extract (~ 80% arabinoxylan oligopeptides) at concentrations of 0.3%, 1.5%, and 7.5%. 3 groups of 20 Wistar rats of the Crl:(WI)BR strain (10 males/group, 10 females/group). Feeding resulted in average daily intakes of 0.2 g/kg (0.3% concentration), 0.9 g/kg (1.5%), and 4.4 g/kg (7.5%) for 13 weeks. No evidence of test substance-related adverse macroscopic or microscopic findings. At histopathological examination, minimal bilateral hypertrophy of renal cortical tubules in males and females, particularly in highest-dose group. Findings were not accompanied by degenerative changes or changes in kidney weight, and were considered non-toxic and suggestive of an adaptive response. No remarkable findings in control rats fed basal diet. NOAEL = 4.4 g/kg/day.[163]

Ghatti Gum: Ghatti gum concentrations of 0, 0.5, 1.5 and 5%. Groups of Sprague-Dawley rats (10 males/group, 10 females/group). Dietary feeding (in basal diet) for at least 90 days. Ghatti gum intake at 5% dietary level ranged from 3044 to 3825 mg/kg body weight/day. Feed consumption among treated and control groups was similar for males and females. 2 of 10 females in 5% ghatti gum group had a single colon ulcer, with associated acute inflammation. Ulcers were considered sporadic occurrences, possibly attributable to basal diet. NOAEL = 5% in diet; NOAELs for males and females estimated at 3044 and 3309 mg/kg/day, respectively.[164]

Ghatti Gum: 5% Ghatti gum. Groups of 20 female Sprague-Dawley rats. Dietary feeding for at least 90 days. Single colon ulcer, with associated acute inflammation, in 1 of 20 control females given basal diet. Colon ulcer considered sporadic, possibly attributable to basal diet. Statistically significant alterations in clinical chemistry were considered sporadic and unrelated to treatment. Feed consumption among treated and control groups similar for each sex. NOAEL = 5% in diet; NOAELs at 3670 and 3825 mg/kg/day for different control diets.[164]

Glucomannan: 10% konjac (plant consisting mostly of glucomannan). Groups of four male Sprague-Dawley rats were fed either 5% cellulose (control), 10% pectin, or 10% konjac for 28 days. After dosing period, rats were fasted for 24 h, fed 5 g/kg body weight brown rice, and killed 5 h later. No indication of toxicity.[165,166]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Branched - Unmodified

Glucomannan: 2.5%, 5%, or 10% refined konjac meal. Groups of 12 five-week-old Sprague-Dawley rats of each sex . Feeding with either a normal basal diet, a hypercholesterolaemic diet (control diet containing 1% cholesterol), or one of three test diets. Because refined konjac meal contains ~ 80% glucomannan, the highest concentration of glucomannan tested was ~ 8%. Four animals of each sex from each group killed after 4, 8, and 12 weeks of feeding. Histological and gross examination of livers from rats fed 1% cholesterol showed spreading fatty degeneration with focal necrosis and a nonspecific inflammation reaction. Similar changes observed in group receiving refined konjac meal at the end of 4 weeks, but the changes disappeared gradually with longer feeding times, and the morphology of the liver was similar to that in the normal control group at the end of 12 weeks. Changes were also observed at gross examination of the liver.[167]

Glucomannan: Basal diet in which 1% of the cornstarch replaced with refined glucomannan (i.e., 1% konjac meal). Groups of 15 Sprague-Dawley rats of each sex. Dietary feeding for 18 months. At the end of feeding period, the animals were killed and the brain, liver, aorta, kidney, spleen, and heart removed. At microscopic examination, the livers of treated rats contained smaller, more lightly stained nuclei and reduced bile-duct proliferation in the portal area. Endothelial cells in the aorta of treated animals were smaller and there was less thickening of the aortic wall. These changes were related to less senescence in the treated group than in the control group. No evidence of treatment-related pathological changes. NOAEL = 1% konjac meal, equivalent to an intake of 500 mg/kg body weight per day.[165]

Pectin and Solanum Tuberosum (Potato) Starch: Test diets containing 5% or 10% pectin-derived acidic oligosaccharides (pAOS). Two groups of F_1 rats (from outbred strain of Wistar rats (Crl:WI(WU); number not stated). Dietary feeding with test (±7 g/kg body weight/day) and control diets for 13 weeks. To keep the total level of added test substance equal in each diet, the low-dose diet (5% pAOS) was adjusted with 5% potato starch. One control group received the standard rodent diet supplemented with 10% potato starch, and the other control group received 10% short-chain FOS (scFOS) in the diet. No treatment- related clinical signs observed, and none of the rats died . Ophthalmoscopic examination did not reveal any treatment-related ocular changes. Neurobehavioral examination and motor activity assessment did not indicate any neurotoxic potential. No relevant differences in body weight, growth rate and feed intake. Macroscopic examination at necropsy did not reveal any adverse effects. Microscopic examination revealed treatment-related histopathological changes in the urinary bladder of animals of the 10% pAOS group. One male and one female of the 5% pAOS group and one male of the control group showed diffuse hyperplasia (very slight). In addition, two males and two females of the 5% pAOS group showed simple hyperplasia in a part of the urinary bladder lining ('focal hyperplasia'). No treatment-related hyperplasia of the transitional epithelium was observed in the kidney. Administration of pAOS at dietary levels up to 10% (equivalent to 7.1 g/kg body weight/day) did not reveal any relevant effects that could be attributed to the ingestion of acidic oligosaccharides.[168]

Starch Acetate: 55% Starch acetate (a chemically modified potato starch) in diet. Mice (75 males and 75 females per test substance). Feeding with starch acetate in the diet for 89 weeks. At week 87, half of the surviving male and female mice placed on control diet (containing 55% pregelatinized potato starch). During feeding period, dietary level of test substance gradually increased until diet contained (by weight) 55% starch acetate. All survivors killed during weeks 89 to 92. Starch acetate caused increased water consumption, distinct caecal and colonic enlargement, and a slightly increased incidence of intratubular nephrosis. Increased incidence of gastric trichobezoars. Concretions in renal pelvis with slight urinary changes, such as increased amounts of amorphous material in the urine and increased urinary calcium content, in the mice fed starch acetate not toxicologically significant. The incidence of intratubular calcinosis or concretions in the pelvic space was not reduced during the recovery period. Caecal and colonic enlargement and changes in urinalysis results were found to be reversible.[162]

Sterculia Urens Gum: 5 non-fasted male Sprague-Dawley rats. Animals intubated with 5 g/kg/day, daily for 5 days. No adverse effects.[153]

Sterculia Urens Gum: 7% (w/w) sterculia urens gum. Albino Wistar rats (rats housed 3 per cage; number tested not stated) Transmission electron microscopy used to study ultrastructure of jejunum, ileum, and cecum after dietary supplementation for 45 days [15 micrographs analyzed] for 45 days. No abnormalities in any of the organelles.[169]

Branched - Modified

Carboxymethyl Inulin: Carboxymethyl inulin (31.1% aqueous). Groups of five male and five female Wistar Crl rats. Doses of 0, 50, 150 and 1000 mg/kg/day (by gavage) for 4 weeks. In all dose groups, no treatment-related effects with respect to: body weight, feed consumption, mortality, hematology, clinical blood chemistry, organ weights or gross or microscopic pathology.[156]

Cyclic

Cyclodextrin: β-cyclodextrin (12,500, 25,000 and 50,000 ppm). Groups of 40 (20 males, 20 females/group) CrI:CD (SD) BR Sprague-Dawley rats. Feeding in the diet for 52 weeks. Control group fed basal diet. The liver and kidney were identified at histopathological examination as target organs for toxicity at concentrations of 50,000 ppm and 25,000 ppm, with the hepatic changes associated with increased plasma liver enzyme and decreased plasma triglyceride concentrations. The only finding for kidneys was a statistically significant ($p < 0.01$) increased incidence of minimal/trace amounts of pigment in the epithelium of the cortical tubules in female rats that received 25,000 ppm or 50,000 ppm β-cyclodextrin in the diet. The "non-toxic dietary inclusion level" of β-cyclodextrin was 12,500 ppm (equivalent to 654 or 864 mg/kg/day for males or females, respectively).[44]

Cyclodextrin: β-cyclodextrin (6200, 12,500 and 50,000 ppm). Groups of 8 (4males, 4 females/group) pure-bred Beagle dogs. Preceding test protocol in rat study used. No pathological evidence of systemic toxicity, although there were minor changes in urinalysis and biochemical parameters and a slightly higher incidence of liquid feces. These changes were considered to be of no toxicological importance. The "non-toxic dietary inclusion level" of β-cyclodextrin was 50,000 ppm (equivalent to 1,831 or 1,967 mg/kg/day for males or females, respectively).[44]

Cycodextrin: γ-cyclodextrin (5%, 10%, or 20%). Groups of 8 (4 males, 4 females) Beagle dogs. Feeding in the diet for 13 weeks. Control group fed basal diet. No treatment-related changes in behavior or appearance and no mortalities. No treatment-related differences with respect to ophthalmoscopic examinations, hematological parameters, clinochemical analyses of the plasma, and semiquantitative urine analyses. Relative ovary weights ignificantly increased in the 10% and 20% concentration groups, but this observation was probably a result of an unusually low ovarian weight in the controls. An increase in relative liver weights in males of the 10% and 20% concentration groups was also considered to lack toxicological relevance, because this observation was not associated with changes in plasma enzyme levels or with histopathological changes. No treatment-related abnormalitiesobserved at necropsy. At microscopic examination, no treatment-related effects in any of the various organs and tissues. Daily consumption of up to 20% γ-cyclodextrin in the diet (≈ 7.7 g/kg body weight in males and 8.3 g/kg body weight in females) did not cause toxicity.[170]

Table 8. Repeated Dose Toxicity Studies on Polysaccharide Gums

Oral - Human

Branched - Unmodified

Sterculia Urens Gum: 5 male volunteers (30 to 56 years old). Ingestion of sterculia urens gum (10.5 g in diet) daily for 21 days. No toxicity or significant effects on plasma biochemistry, hematological indices, or urinalysis parameters were noted.[171]

Branched – Modified

Propylene Glycol Alginate: 5 male volunteers. Following a 7-day control period, the men consumed an amount of propylene glycol alginate equal to 175 mg/kg body weight during the first 7 days of the test period. The amount consumed was increased to 200 mg/kg body weight for the remainder (i.e., 16 days) of the 23 days of dietary supplementation. No significant effect (statistical analysis not performed) on the following: hematological indices, plasma biochemistry parameters, urinalysis parameters, blood glucose levels, plasma insulin concentrations, and expired hydrogen concentrations. Ingestion of propylene glycol alginate caused no adverse dietary or physiological effects. The enzymatic indicators of toxicological effects remained unchanged.[53]

Dermal - Non-Human

Branched - Modified

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs. Maximization test. 5 female guinea pigs (vehicle controls). No mortalities or clinical signs of systemic toxicity were observed. Body weights and weight gains were considered similar when treated and control groups were compared.[156]

Potato Starch Modified: Rats (10 males, 10 females). Applied to skin under occlusive dressing for 28 days (2 g/kg body weight/day) according to OECD 410 test guideline. Sporadic gains and losses of body weight. Compared to the vehicle control group, statistically significant (p value not stated) decrease in body weight gain in treated females during weeks 1 and 4. Clinical biochemical test results indicated statistically significant (p value not stated) decrease in serum triglycerides and slight increase in serum calcium, sodium, and phosphorus in treated males, but not in females. However, none of the other test parameters supported these findings. Decreased organ weights and differences in hematologic test parameters, but these findings were within historical control ranges for this strain of rat. Signs of systemic toxicity not observed at gross examination of treated animals. NOAEL $\geq$ 2,000 mg/kg body weight/day.[155]

Potato Starch Modified: 10% solids aqueous solution. New Zealand albino rabbits (10 males and 10 females) tested; 20 rabbits (controls). Applied to skin under a non-occlusive patch (dose = 2 g/kg bodyweight). Area of application and concentration/dose per cm^2 were not stated. Distilled water, under a non-occlusive patch, applied to controls. Daily evaluations for signs of systemic toxicity, mortality, or morbidity occurred daily; necropsy on day 28. The following considered within normal parameters: body weights, food consumption, gross pathology, and histopathology. Minor differences in organ weight and clinical chemistry changes observed, but considered irrelevant. No significant toxic effects in rabbits.[70]

Table 9. Reproductive and Developmental Toxicity Studies on Polysaccharide Gums

Ingredient	Animals	Procedure	Results
Linear polysaccharides and their salts			
Ammonium Alginate	Fertile eggs from Single-comb White Leghorn chickens	Single injection of ammonium alginate (in corn oil, ≤ 100 µl) into groups of 20 or more eggs; doses up to 0.5 mg/egg)	Injection did not result in significant numbers of abnormal birds.[172]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 22 to 27 pregnant CD-1 mice	Oral doses of 10, 45, 470, or 900 mg/kg body weight/day on days 6-15 of gestation	Number of fetal resorptions and/or fetal deaths increased. Dose-dependent decrease in number of live pups and pup weight. Skeletal maturation was retarded. A no-observed-effect level was not reported.[62]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 21 to 27 pregnant rats (strain not stated)	Oral doses of 40, 100, 240, or 600 mg/kg body weight/day on days 6-15 of gestation	Increased fetal resorptions, with no decrease in the number of live pups. Dose-dependent increase in incidence of missing skeletal sternebrae.[62]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 21 to 24 pregnant rats (strain not stated)	Feeding with 1% or 5% in diet on days 6-16 of gestation	Neither salt was teratogenic.[62]
kappa/lambda-Carrageenan (from *C. crispus*) calcium salt	40 male and 40 female Osborne-Mendel rats	Three-generation study. Feeding with 0.5, 1, 2.5, or 5% in diet 12 weeks prior to mating	In F_{2c} and F_{3c} litters, no specific external, skeletal, or soft-tissue anomaly could be correlated with dosage.[62]
Calcium Carrageenan	Sprague-Dawley rats (number not stated)	Feeding with 0.45, 0.9, or 1.8% in diet prior to mating, during breeding, and throughout gestation, lactation, and post-weaning	No differences between test and negative control groups regarding length of gestation, litter size, or sex distribution.[62,173]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 23 to 30 pregnant hamsters (strain not stated)	Oral doses of 40, 100, 240, or 600 mg/kg body weight on days 6-10 of gestation	No significant effect on nidation or on maternal or fetal survival. Some evidence of dose-dependent delay in skeletal maturation.[62]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 21 to 26 pregnant hamsters	Feeding with 1% or 5% in diet on days 6-11of gestation	Neither salt was teratogenic.[62]
Carrageenan (sodium or calcium salt) or degraded Carrageenan	21 pregnant female Syrian hamsters per dose of carrageenan; 8 pregnant females per dose of degraded carrageenan	Oral doses of 10, 40, 100, or 200 mg/kg body weight on days 6-10 of gestation	No dose-related teratogenic or fetotoxic effects.[62]
kappa/lambda-Carrageenan (from *C. crispus*) sodium or calcium salt	Groups of 12 to 13 pregnant female rabbits (strain not stated)	Oral doses of 40, 100, 240, or 600 mg/kg body weight on days 6-18 of gestation	The numbers of skeletal or soft tissue abnormalities did not differ from those of controls.[62]

Table 9. Reproductive and Developmental Toxicity Studies on Polysaccharide Gums

Ingredient	Animals	Procedure	Results
Branched - unmodified			
Glucomannan (from *Amorphophallus oncophyllus*)	6 pregnant British short-hair domestic cats	Concentration of 2% in the diet during gestation. Actual intake during week prior to parturition ranged from 0.98 to 3.08 mg/kg body weight per day	All pregnant females completed lactation and a normal gestation period. No adverse effect on mean birth weight or mean litter size.[105]
Pectin-derived acidic oligosaccharides (pAOS)	Groups of 24 (16 females, 8 males per group) parental (F_0) Wistar rats of the crl:WI(WU) outbred strain	Concentrations of 5% or 10% in the diet prior to mating, and throughout mating, gestation, and lactation periods	No effect on estral cycle length and normality. No relevant changes in sperm motility, sperm count, or morphologic changes. No effects on reproductive indices, including litter size, pup viability, and difference in sex ratio.[168]
Sterculia Urens Gum (suspension in anhydrous corn oil)	Groups of 87 to 90 pregnant female Dutch-belted rabbits	Oral doses up to 635 mg/kg/day for 13 consecutive days (gestation daysa 8-18).	Not teratogenic.[174]
Sterculia Urens Gum (suspension in anhydrous corn oil)	Groups of 87 to 90 pregnant female albino CD-1 mice	Oral doses up to 170 mg/kg body weight on days 6 through 15 of gestation	No clearly discernible effect on nidation or on maternal or fetal survival. No difference in soft or skeletal tissue abnormalities between test animals and sham-treated controls. Not teratogenic.[174]
Sterculia Urens Gum (suspension in anhydrous corn oil)	28 pregnant female albino CD-1 mice	Oral dose of 800 mg/kg body weight on days 6 through 15 of gestation	Significant number of maternal deaths (9 of 28). Surving dams were completely normal and delivered normal fetuses, with no effect on rate of nidation, or live pup survival *in utero*. Not teratogenic.[174]
Sterculia Urens Gum (suspension in anhydrous corn oil)	Groups of 87 to 89 pregnant female Wistar-derived albino rats	Oral doses up to 900 mg/kg body weight on days 6 through 15 of gestation	Dams were completely normal and delivered normal fetuses, with no effect on rate of nidation, or live pup survival *in utero*. Not teratogenic.[174]
Branched - modified (i.e., added sidechains are larger than acetate)			
Propylene Glycol Alginate	Fertile eggs from Single-comb White Leghorn chickens	Single injection of propylene glycol alginate (in water, ≤ 100 µl) into groups of 20 or more eggs; doses up to 1 mg/egg)	Injection did not result in significant numbers of abnormal birds.[172]
Cyclic			
γ-Cyclodextrin	Groups of 25 pregnant female Wistar Crl (WI)WU BR rats	Concentrations of 1.5%, 5%, 10%, and 20% in the diet on gestation days 0 to 21.	No fetotoxic embryotoxic, or teratogenic effects. NOAEC ≈ 20% in diet (≈ 11 g/kg body weight per day).[175]
α-Cyclodextrin	Groups of 25 pregnant female Wistar Crl (WI)WU BR rats	Concentrations of 1.5%, 5%, 10%, and 20% in the diet on gestation days 0 to 21.	No fetotoxic embryotoxic, or teratogenic effects. NOAEC = 20% in diet (≈ 13 g/kg body weight per day).[176]
γ-Cyclodextrin	Groups of 16 pregnant female New Zealand White rabbits	Concentrations of 5%, 10%, or 20% in the diet on gestation days 0 to 29.	No effect on reproductive performance, and not fetotoxic, embryotoxic, or teratogenic.[177]
α-Cyclodextrin	Groups of 16 pregnant female New Zealand White rabbits	Concentrations of 5%, 10%, or 20% in the diet on gestation days 0 to 29.	No effect on reproductive performance, and not fetotoxic, embryotoxic, or teratogenic.[178]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
		Bacterial Assays		
Linear polysaccharides and their salts				
Carrageenan (natural grade [PNG]) or refined Carrageenan	*Salmonella typhimurium* strain TA100	Ames test	Concentrations up to 100 mg/ml (PNG) and up to 25 mg/ml (refined) without metabolic activation	Not genotoxic.[179]
kappa/lambda-Carrageenan (from *C. crispus*)	*Salmonella typhimurium* strains TA1535, TA1537, and TA1538. *Saccharomyces cerevisiae* strain D4.	Ames test	Test concentrations not stated	Not genotoxic.[62]
PNG or Refined Carrageenan	Mice (strain not stated). *Salmonella typhimurium* strain His G 46	Host-mediated assay	Mice received PNG at oral doses up to 2,500 mg/kg body weight or refined carrageenan at a dose of 700 mg/kg body weight. Bacterial strain tested without metabolic activation	Mutation frequency in injected indicator organism not affected by dosing with carrageenan. Neither PNG nor refined carrageenan was genotoxic.[179]
PNG or Refined Carrageenan	*Bacillus subtilis*	Rec assay for DNA -damaging potential	PNG and refined carrageenan tested at concentrations up to 100 mg/ml and 28 mg/ml, respectively	Neither PNG nor refined carrageenan was genotoxic.[179]
Linear - modified				
Hydrolyzed furcellaran trade name mixture (0.6% hydrolyzed furcellaran, 0.05% concentrate of sea water, 1% phenoxyethanol, and 98.35% water)	*Salmonella typhimurium* strains TA97a, TA98, TA100, and TA 1535; *E. coli* strain WP2uvrA pKM101	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[73]
Branched - unmodified				
Arabinoxylan	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *Escherichia coli* (*E. coli*) strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[163]
Ghatti gum	*Salmonella typhimurium* strains TA97a, TA98, TA100, and TA 1535; *E. coli* strain WP2uvrA pKM101	Ames test	6 mg/plate, with and without metabolic activation	Not genotoxic.[180]
Glucomannan (in konjac flour)	*Salmonella typhimurium* (5 strains, not stated)	Ames test	With and without metabolic activation (doses not stated)	Not genotoxic.[151]
Pectin-derived acidic oligosaccharides (mixture of linear oligomers and small polymers of galacturonic acid) (for genotoxicity evaluation of Pectin)	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *E. coli* strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[168]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
Sterculia urens gum	Mice (strain not stated). *Salmonella typhimurium* strains G46 and TA1530 and *Saccharomyces cerevisiae* strain D3	Host-mediated assay	3 groups of mice intubated with 5,000 mg/kg, 2500 mg/kg, and 30 mg/kg, respectively, followed by injection with tester strains	Not genotoxic in plated tester strains.[153]
Branched - modified (i.e., added sidechains are larger than acetate)				
Carboxymethyl inulin	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *Escherichia coli* (*E. coli*) strain WP2*uvr*A	Ames test	Same as above	Not genotoxic.[156]
Calcium Starch Isododecenylsuccinate	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *E. coli* strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[63]
Corn starch modified (Amaze® [28-1890])	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, or TA 1537; *E. coli* strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[66]
Dextrin myristate (Rheopearl MKL2)	*Salmonella typhimurium* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[67]
Dextrin palmitate (Rheopearl KL2 and Rheopearl TL2)	*Salmonella typhimurium* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[68,69]
Dextrin isostearate (Unifilma HVY)	*Salmonella typhimurium* and *E. coli* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[127]
Sodium Hydrolyzed Potato Starch Dodecenylsuccinate trade name material (PS-111 hydrophobically modified starch powder)	*Salmonella typhimurium* strains TA98, TA 100, TA 1535, and TA 1537; *E. coli* strain WP2*uvr*A	Ames test	up to 5,000 µg/plate, with and without metabolic activation	Not genotoxic.[181]
Stearoyl inulin (Rheopearl ISK2 and Rheopedarl ISL2)	*Salmonella typhimurium* and *E. coli* (strains not stated)	Ames test	Doses and presence/absence of activation not stated	Not genotoxic.[71,72]
	Mammalian Assays			
Linear polysaccharides and their salts				
PNG or Refined Carrageenan	Bone marrow cells from Swiss mice	Micronucleus test	Mice received PNG at doses up to 2,500 mg/kg body weight or refined carrageenan at a dose of 700 mg/kg body weight	Neither PNG nor refined carrageenan was genotoxic.[179]
Branched - modified (i.e., added sidechains are larger than acetate)				
Carboxymethyl inulin	Chinese hamster ovary (CHO-WBL) cells	Chromosome aberrations assay	up to 5,060 µg/ml, with and without metabolic activation	No significant increases in chromosomal aberrations, polyploidy, and endoreduplication.[156]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
Potato starch modified	Mice (strain not stated)	Mouse lymphoma assay. OECD 476 test guideline.	Not stated	Not genotoxic.[155]
Branched - unmodified				
Ghatti gum	Chinese hamster ovary (CHO-WBL) cells	Chromosome aberrations assay	up to 6,000 µg/ml, with and without metabolic activation	Not genotoxic.[180]
Ghatti gum	B6C3F1 mice	Combined micronucleus/Comet assay	Mice dosed orally with up to 2,000 mg/kg/day for 4 days	No effect on micronucleated reticulocyte frequency in peripheral blood. No DNA damage in blood leukocytes or liver.[180]
Glucomannan	L5178Y $tk^{+/-}$ mouse lymphoma cells	Mouse lymphoma assay	Up to 1,000 µg/ml and up to 997 µg/ml with and without metabolic activation, respectively	Not genotoxic.[165]
Glucomannan	CD-1 (ICR) mouse bone marrow cells	Micronucleus test	Mice dosed orally with 5,000 mg/kg body weight	Not genotoxic.[165]
Pectin-derived acidic oligosaccharides (for genotoxicity evaluation of Pectin)	L5178Y mouse lymphoma cells	Mouse lymphoma assay	up to 4370 µg/ml, with and without metabolic activation	Equivocal results.[168]
Pectin-derived acidic oligosaccharides (for genotoxicity evaluation of Pectin)	Chinese hamster ovary cells	Chromosome aberrations assay	up to 4,220 µg/ml, with and without metabolic activation	Clastogenic. Dose-related genotoxicity at ≥ 2,530 µg/ml without metabolic activation. Positive results only at highly cytotoxic concentrations.[168]
Pectin-derived acidic oligosaccharides (for genotoxicity evaluation of Pectin)	F_1 rats (from outbred strain of Wistar rats (Crl:WI(WU))	Micronucleus test	Oral administration of diet containing pectin-derived acidic oligosac-charides (pAOS) (±7 g/kg body weight/day) for 13 weeks.	Compared to control, no increase in mean number of micronuclei in rat erythrocytes.[168]
Sterculia urens gum	Sprague-Dawley rats	Cytogenetic assay	Groups of rats intubated with 5,000 mg/kg, 2500 mg/kg, and 30 mg/kg, respectively. Metapase chromo-somes from rat bone marrow analyzed.	No adverse effect on rat bone marrow chromosomes.[153]
Sterculia urens gum	WI-38 human embryonic lung cells	Cytogenetic assay	up to 1,000 µg/ml	No effect on anaphase chromosomes.[153]

Table 10. Genotoxicity of Polysaccharide Gums

Ingredient/Similar Chemical	Strain/cell type	Assay	Dose	Results
Sterculia urens gum	Sprague-Dawley rats	Dominant lethal gene test	Groups of rats intubated with 5,000 mg/kg, 2500 mg/kg, and 30 mg/kg, respectively	No consistent responses suggestive of genotoxicity.[153]
Wheat bran extract (contains ~ 80% arabinoxylan) (for genotoxicity evaluation of Arabinoxylan)	Chinese hamster lung fibroblasts	Chromosome aberrations assay	up to 5,000 µg/ml, with and without metabolic activation	Not genotoxic or clastogenic.[163]

Table 11. Carcinogenicity of Polysaccharide Gums

Oral

Linear Polysaccharides and Their Salts

Agar: 25,000 ppm or 50,000 ppm agar. Groups of 50 F344 rats and 50 B6C3F1 mice of each sex. Feeding in diet for 103 weeks. Untreated mice and rats served as controls. No clinical signs of toxicity. Increased incidence (not statistically significant) of adrenal cortical adenomas in female rats fed 50,000 ppm agar. Statistically significant increase ($p = 0.007$) in incidence of hepatocellular adenomas in male mice fed 50,000 ppm agar. Incidence of total liver tumors did not differ statistically among control, 25,000 ppm, and 50,000 ppm groups. Increased incidences of adrenal cortical adenomas and liver tumors not considered test substance-related. Agar was non-carcinogenic.[182]

Algin: Up to 25% sodium alginate. Mice (75 males; 75 females). Feeding in diet for 89 weeks (dietary levels gradually increased to maximum concentration of 25%). At week 87, half of surviving male and female mice placed on control diet containing 55% pregelatinized potato starch. Algin was non-carcinogenic.[162]

Carrageenan: 5% ι-carrageenan. Groups of 16 Fischer 344 rats. Feeding for up to 91 days. Proliferating cell nuclear antigen (PCNA) served as a marker of cell proliferation. Immunohistochemical staining for PCNA-positive cells in distal colon performed. Intact layer of columnar epithelial cells lining the mucosa. PCNA-positive cells not found at the luminal surface.[183]

Carrageenan: 0.5%, 1.5%, and 5% ι-carrageenan. Groups of four F344 rats. Feeding in diet for 28 days. Control diet fed to additional group. Thymidine kinase enzymatic activity and PCNA served as markers of cell proliferation. No increase in PCNA-positive cells. Increased thymidine kinase levels observed only in the 5% ι-carrageenan dietary group, corresponding to a 4-fold increase in colonic cell proliferation.[183]

Carrageenan: ι-carrageenan. F344 rats. Feeding in diet for 64 days, followed by 28-day recovery period. During recovery period, proliferating cells returned to level similar to those in rats fed control diet. Results suggest that the quantitative changes in cell proliferation were probably adaptive, and would not contribute to an increased risk of colon neoplasia.[183]

Carrageenan: 0.1, 5, 15, and 25% carrageenan. Groups of 5 male and 5 female mice of two strains. Feeding in the diet for lifespan. Additional group fed control diet. Non-carcinogenic.[184]

Carrageenan: 1, 5, 15, and 25% carrageenan. Groups of 5 male and 5 female mice of two strains. Feeding in diet for up to 24 months. Additional group fed control diet. Hepatic sclerosis at 25% concentration. Non-carcinogenic.[184]

Carrageenan: 0.5, 2.5, and 5% κ-carrageenan. MRC outbred rats and randomly bred Syrian golden hamsters from the Eppley colony (30 males and 30 females per species). Average daily intake of carrageenan estimated to be 4022 mg/kg/day (rats) and 3719 mg/kg/day (hamsters) for lifetime. 100 females and 100 males per control dietary group. No increased mortality, clinical signs of toxicity, or tumor formation.[185]

Carrageenan: Groups of female Fischer 344 rats. Co-carcinogenicity of carrageenan in presence of azoxymethane (AOM) or N- nitrosomethylurea (NMU) evaluated. Treatment groups: control diet (15 rats); 15% carrageenan in control diet (15 rats); 15% carrageenan in control diet + 10 weekly s.c. injections of 8 mg/kg bw (AOM) (30 rats); 2 mg NMU (intrarectal instillations) twice weekly for 3 weeks (30 rats); AOM s.c. alone (30 rats), and NMU i.r. alone (30 rats). Animals killed 40 weeks after the initial injection of AOM or 30 weeks after the initial injection of NMU. Carrageenan enhanced the incidence of colon tumors in AOM- and NMU-treated rats ($p < 0.01$): AOM + carrageenan (26/26, 100%) versus AOM alone (17/30, 57%); NMU + carrageenan (29/29, 100%) versus NMU alone (20/29, 69%); control diet (0/15); and 15% carrageenan in control diet (1/15, 7%).[186]

Carrageenan: Carrageenan (0.25%, 2.5%, or 10%). Aberrant crypt focus (ACF) assay for assessment of initiation and promotion of cancer. 24 rats randomly allocated to 3 groups in initiation experiment: 9 rats given carrageenan (as a 10% jelly [24.7 g/kg body weight per day] for 8 days) in initiation experiment, 9 rats were given pure water (negative controls), and 6 rats received AOM injection (5 mg/kg i.p., positive controls). Promotion experiment: 30 rats received single azoxymethane injection (20 mg/kg i.p.) to initiate colon cancer. Seven days later, the rats were randomly allocated to the following 3 groups of 10: control group (received distilled water), group 1 (received water supplemented with 0.25% carrageenan [liquid] for 100 days), and group 2 (received water supplemented with 2.5% carrageenan [solid gel] for 100 days). In initiation experiment, no ACF found in negative controls or in rats fed carrageenan. In promotion experiment, administration of liquid 0.25% carrageenan reduced number of ACF/rat, and did not change the ACF multiplicity when compared to controls. In contrast, administration of carrageenan jelly (2.5%) for 100 days promoted growth of aberrant crypt foci ($P = 0.016$). Thus, carrageenan jelly did not initiate colon tumors; however, long-term administration of carrageenan jelly enhanced intestinal tumor growth in rats.[187]

Carrageenan: κ-carrageenan (0.5%, 2.5%, or 10%). 54 conventional female Fischer 344 (F-344) rats (harboring a normal rat flora) and 52 germ-free female F-344 rats maintained in isolators. Intiating effect of κ-carrageenan studied by comparing number of ACF in the colon of rats given pure water or κ-carrageenan (as a 10% gel in tap water) for 8 days. Promoting effect of κ-carrageenan studied by comparing multiplicity of ACF (crypts/ACF) in rats that received pure water, liquid κ-carrageenan (0.25% in water), or κ-carrageenan gel (2.5% in water) during 100 days, beginning 7 days after a single AOM injection. κ-carrageenan (10%) did not initiate ACF. In conventional rats, the 2.5% κ-carrageenan gel promoted the growth of ACF as follows: 2.98 ± 0.29 and 3.44 ± 0.48 crypts/AF in control and treated rats, respectively ($p < 0.02$). 0.25% κ-carrageenan gel did not promote ACF.[188]

Carrageenan: 2.5% κ-carrageenan. 8 HFA ratsgiven κ-carrageenan and an additional 8 given water; 4 rats received AOM injection. No promotion effect: $2.81 \pm 0.1$and 2.78 ± 0.38 crypts/ACF in control and treated rats, respectively ($p = 0.80$).[188]

Carrageenan: Carrageenan (1.25%, 2.5%, or 5.0%). Groups of 18 rats or 6 rats. Groups of 18 initiated with DMH, followed by feeding with 1.25%, 2.5%, or 5% in diet for 32 weeks. Groups of 6 received saline and were then treated with 0% and 5.0% carrageenan. Detailed histopathological examination did not demonstrate any carrageenan-induced enhancement of carcinogenesis. Thus, carrageenan did not possess any promoting activity for colorectal carcinogenesis at any dietary concentration.[189]

Carrageenan: In a monograph published by the International Agency for Research on Cancer (IARC) in 1983, IARC concluded that the available data do not provide evidence that native (undegraded) carrageenan is carcinogenic to experimental animals, and, in the absence of epidemiological data, that no evaluation of the carcinogenicity of native carrageenan in humans could be made.[92]

Inulin: Inulin-enriched diet (10% w/w). Group of 10 to 15 Min/+ mice (has heterozygous mutation in the Apc gene, resulting in the truncated Apc protein and development of numerous intestinal adenomas.[190,191]) fed from the age of 5 weeks to 8 or 15 weeks. Additional group fed control diet. Results indicated that dietary inulin can activate mucosal β-catenin signaling, which, in the presence of Apc mutation, induces adenoma growth.[192]

Table 11. Carcinogenicity of Polysaccharide Gums

Inulin: 3 Groups of 10 Sprague-Dawley rats, consisting of control group, group treated s.c.with DMH, and group given DMH and inulin in the diet. When compared to the DMH only group, inulin in diet decreased the expression of IL-2, TNFα, and IL-10 and also decreased the numbers of COX-2- and NFκB-positive cells in the *tunica mucosae* and *tela submucosae* of the colon. Thus, dietary intake of inulin prevented preneoplastic changes and inflammation that promote colon cancer development.[193]

Inulin: Inulin (15 g) in basal diet (85 g). Groups of 20 to 22 Balb/c mice. Feeding for 7 days prior to tumor (TLT and EMT6 tumor cell lines) transplantation. Growth of both tumor cell lines significantly inhibited by supplementing the diet with inulin.[194]

Branched - Unmodified

Arabinoxylan: Groups of 15 rats treated (s.c.) with the colon carcinogen DMH and fed either a control diet or a diet containing arabinoxylan-oligosaccharides (4.8% w/w). Two types of preneoplastic lesions (ACF and mucin-depleted foci [MDF]) detected in colon. Thirteen weeks after DMH treatment, MDF counts significantly lower in entire colon of arabinoxylan-oligosaccharides fed rats (MDF/colon were 7.5 ± 0.6 and 5.5 ± 0.6, in control and arabinoxylan-oligosaccharides groups, respectively; means ± SE [p = 0.05]). Arabinoxylan-oligosaccharides fed rats had significantly fewer ACF in the distal part of the colon than control rats (ACF/distal colon were 135.5 ± 15 and 84.4 ± 11, in control and arabinoxylan-oligosaccharides groups, respectively; means ± SE [p = 0.05]). Thus, dietary intake of arabinoxylan-oligosaccharides by rats reduced the occurrence of two types of preneoplastic lesions, suggesting a chemopreventive effect on colon carcinogenesis.[195]

Arabinoxylan: Groups of 10 ICR male mice. mice were injected i.p. with mouse sarcoma S180 cells, human chronic myelogenous K562 cells, or human leukemia HL-60 cells, and dosed orally with arabinoxylan (100, 200, or 400 mg/kg body weight). All three doses conferred significant inhibitory activity against solid tumor formation in S180 tumor-bearing mice, with inhibitory ratios of 14.34%, 31.37%, and 56.73%, respectively. Arabinoxylan did not have any effect on growth of K562 or HL-60 cells in *vitro*.[196]

Glucomannan: 10% Glucomannan. Groups of 30 C3H/He male mice fed either a powdered commercial diet (control group) or the same diet containing 10% glucomannan. At age 1 year, slight decrease in the number of animals with liver tumors in glucomannan group (control: 63% of 24 mice; glucomannan: 48% of 23 mice) and a statistically significant decrease ($p<0.05$) in the mean number of tumor nodules per mouse in the glucomannan group (control: 1.1; konjac mannan: 0.5). Thus, spontaneous liver tumors in C3H/He mice were inhibited by maintaining the mice on a diet containing 10% glucomannan.[197]

Glucomannan: 5% Glucomannan. Fisher 344 rats (20/group) fed either a commercial diet or similar diet containing 5%glucomannan for 13 weeks. Animals also injected i.p. with DMH weekly. Incidence of DMH-induced colon tumors significantly lower in glucomannan-fed group (39%) when compared to control group (75%). Number of colon adenocarcinomas per rat also significantly lower in glucomannan-fed rats (0.22) than in control rats (0.75). No significant effect on the incidence of tumors of the small intestine, all of which were adenocarcinoma (control: 45%; konjac mannan: 33%).[198]

Pectin: 2.5% Pectin. Male Wistar rats (groups of 4). Feeding in diet for 14 days. Statistically significant increase in the villus height and crypt depth, indicating that feeding with pectin caused mucosal hyperplasia in small intestine.[199]

Starch Acetate: 55% Starch Acetate. Mice (75 males ,75 females) fed starch acetate in diet for 89 weeks. Dietary levels of the test substance gradually increased until diet contained (by weight) 55% starch acetate. At week 87, half ofsurviving male and female mice placed on control diet (containing 55% pregelatinized potato starch). No evidence of carcinogenicity.[162]

Cyclic

Cyclodextrin: 2.5% or 5% β-cyclodextrin. 2 groups of Fischer 344 (F344) rats (50 males and 50 females/group) fed 2.5%and 5% β-cyclodextrin, respectively, for 104 weeks. Control diet fed to additional group. All neoplastic lesions observed were histologically similar to those known to occur spontaneously in this strain of rat; no statistically significant increase in the incidence of any tumor found for either sex in treated groups. It was concluded that the high dose, which was approximately 340-400 times higher than the current daily human intake from ingestion as a food additive and from pharmaceutical use, did not have carcinogenic potential in F344 rats.[111]

Cyclodextrin: β-cyclodextrin . 5 groups of 50 Fischer 344 rats and 52 CD-1 outbred mice of each sex. 4 groups per strain received β-cyclodextrin in the diet at doses of 25, 75, 225, and 675 mg/kg per day, respectively for 93 weeks (males) and between weeks 129 and 130 (females). Fifth group received control diet. No treatment-related carcinogenic effects.[200]

Degraded Polysaccharide Gum

Degraded Carrageenan: Degraded carrageenan (from *Eucheuma spinosum*; degraded by acid hydrolysis). 4 groups of 30 malesand 30 female rats 8fed a diet containing 0 (control), 1 %, 5 %, or 10% degraded carrageenan. Colorectal squamous metaplasia in rats fed degraded carrageenan at concentrations of 10% (59 of 60 rats) and 5% (53 of 60 rats) in the diet. Additionally, colorectal tumors (12 squamous-cell carcinomas, 8 adenocarcinomas and 3 adenomas) found in 19 of 60 rats fed 10% degraded carrageenan in the diet, and these tumors (3 squamous-cell carcinomas, 1 adenocarcinoma and 8 adenomas) also found in 12 of 60 rats fed 5% degraded carrageenan. Neither squamous metaplasia nor colorectal tumors observed in the low-dose group or in controls.[92]

Degraded Carrageenan: Degraded carrageenan (5% in drinking water) administered to 20 male and 20 female rats for 15 months. Colorectal squamous metaplasia observed in all rats after 15 months. Colorectal tumors observed in 11 of 40 treated rats (4 squamous-cell carcinomas, 4 adenocarcinomas, 3 adenomas and 1 myosarcoma); these tumors not observed in control rats (15 males, 15 females).[201]

Degraded Carrageenan: Degraded carrageenan (1 or 5 g/kg body weight) administered by intragastric intubation (frequency of administration not specified) to groups of 15 male and 15 female rats for 15 months. Control rats (15 males, 15 females) dosed intragastrically with distilled water. Squamous colorectal metaplasia observed in all 29 rats in high-dose group and in 11 of 30 rats in low-dose group. Colorectal tumors were observed only in the high-dose group (8 of 29 rats; 5 adenocarcinomas and 4 adenomas).[202]

Degraded Carrageenan 10% degraded carrageenan (in diet that also contained 30% sulfate) fed to Fischer 344 rats. Three groups fed this diet for 2 months (39 rats, group 1), 6 months (42 rats, group 2), and 9 months (42 rats, group 3). Control group (46 rats) received the same diet without carrageenan, and the same was true for all other groups after cessation of feeding. 100% incidence of colorectal squamous metaplasia observed in all treatment groups. Tumors also observed in 5 of 39 rats in group 1 (3 squamous-cell carcinomas, 1 adenoma, 1 anaplastic carcinoma), 8 of 42 rats in group 2 (6 squamous-cell carcinomas, 1 adenocarcinoma, 1 adenoma) and in 17 of 42 rats in group 3 (14 squamous-cell carcinomas, 4 adenocarcinomas). Colorectal changes not observed in control rats.[92,203]

Table12. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Skin Irritation and Sensitization - Non-Human

Linear Polysaccharides and Their Salts

Algin: 2% algin. Rabbits (number not stated). 3 primary skin irritation experiments. Occlusive patches applied to the skin. Mean skin irritation score of < 0.5 = non-irritating; 0.5 to 2.0 = slightly irritating. Primary irritation index (PII) values calculated. PII of < 0.5 deemed satisfactory, but PII no greater than 1 is also acceptable. PII values of 0, 0, and 0.08 were reported in the 3 experiments, respectively.[61]

Algin: 2% algin. Rabbits (3 per experiment). Test substance (2 ml) applied to flanks 5 days per week for 6 weeks. Mean maximum irritation index (MMII) values calculated. Macroscopic and histological examinations of test sites performed. MMII values of 0.67, 0, and 0.67 were reported in 3 experiments, respectively. Daily application of test substance did not induce a severe reaction at either macroscopic or histological examination.[61]

Carrageenan: Food grade iota-carrageenan (one subtype of carrageenan with a specific number and position of sulfate groups on the repeating galactose units). Guinea pigs (number not stated). Study details not included. No skin sensitization.[62]

Branched - Unmodified

Glucomannan (in konjac flour [mechanically ground]). Guinea pigs (number not stated). Application to skin according to the Buehler closed patch method. No sensitization.[151]

Branched - Modified

Corn Starch Modified: Corn starch modified in distilled water (30% solids). 10 Zealand White rabbits (5 males and 5 females). Application to skin (2,000 mg/kg); dose per cm^2 not stated. Dermal reactions either absent or classified as barely perceptible at 24-h and 48-h readings, and absent at the 74-h reading. Mild skin irritant (primary irritation index = 0.25).[66]

Corn Starch Modified: Corn Starch Modified (up to 30%). 20 guinea pigs (strain not stated; 10 males, 10 females). Maximization test (OECD protocol 406.) During induction,10% solution injected and 30% solution applied topically. Concentration per cm^2 was not stated. During challenge, application of 20% solution for 24 h. Reactions scored at 48 h and 72 h post-application. Control group (5 males, 5 females) tested with distilled water during induction and challenged with test substance. Reactions ranging from no erythema to moderate erythema observed after induction with the control or test substance. Erythema observed after challenge with test substance. However, rechallenge with same test substance concentration did not cause erythema. Not a sensitizer.[66]

Corn Starch Modified: 50% corn starch modified paste. 25 female Hartley guinea pigs. RIPT according to Buehler method (OECD protocol 4067). 10 guinea pigs treated with distilled water (control). Positive control (isoeugenol) tested in study performed within 6 months of current study. During induction, test material applied topically to shoulder area (~ 0.4 g on occlusive patch; area of application site not stated) . Topical challenge with 50% corn starch modified paste for 6 h. Challenge reactions scored at 24 h and 48 h post-application. No erythema or edema during induction or challenge. Non-sensitizer. Positive control induced sensitization.[63]

Carboxymethyl Inulin: Carboxymethyl inulin (1% to 100%). Groups of 2 adult Dunkin–Hartley albino guinea pigs. Test substance injected into clipped scapular region; reactions scored at 24 h and 48 h. Also, series of test article concentrations (0.5 ml) applied topically for 24 h to clipped external flank using Metalline patches secured with tape and an elastic bandage. Test material was removed after 24 h and signs of irritation recorded at 24 h and 48 h after treatment. Undiluted carboxymethyl inulin produced necrosis after intradermal injection, observed both after 24 h and 48 h; 20% to 50% did not cause necrosis, but grade 2 erythema was observed at either 24 h or 48 h. Signs of irritation were not observed at 24 h or 48 h at concentrations up to 100% in the patch tests.[156]

Carboxymethyl Inulin: 31.1% aqueous carboxymethyl inulin. 10 adult Dunkin–Hartley albino guinea pigs. Maximization test. Five female guinea pigs served as vehicle controls. No evidence of sensitization.[156]

Potato Starch Modified: 10 rats received single dose of potato starch modified (dose = 2 g/kg) dermally. Very slight to well-defined erythema and edema observed in all animals after 24 h. At 48 h, very slight erythema and very slight edema in 5 and 3 rats, respectively. All reactions had cleared by 72 h.[155]

Potato Starch Modified: Rats (10 males, 10 females). Dose of 2 g/kg body weight/day applied to the skin, under occlusive dressing, for 28 days . Neither erythema nor edema observed. However, small scabs observed on 5 males and 6 females, attributed to adhesion of test material to skin.[155]

Potato Starch Modified: Potato starch modified (18.5% aqueous suspension). 20guinea pigs. Buehler test (OECD 406 test guideline). Faint erythema (non-confluent) observed in 6 of 20 animals after second or third induction application. No evidence of sensitization.[155]

Potato Starch Modified: Potato Starch Modified (10% solids aqueous solution). 10 male and 10 female New Zealand albino rabbits (test animals)). Using non-occlusive patch, test substance (2 g/kg body weight) applied to the skin. The area of application and dose per cm^2 not stated. 20 control animals tested with distilled water under non-occlusive patch. Neither erythema nor edema observed in treated or control animals. No adverse morphologic effects on the skin.[70]

Potato Starch Modified: Potato starch modified (18.5% solids). 20 guinea pigs (10 males, 10 females). RIPT according to Buehler method (OECD 406 protocol). Concentration per cm^2 not stated. 10 control animals (5 males, 5 females) treated with distilled water. During induction, very faint erythema in 6 of 20 animals; reactions not observed in controls. Very faint erythema observed in 2 of 20 treated animals and in 2 of 10 controls during challenge phase. Non-sensitizer.[70]

Dextrin Myristate: 6 New Zealand white rabbits. Skin irritation study (test protocol not stated). Non-irritant.[67]

Dextrin Myristate: Guinea pigs (number and strain not stated). Magnusson-Kligman maximization test. No evidence of skin sensitization.[67]

Dextrin Palmitate: 3 New Zealand white rabbits. Skin irritation study (test protocol not stated). Non-irritant.[68,69]

Table12. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Branched - Modified

Dextrin Palmitate: Guinea pigs (number and strain not stated). Magnusson-Kligman maximization test (test concentrations not stated). No evidence of skin sensitization.[68,69]

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate: Test Material: Material (corn starch modified) described as structurally similar to sodium hydrolyzed starch dodecenylsuccinate and as the calcium salt of the ester formed from the reaction of 3-(dodecenyl)dihydro-2,5-furandione and corn starch, in which the degree of substitution per glucose unit is less than 0.1. 6 New Zealand White rabbits. OECD 404 test protocol. 50% slurry of test material (1 ml) applied topically (on occlusive patch, area of application site not stated) for 24 h to intact and abraded skin sites on the back of each animal. Reactions scored for up to 72 h after patch application. Erythema observed at intact and abraded sites on one animal, and reactions had cleared by 48 h. Mildly irritating to the skin (primary irritation index = 0.09).[63,204]

Stearoyl Inulin: 6 Japanese white rabbits. Skin irritation potential evaluated (concentrations and test protocol not stated). Non-irritant.[71,72]

Stearoyl Inulin: Guinea pigs (number and strain not stated). Skin sensitization potential evaluated (concentrations not stated) according to adjuvant and patch method. Skin irritation classified as weak. Very low skin sensitization potential.[71,72]

Skin Irritation and Sensitization - Human

Linear Polysaccharides and Their Salts

Algin: 20% aqueous sodium alginate. 12 male subjects with no history of allergy. Patch-testing (Finn chambers) with 20% aqueous sodium alginate according to International Contact Dermatitis Research Group (ICDRG) recommendations. Area (cm^2) of application and dose per cm^2 not stated. Reactions scored at 2 and 3 days post-application. ± reaction observed in one subject on days 2 and 3. Results negative for skin irritation and allergic contact dermatitis.[205]

Linear - Modified

Hydrolyzed Furcellaran: Mixture containing 1.35% furcellaran powder and 1% phenoxyethanol. 10 adults. Mixture applied (under occlusive patch) for 48 h to back. Area (cm^2) of application and dose per cm^2 not stated. Non-irritant.[73]

Hydrolyzed Furcellaran: Mixture containing 1.35% furcellaran powder, 0.1% potassium sorbate, and 0.05% citric acid. 10 adults. Mixture applied (under occlusive patch) for 48 h to back. Area (cm^2) of application and dose per cm^2 not stated. Non-irritant and non-sensitizer.[73]

Hydrolyzed Furcellaran: Mixture containing 0.6% hydrolyzed furcellaran, 0.05% concentrate of sea water, 1% phenoxyethanol, and 98.35% water. 100 subjects. Mixture applied 9 times to each subject. Area (cm^2) of application and dose per cm^2 not stated. Non-irritant and non-sensitizer.[73]

Maltodextrin: Eye gel containing 2.45% maltodextrin. 103 subjects. HRIPT. Patch type, area (cm^2) of application, and dose per cm^2 not stated. Challenge patches applied to original and alternate sites, and challenge reactions scored at approximately 48 h and 96 h post-application. Five instances of erythema (grade 1) during induction. At 48-h challenge reading, a grade of 1 reported for alternate challenge site of one subject. Gel did not induce allergic contact dermatitis.[206]

Branched - Modified

Corn Starch Modified: 7.5% solution in distilled water. 26 female subjects. 21-day cumulative irritation study. Test material (0.2 ml per 24-h patch) applied topically. Area (cm^2) of application and dose per cm^2 not stated. Reactions ranged from no erythema to minimal erythema. Non-irritant. Distilled water (vehicle control) did not cause erythema. Sodium lauryl sulfate (positive control) induced marked erythema and papules.[66]

Corn Starch Modified: 7.5% solution in distilled water. 113 subjects (86 females, 27 males). HRIPT. Patch type, area (cm^2) of application, and dose per cm^2 not stated. Challenge eactions scored at 48 h and 96 h post-application. Test substance and distilled water caused slight erythema in 3 subjects. Test substance and distilled water classified as non-sensitizers.[66]

Dextrin: Rinse-off facial product containing 42.6919 % dextrin (1% aqueous; effective concentration ≈ 0.4%). 54 subjects (46 females, 8 males). HRIPT. During induction, product (0.1-0.15 g on occlusive patch) applied for 24 h to the back.. Dose/concentration per cm^2 not stated. Challenge patch applied to new test site and reactions scored at 24 h and 72 h post-application. Transient, barely perceptible erythema, in 1 subject, during induction. No reactions observed during challenge phase. No clinically significant skin irritation or evidence of allergic contact dermatitiss.[207]

Dextrin Myristate: Leave-on facial product containing 0.3% dextrin myristate. 51 subjects (40 females, 11 males). HRIPT. During induction, product (0.1-0.15 g on occlusive patch) applied for 24 h to the back.. Dose/concentration per cm^2 not stated. Challenge patch applied to new test site and reactions scored at 24 h and 72 h post-application. Skin reactivity was not observed during the induction or challenge phase. Product did not cause skin irritation or allergic contact dermatitis.[208]

Hydroxypropyltrimonium Hydrolyzed Corn Starch: 15% hydroxypropyltrimonium hydrolyzed corn starch. 47 male and female subjects. HRIPT. During induction, semi-occlusive patch (1" x 1") containing approximately 0.2 ml of test material applied for 24 h to upper back. 24-h challenge patch applied to new test site, adjacent to induction patch site. No reactions during study. No skin irritation or allergic contact sensitization potential.[209]

Calcium Starch Isododecenylsuccinate: Test material (powder) and a 50% w/v slurry of test material in baby oil tested. 23 subjects. Powder applied topically (0.2 g, moistened with distilled water; area of application site not stated) under occlusive conditions for 21 days. 50% w/v slurry applied acccording to same procedure. Powder caused dermal effects that ranged from no irritation to erythema and papules cumulative irritation score = 177). Superficial layer effects ranged from none to glazing with peeling and cracking. 50% w/v slurry caused milder reactions (cumulative irritation score = 50.6). Both test materials classified as probable mild irritants under normal use conditions.[63,64,210]

Branched - Modified

Sodium Hydrolyzed Potato Starch Dodecenylsuccinate: Cleanser containing 10 wt% sodium hydrolyzed potato starch dodecenylsuccinate. 227 subjects (18 to 69 years old; 165 females, 62 males). HRIPT. During induction, occlusive patch containing ~ 0.2 g of the test material was applied to the back (area of application site not stated) for 24 h. week non-treatment period. Occlusive challenge patch containing the test material (~ 0.2 g) applied for 24 h to new site on back. Reactions were scored for up to 96 h post-application. Four subjects had low-level (±) reactions during induction, and 2 subjects had ± reactions during challenge phase. Non-sensitizer.[211]

Table12. Skin Irritation/Sensitization Potential of Polysaccharide Gums

Unknown Structural Configuration

Algae Exopolysaccharides: 1% solution of algae exopolysaccharides. 50 subjects. HRIPT. During induction, occlusive patch containing test substance (0.2 ml or 0.2 g) applied for 24 h to infrascapular region of back. Dose per cm^2 not stated. Challenge dose (equivalent to induction application) of test substance applied once to new test site. Reactions scored at 24 h to 48 h post-application. No evidence of adverse reactions. Not a primary skin irritant or sensitizer.[212]

In Vitro

Branched - Modified

Hydroxypropyltrimonium Hydrolyzed Corn Starch: MatTek Corporation EpiDerm™ skin model *in vitro* toxicity testing system. Skin model consists of normal, human-derived epidermal keratinocytes (NHEK) that have been cultured to form a multilayered, highly differentiated model of the human epidermis. Test procedure utilizes a water-soluble, yellow tetrazolium salt MTT. In the mitochondria of viable cells, MTT is reduced by succinate dehydrogenase to an insoluble formazan derivative (purple color). Substances that damage this enzyme inhibit reduction of the tetrazolium salt. Undiluted test substance (100 µl) added to millicells containing EpiDerm™ samples; time at which % viability would be 50% (ET_{50}) estimated. Mild irritant (ET_{50} = 18.1h).[213]

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SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 6.2
Revision Date 07.06.2021
Print Date 27.02.2023
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name	:	Maltodextrin
Product Number	:	419699
Brand	:	Aldrich
REACH No.	:	A registration number is not available for this substance as the substance or its uses are exempted from registration, the annual tonnage does not require a registration or the registration is envisaged for a later registration deadline.
CAS-No.	:	9050-36-6

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses	:	Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet

Company	:	Sigma-Aldrich Chemie GmbH Industriestrasse 25 CH-9471 BUCHS
Telephone	:	+41 81 755 2511
Fax	:	+41 81 756 5449
E-mail address	:	technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone #	:	+41 43-508-2011 (CHEMTREC) +41 44-251-5151 (Tox-Zentrum) 145(Tox Info Suisse)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

CAS-No. : 9050-36-6
EC-No. : 232-940-4

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

4.2 Most important symptoms and effects, both acute and delayed

The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed

No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Water Foam Carbon dioxide (CO2) Dry powder

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture

Carbon oxides
Combustible.
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters

In the event of fire, wear self-contained breathing apparatus.

5.4 Further information

Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Avoid inhalation of dusts. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Dry.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
required when dusts are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.
Recommended Filter type: Filter type P1

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: solid
b)	Odor	No data available
c)	Odor Threshold	No data available
d)	pH	No data available
e)	Melting point/freezing point	Melting point/range: 240 °C - dec.
f)	Initial boiling point and boiling range	No data available
g)	Flash point	No data available
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	No data available
k)	Vapor pressure	No data available
l)	Vapor density	No data available
m)	Relative density	No data available
n)	Water solubility	No data available
o)	Partition coefficient: n-octanol/water	No data available
p)	Autoignition temperature	No data available
q)	Decomposition	No data available

	temperature	
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information
No data available

SECTION 10: Stability and reactivity

10.1 Reactivity
The following applies in general to flammable organic substances and mixtures: in correspondingly fine distribution, when whirled up a dust explosion potential may generally be assumed.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
no information available

10.5 Incompatible materials
No data available

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
Oral: No data available
Inhalation: No data available
Dermal: No data available

Skin corrosion/irritation
No data available

Serious eye damage/eye irritation
No data available

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure

No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

No data available

SECTION 12: Ecological information

12.1 Toxicity
No data available

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name
ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)
ADR/RID: - IMDG: - IATA: -

14.4 Packaging group
ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards

ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information

Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

15.2 Chemical Safety Assessment

For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

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European Commission

Combined Draft Renewal Assessment Report prepared according to Regulation (EC) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008

Maltodextrin

Volume 3 – B.6 (AS)

Rapporteur Member State: Ireland
Co-Rapporteur Member State: France

VERSION HISTORY

Date	Version	Reason for revision
11/11/2022	Version 1.0	Initial RAR
02/02/2023	Version 1.1	Updated in response to EFSA's completeness check of the RAR.

TABLE OF CONTENTS

B.6. TOXICOLOGY AND METABOLISM DATA

Introduction

Maltodextrins are partially hydrolysed starches, composed of chains of D-glucose of variable length. The degree of hydrolysis of starches is measured as a Dextrose Equivalent (DE) and maltodextrins have a DE of between 3 and 20 (i.e. equivalent to between 3 and 20 glucose molecules). They belong to the polysaccharide chemical group and have the same general formula as carbohydrates but are of shorter chain length. The source of maltodextrin being supported in this renewal ([redacted] is produced from maize starch and has a dextrose equivalent of 18-20.

Maltodextrins are ubiquitous in nature and the food chain and are accepted as being part of the normal diet. They are permitted for use as a food additive within Council Directive 89/107/EEC, and in infant formulae and follow-on formulae under Annex 1 Section 4 Carbohydrates Point 4.1 of Commission Directive 91/321/EEC. In the United States, maltodextrins are regulated under the Food and Drug Administration's (FDA's) Code of Federal Regulations (CFR) as a GRAS substance, meaning it is Generally Recognized As Safe. They are used as food additives for their texturizing, gelling, emulsifying and non-crystallizing properties and as a partial substitute for fats in specialised nutrition such as infant nutrition, sports nutrition and clinical applications. Maltodextrin is also listed under Directive 96/335/EC as a permitted ingredient for use in cosmetics and in the European Pharmacopoeia (Monograph 1970). [redacted] the subject of this renewal, is considered as "food grade", including use in infant formulae.

Following ingestion, maltodextrins are digested in the same way as any other starch hydrolysis product, yielding simple sugars such as glucose. Maltodextrins are rapidly metabolised and [redacted] has even been used as a control oligosaccharide in the investigation of enzymatic hydrolysis of human milk oligosaccharides in the upper gastrointestinal tract. In an *in vitro* system there was complete recovery of glucose from the hydrolysis of maltodextrin ([redacted] by 20 hours, demonstrating this rapid breakdown (Engfer et al., 2000).

The wide range of authorised uses of maltodextrins highlights their safety, which was noted during the previous EU evaluation of maltodextrin as a plant protection product. No toxicology data on the active substance were considered necessary to support its safety and the peer review report published by EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin were supported, reference values were not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

As part of the renewal application for maltodextrin, and to provide support to the previous EFSA conclusion that maltodextrin is of low toxicological concern, a review of the existing extensive uses of maltodextrin in food, feed and other applications has been undertaken and is summarised below (B.6.0.1).

B.6.0.1. Review of the Uses of Maltodextrins

Data point:	CA 5.0/2
Report author	Evans, R. and Hearty, A. (Prepared by Exponent International Ltd)
Report year	(2020)
Report title	Review of existing food and non-food uses of maltodextrins
Report No	1905806.UK0 - 4797
Document No	None
Guideline followed in study:	N/A
Deviations from current test guideline	N/A
Previous evaluation	No, not previously submitted
GLP/Officially recognised testing facilites	N/A
Acceptability/Reliability:	Yes

EXECUTIVE SUMMARY

Exponent has undertaken a review of the existing uses of maltodextrin. Maltodextrin is widely used with extensive applications in food as an ingredient or for its technical properties, in infant formula, in medicines and cosmetics and in animal feed. Exposure to maltodextrin is widespread and a conservative estimate indicates that maltodextrin intake could be in the range of 5 – 14 g per person per day in the general population.

MATERIALS AND METHODS

1. Materials:

Test Material	N/A
Test System	N/A
2. Methods	Exponent has undertaken a review of the existing extensive uses of maltodextrin in food, feed and other applications. The method of how the review was performed is not stated.
In life dates:	N/A
Data:	No data available
Analysis:	No data available
Statistics:	No data available

RESULTS

Applications

1) Use in food

Use as a food ingredient: Maltodextrins are considered as food ingredients and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008), as are all starches treated with amylolytic enzymes. There are no specified purity criteria or specifications for maltodextrins intended for food use in the EU other than they should not be injurious to health, or unfit or unsafe by way of contamination (in line with the general requirements for all foodstuffs set out in Regulation (EC) No 178/2002 on the general principles of food law). There is no upper level on their use as a food ingredient and there are few restrictions on the types of products in which they can be used. In the USA, maltodextrins are GRAS (Generally Regarded as Safe) and the associated conditions of use are set out under 21 CFR184.1444. Maltodextrins are used variously as an ingredient in products such as ice cream, dried instant foods, confectionary, cereals, snacks, and beverages. Maltodextrins are used extensively in certain specialist nutrition product categories, including sports nutrition such as energy and recovery drinks, where their easy digestibility and absorption provides a rapidly available energy source.

Use as a carrier / encapsulating material: The neutral taste and technical properties mean that maltodextrins are commonly used to help incorporate other ingredients into foods. Maltodextrins are widely employed as part of the microencapsulation system for food constituents such as flavours and bioactive compounds. As with the use of maltodextrins as a food ingredient, there is no regulatory restriction on the amounts that can be used, and so overall use in these food applications is difficult to quantify.

Use in infant formula and follow-on formula: Maltodextrin is permitted to be used as a carbohydrate source in both infant formula and follow-on formula in the EU, as set out in Delegated Regulation (EU) No. 2016/127 on the compositional and information requirements for infant formula and follow-on formula. Article 3 of the regulation states that infant formula and follow-on formula may only be manufactured from food ingredients whose suitability for infants from birth and infants aged over 6 months respectively, "has been established by generally accepted scientific data". The EFSA Opinion (2014) on the essential composition of infant and follow-on formulae agreed with the SCF Opinion (2003) on the same topic that it was not necessary to propose any minimum or maximum amounts of maltodextrins in either infant or follow-on formulae, as long as the maximum content of carbohydrates in either product type was not exceeded.

2) Use in medicines and cosmetics

Maltodextrins are used as excipients (non-active substances) in pharmaceutical preparations and a specification for the substance has been established in the European Pharmacopoeia.

Regulation (EC) No 1223/2009 does not restrict the use of maltodextrins in cosmetic products where they are frequently used as viscosity increasing agents, and as such there is no maximum limit established for their presence in products. In terms of an assessment of the safety in use of maltodextrins in cosmetics, the USA Cosmetic Review Panel undertook a safety assessment of polysaccharide gums, and as part of that assessment were able to conclude that maltodextrin was safe to use in the present practices of use and concentrations in cosmetics based on a detailed safety assessment (Cosmetic Ingredient Review (CIR) Expert Panel, 2015).

3) Use in animal feed

Maltodextrins are listed as a recognized component of animal feed in the EU. They are listed in the EU feed material catalogue contained in Commission Regulation (EU) No 68/2013. There are no specific restrictions on the use of maltodextrins in food, and they find use in products such as premixes and milk replacers and are used for both their nutritional and technical properties. Maltodextrins are also extensively used in pet food, i.e. for animals not intended for the food chain, and again they are used for both nutritive and technical properties, including as a thickener and binder, as well as a carrier for other components included in the pet food where these may be susceptible to production processes or long term storage.

Exposure

Since maltodextrin use is extensive in food, and there are no upper use limits for the substance set out in legislation, it is difficult to estimate dietary exposure. The use of maltodextrin as an ingredient in food is ubiquitous and can be added to many types of processed food products, in addition to infant, clinical and sports nutrition products as a source of readily digestible carbohydrate. In addition, it is widely used as bulking agent and a thickener for many foodstuffs and food supplement products. There is no maximum level of use for maltodextrin in foods other than to comply with GMP requirements. These two aspects (i.e. its widespread use and no quantitative limits on its use) highlight the difficulties associated with conducting a realistic intake assessment for this substance and may be one of the reasons why maltodextrin intake has not previously been examined.

As there is no direct information on intake of maltodextrin available, for a conservative estimate of exposure, the intake can be based on the total intake of carbohydrate in the diet. In the EU, the dietary recommended value (DRV) for carbohydrate is 45-60% total energy (EFSA, 2010). Based on a reference intake of total energy of 2000 kcal per day for an adult, this leads to a reference intake of 225 - 300 g carbohydrate per day. On review of actual dietary data from food consumption surveys across Europe, average carbohydrate intakes in adults were slightly lower (190 – 280 g per day). The main source of carbohydrate intake in the diet is from staple foods such as cereal based foods, including bread, potatoes, tubers and pulses and also from fruits, vegetables, dairy and sweets, soft drinks etc. For the total daily intake of carbohydrates, maltodextrins would only contribute to a relatively small proportion of this, mainly from its use in various processed foods and to foods for special groups (e.g. sports nutrition products, medical foods and food supplements). This Scientific Opinion (EFSA, 2010) also reported that in adults, the intake of mono and disaccharides varied between 17 - 26% total energy and the intake of polysaccharides between 20 - 27% total energy. If we consider that maltodextrin intake forms part of this intake of polysaccharides (along with longer chain molecules such as starch, non-starch polysaccharides, and other oligosaccharides), then we can make a conservative assumption that maltodextrins could account for up to 5-10% of total polysaccharide intake, i.e. 1.0 – 2.7% total energy. This conservative assessment indicates that maltodextrin intake could be in the range of 5 – 14 g per person per day in the general population.

Intakes of maltodextrin may even be higher than this range for certain adult consumers, for example those individuals who consume sports nutrition products containing maltodextrin, and would be substantially higher for infants consuming infant or follow-on formula. High consumption of liquid infant formula is assumed to be 260 mL/kg bw per day for infants aged 0-16 weeks (EFSA, 2017). If one assumes all carbohydrate in the formula is maltodextrin, which is a realistic scenario for certain products, the level of total carbohydrate (and thus in this case maltodextrin) permitted in infant formula is 9 – 14 g per 100 kcal. The energy requirements for infant formula are 60 – 70 kcal per 100 ml (Annex I of Delegated Regulation (EU) No. 2016/127), therefore the potential intake of carbohydrate (i.e. maltodextrins where this is the sole source of carbohydrate in the formula) could range from 14.0 – 25.5 g per kg body weight. If one assumes average bodyweights of 16-week old infants are 5.9 kg for boys and 5.4 kg for girls (EFSA, 2017) then this gives potential total maximum daily maltodextrin intakes of 82.8 g -150.3 g for infant boys and 75.8 g – 137.6g for infant girls.

Assessment and conclusion by the applicant:

Assessment:

Maltodextrins are food ingredients and are ubiquitous in many processed food products. They are considered a very 'safe' ingredient with widespread applications (including infant nutrition products) and are derived from conventional crops with a long history of intake, as in the case of [redacted] from partial hydrolysis of maize starch. They also have widespread uses in animal feed, cosmetics and as an inert in medicinal preparations.

Conclusion:

Considering the widespread food uses and the extremely rapid breakdown after ingestion to glucose, it is not necessary to address each of the data requirements listed in Commission Regulation (EU) No. 283/2013 with mammalian toxicity data. The only potential hazard reported on the MSDS is related to rubbing, possibly causing mechanical skin irritation for hypersensitive individuals. This would result from a physical action rather than to any intrinsic irritancy properties of the substance itself.

Assessment and conclusion by the RMS (IE, 2022):

This study highlights the many applications of maltodextrin. Given the wide range of uses in regulated goods, the rapid breakdown to glucose and EFSA's conclusion from the last EU review, the RMS accepts that it is not necessary to address each of the data requirements listed in Commission Regulation (EU) No. 283/2013 for mammalian toxicity data.

B.6.1. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION IN MAMMALS

Previously Evaluated Studies

No studies were submitted for the original review in DAR (2011). This was considered acceptable considering the widespread use of maltodextrin in food, feed, cosmetics and medicinal preparations and because metabolites of maltodextrins are a standard energy source. In the previous review EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies

A study from the literature has been submitted and is discussed below in section B.6.1.1.1. No other studies have been performed. This is considered acceptable since the source of maltodextrin is unchanged and is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

B.6.1.1. Absorption, distribution, metabolism and excretion by oral route

During the previous EU review it was accepted by EFSA that maltodextrin is rapidly metabolised to glucose following ingestion. No further investigation of its absorption, distribution, metabolism or excretion by oral exposure is considered necessary, but a paper identified in the literature search was considered relevant by the applicant so was submitted. The paper is a review of the Nutrition, Health, and Regulatory Aspects of Digestible Maltodextrins (Hofman et al., 2016), however the RMS does not consider it sufficiently relevant for this endpoint.

B.6.1.1.1. Review of Nutrition, Health and Regulatory Aspects of Maltodextrin

Data Point	CA 5.1.1
Report Author	Hofman, D.L, van Buul, V.J., Brouns, F.J.P.H
Report Year	2016
Report Title	Nutrition, Health, and Regulatory Aspects of Digestible Maltodextrins

Report No	Critical Reviews in Food Science and Nutrition 56:2091-2100
Document No	N/A
Guidelines followed in study	N/A
Deviations from test guideline	N/A
Previous Evaluation	No, not previously submitted
GLP/Officially recognised testing facilities	N/A
Acceptability/Reliability:	Supportive only (not sufficiently relevant)

EXECUTIVE SUMMARY

Digestible maltodextrins (MDs) are low-sweet saccharide polymers consisting of D-glucose units linked primarily linearly with alpha-1,4 bonds, but can also have a branched structure through alpha-1,6 bonds. Often, maltodextrins are classified by the amount of reducing sugars present relative to the total carbohydrate content; between 3 and 20 percent in the case of digestible maltodextrins. These relatively small polymers are used as food ingredients derived by hydrolysis from crops naturally rich in starch. Through advances in production technology, the application possibilities in food products have improved during the last 20 years. However, since glucose from digested maltodextrins is rapidly absorbed in the small intestine, the increased use has raised questions about potential effects on metabolism and health. Therefore, up-to-date knowledge concerning production, digestion, absorption, and metabolism of maltodextrins, including potential effects on health, were reviewed. Exchanging unprocessed starch with maltodextrins may lead to an increased glycemic load and therefore post meal glycaemia, which are viewed as less desirable for health. Apart from beneficial food technological properties, its use should accordingly also be viewed in light of this. Finally, this review reflects on regulatory aspects, which differ significantly in Europe and the United States, and, therefore, have implications for communication and marketing.

Conclusion:

The decrease in the consumption of 'whole' foods and dietary fibre, along with a rise in the consumption of rapidly digestible and absorbable CHO sources such as isolated starches, starch derivatives, and sugars, parallels an increase in the global prevalence of obesity, diabetes, and cardiovascular disease. Due to their characteristics and physicochemical, functional, technological, and nutritional properties, MDs have numerous applications in food products. Accordingly, the rise in the overall consumption of MDs, amongst other refined CHO sources, can be attributed to a broader variety of foods containing them, thus potentially increased consumption. A frequent consumption of these products should be judged in the light of the potential effects that this may have on health.

MATERIALS AND METHODS

1. **Materials:**

Test Material	N/A
Test System	N/A
2. Methods	No data available. The method of how the review was performed is not stated.
In life dates:	N/A
Data:	No data available
Analysis:	No data available
Statistics:	No data available

RESULTS

Production and composition of maltodextrins

Maltodextrins (MDs) are produced by hydrolysis of starch from different botanical sources. During the production process, native starch is heated in the presence of water, causing the crystalline structure of starch granules to swell and be broken irreversibly. This gelatinization process makes starch available for enzymatic or acidic degradation, or a combination of both. After degradation, chains of D-glucose units are left with varying length and appearance. Digestible MDs ((C6H10O5)nH2O) have a relatively short chain length and can be defined as saccharide polymers obtained from edible starch having a so-called dextrose equivalency (DE) of less than 20.

Starch granules mainly contain varying amounts of two types of glucose polymers: amylose and amylopectin, which differ in molecular structure. In amylose, glucose units are linked in a linear structure by α1,4 glycosidic links while some glucose units in amylopectin are linked by α1,6 bonds, resulting in branched structures. Most starches contain approximately 70–80% amylopectin and roughly 20–30% amylose. The latter is known to be less rapidly digested by pancreatic a-amylase. Thus, depending on the amylose content of the native starch (some specific selected crops have a high amylose starch content of up to 70%) differences in blood glucose response will occur. Accordingly, high amylose rice has a lower glycemic index (GI D 38) than low amylose rice (GI D 57).
The amylose/amylopectin ratio in different native starches can also influence the properties and therefore technological applications of the MDs derived from these starches as well as their digestive properties. When discussing the production process of MDs, differences in composition are often expressed by the dextrose equivalent (DE). This crude yet relatively simple measurement is often used to express the degree of hydrolysis of starch; the higher the degree of hydrolysis, the higher the DE. The DE corresponds to the amount of reducing sugars (in g) expressed as dextrose on 100 g dry matter in the product as shown in Equation 1.

Equation 1: Equation for calculation of the dextrose equivalent (DE) of a carbohydrate (CHO)

$$DE = 100 \times \frac{Reducing\ sugar, pressed\ as\ dextrose}{Total\ carbohydrate}$$

Given this equation, free D-glucose (dextrose) has a DE of 100. In glucose polymers, reducing sugars can be present in the 'tail' of the molecule, a so-called reducing end. As such, branched MDs are more likely to have high amounts of reducing sugars. With respect to the amylose and amylopectin content, the DE of a MD correlates to the ratio of amylose and amylopectin content in the starch used to produce it; a higher amylopectin content correlates to a higher DE of a MD. Dried glucose syrups are, by definition, dried starch hydrolysis products with a DE greater than 20, whereas MDs are defined as dried starch hydrolysis products with a DE equal to or lower than 20, but higher than 3.

Maltodextrins in the human diet
The digestive end product of MDs, glucose, is not considered to be an essential nutrient. Yet, glucose participates in many basic metabolic processes in the body. MDs are considered to be a good source of energy since glucose obtained from its digestion is readily absorbed in the small intestine and subsequently used in metabolism. Although, large differences also occur here in the rate of branching of MDs. Since MDs are partially depolymerized starch granules, their digestion requires the same enzymes as required for the digestion of starch in vivo. Furthermore, starch, MDs and glucose all have a similar energy value of 4 kcal/g or 16 kJ/g.
It is often suggested that there are differences in the rate of digestion and absorption of oral MDs compared to oral glucose. While glucose will be immediately available for absorption upon arrival in the small intestine, MDs need to be digested by a-amylase and maltase first. The digestion of starch and MDs starts in the mouth by salivary a-amylase. This enzyme has the ability to breakdown MDs into maltose, a disaccharide consisting of two-linked D-glucose units. It appears that salivary amylase plays a rather small role in the MD breakdown due to the relatively short time that MDs reside in the mouth. Subsequent to arrival in the stomach, the gastric contents need to be transferred into the small intestinal duodenum for digestion and further transit in the gut. The rate of gastric emptying is regulated by volume effects activating stretch receptors and small intestinal receptors, which sense the composition and quantity (load) of the macronutrients in the gastric effluent. As a result, the gastric emptying of CHO solution is regulated in such a way that an almost constant energy output from the stomach is realized, explaining why diluted drinks (low macronutrient- energy content) empty more rapidly from the stomach than concentrated drinks (high macronutrient-energy content).
Pancreatic amylase, secreted in the small intestine, plays a final role in hydrolyzing the α, 1–4 linkages of MDs, a process that leads to the formation of maltose units. Maltose is either taken up by the gut epithelium directly or further broken down by brush border maltase, resulting in free glucose. The obtained free glucose is actively transported across the apical membrane of the enterocytes, and subsequently across their basement membrane into blood. Due to the difference in digestion and absorption, when compared to glucose, it has often been suggested that low-DE MDs, as complex CHOs, will require more time for digestion and absorption, resulting in a lower glycemic response.
This suggestion, however, is a misconception and is not supported by any research data. In contrast, the enzymic digestion of MDs appears to take place at a high rate leading to an absorption rate not being different from absorption after ingestion of pure glucose, as reflected also by comparable post-ingestive insulin responses at rest and during exercise, as well as oxidation rates during exercise. During absorption, a small fraction of glucose may be converted to lactic acid by the small intestinal cells or subsequently be taken up by liver, muscle,

brain, and red blood cells, to serve as energy source. The nonmetabolized fraction of absorbed glucose will either be stored as liver and muscle glycogen under the influence of insulin or converted to lipid.

Health Aspects of Digestible Maltodextrins Consumption: The rise in consumption of refined CHO sources has been linked to an increased health risk. Although no causal relationship between the consumption of MDs and negative health effects has been reported, this does not mean that overconsumption of foods containing MDs will have no effect. The regular intake of calorie dense, low-fibre/protein foods or drinks with high levels of refined added CHOs, in particular soft drinks and sweet snacks, may easily induce a persistent positive energy balance resulting in weight gain, impaired insulin sensitivity as well as increased blood cholesterol and blood lipids. Accordingly, consumers should consume in moderation and food and beverage producers should reduce the energy density of food and beverage while taking care for an appropriate nutrient, fibre, and protein level where possible.

Application of Maltodextrins in Food Products
Through advances in science and technology, the knowledge on the (functional) application possibilities of MDs in food and beverage products has improved significantly during the last 20 years. Due to their specific technological/functional properties and easy applicability, MDs can substitute sucrose or fat, and are being used in ice cream, dried instant food formulations, confectionary, cereals, snacks, and beverages.

Infant Nutrition: There is a strong nutritional reliance on lactose as a source of energy in early human development, preferably as part of the mother's breast milk. However, lactase deficiency resulting in the inability to digest may lead to malabsorption-induced osmotic diarrhea in which approximately 40% of the energy provided may be lost. In such cases, MDs can be used as a substitute for lactose to provide energy. In this respect, it is suggested also that the use of MDs, instead of glucose is favorable since this helps reduce osmotic load and related intestinal distress. MDs are also used as a CHO source in nonallergic infant formulae containing nondairy proteins (soy) or hydrolyzed proteins (hypoallergenic formulas).

Clinical Nutrition: In clinical nutrition, MDs are applied in enteral and parenteral nutrition in which they can be combined with proteins for use of preoperative feeding and drinks. Administering preoperative drinks containing MDs and protein, instead of using the conventional method of preoperative fasting, to patients undergoing major surgery for gastrointestinal malignancies seems to be a practical approach. For example, in one study, patients undergoing gastrointestinal surgery either received preoperative drinks containing 11% proteins, 70% MDs, and 19% sucrose (intervention group) or fasted prior to their surgery (control group). Results showed that the average postoperative hospital stay of patients in the intervention group was 50% lower compared to the controls. In addition, the patients in the intervention group had a lower postoperative inflammatory reaction than the patients who did not receive the preoperative drinks. A different study investigated the effects of the administration of a preoperative drink containing MD and glutamine (GLN group) or only MD (CHO group) prior to laparoscopic cholecystectomy. Patients included in the control group fasted prior to their surgery. Results showed a reduced biological response to surgical trauma by improving insulin sensitivity in patients in the GLN group, but not the CHO group, compared to the control group.

Oral Rehydration Drinks: Early studies have indicated benefits of using MDs in oral rehydration solutions (ORS) for individuals suffering from diarrhea over the use of glucose.

Sports Rehydration Drinks: A low beverage osmolality supports gastric emptying rate and helps reduce gastrointestinal stress. Accordingly, aiming at a low beverage osmolality, MDs are being used to replace sucrose or glucose in sport drinks.

Additional applications include **Sports Energy Drinks**, **Sports Recovery Drinks**, **Applications related to Oral Health**, **as Fat Replacer** and **related to Appetite Control**.

Food Regulatory Aspects Relevant to Maltodextrins in Europe and the United States are also discussed in this paper but are not viewed as relevant to the renewal of maltodextrin so are not summarized.

CONCLUSION
The decrease in the consumption of 'whole' foods and dietary fibre, along with a rise in the consumption of rapidly digestible and absorbable CHO sources such as isolated starches, starch derivatives, and sugars, parallels an increase in the global prevalence of obesity, diabetes, and cardiovascular disease. Due to their characteristics and physicochemical, functional, technological, and nutritional properties, MDs have numerous applications in

functional foods and beverages, as well as clinical nutrition, sports nutrition and infant nutrition. Accordingly, the rise in the overall consumption of MDs, amongst other refined CHO sources, can be attributed to a broader variety of foods containing them, thus potentially increased consumption. The use of MDs in specific circumstances, such as the use of concentrated energy drinks during endurance sports, may help reduce the risk of gastrointestinal distress compared to the use of glucose or sucrose, which would induce a high gastro-intestinal osmolality which may potentially induce gastrointestinal distress. Next to their use as an energy source, applications of MDs include their uses in replacing fat, encapsulating vitamins, minerals and flavorants, enhancing shelf life, and increasing bulk of products, amongst other things. Furthermore, even though the use of MDs as CHO source is preferred to that of common sugars and their use as fat replacers leads to a reduction in the energy density (kJ/g) of food products containing them, a frequent consumption of these products should be judged in the light of the potential effects that this may have on health.

Assessment and conclusion by the applicant:
Assessment: This review provides a summary of the nutrition, health, and regulatory aspects of digestible maltodextrins including vital background information on kinetic and biochemical processes related to the consumption of maltodextrin containing products. Also, the paper discusses that due to the use of maltodextrins in various food products, certain consumer groups may take up considerable amounts of maltodextrins. Overall, the data provided in this study and included in this summary are considered to be scientifically valid and reliable to support the assessment of maltodextrin. This paper also discusses regulatory aspects relating to food but they were not viewed as relevant to the renewal of maltodextrin so were not summarized above. **Conclusion:** Due to their characteristics and physicochemical, functional, technological, and nutritional properties, MDs have numerous applications in food products. Since glucose from digested maltodextrins is rapidly absorbed in the small intestine, the increased use in the diet has raised questions about potential effects on metabolism and health.

Assessment and conclusion by the RMS (IE, 2022):
This paper reviews literature from food technology, food chemistry, behavioural nutrition and biological sciences sources, and discusses the production and composition of maltodextrins, digestion of maltodextrins, applications in food products and food regulatory aspects of maltodextrins in the EU and US. Little of the discussion focuses on the absorption and metabolism of maltodextrin, and no information on distribution or excretion is provided. In the opinion of the RMS, the paper does not provide sufficient relevant, new information to contribute to this endpoint.

B.6.1.2. Absorption, distribution, metabolism and excretion by other routes
No data required for the reasons given under B.6.1.

B.6.2. ACUTE TOXICITY

Previously Evaluated Studies
For the original review, studies determining the acute oral, dermal and inhalation toxicity and the skin irritation properties were provided. They were performed with an alternative source of maltodextrin called Hugtite (also referred to as Avadex 58 MD G), which is a 50% aqueous solution of maltodextrin derived from potato starch rather than maize starch. EFSA concluded that these data did not provide evidence of acute toxic properties but they noted that 'Hugtite' had not been demonstrated to be equivalent to the representative plant protection product 'Eradicoat' (EFSA Journal 2013;11(1):3007). These studies are summarised below for completeness but are not considered necessary for decision making based on EFSA's conclusion, which states:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies

During the previous review, an issue was raised regarding the use of alpha amylase, a known skin sensitiser, in the manufacturing process of [redacted] A request for 5 batch analysis data was made to discern the levels of this potentially toxicologically relevant impurity in the active substance. This data has now been submitted and is discussed in section B.6.2.6. No other studies have been submitted and this is considered acceptable as the source of maltodextrin is unchanged and is supplied to the food industry, and because maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

Summaries of all acute toxicity studies and details on classification according to CLP Regulation (EC) No.1272/2008 are presented below and detailed in the following sections.

Table 1: Summary of Acute Toxicity Studies

Test	Species	Result	Classification	Previously evaluated	Reference
Acute Oral	Rat	LD_{50} > 2000 mg/kg bw	None	Yes	[redacted] (1991a)
Acute Dermal	Rat	LD_{50} > 2000 mg/kg bw	None	Yes	[redacted] (1991)
Acute Inhalation	Rat	LC_{50} > 5.16 mg/litre	None	Yes	[redacted] (1991)
Skin Irritation	Rabbit	Non-irritating	None	Yes	[redacted] (1991b)
Eye Irritation	-	-	None	-	No study performed
Skin Sensitisation	-	-	None	-	No study performed

B.6.2.1. Oral

Data Point	CA 5.2.1_1
Report Author	[redacted]
Report Year	1991a
Report Title	Acute Oral Toxicity (Limit Test) in the Rat
Report No	373/1
Document No	-
Guidelines followed in study	OECD 401 (1981)
Deviations from test guideline	None
Previous Evaluation	Yes, evaluated and accepted in the DAR (2011)
GLP/Officially recognised testing facilities	Yes
Acceptability	Acceptable, though noting this is a formulation study

EXECUTIVE SUMMARY

In an acute oral toxicity study, groups of fasted, young adult Sprague-Dawley rats 5/sex/dose were given an oral dose (gavage) of Hugtite (50% w/w maltodextrin) using a single dose of 2,000 mg/kg bw and were observed for 14 days.

Oral LD_{50}	males	=	> 2000 mg/kg bw
	females	=	> 2000 mg/kg bw
	combined	=	> 2000 mg/kg bw

Hugtite was found to be of a low order of acute oral toxicity following exposure of rats. There were no mortalities and no clinical signs in any animals. Body weight gain was normal. On the basis of this study, Hugtite does not warrant classification as being harmful or toxic.

MATERIALS AND METHODS

1. Test Material:	Hugtite
Description:	Brown viscous liquid
Lot/Batch#:	8225
Purity:	Not given
CAS#:	9004-53-9
Stability of test compound	Not determined
2. Vehicle:	None
3. Test animals -	
Species:	Rat
Strain:	Sprague-Dawley
Sex:	Male and Female
Age:	Young adult (5 to 8 weeks old)
Weight at dosing:	143 – 173 g males; 142 – 153 g females
Source:	[redacted]
Acclimation period:	5 days
Diet:	Rat and Mouse Expanded Diet No. 1, Special Diet Services Ltd, UK, *ad libitum*
Water:	Tap water, *ad libitum*
4. Housing:	Animals were housed in groups of 5 by sex in solid-floor polypropylene cages with sawdust bedding
Temperature:	21-24 °C
Humidity:	Relative humidity ranged from 34 to 62%
Air changes:	~15 changes per hour
Photoperiod:	Alternating 12-hour light and dark cycles
5. Methods	
In life dates:	2 May to 23 May 1991
Animal assignment and treatment	Following a range-finding preliminary test in which no animals died (2000 mg/kg bw), a single dose of 2000 mg/kg bw was selected for the main study. Animals were assigned to the test groups listed in Table 2. Rats were given a single dose of Hugtite by gavage. The test substance was administered as supplied. Animals were observed for gross toxicity, behavioural changes and/or mortality at 0.5, 1, 2 and 4 hours after dosing and at least once daily for the remainder of the 14-day study. Body weights were recorded at day 0 (prior to dosing), 7 and 14. On day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.
6. Statistics	The data did not warrant statistical analysis.

RESULTS

Table 2: Doses, mortality / animals treated

Dose (mg/kg bw)	Males	Females	Combined
0	0/5	0/5	0/10
2,000	0/5	0/5	0/10

1. Mortality	Details are provided in Table 2. No mortalities occurred at 2,000 mg/kg bw, the only dose level tested.

2.	**Clinical Observations**	There were no clinical signs of systemic toxicity.
3.	**Bodyweight**	All animals gained weight 7 and 14 days following dosing.
4.	**Necropsy**	No internal abnormalities were observed at gross necropsy.

CONCLUSION
The oral LD50 of Hugtite was found to be in excess of 2,000 mg/kg bw. Hugtite does not warrant classification as being toxic or harmful on the basis of its acute oral toxicity.

Assessment and conclusion by the applicant:
Assessment: This study was evaluated and accepted for the first EU approval review of maltodextrin (DAR Vol. 3 B6, 2011). The study was performed according to OECD 401 (1981) which was deleted in 2002 and replaced by OECD 420, 423 and 425. However, the results of this OECD 401 study are still scientifically valid for estimation of the acute oral LD50 for Hugtite (50% aqueous solution of maltodextrin). **Conclusion:** The study complies with the data requirements given in Commission Regulation No 283/2013. Under the conditions of this study, the acute oral LD50 value for Hugtite (50% aqueous solution of maltodextrin) was found to be in excess of 2,000 mg/kg bw. Classification under Regulation (EC) No. 1272/2008 for acute oral toxicity is not warranted.

Assessment and conclusion by the RMS (IE, 2022):
The guideline followed in this study was replaced in 2002 but the study was evaluated and accepted in the DAR (2011) and still remains valid. The oral LD_{50} was found to be >2000 mg/kg bw in both male and female Sprague-Dawley rats. Based on this study, classification of Maltodextrin according to CLP Regulation (EC) No.1272/2008 is not required.

B.6.2.2. Dermal

Data Point	CA 5.2.2_1
Report Author	[redacted]
Report Year	1991
Report Title	Acute Dermal Toxicity (Limit Test) in the Rat
Report No	373/2
Document No	-
Guidelines followed in study	OECD 402 (1981)
Deviations from test guideline	None. However, the updated guideline (OECD Guideline No. 402 (2017)) requires use of female animals only, stepwise dosing, observation after 30 mins and Draize scoring at 24, 48 and 72 hours. These deviations are not expected to alter the validity or outcome of the study.
Previous Evaluation	Yes, evaluated and accepted in the DAR (2011)
GLP/Officially recognised testing facilities	Yes
Acceptability	Acceptable, though noting this is a formulation study

EXECUTIVE SUMMARY
Five male and five female Sprague Dawley rats were treated with a single, semi occlusive dermal application of Hugtite (50% aqueous solution of maltodextrin) at a dose of 2000 mg/kg bw. The test substance was applied as supplied. The application period was 24 hours, followed by a 14-day observation period.

Clinical observations along with a check of viability and mortality were performed on all animals at 1 and 5 hours after dosing and daily for 14 days thereafter. Body weight was measured prior to dosing on Day 0 and on Days 7 and 14. Rats were euthanized and subjected to a gross macroscopic examination at the end of the 2-week observation period (Day 14).

No mortality occurred during the 14-day observation period. No clinical signs were observed after treatment with the test substance or during the 14-day observation period. All rats were symptom-free during the entire study.

The median lethal dose of Hugtite after a single dermal administration was found to be greater than 2000 mg/kg bw in male and female Sprague Dawley rats.

MATERIALS AND METHODS

3.	**Test Material:**	HUGTITE
	Description:	Brown viscous liquid
	Lot/Batch#:	8225
	Purity:	Not given
	CAS#:	9004-53-9
	Stability of test compound	Not determined
4.	**Vehicle:**	Test material dosed as received
5.	**Test animals -**	
	Species:	Rat
	Strain:	Sprague-Dawley
	Sex:	Male and Female
	Age:	Young adult (10 to 14 weeks old)
	Weight at dosing:	221 – 246 g males; 201 – 218 g females
	Source:	[redacted]
	Acclimation period:	5 days
	Diet:	Rat and Mouse Expanded Diet No. 1, Special Diet Services Ltd, UK, *ad libitum*
	Water:	Tap water, *ad libitum*
6.	**Housing:**	Animals were housed individually in solid-floor polypropylene cages with sawdust bedding during the exposure period. For the remainder of the study the animals were housed in groups of 5 by sex.
	Temperature:	19-23 °C
	Humidity:	Relative humidity ranged from 50 to 61%
	Air changes:	~15 changes per hour
	Photoperiod:	Alternating 12-hour light and dark cycles
7.	**Methods**	
	In life dates:	14 May to 28 May 1991
	Animal assignment and treatment:	Sprague-Dawley rats (5/sex) were given a single 24 hour, semi-occluded dermal application to intact skin at a dose level of 2000 mg/kg body weight. On the day prior to dosing, the fur was clipped from the back and flanks of each animal to expose a skin area of approximately 5 cm × 4 cm. The clipped area accounted for approximately 10% of each animal's body surface. The undiluted test substance was applied uniformly using a graduated syringe and a piece of surgical gauze placed over the treated area. After an exposure period of 24 hours, the occlusion was removed and residual test material was removed with distilled water. Animals were observed for gross toxicity and behavioural changes on four occasions on the day of dosing (0.5, 1, 2 and 4 hours after dosing) and once daily thereafter for the duration of the study. Individual body weights were measured and recorded on days 0, 7 and 14. On day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.
8.	**Statistics:**	The data did not warrant statistical analysis.

RESULTS

Table 3: Doses, mortality / animals treated

Dose Level (mg/kg bw)	Day Number	Number of Deaths	
		Male	Female
2000	1	0/5	0/5
	Total at day 14	0/5	0/5

1. **Mortality** — Details are provided in Table 3. No mortalities occurred at 2,000 mg/kg bw, the only dose level tested.
2. **Clinical Observations** — There were no clinical signs of systemic toxicity or skin irritation.
3. **Bodyweight** — There were no treatment related effects on body weight or body weight gain during the observation period.
4. **Necropsy** — No internal abnormalities were observed at gross necropsy.

CONCLUSION

The dermal LD50 of Hugtite was found to be in excess of 2,000 mg/kg bw. Hugtite does not warrant classification as being toxic or harmful on the basis of its acute dermal toxicity.

Assessment and conclusion by the applicant:

Assessment:

This study was evaluated and accepted for the first EU approval review of maltodextrin (DAR Vol. 3 B6, 2011). The study was performed according to OECD 402 (1981). Therefore, the present study is considered to be scientifically valid to derive a dermal LD50 for Hugtite (50% aqueous solution of maltodextrin).

Conclusion:

The study complies with the data requirements given in Commission Regulation No 283/2013. Under the conditions of this study, the acute dermal LD50 value for Hugtite (50% aqueous solution of maltodextrin) was found to be in excess of 2,000 mg/kg bw. Classification under Regulation (EC) No. 1272/2008 for acute dermal toxicity is not warranted.

Assessment and conclusion by the RMS (IE, 2022):

This study was evaluated and accepted in the DAR (2011) however since then a new acute dermal toxicity guideline (OECD Guideline No. 402, 2017) has been released. Deviations in this study from the new guideline are not expected to alter the validity or outcome of the study, therefore it is still acceptable.

The study complies with the data requirements set in Commission Regulation No 283/2013. Under the conditions of this study, the acute dermal LD50 value for Hugtite (50% aqueous solution of maltodextrin) was found to be in excess of 2,000 mg/kg bw. The criteria for classification under Regulation (EC) No. 1272/2008 have not been met therefore classification of maltodextrin for acute dermal toxicity is not warranted.

B.6.2.3. Inhalation

Data Point	CA 5.2.3_1
Report Author	[redacted]
Report Year	1991
Report Title	Acute Inhalation toxicity Study Four-Hour Exposure (Nose Only) in the Rat
Report No	373/3
Document No	-

Guidelines followed in study	OECD 403 (1981)
Deviations from current test guideline	None
Previous evaluation	Yes, evaluated and accepted in the DAR (2011)
GLP/Officially recognised testing facilities	Yes
Acceptability	Acceptable, though noting this is a formulation study

EXECUTIVE SUMMARY

This study was performed to assess the acute inhalation toxicity of Hugtite (50% aqueous solution of maltodextrin) in male and female Sprague Dawley rats following a single 4-hour nose-only exposure followed by a 14-day observation period. The day of exposure was designated Day 0. Aerosol concentrations were measured gravimetrically. The particle size distribution of the test aerosol was determined twice during the exposure period using a Cascade Impactor. Clinical observations and body weights were recorded throughout the study and at the end of the scheduled period the animals were euthanised and subjected to a gross examination post mortem.

Table 4: Mean achieved atmosphere concentration and particle size distribution

Group	Mean achieved concentration (mg/L)	Mean Mass Median Aerodynamic Diameter (MMAD) (µm)	Inhalable Fraction (% < 4 µm)
0 (control)	NA	NA	NA
5.16 mg/L	5.16	2.7	68.2

During exposure and on removal from the chambers, incidents of wet fur were noted. On removal there were also isolated signs of red/brown staining around the snout and/or eyes. Seven animals showed no abnormalities one hour after completion and all animals showed no abnormalities on Day 1 following exposure or during the remainder of the study. There were no mortalities and therefore the acute inhalation LD50 was > 5.16 mg/L.

MATERIALS AND METHODS

1. **Test Material:** HUGTITE

   Description: Brown viscous liquid
   Lot/Batch#: 8225
   Purity: Not given
   CAS#: 9004-53-9
   Stability of test compound Not determined
2. **Vehicle:** Test material dosed as received
3. **Test animals:**

   Species: Rat
   Strain: Sprague-Dawley
   Age: Young adult (8 to 10 weeks old)
   Sex: Male and Female
   Weight at dosing: 230 – 248 g males; 211 – 226 g females
   Source: [redacted]
   Acclimation period: 5 days
   Diet: Rat and Mouse Expanded Diet No. 1, Special Diet Services Ltd, UK, *ad libitum*
   Water: Tap water, *ad libitum*
4. **Housing:** Animals were housed in groups of five in solid-floor polypropylene cages with sawdust bedding during the exposure period.

   Temperature: 20-23 °C
   Humidity: Relative humidity ranged from 52 to 76%
   Air changes: ~15 changes per hour
   Photoperiod: Alternating 12-hour light and dark cycles

5. Methods

In life dates:	19 April to 31 July 1991
Animal assignment and treatment	A group of ten Sprague-Dawley rats (5/sex) were exposed to an achieved atmosphere of 'Hugtite' 5.16 mg/litre (SD 0.17). The characteristics of the test atmosphere were MMAD 2.7 μm (68.2% <4 μm) and GSD 0.42 μm. Each rat was individually held in a tapered, polycarbonate restraining tube fitted onto a single tier exposure chamber and sealed by means of a rubber 'O' ring. Only the noses of the animals were exposed to the test atmosphere. Animals were observed approximately hourly during the 4-hour exposure period. Thereafter mortality and moribundity checks were conducted twice daily. Observations for signs of toxicity were conducted immediately following exposure and daily thereafter. Individual body weights were measured and recorded on days 0, 7 and 14. On day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.
6. Statistics	The data did not warrant statistical analysis.

RESULTS

Table 5: Doses, mortality / animals treated

Dose (mg/L)	Males	Females	Combined
0	0/5	0/5	0/10
5.16*	0/5	0/5	0/10

* Mean achieved against nominal of 5 mg/L

1. Mortality	Details are provided in **Table 5**. No mortalities occurred at 5.16 mg/L, the only dose level tested. The 4-hour inhalation LC50 for males and females was >5.16 mg / L.
2. Clinical Observations	During exposure and on removal from the chambers, incidents of wet fur were noted. On removal there were also isolated signs of red/brown staining around the snout and/or eyes. Seven animals showed no abnormalities one hour after completion and all animals showed no abnormalities on Day 1 following exposure or during the remainder of the study.
3. Bodyweight	There were no treatment related effects on body weight or body weight gain during the observation period.
4. Necropsy	No internal abnormalities were observed at gross necropsy.

CONCLUSION

The 4-hour inhalation LC50 of Hugtite was found to be in excess of 5.16 mg/L. Hugtite does not warrant classification as being toxic or harmful on the basis of its acute inhalation toxicity.

Assessment and conclusion by the applicant:

Assessment:

This study was evaluated and accepted for the first EU approval review of maltodextrin (DAR Vol. 3 B6, 2011). The study was performed according to OECD 403 (1981). Therefore, the present study is considered to be scientifically valid to derive an acute inhalation LC50 for Hugtite (50% aqueous solution of maltodextrin).

Conclusion:

The study complies with the data requirements given in Commission Regulation No 283/2013. Under the conditions of this study, the acute inhalation LC50 value for Hugtite (50% aqueous solution of maltodextrin) was found to be in excess of 5.16 mg/L. Classification under Regulation (EC) No. 1272/2008 for acute inhalation toxicity is not warranted.

Assessment and conclusion by the RMS (IE, 2022):

The guideline followed in this study was updated in 2009 but the study was evaluated and accepted in the DAR (2011) and still remains valid. The 4-hour inhalation LC50 of Hugtite was found to be >5.16 mg/litre in both male and female Sprague-Dawley rats. Based on this study, classification of maltodextrin for acute inhalation toxicity according to CLP Regulation (EC) No.1272/2008 is not warranted.

B.6.2.4. Skin irritation

Data Point	CA 5.2.4_1
Report Author	[redacted]
Report Year	1991b
Report Title	Acute Dermal Irritation in the Rabbit
Report No	373/4
Document No	N/A
Guidelines followed in study	OECD 404 (1981)
Deviations from current test guideline	None
Previous evaluation	Yes, evaluated and accepted in the DAR (2011)
GLP/Officially recognised testing facilities	Yes
Acceptability	Acceptable, though noting this is a formulation study

EXECUTIVE SUMMARY

In a primary skin irritation study, young adult New Zealand White rabbits (2 female, 1 males) were dermally exposed to 0.5 mL of Hugtite (50% aqueous solution of maltodextrin), applied to the intact shaved skin under a semi-occlusive dressing, for 4 hours. Skin reactions were scored at 1, 24, 48 and 72 hours after removal of the dressing. Irritation was scored by a numerical scoring system and the Primary Irritation Index (PII) was calculated.

Very slight erythema was noted in one treated skin site at one hour post treatment and at one other site at the 24 hour observation. All treated sites had resolved by 48 hours. No other effect was seen. According to the Draize classification criteria, Hugtite is considered to be a Mild Irritant to rabbit skin (PII = 0.2) but is not classified for skin irritancy under Regulation (EC) 1272/2008.

MATERIALS AND METHODS

1. **Test Material:** HUGTITE

   Description: Brown viscous liquid
   Lot/Batch#: 8225
   Purity: Not given
   CAS#: 9004-53-9
   Stability of test compound Not determined
2. **Vehicle:** Test material dosed as received

3. Test animals -

Species:	Rabbit
Strain:	New Zealand Whites (NZW)
Sex:	Male and Female
Age:	Young adult (12 to 16 weeks old)
Weight at dosing:	2.50 – 2.66 kg
Source:	[redacted]
Acclimation period:	5 days
Diet:	Spillers rabbit diet, *ad libitum*
Water:	Tap water, *ad libitum*

4. Housing: Animals were individually housed in suspended metal cages.

Temperature:	17-21 °C
Humidity:	Relative humidity ranged from 57 to 63%
Air changes:	~15 changes per hour
Photoperiod:	Alternating 12-hour light and dark cycles

5. Methods:

In life dates:	10 April to 13 April 1991
Animal assignment and treatment	New Zealand White rabbits (3) were given a single 4-hour, semi-occluded dermal application (2.5 x 2.5 cm gauze patch) with 0.5 ml of undiluted test material was applied to intact, shorn skin. On the day prior to dosing, the fur was clipped from the dorsal/flank area of the trunk of each animal using veterinary clippers. The test material was applied, semi-occluded, as a single dermal administration. The application rate was 0.5 ml per animal. The substance was applied under a 2.5 x 2.5 cm gauze patch. After an exposure period of 4 hours, the occlusion was removed and residual test material was removed with distilled water. The test sites were examined for signs of erythema and oedema at 1, 24, 48 and 72 hours following patch removal.

6. Statistics The data did not warrant statistical analysis.

RESULTS

Very slight erythema was noted in one treated skin site at one hour post treatment and at one other site at the 24 hour observation. All treated sites had resolved by 48 hours. No other effect was seen.

Table 6: Individual and mean skin irritation scores according to the Draize scheme

	Erythema			Oedema		
Animal no.	**20 female**	**23 female**	**37 male**	**20 female**	**23 female**	**37 male**
after 1 hr	0	0	1	0	0	0
after 24 hr	0	1	0	0	0	0
after 48 hr	0	0	0	0	0	0
after 72 hr	0	0	0	0	0	0
Average per animal	0	0.3	0	0	0	0
Overall mean score 24-72 hr	0.1			0.0		

CONCLUSION

Hugtite produced a primary irritation index of 0.2 and was classified as a mild irritant to rabbit skin according to the Draize classification scheme. Based on this study, Hugtite is not classified for skin irritancy under Regulation (EC) 1272/2008.

Assessment and conclusion by the applicant:
Assessment: The study was previously evaluated and accepted in the DAR (2011). The previous evaluation considered Hugtite (50% aqueous solution of maltodextrin) to be "Non Irritant". This was a GLP and guideline compliant study performed in accordance with OECD 404 (1981) guideline in force at the time of submission of the dossier. The study complies with the data requirements given in Commission Regulation No 283/2013. There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study. **Conclusion:** The application of Hugtite (50% aqueous solution of maltodextrin) did not result in any signs of skin irritation. According to the Draize classification criteria, Hugtite is considered to be a Mild Irritant to rabbit skin but is not classified for skin irritancy under Regulation (EC) 1272/2008.

Assessment and conclusion by the RMS (IE, 2022):
The guideline followed in this study was updated in 1992 and 2002 but the study was evaluated and accepted in the DAR (2011) is still deemed valid. The application produced very slight erythema in two females which was reversible within 48 h, which does not meet the criteria set in CLP Regulation (EC) No.1272/2008 for classification as skin irritant. Based on this study, classification of Maltodextrin as a skin irritant is not warranted.

B.6.2.5. Eye irritation

Previously Evaluated Studies

No data on the eye irritation properties of maltodextrin were required during the original review. It was concluded that the technical material might be irritating as a dust cloud.

New Studies

No new studies have been submitted for the purpose of renewal. This is considered acceptable since the source of maltodextrin is unchanged and is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products. Classification for Eye Irritation according to CLP Regulation (EC) No.1272/2008 is not warranted.

B.6.2.6. Skin sensitization

Previously Evaluated Studies

No skin sensitization studies were submitted during the original review. This was considered acceptable except for the concern regarding the presence of alpha amylase, a known sensitiser, in the manufacturing process of [redacted] When present at >1%, alpha amylase can trigger a classification for sensitising properties due to the potential for skin sensitisation in gluten sensitive individuals. At the time of the original review, preliminary batch analysis demonstrated that alpha amylase in the technical material were <0.125% and hence no classification was triggered. Instead, the supplemental hazard information statement "Contains alpha-amylase. May produce an allergic reaction" was added to the label. To address this, complete 5 batch data was requested.

New Studies

For this renewal process, no skin sensitization studies have been performed but a relevant EFSA conclusion and the complete 5 batch analysis data have been submitted. EFSA's Panel on Food Contact Materials, Enzymes, Processing Aids has reviewed numerous applications for authorisation of α-amylase preparations submitted under EU legislation on enzymes in foodstuffs (Regulation (EC) 1332/2008), and has concluded that whilst "allergic reactions upon oral ingestion of the α-amylase preparations in individuals sensitised by inhalation to α-amylase cannot be ruled out, the likelihood of such reaction to occur is considered to be low"(EFSA, 2019). The 5 batch analysis report provides further evidence that sensitisation is not a concern. The data is not included as it is confidential, however it demonstrates that residual alpha-amylase in the technical material is <0.1%, below the cut-off for classification and for inclusion of a supplementary hazard information statement. Based on this evidence, maltodextrin is not considered to be a skin sensitizer and classification according to CLP Regulation (EC) No.1272/2008 is not required.

B.6.2.7. Phototoxicity

Previously Evaluated Studies
During the previous EU review it was not necessary to provide any data on the toxicological properties of maltodextrin. EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies
No new studies have been submitted. This is considered acceptable since the source of maltodextrin is unchanged and is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

B.6.3. SHORT-TERM TOXICITY

Previously Evaluated Studies
During the previous EU review it was not necessary to provide any data on the toxicological properties of maltodextrin. EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies
No new studies have been submitted. This is considered acceptable since the source of maltodextrin is unchanged and is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

B.6.3.1. Oral 28-day study

No data required for the reasons given under B.6.3.

B.6.3.2. Oral 90- day study

No data required for the reasons given under B.6.3.

B.6.3.3. Other routes

No data required for the reasons given under B.6.3.

B.6.4. GENOTOXICITY

Previously Evaluated Studies
During the previous EU review it was not necessary to provide any data on the toxicological properties of maltodextrin. EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from

> its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies
No new studies have been submitted. This is considered acceptable since the source of maltodextrin is unchanged and is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

B.6.4.1. In vitro studies

No data required for the reasons given under B.6.4.1.

B.6.4.2. In vivo studies in somatic cells

No data required for the reasons given under B.6.4.1.

B.6.4.3. In vivo studies in germ cells

No data required for the reasons given under B.6.4.1.

B.6.5. LONG-TERM TOXICITY AND CARCINOGENESIS

Previously Evaluated Studies
During the previous EU review it was not necessary to provide any data on the toxicological properties of maltodextrin. EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies
No new studies have been submitted. This is considered acceptable since the source of maltodextrin is unchanged and is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

B.6.6. REPRODUCTIVE TOXICITY

Previously Evaluated Studies
During the previous EU review it was not necessary to provide any data on the toxicological properties of maltodextrin. EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies
No new studies have been submitted. This is considered acceptable since the source of maltodextrin is unchanged and is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

B.6.6.1. Generational studies

No data required for the reasons given under B.6.6.

B.6.6.2. Developmental toxicity studies

No data required for the reasons given under B.6.6.

B.6.7. NEUROTOXICITY

Previously Evaluated Studies
During the previous EU review it was not necessary to provide any data on the toxicological properties of maltodextrin. EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies
No new studies were performed. This is considered acceptable since the source of maltodextrin is unchanged, is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

B.6.7.1. Neurotoxicity studies in rodents

No data required for the reasons given under B.6.7.

B.6.7.2. Delayed polyneuropathy studies

No data required for the reasons given under B.6.7.

B.6.8. OTHER TOXICOLOGICAL STUDIES

Previously Evaluated Studies
For the original review it was not necessary to provide any data on the toxicological properties of maltodextrin. EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

New Studies
The literature search conducted by the applicant identified four papers which were deemed relevant and have been included in section B.6.8.2. These papers discuss potential effects of maltodextrin on the intestinal tract when consumed as a food stuff as part of a maltodextrin enriched diet. A fifth paper which discusses metabolic and cognitive effects of sucrose and maltodextrin in rats is included in section B.6.8.2.5. The paper was not identified by the applicant but was considered relevant by the RMS.

Summaries of all five papers and their impact on the evaluation of maltodextrin as a plant protection product are presented in section B.6.8.2.

B.6.8.1. Toxicity studies on metabolites and relevant impurities

No studies have been submitted. This is considered acceptable as metabolites of maltodextrin are either shorter chain lengths of glucose or glucose itself and therefore metabolites are not relevant, and there are no relevant impurities that require testing (the source of maltodextrin is supplied to the food industry).

B.6.8.2. Supplementary studies on the active substance

B.6.8.2.1. Supplementary Study 1

Data Point	CA 5.8.2_1
Report Author	Laudisi et al.
Report Year	2019
Report Title	The Food Additive Maltodextrin Promotes Endoplasmic Reticulum Stress-Driven Mucus Depletion and Exacerbates Intestinal Inflammation
Report No	Cellular and Molecular Gastroenterology and Hepatology 2019;7:457–473.
Document No	N/A
Guidelines followed in study	None
Deviations from current test guideline	N/A
Previous evaluation	No, not previously submitted
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities (research study)
Acceptability	Yes; Reliable with restriction

EXECUTIVE SUMMARY

Background and aims: Food additives, such as emulsifiers, stabilizers, or bulking agents, are present in the Western diet and their consumption is increasing. However, little is known about their potential effects on intestinal homeostasis. In this study we examined the effect of some of these food additives on gut inflammation. Mice were given drinking water containing maltodextrin (MDX), propylene glycol, or animal gelatin, and then challenged with dextran sulfate sodium or indomethacin. In parallel, mice fed a MDX-enriched diet were given the endoplasmic reticulum (ER) stress inhibitor tauroursodeoxycholic acid (TUDCA). Transcriptomic analysis, real-time polymerase chain reaction, mucin-2 expression, phosphorylated p38 mitogen-activated protein (MAP) kinase quantification, and H&E staining was performed on colonic tissues. Mucosa associated microbiota composition was characterized by 16S ribosomal RNA sequencing. For the *in vitro* experiments, murine intestinal crypts and the human mucus-secreting HT29-methotrexate treated cell line were stimulated with MDX in the presence or absence of TUDCA or a p38 MAP kinase inhibitor.

Diets enriched in MDX, but not propylene glycol or animal gelatin, exacerbated intestinal inflammation in both models. Analysis of the mechanisms underlying the detrimental effect of MDX showed up-regulation of inositol requiring protein 1b, a sensor of ER stress, in goblet cells, and a reduction of mucin-2 expression with no significant change in mucosa associated microbiota. Stimulation of murine intestinal crypts and HT29-methotrexate treated cell line cells with MDX induced inositol requiring protein 1b via a p38 MAP kinase–dependent mechanism. Treatment of mice with TUDCA prevented mucin-2 depletion and attenuated colitis in MDX-fed mice.

MDX increases ER stress in gut epithelial cells with the downstream effect of reducing mucus production and enhancing colitis susceptibility.

MATERIALS AND METHODS

Test Material: Maltodextrin (dextrose equivalent)
Lot/Batch#: No data available
CAS # No data available
Source Sigma Milan, #419672
Vehicle: Drinking water

Test animals -

Species:	Mouse
Strain:	Balb/c
Age:	6-7 weeks
Source:	Charles River Laboratories Italia Srl (Rozzano, MI), Italy

Methods

In life dates:	No data available

Test System:

Animal treatment:	Mice were exposed to MDX (concentration range, 1%–5%), PG (0.5%), and GEL (5 g/L) in drinking water for 45 days. Water was changed every second day. During the last 10 days, animals received DSS (1.75%, #160110; MP Biomedicals, Santa Ana, CA) either in normal drinking water, or MDX-, PG-, or GEL-enriched drinking water. Mice were weighed daily. Mice were killed after 10 days of treatment with DSS and colon samples were collected for histology, protein and RNA extraction, and isolation of IECs and LPMCs. In parallel, mice receiving a MDX-enriched diet, together with control mice, were given 250 mg/kg TUDCA (Carbosynth Ltd, Berkshire, UK) intraperitoneally every other day starting from day 21 of diet. In additional experiments, mice were exposed to drinking water in the presence or absence of MDX 5% for 35 days and then injected subcutaneously with indomethacin (5 mg/kg, #I7378; Sigma). Mice were killed 24 hours later and ileal samples were collected for histologic analysis.
Cell Culture:	Intestinal Epithelial Cells (IECs) and Lamina Propria Mononuclear Cells (LPMCs) were isolated from murine colons. The mucous-secreting HT29-MTX cell line was obtained from the European Collection of Authenticated Cell Cultures (Public Health England, Porton Down, Salisbury, UK). In some experiments, HT29-MTX cells were pretreated with TUDCA (10 mmol/L) or a p38-MAPK inhibitor (S202190; Calbiochem, San Diego, CA) for 1 hour or transfected with p38 or a control siRNA (Santa Cruz Biotechnology, Dallas, TX) using Lipofectamine 3000 reagent (Invitrogen, Carlsbad, CA).
Measurements Taken:	Transcriptomic Analysis, Real-Time PCR, Quantification of Fecal Lipocalin-2 by Enzyme-Linked Immunosorbent Assay, Western Blot, Histopathologic Scoring and Immunohistochemistry, Immunofluorescence and Periodic Acid-Schiff–Alcian Blue Staining, Microbiota Analysis by 16S Ribosomal RNA Gene Sequencing, Overnight Fasting Blood Glucose Measurement
Statistics:	Parametric data were analyzed using the 2-tailed Student t test for comparison between 2 groups or 1-way analysis of variance followed by the Bonferroni post hoc test for multiple comparisons. Nonparametric data were analyzed using the Mann–Whitney U test for comparison between 2 groups or the Kruskal–Wallis test for multiple comparisons. Significance was defined as a P value less than .05.

RESULTS

Maltodextrin (MDX) Enriched Diet Exacerbates Intestinal Inflammation

The selected compounds induced neither clinical nor histologic signs of intestinal inflammation, nor changes in inflammatory cytokines. Analysis of Lipocalin-2 (Lcn-2), a sensitive and non-invasive biomarker of intestinal inflammation, in stool samples collected from mice exposed to MDX (5%), PG (0.5%), and GEL (5 g/L) showed

no significant change as compared with control mice, thus confirming the absence of colitis in mice fed such additives. However, MDX-fed mice developed a more severe colitis when challenged with dextran sulfate sodium (DSS), as shown by significantly greater weight loss, more pronounced infiltration of inflammatory cells, and greater epithelial damage. The MDX-fed mice also showed up-regulation of interleukin (IL)1b and Lcn-2 as compared with mice receiving PG- or GEL-enriched diet or controls. The deleterious effect of MDX on intestinal inflammation was more evident when it was used at a concentration of 5%, even though mice given 3% MDX showed a more pronounced inflammatory infiltrate as compared with control mice receiving drinking water. Therefore, all subsequent experiments were performed with 5% MDX. To exclude that the more severe colitis in MDX-treated mice was owing to increased uptake of DSS, we used another model of intestinal inflammation induced by a single subcutaneous injection of indomethacin. MDX-fed mice showed a more pronounced ileal mucosal injury compared with controls. Altogether, these data indicate that consumption of MDX in drinking water exacerbates gut inflammation.

MDX Activates an Endoplasmic Reticulum Stress Response in Intestinal Epithelial Cells

To dissect the mechanisms by which MDX enhances susceptibility to intestinal damage, a microarray analysis of colonic samples isolated from mice receiving MDX was performed. Several genes involved in the lipid and carbohydrate metabolism and in protein glycosylation were upregulated in MDX-treated mice. Mice given MDX also showed increased transcripts of molecules involved in the unfolded protein response (UPR), usually activated during a phenomenon termed endoplasmic reticulum(ER) stress. Among the UPR-related genes, Ern-2, which encodes for inositol-requiring enzyme (IRE)1b protein, was the most differentially expressed gene. Real-time polymerase chain reaction (PCR) assay of colonic samples confirmed the microarray results and showed up-regulation of Ern-1 and Xbp1s, 2 other IRE1/UPR-related genes. Further analysis of RNA transcripts in intestinal epithelial cells (IECs) and lamina propria mononuclear cells (LPMCs) isolated from colonic samples showed that induction of IRE1b/IRE1a was restricted to the intestinal epithelium compartment. *In vitro* stimulation of intestinal crypts from untreated mice with MDX enhanced RNA transcripts for Ern-1, Ern-2, and Xbp1s.

MDX-Enriched Diet Alters the Intestinal Mucus Barrier

The major macromolecular component of the gut mucus layer is the mucin glycoprotein Mucin-2 (Muc-2), and immunofluorescence analysis of colonic sections showed that MDX markedly reduced Muc-2 staining, as well as expression of glycosylated (mature) Muc-2. Moreover, periodic acid-Schiff/Alcian blue staining confirmed the negative effect of a MDX-enriched diet on mucus content. In contrast, MDX up-regulated Muc-2 RNA transcripts, a finding that could reflect activation of a compensatory mechanism to the reduced Muc-2 protein secretion. Enhanced staining for cleaved caspase-3, indicative of induction of intestinal epithelial apoptosis, was seen in colonic sections of MDX-treated mice.

Induction of ER Stress by MDX Is Mediated by p38 Mitogen-Activated Protein Kinase

The pathway(s) of MDX induced ER stress was also investigated. Stimulation of the mucus-secreting HT29-methotrexate treated cell line (HT29-MTX) cell line with 3% and 5% MDX up-regulated Ern-2 RNA transcripts. Treatment of HT29-MTX cells with MDX caused a time-dependent increase in the expression of phosphorylated (p)-p38, while extracellular signal–regulated kinase 1/2 and c-Jun N-terminal kinase activation remained unchanged. Pharmacologic inhibition of p38 downregulated MDX-induced Ern-2 RNA expression. Similar results were seen in MDX-treated cells transfected with p38 small interfering RNA (siRNA). Immunofluorescence of mouse colonic sections showed that daily consumption of MDX enhanced p-p38 expression in epithelial cells.

ER Stress Inhibition Improves Colitis in MDX-Fed Mice

To mechanistically prove that the enhanced susceptibility of mice to colitis after MDX administration relies on the ER stress/UPR pathway, ER stress was inhibited with the chemical chaperone tauroursodeoxycholic acid (TUDCA). Pretreatment of HT29-MTX cells with TUDCA significantly reduced MDX-mediated Ern-2 RNA expression. Administration of TUDCA to MDX treated mice resulted in diminished induction of Ern-2, Ern-1, and Xbp1s RNA expression and normalization of Muc-2 production. Mice receiving TUDCA showed a marked attenuation of DSS colitis after MDX administration, as evidenced by less changes in body weight, improved histology, and lower IL1b and Lcn-2 transcripts.

MDX-Enriched Diet Does Not Affect Mucosa-Associated Microbiota

Interrogation of microbiota composition with 16S RNA sequencing in colonic samples showed that MDX-fed mice did not show any changes in microbiota composition in terms of phyla and related classes, with low

frequency (<0.1%) of the genus E coli among groups. TUDCA treatment was associated with no change in microbiota composition.

Prolonged MDX-Enriched Diet Induces Low-Grade Intestinal Inflammation
Mice fed with MDX for 10 weeks showed no significant change in body weight and stool consistency. However, such animals showed low-grade intestinal inflammation, which was characterized by focal inflammatory infiltrates, distortion of gland architecture, edema, and increased transcripts for IL1b, Lcn-2, and Ern-2 as compared with control mice. As expected, mice receiving MDX had a marked reduction of Muc-2 protein. Because recent studies reported that low-grade inflammation induced by food additives was associated with metabolic alterations, we investigated whether a prolonged MDX-enriched diet could alter blood glycemic levels. Data indicate that the 15-hour fasting blood glucose level was higher in MDX-treated mice as compared with controls.

CONCLUSION
This study shows that a MDX-enriched diet reduces the intestinal content of Muc-2, thus making the host more sensitive to colitogenic stimuli. These data together with the demonstration that MDX can promote epithelial intestinal adhesion of pathogenic bacteria21 supports the hypothesis that Western diets rich in MDX can contribute to gut disease susceptibility

Assessment and conclusion by the applicant:

Assessment:

This study is considered relevant for the evaluation of Maltodextrin (MDX) as it investigates intestinal toxicity endpoints relevant to exposure of MDX. Presented studies were conducted in an appropriate species (mice), with a relevant route of exposure (via the diet) and at appropriate and conservative doses since the concentration of MDX selected for this study (i.e. 5%) is equivalent to levels commonly found in infant formulas, even though it is highly likely that the amount of MDX reaching the distal intestine from the ingestion of infant formula is lower than what was administered to mice. The data provide insights into the dose-response relationship of MDX inducing intestinal inflammation. The study is considered to be reliable with restriction (Klimisch score 2) as it was not stated whether the study follows an OECD test guideline or GLP. Also, the study is well documented and meets generally accepted scientific principles and statistical methods.

Conclusion:

This study shows that a Maltodextrin-enriched diet increased severity of intestinal inflammation and reduced the content of Muc-2 in the intestinal mucus barrier, thus making the host more sensitive to colitogenic stimuli. Maltodextrin activates endoplasmic reticulum stress in intestinal epithelial cells mediated by p38 mitogen-activated protein kinase. These data together with the demonstration that MDX can promote epithelial intestinal adhesion of pathogenic bacteria support the hypothesis that Western diets rich in Maltodextrin can contribute to gut disease susceptibility.

Assessment and conclusion by the RMS (IE, 2022):

The RMS agrees that the study is relevant to this evaluation and sufficiently reliable for evaluation. The findings of the study imply that maltodextrin can contribute to gut disease susceptibility. This raises concerns for human health because maltodextrin is a common additive in the Western diet, but should not impact this evaluation of maltodextrin as a plant protection product, where exposure would be meaningfully lower.

In an effort to quantify the exposure from use as a plant protection product compared to the exposure in the diet, the EFSA 'Calculator for non-dietary exposure to plant protection products' was used. As no reference values were allocated, a value of 83 mg/kg bw/day (taken from the conservative estimate of 5g consumed in the diet per person per day, (Evans and Hearty, 2020)), was set as a de facto reference value. Dermal absorption was set to the default value of 50% (EFSA, 2017) and all other variables followed the application data for the representative product Eradicoat. Using this approach, the exposure to operator was 3.01% of the RVNAS (Reference Value Non acutely toxic Active Substance) and to resident was 5.96% of the RVNAS, translating to exposure values of 2.5 and 6.8 mg/kg bw/day, respectively.

Given that the exposure is likely to be less than 6% of estimated daily food consumption of maltodextrin, use of

maltodextrin as a plant protection product is not likely to contribute to adverse effects on gut health.

B.6.8.2.2. Supplementary Study 2

Data Point	CA 5.8.2_2
Report Author	Nickerson, K.P. and McDonald, C., 2012
Report Year	2012
Report Title	Crohn's Disease-Associated Adherent-Invasive Escherichia coli Adhesion Is Enhanced by Exposure to the Ubiquitous Dietary Polysaccharide Maltodextrin
Report No	PLoS ONE 7(12): e52132
Document No	N/A
Guidelines followed in study	None
Deviations from current test guideline	N/A
Previous evaluation	No, not previously submitted
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities (research study)
Acceptability	Yes; Reliable with restriction

EXECUTIVE SUMMARY

Crohn's disease (CD) is associated with intestinal dysbiosis evidenced by an altered microbiome forming thick biofilms on the epithelium. Additionally, adherent-invasive E. coli (AIEC) strains are frequently isolated from ileal lesions of CD patients indicating a potential role for these strains in disease pathogenesis. The composition and characteristics of the host microbiome are influenced by environmental factors, particularly diet. Polysaccharides added to food as emulsifiers, stabilizers or bulking agents have been linked to bacteria-associated intestinal disorders. The escalating consumption of polysaccharides in Western diets parallels an increased incidence of CD during the latter 20th century. In this study, the effect of a polysaccharide panel on adhesiveness of the CD-associated AIEC strain LF82 was analyzed to determine if these food additives promote disease-associated bacterial phenotypes. Maltodextrin (MDX), a polysaccharide derived from starch hydrolysis, markedly enhanced LF82 specific biofilm formation. Biofilm formation of multiple other E. coli strains was also promoted by MDX. MDX-induced E. coli biofilm formation was independent of polysaccharide chain length indicating a requirement for MDX metabolism. MDX exposure induced type I pili expression, which was required for MDX-enhanced biofilm formation. MDX also increased bacterial adhesion to human intestinal epithelial cell monolayers in a mechanism dependent on type 1 pili and independent of the cellular receptor CEACAM6, suggesting a novel mechanism of epithelial cell adhesion. Analysis of mucosa-associated bacteria from individuals with and without CD showed increased prevalence of malX, a gene essential for MDX metabolism, uniquely in the ileum of CD patients. These findings demonstrate that the ubiquitous dietary component MDX enhances E. coli adhesion and suggests a mechanism by which Western diets rich in specific polysaccharides may promote dysbiosis of gut microbes and contribute to disease susceptibility.

MATERIALS AND METHODS

Test Material: Maltodextrin
Source: Spectrum chemicals
Test Material: Maltodextrin (fractionated)
Source: Sigma
Vehicle: No data available
Test system -
Species/strain: Human gastrointestinal tissue
Source: Cleveland Clinic Tissue Procurement Service (protocol IRB#12-383)
Tissue: Ileum, colon of Crohn's Disease patients
Age: Ileum: median: 34.9; range: 17-76
Colon: median: 32; range: 22-67
Sex: Ileum: 9 females, 9 males
Colon: 8 females, 8 males
Test system -

Cell culture:	HT29 cells Caco2 cells Raw264.7 cells Caco2:shCeacam6 cells Caco2:shControl stable knockdown cells
Methods	
In life dates:	No data available
Measurements Taken:	Quantitative Real Time PCR, Biofilm Formation Assays, Scanning Electron Microscopy, Type 1 Pili Expression Analysis, Cell Adhesion And Invasion Assays, Immunofluorescence
Statistical Analyses	Experiments were performed in triplicate and significance determined by ANOVA with post-hoc analysis using unpaired t-tests with equal variance. qPCR data was analyzed by non-parametric Wilcoxon test to accommodate the non-Gaussian distribution of the data set.

RESULTS

Maltodextrin enhances biofilm formation of CD-associated E. coli *in vitro*

Specific biofilm formation was strikingly enhanced in medium containing MDX relative to glucose-supplemented medium and more modestly increased in mannitol-containing medium. Biofilm formation was confirmed by microscopy in wells stained with Congo red to visualize exopolysaccharide matrix production, a hallmark of biofilm formation.

MDX is included as a bulking agent in the no-calorie sweeteners Equal® (aspartame) and Splenda® (sucralose). Using these commercial sources of MDX, the growth and biofilm formation of LF82 was assessed. LF82 grew robustly in media supplemented with Equal® or Splenda® and specific biofilm formation was strikingly enhanced in medium containing Equal® or Splenda® relative to glucose-supplemented medium. These findings indicate that MDX found in commercial sources can stimulate LF82 biofilm formation.

MDX promotes biofilm formation of multiple E. coli strains in a process dependent on MDX metabolism

A panel of E. coli strains including laboratory reference strains, additional AIEC strains, clinical isolates from individuals without inflammatory bowel disease and the probiotic E. coli Nissle 1917 were evaluated for growth and biofilm formation in medium supplemented with glucose or MDX. A majority of the strains tested (75%) showed a significant increase in MDX-stimulated specific biofilm formation relative to glucose-supplemented medium. These findings suggest that MDX affects a wide variety of E. coli strains and that this is not a unique feature of disease-associated strains.

Since the MDX tested is a heterogeneous mix of chain lengths, the effectiveness of different size MDXs to stimulate biofilm formation was investigated to determine whether a specific size range of MDX was required for this effect. All MDX-supplemented media, regardless of chain length, were sufficient to increase LF82 biofilm formation relative to glucose-supplemented medium in specific biofilm formation assays and confirmed by staining of biofilms with crystal violet or Congo red. While all MDX-supplemented media promoted biofilm formation, longer MDX chains were more effective, suggesting that metabolism of MDX may be important for biofilm enhancement.

MDX promotes type 1 pili expression which is required for enhanced biofilm formation

To identify candidate bacterial adhesins responsible for MDX-mediated biofilm formation, LF82 biofilms were visualized by scanning electron microscopy (SEM). At high magnification, an increase in short, thin, hair-like projections ranging between 0.5 mm to 1.5 mm in length could be seen protruding from the surface of LF82 grown in medium supplemented with MDX. One adhesin with these characteristics is type 1 pili, which has been described as a major adhesive structure of LF82.

Expression of type 1 pili is regulated by an invertible DNA element in the *fim* operon of the bacterial genome. The bacteria in MDX supplemented medium were more homogenous with the *fim* invertible element in the ‘‘on’’ position, suggesting that type 1 pili are adhesins upregulated by LF82 when grown in MDX-containing medium.

This adhesin was confirmed to be type 1 pili through the evaluation of isogenic mutant strains of LF82. A type 1 pili adhesin *fim*H knockout strain (Δ*fim*H) formed biofilms that were unaffected by the addition of MDX, whereas a flagellin knockout strain (Δ*fli*C) increased biofilm formation in MDX-containing medium. Taken together, this data demonstrates that MDX increases biofilm formation through the upregulation of type 1 pili expression.

Bacteria with genes for MDX metabolism are more prevalent in the ileal mucosa of CD patients

AIEC strains have been isolated from CD patients with ileal disease and are implicated in CD pathogenesis. A recent study observed that these AIEC strains are present at the time of disease diagnosis and these strains were associated with carriage of a virulence factor, malX. MalX is a MDX-binding component of the maltose/MDX metabolism system. As MDX-grown LF82 form robust biofilms, the authors hypothesized that MDX metabolism may be beneficial for colonization of E. coli in the terminal ileum of CD patients. DNA samples from intestinal mucosa were analyzed by qPCR for the presence of malX. Specifically in ileal samples, increased levels and prevalence of the malX gene in CD patients were observed as compared to controls (18% positive in ileal controls vs. 71% positive in ileal CD). The prevalence of E. coli 16S DNA was not increased in these samples, indicating that malX is not a marker for E. coli. These findings suggest a link between MDX utilization and microbial changes in ileal CD.

Additional Findings

Additional experiments conducted by the authors were able to further characterise the mechanism for these effects. They are considered by the RMS as beyond the scope of this review so are not discussed in detail, but can be summarised as showing that MDX enhances LF82 adhesion to intestinal epithelial cells and macrophages but does not promote invasion, LF82 adhesion to intestinal epithelial cells is enhanced by MDX in a type 1 pili dependent manner, MDX-enhanced LF82 adhesion to intestinal epithelial cells is independent of CEACAM6.

CONCLUSION

CD is a complex and multi-factorial disease with genetic, bacterial, and environmental factors contributing to disease pathogenesis, and the factors that contribute to changes in the microbiome of CD patients are not well understood. This study's findings, which showed increased adhesiveness and biofilm formation of E. coli grown in MDX, would suggest that exposure to MDX may be one factor which promotes the colonization of pathobionts, such as AIEC LF8. Overall, it describes a potential disease mechanism linking the ubiquitous dietary additive MDX to microbial changes in the intestine of CD patients.

Assessment and conclusion by the applicant:

Assessment:

This study is considered relevant for the evaluation of maltodextrin as it investigates whether maltodextrin promotes alterations in E. coli adhesion to human intestinal epithelium associated with Crohn's Disease. This toxicological endpoint is considered relevant as the gut is a likely target of exposure when maltodextrin is used as plant protection product. The selection of doses was based on consumption estimates. The study is considered adequate to support the assessment of maltodextrin as results provide insights into the potential and related mechanisms of maltodextrin contributing to factors associated with intestinal disease. The study is considered to be reliable with restriction (Klimisch score 2) as it was not stated whether the study follows an OECD test guideline or GLP. Experiments conducted under this study are well documented and meet generally accepted scientific principles and statistical methods.

Conclusion:

The study shows that Maltodextrin enhances biofilm formation of CD-associated E. coli *in vitro*, promotes biofilm formation of multiple E. coli strains in a process dependent on maltodextrin metabolism, type 1 pili expression which is required for enhanced biofilm formation, and enhances LF82 adhesion to intestinal epithelial cells and macrophages. These findings suggest a mechanism by which consumption of maltodextrin may promote intestinal disease in susceptible individuals.

Assessment and conclusion by the RMS (IE, 2022):

The RMS agrees that the study is relevant to this evaluation and sufficiently reliable for evaluation. It provides evidence to suggest that consumption of maltodextrin may promote intestinal disease in susceptible individuals. The authors note that CD is a complex and multi-factorial disease and that factors that contribute to changes in the microbiome of CD patients are not still not well understood. Taking this into consideration, the findings

should not impact the outcome of this evaluation of maltodextrin as a plant protection product. The study is included for the sake of completeness and should only be considered as supportive.

B.6.8.2.3. Supplementary Study 3

Data Point	CA 5.8.2_3
Report Author	Nickerson et al.
Report Year	2014
Report Title	The Dietary Polysaccharide Maltodextrin Promotes Salmonella Survival and Mucosal Colonization in Mice
Report No	PLoS ONE 9(7): e101789
Document No	N/A
Guidelines followed in study	None
Deviations from current test guideline	N/A
Previous evaluation	No, not previously submitted
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities (research study)
Acceptability	Yes; Reliable with restriction

EXECUTIVE SUMMARY

In the latter half of the 20th century, societal and technological changes led to a shift in the composition of the American diet to include a greater proportion of processed, pre-packaged foods high in fat and carbohydrates, and low in dietary fibre (a ‘‘Western diet’’). Over the same time period, there have been parallel increases in *Salmonella* gastroenteritis cases and a broad range of chronic inflammatory diseases associated with intestinal dysbiosis. Several polysaccharide food additives are linked to bacterially driven intestinal inflammation and may contribute to the pathogenic effects of a Western diet. Therefore, we examined the effect of a ubiquitous polysaccharide food additive, maltodextrin (MDX), on clearance of the enteric pathogen Salmonella using both *in vitro* and *in vivo* infection models. When examined *in vitro*, murine bone marrow derived-macrophages exposed to MDX had altered vesicular trafficking, suppressed NAPDH oxidase expression, and reduced recruitment of NADPH oxidase to Salmonella-containing vesicles, which resulted in persistence of Salmonella in enlarged Rab7+ late endosomal vesicles. *In vivo*, mice consuming MDX-supplemented water had a breakdown of the antimicrobial mucous layer separating gut bacteria from the intestinal epithelium surface. Additionally, oral infection of these mice with Salmonella resulted in increased cecal bacterial loads and enrichment of lamina propria cells harbouring large Rab7+ vesicles. These findings indicate that consumption of processed foods containing the polysaccharide MDX contributes to suppression of intestinal anti-microbial defence mechanisms and may be an environmental priming factor for the development of chronic inflammatory disease.

MATERIALS AND METHODS

Test Material: Maltodextrin, (4.5 g/L)
Source: Spectrum Chemicals, New Brunswick, New Jersey
Test Material: Maltodextrin (MDX) and glucose mixture
Source: MDX: Spectrum Chemicals, New Brunswick, New Jersey
Glucose: Sigma, Saint Louis, Missouri
Mixture composition: 25% MDX= 1.125 g/L MDX, 3.375 g/mL glucose for a total of 4.5 g/L
Test system -
Cell culture: HCT116 cells
HT29 cells
Test system -
***In vitro* system:** Primary human peripheral blood monocytes
Source: Cleveland Clinic Clinical and Translational Sciences Collaborative (protocol IRB#08-957)
Test system -
***In vitro* system:** Murine bone marrow-derived macrophages (BMDM)

Species:	Mouse
Strain:	C57BL/6 and AKR
Sex:	C57BL/6 mice: Female
Age:	C57BL/6 mice: 6 weeks
Source:	C57BL/6 mice: Jackson Laboratories, Bar Harbor, Maine (stock number 000664) AKR mice: Case Western Reserve University, Cleveland, Ohio
Diet:	Harlan Teklad Global Irradiated Rodent Diet 2918
Water:	No data available

Methods

In life dates:	No data available
Measurements/Procedures:	*Salmonella* Infections, Immunofluorescent staining and confocal microscopy, Reactive oxygen species measurement, Immunoblot analysis of NADPH oxidase expression, Fluorescent *in situ* hybridization
Statistical analysis	Statistical analyses were performed using Prism software (Graph Pad) and p values ≤0.05 were considered significant. *In vitro* experiments were performed in triplicate in a minimum of three independent experiments and analyzed by either ANOVA or two-tailed, unpaired t-test to determine significance. *In vivo* experiments were conducted with a total of 6 control mice and 7 experimental group mice and analyzed using a two-tailed Mann-Whitney test to account for unequal variance. Data is presented as averages with standard error unless noted in the figure legend.

RESULTS

MDX exposure impairs *Salmonella* clearance from intestinal epithelial cells and macrophages

MDX exposure enhanced intracellular *Salmonella* survival in human intestinal epithelial cell lines, primary human monocyte-derived macrophages, and murine bone marrow-derived macrophages (BMDM). These results were confirmed by visualization of bacterial loads in BMDM by confocal microscopy. The effects of MDX on *Salmonella* clearance were also dose-dependent, with impaired clearance observed in BMDM cultured in media reconstituted with a 25% MDX/75% glucose mix and further suppressed as the proportion of MDX increased in the media.

***Salmonella* entry and trafficking to early endosomes are unaffected by MDX exposure**

Increased intracellular bacterial loads in MDX exposed cells could be a result of defective bacterial clearance or enhanced bacterial entry. To discriminate between these two possibilities, the initial cellular entry of *Salmonella* was assessed by confocal microscopy and gentamycin protection assays in BMDM. Analyses of confocal micrographs showed that *Salmonella* is immediately trafficked to a $Rab5^+$ early endosome in both media conditions. As early as 15 minutes post-infection, equivalent numbers of *Salmonella* co-localize with $Rab5^+$ vesicles in both control and MDX exposed cells. These findings indicate that MDX does not affect *Salmonella* entry or early trafficking events.

MDX promotes a new replicative niche for *Salmonella*

Salmonella is a facultative intracellular pathogen that replicates within specialized, *Salmonella*-containing vesicles (SCV). These SCV acquire markers of late endosomes (Rab7) and selective lysosome-associated membrane proteins (LAMPs) without accumulation of lysosomal hydrolytic enzymes through the action of bacterial effector proteins. The co-localization of *Salmonella* with $Rab7^+$ vesicles was assessed in BMDM cultured in glucose- or MDX-supplemented media. At 90 minutes post-infection, a dramatic difference in the total number of $Rab7^+$ vesicles was apparent (~2 fold increase). In addition to a greater intracellular *Salmonella* load, MDX exposed BMDM had more enlarged (>0.5 μm), $Rab7^+$ vesicles as compared to glucose cultured cells. Quantitation of confocal micrographs demonstrated an enrichment of *Salmonella* within large, $Rab7^+$ vesicles in MDX cultured cells. Rab7 is essential for the recruitment and transfer of LAMPs to the SCV. Surprisingly, although MDX enhanced Rab7 accumulation on SCVs, the total number of *Salmonella* co-localized with $Lamp2^+$ vesicles was not different between glucose or MDX exposed cells. These results suggest that MDX does not block SCV maturation, but promotes accumulation of *Salmonella* in enlarged $Rab7^+$ vesicles that may function as a new replicative niche for these bacteria.

Dietary MDX consumption alters the intestinal antimicrobial barrier and enhances mucosal *Salmonella* colonization

The effect of MDX consumption on the clearance of an enteric pathogen *in vivo* was assessed using the streptomycin pre-treatment mouse model of Salmonella colitis. The drinking water of 6 week old female C57BL/6 mice was supplemented with 5% MDX for 2 weeks. Confocal micrographs visualized a striking decrease in the separation of bacteria from the epithelial layer in MDX-supplemented mice. The enhanced infiltration of bacteria into the anti-microbial zone in these mice was quantitatively confirmed using an established scoring system, suggesting that MDX consumption alters the intestinal antimicrobial barrier.

Upon *Salmonella* infection, MDX-supplemented mice had enhanced cecal *Salmonella* colonization relative to control mice 48 hours post-infection, as demonstrated by a ~2.5-log increase in viable bacteria recovered from cecal homogenates.

CONCLUSION

These findings demonstrate that MDX exposure promotes the formation of a novel protective niche for *Salmonella* through dampening host anti-microbial responses to enhance intracellular survival and mucosal colonization. These results suggest that consumption of processed foods containing the polysaccharide MDX may contribute to a greater risk for enteric infection may be an environmental priming factor for the development of chronic inflammatory diseases, such as inflammatory bowel disease.

Assessment and conclusion by the applicant:
Assessment: This study investigated effects of Maltodextrin on intestinal anti-microbial defence mechanisms, specifically the clearance of the enteric pathogen Salmonella, using both *in vitro* and *in vivo* infection models. This study is considered relevant for the evaluation of Maltodextrin as the gut is a likely target of exposure when Maltodextrin is used as plant protection product. The experiments presented in this study were conducted in human and murine cells and cell lines. In the drinking water study in mice, the concentration of Maltodextrin selected was based on the amount of Maltodextrin commonly used in infant formulas which results in exposure considerably higher than human exposure expected from the substance's use as plant protection product. The data presented in this study are considered adequate to support the assessment of Maltodextrin as results provide insights into the potential and related mechanisms of Maltodextrin contributing to intestinal disease. The study is considered to be reliable with restriction (Klimisch score 2) as it was not stated whether the study follows an OECD test guideline or GLP. Experiments conducted under this study are well documented and meet generally accepted scientific principles and statistical methods. **Conclusion:** The study shows that Maltodextrin consumption may be a contributory factor in bacterially-driven pathologies by reducing host anti-microbial defences, resulting in a new niche for *Salmonella* survival in macrophages and the intestinal mucosa.

Assessment and conclusion by the RMS (IE, 2022):
The RMS agrees that the study is relevant to this evaluation and sufficiently reliable for evaluation. The findings of the study indicate that consumption of processed foods containing maltodextrin may act as an environmental priming factor for the development of chronic inflammatory disease. They do not however provide evidence that maltodextrin, when used as a plant protection product, contributes to this. The study is included for the sake of completeness but should only be considered as supportive.

B.6.8.2.4. Supplementary Study 4

Data Point	CA 5.8.2_4
Report Author	Nickerson et al., 2015
Report Year	2015
Report Title	Deregulation of intestinal anti-microbial defence by the dietary additive, maltodextrin
Report No	Gut Microbes 6:1, 78-83
Document No	N/A

Guidelines followed in study	None
Deviations from current test guideline	N/A
Previous evaluation	No, not previously submitted
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities (research study)
Acceptability	Yes; Reliable with restriction

EXECUTIVE SUMMARY

Inflammatory bowel disease (IBD) is a complex, multi-factorial disease thought to arise from an inappropriate immune response to commensal bacteria in a genetically susceptible person that results in chronic, cyclical, intestinal inflammation. Dietary and environmental factors are implicated in the initiation and perpetuation of IBD; however, a singular causative agent has not been identified. As of now, the role of environmental priming or triggers in IBD onset and pathogenesis are not well understood, but these factors appear to synergize with other disease susceptibility factors. Previous work determined that the polysaccharide dietary additive, maltodextrin (MDX), impairs cellular anti-bacterial responses and suppresses intestinal anti-microbial defence mechanisms. This addendum reviews potential mechanisms for dietary deregulation of intestinal homeostasis and how dietary and genetic risk factors may combine to result in disease pathogenesis, and discusses these ideas in the context of recent findings related to dietary interventions for IBD.

METHOD

No data available. The method of how the review was performed is not stated.

RESULTS

Maltodextrin (MDX) is a Common Food Additive That Alters Both Microbial Phenotype and Host Anti-Bacterial Defences

Since the mid-1950s, MDX has been added to foods as a filler, thickener, texturizer, or coating agent and is generally recognized as safe (GRAS) by the Federal Drug Agency (FDA). In a survey of grocery store food, it was found that ~60% of all packaged items had "maltodextrin" or "modified (corn, wheat, etc.) starch" included in their ingredients list. Furthermore, results of a food frequency questionnaire indicated that 98.6% (210/213) of respondents routinely consume food items containing MDX, with an average consumption of 2.6 MDX-containing items per day. These surveys demonstrate that MDX is currently a ubiquitous and frequently consumed dietary polysaccharide additive in the general population.

Increasing evidence supports a modulatory relationship between commensal bacteria, host immune responses, and diet. The authors found in previous work that patients with ileal CD have a mucosal microbiome enriched for MDX metabolism, as compared to colonic CD patients and non-IBD controls (Nickerson KP and McDonald, 2012). MDX consumption also influences cellular functions and shapes host-microbial interactions, as demonstrated by the increased viability of intracellular Salmonella in macrophages and epithelial cells cultured in MDX-supplemented media. When the effects of MDX exposure were further examined *in vivo* using a murine Salmonella infection model, alterations in intestinal homeostasis were observed. These findings indicate that although MDX consumption does not cause intestinal disease in healthy, adult mice, it may prime the intestine for disease development through impairment of anti-bacterial cellular responses, decreases in mucosal barrier defences, and promotion of E. coli strain adhesion (Nickerson et al., 2014).

Diet-Driven Mucosal Barrier Alterations Related to IBD Pathogenesis

Consumption of carbohydrates and simple sugars directly alter cellular sugar concentrations, which can alter glycosylation patterns and amounts of glycosylated proteins produced by goblet cells. Modifications in mucosal glycosylation patterns can lead to enhanced degradation by mucolytic bacteria, and a survival advantage for these microbes in close proximity to the epithelium. It has been hypothesized that bacterial infection acts as an initiating event in the development of IBD, where inflammation is unresolved despite clearance of the offending pathogen. The authors postulate that defects in mucosal barrier integrity would occur in MDX-supplemented mice and that they would be more prone to expansion of pathobionts, such as AIEC. It may be that a diet rich in MDX leads to alterations in the commensal microbiome and cellular glycome which leads to increased susceptibility to enteric pathogen infection and IBD development.

Dietary Studies: From *In Vitro* Observations to Clinical Efficacy

Recent studies of dietary interventions in IBD patients have demonstrated promising results in promoting clinical remission of IBD, which include the Specific Carbohydrate Diet (SCD) and the IBD-Anti-Inflammatory Diet (IBDAID). Interestingly, in context of our studies, both of these dietary paradigms exclude pre-packaged and commercially processed food products, effectively eliminating MDX (and other related emulsifiers and texturizers) from their diet as well.

Cultivating a Greater Understanding of the Effect of Diet on Human Health
The authors postulate that dietary additives, such as MDX, are potentiators of disease and, if true, could explain the suggested efficacy of seemingly disparate diets (i.e. enteral nutrition, parenteral nutrition, gluten-free diets, elemental diets, etc.) on intestinal inflammation. Uncovering these mechanisms of disease and examining how they interact with other IBD risk factors, such as genetics, would provide us with opportunities to more effectively resolve existing disease and the exciting possibility to prevent it in susceptible individuals.

Assessment and conclusion by the applicant:
Assessment: In this addendum, the authors review potential mechanisms for dietary deregulation of intestinal homeostasis, postulate how dietary and genetic risk factors may combine to result in disease pathogenesis, and discuss these ideas in the context of recent findings related to dietary interventions for inflammatory bowel disease (IBD). Maltodextrin is discussed as one of various factors potentially contributing to IBD. It also needs to be considered that this review primarily assesses data which are related to maltodextrin exposure from food which is considerably higher than human exposure expected from the substance's use as plant protection product. Therefore, this study is considered reliable with restriction. **Conclusion:** Potential mechanisms for dietary deregulation of intestinal homeostasis caused by maltodextrin as well as other additives (e.g. emulsifiers and thickeners) are discussed. The authors postulate that dietary additives, such as maltodextrin, are potentiators of disease and, if true, could explain the suggested efficacy of seemingly disparate diets (i.e. enteral nutrition, parenteral nutrition, gluten-free diets, elemental diets, etc.) on intestinal inflammation.

Assessment and conclusion by the RMS (IE, 2022)
The RMS agrees that the study is relevant to this evaluation and sufficiently reliable for evaluation. It reviews the role of dietary maltodextrin in deregulation of intestinal homeostasis, how this interacts with other IBD risk factors and how specialised diets can open the possibility for prevention in susceptible individuals. The review focuses on dietary maltodextrin, which is a ubiquitous and frequently consumed dietary polysaccharide additive in the general population. Considering the ubiquity of maltodextrin in the diet, exposure as a plant protection product is expected to be low in comparison. The study is included for the sake of completeness but should only be considered as supportive.

B.6.8.2.5. Supplementary Study 5

Data Point	CA 5.8.2_5
Report Author	Kendig et al.
Report Year	2014
Report Title	Maltodextrin can produce similar metabolic and cognitive effects to those of sucrose in the rat
Report No	Appetite 77C (2014) 1–12
Document No	N/A
Guidelines followed in study	None
Deviations from current test guideline	N/A
Previous evaluation	No, not previously submitted
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities (research study)
Acceptability	Yes; Reliable with restriction

EXECUTIVE SUMMARY

In the context of the well-documented metabolic and behavioural effects of supplementing rats' diets with access to a sucrose solution, the aim of this study was to compare the impact of 10% sucrose with that of an isoenergetic (10.4%) solution of hydrolysed starch, maltodextrin. This polysaccharide is metabolised at least as rapidly as sucrose and is also very palatable to rats, but does not contain fructose. Each of three experiments contained three groups: one given a sucrose solution, one given a maltodextrin solution and a control group maintained on standard chow and water alone. In Experiment 1 the sucrose and maltodextrin groups were given their supplementary drinks for 2 h each day, while in Experiments 2 and 3 these groups had 24-h access to their supplements. Ad libitum access to maltodextrin produced at least as rapid weight gain as sucrose and in Experiment 2 retroperitoneal fat mass was greater in the two carbohydrate groups than in the control group. Moreover, in Experiment 3, impaired performance on a location recognition task was also found in both carbohydrate groups after only 17 days on the diets. These results indicate that the harmful effects of excess sucrose consumption can also be produced by another rapidly absorbed carbohydrate that does not contain fructose.

METHODS

Male albino Wistar rats were group-housed (n = 4 or 5/cage) in a room on a 12:12-h light-dark cycle (lights on at 06:00 h), at temperature of 23–25°C and humidity of 40–45%. After 8 days of acclimatisation, the animals were weighed and transferred to individual cages measuring 46 × 27 × 32 cm. The 30 rats used in each experiment were 8–11 weeks old when randomly allocated to three groups (each n = 10) of similar mean body weights.

Table 7: Experimental Set Up

Experiment	Exposure	Test
1	2 h access for 78 days	MWM Test + Metabolic Measures
2	Unrestricted access for 77 days	MWM Test + Metabolic Measures
3	Unrestricted access for 18 days	Hippocampus-Dependent Spatial and Memory Test

Dietary Interventions

The solutions were given in 100-ml plastic bottles with metal ball-bearing spouts inserted into the animals' individual home cages. Both carbohydrate solutions provided an energy density of approx. 1.65 kJ/g and were made in tap water with 10% w/v sucrose (16.5 kJ/g, Coles white sugar; Victoria, Australia) or 10.4% w/v maltodextrin powder (15.9 kJ/g, Polycose® from Ross Nutrition, Abbott Laboratories; Columbus, Ohio, USA). Control rats received an additional bottle of tap water. Standard laboratory chow (Speciality Feeds®, 14.24 kJ/g; 20% protein, 4% fat, 60% carbohydrate) and tap water were available *ad libitum* throughout the protocol. For the first 48 days of the 77-day dietary intervention in Experiment 2 the source of maltodextrin was still Polycose®, but, when this became unavailable in Australia, a local source (Myopure; http://www.myopure.com.au) provided maltodextrin of the same energy density for the remaining 29 days. This source was also used for the maltodextrin used in Experiment 3, where the dietary intervention was for only 18 days.

Metabolic Measures

In Experiment 1, fasting blood glucose, insulin and leptin were measured following 6-h fasting periods. The same measures were taken in Experiment 2 following the 12-h fasting periods, except that leptin was not measured. In Experiments 1 and 2 retroperitoneal fat pad mass was measured post-mortem on the day following completion of the dietary interventions. Rats were sacrificed by intraperitoneal injection of 500 µl pentobarbitone sodium anaesthetic euthanasia solution and retroperitoneal fat pads were excised and weighed.

Behavioural Measures

Morris Water Maze Test: In Experiment 1 the 12-day Morris water maze training and test procedure consisted of three blocks (repetitions) of three training days and one test day. The maze was a large circular pool 200 cm in diameter and 60 cm in height filled with 50 cm depth of warm (25 +/- 1 deg) water that was made opaque by adding a small amount of nontoxic white paint. A small clear platform (diameter 15.8 cm) was located in the centre of one quadrant of the maze. This was submerged just below the surface of the water so that rats could rest there safely after locating it. Maze training began on Day 65, with rats continuing to receive 2-h drinking sessions of sucrose, maltodextrin or water control after the conclusion of maze training. On training days, the animals were trained twice a day between 10:00 and 16:00 h and entered the water maze from either quadrant adjacent to the target quadrant. The entrance to the water maze for each rat alternated between each trial and was

consistent between groups. Trials ended after 2 min of searching in the maze or when the rats located the target platform. Rats were placed on the platform for 10 sec if they did not locate the target within 2 min. All animals were then dried and returned to their home cages. On the three test days, the animals were tested between 10:00 and 12:00 h and entered the water maze from the opposite quadrant to the target quadrant. The target platform was removed and rats were given a 1-min probe trial. The outcome measures were latency to reach to target quadrant, latency to reach the target annulus (circular region of 30 cm in diameter around the target platform area), latency to reach the target platform location, time spent in target quadrant, and average distance to target platform location.

Hippocampus-Dependent Spatial and Memory Test: Testing was carried out in a black wooden arena with a black PVC base marked with a white grid dividing the arena into 16 equal sized squares. The sets of objects used were commercial products (e.g. lunch box container, cooking sauces, tinned food) made of a variety of materials (plastic, glass, aluminium and porcelain) and varied in both height and width. Each object was only used for one trial per rat. Rats were first given two 10-min habituation sessions (Days 1 and 2) in the empty arena on consecutive days. On Day 3 half of the rats received an object test and the remainder received a location recognition test. On Day 4 rats that had received the object test now received the location test and vice versa. Every test throughout the experiment contained a 5-min familiarisation phase followed 5 min later by a 3-min test phase. In the familiarisation phase the rat was placed into the centre of the arena with two identical sample objects, which were located in two of the middle four squares, and allowed to explore. The rat was then removed and the arena and objects were cleaned with a 50% ethanol solution. For the object test phase, two objects were placed in the same position as in the familiarisation trial. While one of these objects was identical to the sample object previously presented, the other was a novel object. In the location test phase, the two objects were the same as in familiarisation, but one was moved to one of the corners of the arena. The dietary manipulation began after the completion of baseline testing on Day 4. The object and place recognition tests were repeated on Days 12 and 13, i.e. after 8 to 9 days on the diet, and on Days 21 and 22, i.e. after 17 to 18 days on the diet. The time of day for testing an individual rat was held constant across sessions and the object order and location were counterbalanced between rats and across trials. Exploration was defined as a rat's head within 2 cm of the object with the neck extended and vibrissae moving around the object. Recognition was measured in terms of an Exploration Ratio: time spent exploring the novel object (or object in the novel location) divided by the time spent exploring both objects ($t_{novel}/(t_{novel} + t_{old})$. Individual rat data were excluded if an object was knocked over during either a familiarisation or test phase.

Statistical Analysis

One-way and mixed ANOVAs were followed by post hoc Tukey tests to evaluate the data reported below. In all experiments critical F was chosen to maintain the type 1 error rate at less than 0.05. Data were analysed with IBM SPSS Statistics 20.

RESULTS

Bodyweight, fluid consumption and energy intake

In Experiment 1 there were no differences between the groups in terms of body weight at any stage of the intervention. The contribution of the carbohydrate drinks to total energy intake remained less than 10%. In Experiment 2, body weight gain by the Maltodextrin group was greater than the gain by the Sucrose group, but not significantly different from the gain by the Control group. Consumption of maltodextrin, with an overall mean 24-h intake of 130.15 ml, was consistently higher than of sucrose, with an overall 24-h intake of 100.89 ml, throughout the diet intervention. Maltodextrin rats derived a greater proportion of total energy from their carbohydrate drink, 46.5%, than sucrose rats did from sucrose, 38.8%, $F(1,17) = 6.88$, $P = 0.018$. Consumption of maltodextrin. In Experiment 3, the two carbohydrate groups gained weight at a faster rate than the Control group. there were no significant differences in energy intake between the Sucrose and Maltodextrin groups, with both groups deriving around 37% of their energy from the carbohydrate solutions, $F < 1$.

Metabolic Measures

In Experiment 1, there were no significant differences between groups in any metabolic measurement. In Experiment 2, fasting blood glucose levels were higher in the Maltodextrin group than in the Sucrose and Control groups, but not significantly. For retroperitoneal fat mass, the Maltodextrin group had higher g/kg fat than the Control group, $P = 0.006$, but did not differ significantly from the Sucrose group. No metabolic measures were taken in Experiment 3.

Spatial Learning and Memory Tests

In neither Experiment 1 nor Experiment 2 did the groups differ on any measure of spatial learning in the Morris Water Maze, all Fs < 1. For the object and location recognition tests used in Experiment 3, baseline recognition ratios and total exploration times were similar across the diet groups and across the two tasks. After 8-9 days on the diets, recognition ratios were still similar across the groups and on both tests, largest F=1.14. After 17–18 days on the diets, all groups were still performing well on the object task and at a comparable level, $F(2,26) = 3.230$, $P = 0.056$, but they differed considerably on the location task, $F(2,27) = 14.254$, $P < 0.001$. Specifically, the ability of the Sucrose and Maltodextrin groups to recognise that an object was in a new location was near chance, while the Control group continued to perform at a high level, all ps < 0.001.

CONCLUSION

In terms of bodyweight and metabolic measures, the study showed that when rats derived < 10% of their energy from carbohydrate solutions, as in Experiment 1, they could reduce their chow intake to compensate and prevent impact on their weight and metabolism compared to controls. Conversely, when the rats derived a large proportion of their energy from carbohydrate solutions, as in Experiment 2, they did not reduce their intake of chow sufficiently, and deposited more retroperitoneal fat than controls. For behaviour, the study shows that consumption of 10% sucrose or maltodextrin solution for less than 3 weeks can impair performance on a hippocampus-dependent short-term location recognition task, but does not impair a very similar object recognition task. The lack of effect observed in the MWM tests may be because it is insensitive to hippocampal damage.

Assessment and conclusion by the RMS (IE, 2022):
This study was exploratory in nature and not intended to inform a regulatory toxicology endpoint. It is considered relevant by the RMS because it investigates metabolic and behavioural effects of maltodextrin using a well-defined test material in a relevant test species (mice) and using a relevant route of exposure (in drinking water). The study is also considered reliable because it follows scientifically valid principles (use of control group, randomisation, blinded scoring) and is well documented. As the experiments were not conducted under GLP condition and did not follow an OECD Guideline, the study is considered reliable with restriction. The results of the study indicate that, just like sucrose, excessive intake of a maltodextrin solution can produce faster weight gain, larger retroperitoneal fat pads and poorer spatial cognition compared to control animals. This potential neurotoxicity is an interesting finding but, in the view of the RMS, this single study does not provide sufficient information on this endpoint to draw a clear conclusion. Furthermore, the dose to mice in this study from a 10.4% drinking solution is equivalent to approximately 13g maltodextrin/day, which is considerably higher than predicted exposure as a plant protection product. The study is included for the sake of completeness but should only be considered as supportive.

B.6.8.2.6. Overall Conclusion

Five supplementary studies on maltodextrin have been obtained from the literature. Four of these examine the role of maltodextrin in chronic intestinal disorders such as Crohn's disease (CD) and ulcerative colitis (UC), which are the principal forms of inflammatory bowel diseases (IBD). In recent years, the frequency of intestinal and systemic immune-inflammatory disorders has increased in previously low incidence areas, likely due in part to the Westernization of dietary habits. Maltodextrin is a food additive commonly used within the Western diet and accumulating evidence suggests that MDX can impair gut homeostasis and promote intestinal pathologies (Laudisi et al, 2019b). In an investigation into the effect of MDX on gut inflammation, Laudisi et al. (2019a, Supplementary Study 1) demonstrated that mice receiving MDX for 5 weeks in drinking water exhibited ERS activation in goblet cells, which was accompanied by decreased mucus production and increased susceptibility to colitogenic stimuli. It was further shown that long-term oral intake of MDX (i.e., 10 weeks) can promote low-grade intestinal inflammation in mice, with alterations of colonic morphology and increased expression of the inflammatory markers. When researching Crohn's Disease, Nickerson and McDonald observed that that MDX favours the adhesiveness of the CD-associated adherent and invasive E. coli (AIEC) strain LF82, which have been isolated from CD patients with ileal lesions and are supposed to play a pathogenic role in this disorder. Furthermore, AIEC strains carry the virulence factor MalX, which is an MDX-binding component of the maltose/MDX metabolism system, and MDX-grown LF82 form robust biofilms, suggesting that MDX metabolism may help colonization of E. coli in the terminal ileum (Nickerson and McDonald, 2012, Supplementary Study 2). The same researchers later recorded an impaired anti-bacterial response to Salmonella infection in mice receiving oral MDX, as well as an increase in bacteria mucosal colonization through alterations

of the intestinal epithelial barrier (Nickerson et al., 2014, Supplementary Study 3). These studies document an ability of MDX to exacerbate intestinal inflammation and deregulate intestinal anti-microbial defences. Taking all of this evidence into consideration, it appears that MDX may contribute to Inflammatory Bowel Disease (IBD) by acting as an environmental priming factor and potentiator of disease (Nickerson et al., 2015, Supplementary Study 4). However, IBD is a complex, multi-factorial disease and our understanding of the role of MDX in IBD is still rudimentary in nature. Additionally, predicted exposure from use as a plant protection product is relatively low (<6% of daily consumption from the diet) and not via the oral route of exposure, so it is concluded that use of maltodextrin as a PPP is not likely to contribute to adverse effects on gut health.

The fifth study reported on metabolic and cognitive effects of maltodextrin in rats and compared them with those of sucrose. The only important findings on metabolic effects were a higher g/kg retroperitoneal fat mass in the maltodextrin group than the control group, however this was not significantly different from the sucrose group. In the assessment of cognitive effects, it was shown that consumption of either 10% sucrose or maltodextrin solution for less than 3 weeks can impair performance on a hippocampus-dependent short-term location recognition task, but not a similar object recognition task. In the opinion of the RMS, this finding alone is not substantive enough to be toxicologically relevant for this evaluation of maltodextrin.

B.6.8.3. Studies on endocrine disruption

No data required. The source of maltodextrin is unchanged and is supplied to the food industry and maltodextrins continue to have widespread uses in food, feed, cosmetics and medicinal products. They are considered to be food ingredients, and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008) as are all starches treated with amylolytic enzymes. There is no upper level on their use as a food ingredient and there are few restrictions on the types of products in which they can be used. It is therefore not necessary to provide any data/information on endocrine disrupting properties.

B.6.9. MEDICAL DATA AND INFORMATION

Medical data are not considered necessary. During the previous EU review it was not necessary to provide any data on the toxicological properties of maltodextrin. EFSA concluded:

> "Considering the fact that maltodextrin is rapidly metabolised with metabolites being a standard energy source (e.g. glucose), and considering also its uses as a food additive, in cosmetics and in medicinal products, maltodextrin is of low toxicological concern and no risks to human health are expected from its use as a plant protection product. Therefore, data waivers for specific toxicological studies with maltodextrin are supported, reference values are not allocated, and no quantitative risk assessment for operator, worker and bystander exposure is considered necessary" (EFSA Journal 2013;11(1):3007).

This approach remains valid. The source of maltodextrin is unchanged and is supplied to the food industry and maltodextrin continues to have widespread uses in food, feed, cosmetics and medicinal products.

B.6.9.1. Medical surveillance on manufacturing plant personnel and monitoring studies

No data required. The source of maltodextrin is unchanged and is supplied to the food industry and maltodextrins continue to have widespread uses in food, feed, cosmetics and medicinal products. They are considered to be food ingredients, and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008) as are all starches treated with amylolytic enzymes. There is no upper level on their use as a food ingredient and there are few restrictions on the types of products in which they can be used. For these reasons, no data are available on medical surveillance. The literature search also did not find any relevant articles other than those summarised under B.6.8.2.

B.6.9.2. Data collected on humans

No data required. The source of maltodextrin is unchanged and is supplied to the food industry and maltodextrins continue to have widespread uses in food, feed, cosmetics and medicinal products. They are considered to be food ingredients, and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008) as are all starches treated with amylolytic enzymes. There is no upper level on their use as a food ingredient and there are few restrictions on the types of products in which they can be used. The literature search also did not find any relevant articles other than those summarised under B.6.8.2.

B.6.9.3. Direct observation

No data required. The source of maltodextrin is unchanged and is supplied to the food industry and maltodextrins continue to have widespread uses in food, feed, cosmetics and medicinal products. They are considered to be food ingredients and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008) as are all starches treated with amylolytic enzymes. There is no upper level on their use as a food ingredient and there are few restrictions on the types of products in which they can be used. The literature search also did not find any relevant articles other than those summarised under B.6.8.2.

B.6.9.4. Epidemiological studies

No data required. The source of maltodextrin is unchanged and is supplied to the food industry and maltodextrins continue to have widespread uses in food, feed, cosmetics and medicinal products. They are considered to be food ingredients and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008) as are all starches treated with amylolytic enzymes. There is no upper level on their use as a food ingredient and there are few restrictions on the types of products in which they can be used. The literature search also did not find any relevant articles other than those summarised under B.6.8.2.

B.6.9.5. Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical test

No data required. The source of maltodextrin is unchanged and is supplied to the food industry and maltodextrins continue to have widespread uses in food, feed, cosmetics and medicinal products. They are considered to be food ingredients and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008) as are all starches treated with amylolytic enzymes. There is no upper level on their use as a food ingredient and there are few restrictions on the types of products in which they can be used. Information on signs of poisoning is therefore not relevant.

B.6.9.6. Proposed treatment: first aid measures, antidotes, medical treatment

No data required. The source of maltodextrin is unchanged and is supplied to the food industry and maltodextrins continue to have widespread uses in food, feed, cosmetics and medicinal products. They are considered to be food ingredients and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008) as are all starches treated with amylolytic enzymes. There is no upper level on their use as a food ingredient and there are few restrictions on the types of products in which they can be used. Proposed treatments are therefore not relevant.

B.6.10. REFERENCES RELIED ON

B.6.10.1. Literature Review

Evaluation the Literature Review
Under Article 8(5) of (EU) 1107/2009 the applicant is required to submit peer reviewed studies published in the open literature in the past ten years that are relevant to the assessment of maltodextrin. EFSA has provided guidance on conducting an acceptable literature search (EFSA Journal 2011; 9(2):2092). A literature search was conducted by the applicant in accordance with this guidance and five papers relevant to toxicology and metabolism were identified.

1. Search Strategy
Acceptable. Included maltodextrin and corresponding trade names and CAS numbers which produced 946 hits. The active ingredient name and CAS number were used in order to obtain relevant hits, as maltodextrin is prevalent in the scientific literature due to its use in nearly all food categories and as a drying aid in various food processing methods. The time period of the primary search was limited to studies published in or after 2010 up to 27th December 2019. A subsequent secondary (top-up) search to capture literature beyond the 27th December 2019 and in the months prior to submission, was performed on the 30th October 2020 using the same search criteria.

Table 8: Input parameters

Description/justification of search terms	Search terms	Search engine	Fields searched
Substance name	Maltodextrin	Proquest Dialog	Title
Trade names	Eradicoat Eradicoat Max Majestik	STN and Proquest Dialog	Full text
CAS numbers:	9050-36-6	STN and Proquest Dialog	Title, subject and abstract

The following refinement criteria were applied to each search: Toxicity OR rat OR mouse OR dog OR rabbit OR hamster OR "repeat dose" OR genotox* OR mutagen* OR carcinogen* OR acute OR irritation OR chronic OR toxicokinetic* OR reproduct* OR development* OR oncogen* OR neurotox* OR adverse OR human OR medical OR endocrine OR biotransformation OR poison
Trade name specific search terms, however, were also refined with "AND Maltodextrin" before applying the above refinement criteria.

Table 9: Reporting of the Search Process for Scientific Peer-Reviewed Open Literature in Bibliographic Databases

	STN	Dialog	STN	Dialog
	Primary search	Primary search	Secondary (top-up) search	Secondary (top-up) search
Justification for choice of the database:	Table 11	Table 11	Table 11	Table 11
Date of the search:	27th December 2019	27th December 2019	30th October 2020	30th October 2020
Date span of the search:	10 years	10 years	27 Dec 2019 – 30 Oct 2020	27 Dec 2019 – 30 Oct 2020
Date of the latest database update included in the search:	Table 10	Table 10	Table 10	Table 10
Fields searched	[Full text], [Title and Abstract]	[Title]	[Full text], [Title and Abstract]	[Title]
Number of summary records retrieved after removing duplicates	204	382	44	316

	STN	Dialog	STN	Dialog
	Primary search	**Primary search**	**Secondary (top-up) search**	**Secondary (top-up) search**
Total number of summary records retrieved after removing duplicates	586		360	
Total number of summary records retrieved after removing duplicates	946			

2. Databases searched

Acceptable. 27 databases were searched and justification for choice of database was given. Further information on the databases utilised are presented below.

Table 10: List of Databases Searched

a) STN Databases

STN-DATABASES:	**FREQUENCY OF UPDATES**
BIOSIS (BIOSIS PREVIEWS®)	Updated weekly
CABA (CA Abstracts)	Updated weekly
CAplus (Toxicology focus)	Updated daily
EMBASE (Excerpta Medica)	Updated daily
ESBIOBASE (Elsevier Current Research in Biology and BioScience)	Updated weekly
MEDLINE	Updated daily
SCISEARCH (Science Citation Index)	Updated weekly
TOXCENTER (Toxicology Center produced by American Chemical Society CAS)	Updated weekly

b) Dialog Databases

DIALOG DATABASES:	**UPDATES**
AGRICOLA	All PROQUEST databases are current and updated regularly
AGRIS	
Aqualine	
Aquatic Science & Fisheries Abstracts (ASFA)	
BIOSIS® Toxicology	
CAB ABSTRACTS	
Ecology Abstracts	
EMBASE	
Environment Abstracts	
FSTA®	
FOODLINE®: Science	
GEOBASE(TM)	
GeoRef	
Kosmet	
MEDLINE®	
Pollution Abstracts	
ToxFile	
Toxicology Abstracts	
TOXLINE	
Water Resources Abstracts	

Table 11: Justification for Choice of Databases Used

a) STN Databases

Provider	Database	Justification
STN*	**BIOSIS**	BIOSIS Previews® is the largest and most comprehensive life science database in the world. Amongst other subject coverage includes Agriculture, Biochemistry, Biophysics, Botany, Environmental Biology, Physiology, Toxicology. Sources include periodicals, journals, conference proceedings, reviews, reports, patents and short communications. Nearly 6,000 life science journals, 1,500 international meetings as well as review articles, books, and monographs are reviewed for inclusion. Bibliographic information, indexing terms, abstracts, and CAS Registry Numbers are all searchable.
STN*	**CAB Abstracts**	The CAB Abstracts database covers worldwide literature from all areas of agriculture and related sciences including biotechnology, forestry, and veterinary medicine. Sources for CABA include journals, books, reports, published theses, conference proceedings, and patents. Bibliographic information, indexing terms, abstracts and CAS Registry Numbers are searchable.
STN*	**CAPLUS**	The Chemical Abstracts (CA) database covers all areas of Biochemistry, Chemistry and Chemical engineering, and related sciences. Sources include over 8,000 journals, patents from 38 national patent offices and two international patent organizations, technical reports, books, conference proceedings, and dissertations. Electronic only journals and Web preprints are also covered. Bibliographic terms, indexing terms, roles, CAS Registry Numbers, International Patent Classification and abstracts are searchable.
STN*	**EMBASE**	The Excerpta Medica database covers worldwide literature in the biomedical and pharmaceutical fields, including biological science, biochemistry, human medicine, forensic science, paediatrics, pharmacy, pharmacology and drug therapy, pharmacoeconomics, psychiatry, public health, biomedical engineering and instrumentation and environmental science. Sources for EMBASE include more than 4,000 journals from approximately 70 countries, monographs, conference proceedings, dissertations and reports.
STN*	**ESBIOBASE**	Elsevier BIOBASE is a bibliographic current awareness database providing comprehensive coverage of the entire spectrum of biological research worldwide. Coverage includes the following areas: applied microbiology, biotechnology, cancer research, cell & developmental biology, clinical chemistry, ecological & environmental sciences, endocrinology, genetics, immunology, infectious diseases, metabolism, molecular biology, neuroscience, plant and crop science, protein biochemistry and toxicology. Records are selected from over 1,700 international scientific journals, books and conference proceedings.
STN*	**MEDLINE**	MEDLINE contains information on every area of medicine. The MEDLINE database corresponds to Index Medicus, Index to Dental Literature and International Nursing Index; OLDMEDLINE, with data from NLM's from the Cumulated Index Medicus (1960-1965) and Current List of Medical Literature (1958-1959); and, since August 2001, IN-PROCESS records, the latest documents before they have been completely indexed for inclusion on MEDLINE. Sources include journals and chapters in books or symposia. Bibliographic information, indexing terms, abstracts, chemical names and CAS Registry Numbers are all searchable.
STN*	**SCISEARCH**	Science Citation Index, one of the largest multidisciplinary scientific databases, is an international index to the literature covering virtually every subject area within the broad fields of science, technology and biomedicine. Records include references from over 5,600 scientific, technical and medical journals are contained in the database.

Provider	Database	Justification
STN*	**TOXCENTER**	Toxicology Center covers the pharmacological, biochemical, physiological, and toxicological effects of drugs and other chemicals. TOXCENTER is composed of the following subfiles: BIOSIS (1969 to date), CAplus (1907 to date), IPA (1970 to date), and MEDLINE (1953 to date). Sources include abstracts, books and book chapters, bulletins, conference proceedings, journal articles, letters, meetings, monographs, notes, papers, patents, presentations, research and project summaries, reviews, technical reports, theses, translations, unpublished material, web reprints. Records contain bibliographic data, abstracts, indexing terms, chemical names and CAS Registry Numbers

* *http://www.stn-international.de/database_list.html?&no_cache=1&cHash=*

b) Dialog Databases

Dialog is the premier online retrieval service with the most comprehensive content collection and most powerful search language available. Dialog is the worldwide leader in providing online-based information in science. The database holds data from more than 800 million unique records of key information, accessible via the Internet. Content areas include, but are not limited to, biomedical research, biotechnology, chemicals, environment, food and agriculture, medicine and science and technology.

Provider	Database	Justification
Dialog	**AGRICOLA (AGRICultural OnLine Access)**	AGRICOLA (AGRICultural OnLine Access) is an extensive international bibliographic database consisting of records for literature citations of journal articles, monographs, theses, patents, translations, microforms, audiovisuals, software and technical reports. Available since 1970, AGRICOLA serves as a document locator and bibliographic access and control system for the U.S. National Agricultural Library (NAL) collection, but since 1984 the database has also included some records produced by cooperating institutions for documents not held by NAL.
Dialog	**AGRIS International**	AGRIS International is the international information system for agricultural sciences and technology. The AGRIS International database has served since 1974 as a comprehensive inventory of worldwide agricultural literature which reflects research results, food production, and rural development to help users identify problems involved in all aspects of world food supply. Emphasis in AGRIS International is non-U.S. This file corresponds in part to the printed publication, Agrindex, published monthly by the Food and Agriculture Organization (FAO) of the United Nations. AGRIS is a cooperative, decentralised system in which over 100 national and multinational centers take part. It collects and makes available current information on the agricultural literature of the world appearing in journals, books, reports, and conference papers. Each country which participates in AGRIS does so by submitting information about documents published within its own territories. All contributing sources are of non-U.S. origin. FAO acts as a coordinating agency within this global information system, facilitating the exchange of agricultural information to its member countries.

Provider	Database	Justification
Dialog	**Aqualine**	Aqualine contains abstracts and bibliographic citations from approximately 300 journals as well as from conference proceedings, scientific reports, books and theses. Major subjects of coverage include water resources and supplies management, water legislation, water quality, potable water distribution, wastewater collection, water treatment technologies, wastewater and sewage treatment, and ecological and environmental effects of water pollution. Previously published by the well-known and respected WRc in England, Aqualine is now produced in joint cooperation with WRc and CSA.
Dialog	**ASFA (Aquatic Sciences and Fisheries Abstracts)**	ASFA (Aquatic Sciences and Fisheries Abstracts) series is the premier international reference in the field of aquatic resources. Since 1966 input to ASFA has been provided by a growing international network of information centers monitoring more than 5,000 serial publications, books, reports, conference proceedings, translations and limited distribution literature. ASFA is a component of the Aquatic Sciences and Fisheries Information System (ASFIS), formed by four United Nations agency sponsors of ASFA and a network of international and national partners.
Dialog	**BIOSIS® Toxicology**	BIOSIS Previews® is the largest and most comprehensive life science database in the world. Amongst other subject coverage includes Agriculture, Biochemistry, Biophysics, Botany, Environmental Biology, Physiology, Toxicology. Sources include periodicals, journals, conference proceedings, reviews, reports, patents and short communications. Nearly 6,000 life science journals, 1,500 international meetings as well as review articles, books, and monographs are reviewed for inclusion. Bibliographic information, indexing terms, abstracts, and CAS Registry Numbers are all searchable.
Dialog	**CAB Abstracts**	The CAB Abstracts database covers worldwide literature from all areas of agriculture and related sciences including biotechnology, forestry, and veterinary medicine. Sources for CABA include journals, books, reports, published theses, conference proceedings, and patents. Bibliographic information, indexing terms, abstracts and CAS Registry Numbers are searchable.
Dialog	**Ecology Abstracts**	Ecologists will find in this journal the essence of current ecology research across a wide range of disciplines, reflecting recent advances in light of growing evidence regarding global environmental change and destruction. Ecology Abstracts focuses on how organisms of all kinds - microbes, plants, and animals - interact with their environments and with other organisms. Included are relevant papers on evolutionary biology, economics, and systems analysis as they relate to ecosystems or the environment. With coverage ranging from habitats to food chains, from erosion to land reclamation, the journal provides an important cross-section of current findings in target research areas. Detailed information on resource and ecosystems management and modeling contributes to the journal's practical value, as does material on the impact of climate, water resources, soil, and man or growing environmental problems such as depletion, erosion, and pollution all topics which are covered in depth. Comprehensive, yet carefully focused coverage makes this an essential resource for scientists concerned with preserving the environment.
Dialog	**EMBASE**	The Excerpta Medica database covers worldwide literature in the biomedical and pharmaceutical fields, including biological science, biochemistry, human medicine, forensic science, paediatrics, pharmacy, pharmacology and drug therapy, pharmacoeconomics, psychiatry, public health, biomedical engineering and instrumentation and environmental science. Sources for EMBASE include more than 4,000 journals from approximately 70 countries, monographs, conference proceedings, dissertations and reports.

Provider	Database	Justification
Dialog	**Environment Abstracts**	Environment Abstracts (formerly Environment Abstracts published by LexisNexis) encompasses all aspects of the impact of people and technology on the environment and the effectiveness of remedial policies and technologies. As of 1994, the database also provides expanded coverage of energy-related issues. Environment Abstracts provides access to more than 950 journals published in the U.S. and abroad. The database also covers conference papers and proceedings, special reports from international agencies, non-governmental organizations, universities, associations and private corporations. Other materials selectively indexed include significant monographs, government studies and newsletters. Environment Abstracts customers will also receive access to Sustainability Science Abstracts and EIS: Digests of Environmental Impact Statements. Environment Abstracts also includes a special collection of over 4,000 full text government reports.
Dialog	**FSTA®**	FSTA® is produced by IFIS (UK) - core food information, an independent, not-for-profit organisation whose primary objective is to provide quality information products and services designed to meet the needs of all those working in the food sector. FSTA® is the largest and most respected collection of food science, food technology and food related human nutrition abstracts, providing content since 1969. It is compiled by a team of specialist scientists dedicated to producing a database of consistent high quality and timeliness. Continual development of coverage allows FSTA® to maintain its position as the market-leading food science database. There are more than 109,000 patent records including more than 11,000 Japanese patents. FSTA® covers journal articles (approximately 80%), patents, theses, standards, legislation, books, reviews and conference proceedings.
Dialog	**Foodline®: SCIENCE**	Foodline®: SCIENCE is a vital resource for keeping up-to-date with published information on food science and technology worldwide. All aspects of the food and drink industry are covered, including ingredients and process technology, microbiology, packaging, food chemistry, biotechnology, food safety and nutrition. A key strength of the database is its currency, key journals being abstracted and available online within two weeks of delivery. More than 250 current periodicals are scanned extensively for FoodlineScience. In total, more than 1,800 records are added to FoodlineScience each month, including scientific journals, trade journals, books, book chapters, standards, technical reports and PCT, European, UK, US and Japanese patents. Produced by the Leatherhead Food Research since 1972.
Dialog	**GEOBASE**	GEOBASE is a unique bibliographic database covering worldwide research literature since 1980 in physical and human geography, earth and environmental sciences, ecology, and related disciplines. In addition to providing comprehensive coverage of the core scientific and technical periodicals, Geobase has a unique coverage of non-English language and less readily available publications. Over 2,000 journals are fully covered with an additional 3,000 having partial coverage. Over 2,000 books, monographs, conference proceedings, and reports are also included.

Provider	Database	Justification
Dialog	**GeoRef**	GeoRef, the database of the American Geosciences Institute (AGI), covers worldwide technical literature on geology and geophysics. GeoRef corresponds to the print publications: Bibliography and Index of North American Geology, Bibliography of Theses in Geology, and the Geophysical Abstracts, Bibliography and Index of Geology Exclusive of North America. GeoRef organizes and indexes papers from more than 13,000 serials and other publications representative of the interests of the 50 professional geological and earth science societies that are members of the AGI. GeoRef is international in coverage with about 40% of the indexed publications originating in the United States and the remainder from outside the U.S. Publications of international organizations represent about 7% of the file. The database includes current coverage of more than 3,500 journals as well as books and book chapters, conference papers, government publications, theses, dissertations, reports, maps, and meeting papers.
Dialog	**KOSMET**	Cosmetic & Perfume Science & Technology (KOSMET) is a bibliographic database containing citations to the worldwide literature on cosmetics and perfumes, with an emphasis on scientific and technical research and studies. Citations, mostly with abstracts, include bibliographic data, indexing information and CAS Registry Numbers. For literature of non-English origin the original title is given additionally. Coverage includes product development, knowledge of healthy skin and its adnexa (hair, nails, teeth, glands), trading of perfumes and cosmetics, research and development of raw materials, active ingredients, formulations, manufacture, analysis, safety, *in vitro* toxicology, physiochemical properties, biological properties, stability, packaging and clinical studies. Sources include periodicals, technical publications, conference proceedings and all reports from IFSCC congresses and meetings.
Dialog	**MEDLINE (Medical Literature, Analysis, and Retrieval System Online)**	MEDLINE is produced by the U.S. National Library of Medicine (NLM) and is the U.S. National Library of Medicine's premier bibliographic database that contains more than 15 million references to journal articles in life sciences with a concentration on biomedicine. The broad coverage of the database includes basic biomedical research and the clinical sciences since 1950 including nursing, dentistry, veterinary medicine, pharmacy, allied health and pre-clinical sciences. MEDLINE also covers life sciences that are vital to biomedical practitioners, researchers and educators, including some aspects of biology, environmental science, marine biology, plant and animal science as well as biophysics and chemistry. Increased coverage of life sciences began in 2000. MEDLINE is indexed using NLM's controlled vocabulary, MeSH® (Medical Subject Headings). Approximately 400,000 records are added per year, of which more than 76% are in English.
Dialog	**Pollution Abstracts**	Pollution Abstracts provides fast access to the environmental information necessary to ensure ongoing compliance and handle emergency situations more effectively. Pollution Abstracts combines information on scientific research and government policies in a single resource. Topics of growing concern are extensively covered from the standpoints of atmosphere, emissions, mathematical models, effects on people and animals, toxicology and health and environmental action in response to global pollution issues. To ensure comprehensive coverage, material from conference proceedings and hard-to-find documents has been summarised along with information from primary journals in the field. Published since 1966 by CSA (Cambridge Scientific Abstracts).

Provider	Database	Justification
Dialog	**ToxFile**	ToxFile covers 1965 to the present of the toxicological, pharmacological, biochemical and physiological effects of drugs and other chemicals: adverse drug reactions, chemically induced diseases, carcinogenesis, mutagenesis, teratogenesis, environmental pollution, pesticides, waste disposal, radiation, and food contamination. ToxFile includes toxicology records derived from MEDLINE and also includes citations referred to as TOXNET records from the following organizations and data repositories: Aneuploidy File (ANEUPL), International Labor Office (CIS), Toxicology Research Projects (CRISP), Developmental and Reproductive Toxicology (DART), Environmental Mutagen Information Center File (EMIC), Epidemiology Information System (EPIDEM), Environmental Teratology Information Center File (ETICBACK), Federal Research in Progress (FEDRIP), Health Aspects of Pesticides Abstract Bulletin (HAPAB), Toxicological Aspects of Environmental Health (HEEP), Hazardous Materials Technical Center File (HMTC), National Institute for Occupational Safety and Health (NIOSH), Toxicology Document and Data Repository (NTIS), Pesticides Abstracts (PESTAB), Poisonous Plants Bibliography (PPBIB), Swedish National Chemicals Inspectorate (RISKLINE), and Toxic Substances Control Act Test Submissions (TSCATS).
Dialog	**Toxicology Abstracts**	Toxicology Abstracts is the only comprehensive print resource for professionals in this field who must be aware of every new finding. Specifically focused to meet the needs of toxicologists, Toxicology Abstracts covers issues from social poisons and substance abuse to natural toxins, from legislation and recommended standards to environmental issues. Surveying the literature for toxicology studies of industrial and agricultural chemicals, household products, pharmaceuticals, and myriad other substances, each issue publishes information concerning the in vivo effects of toxic substances. Topics of current concern such as the effects of alcohol and smoking, drug abuse, hydrocarbon studies, nitrosamines, radiation and radioactive materials, and much more are extensively examined. Toxicity testing methodology and analytical procedures for toxic substances are also covered. Through many years of delivering crucial information on the tough, far-reaching issues of toxicology, Toxicology Abstracts has become the single most widely-used journal in this field.
Dialog	**TOXLINE**	Bibliographic citations to toxicological, pharmacological, biochemical and physiological effects of drugs and other chemicals. Coverage is international but contains primarily English language items; Updates are monthly, with about 9,300 new citations added each month; the file contains over 2.4 million records. The records are derived from about 16 secondary sources.
Dialog	**Water Resources Abstracts**	Water Resources Abstracts offers a comprehensive range of water-related topics summarising the world's technical and scientific literature on water-related topics covering the characteristics, conservation, control, pollution, treatment, use and management of water resources in the life and physical sciences, as well as the engineering and legal aspects of the conservation, control, use, and management of water. The database was originally produced by the U.S. Geological Survey starting in 1968 when it was generally known as Selected Water Resources Abstracts. Since 1994, Water Resources Abstracts has been produced by CSA (Cambridge Scientific Abstracts), which broadened the scope by including more material published outside the U.S.A. This database, which concentrates on water supply and water treatment, complements the Aquatic Sciences & Fisheries Abstracts database, ASFA, where there is greater coverage of the marine environment and biological material.

3. Relevance criteria

The 946 papers were rapidly assessed by a manual review of the titles/abstracts and obviously irrelevant titles were discarded, this left 24 papers either relevant or of unclear relevance. The applicant provided copies of the abstracts of these 24 papers which were further assessed.

The abstract/full text of these papers were considered to

a) determine their relevance and

b) if the study could impact on the endpoints and risk assessment of the active substance

The criteria considered for relevancy of studies relating to individual toxicology data requirements are detailed in the table below. The RMS agrees with these relevancy criteria.

Table 12: Relevancy Criteria

Data requirement (data point)	Relevancy criteria considered
Active substance	
Studies on absorption, distribution, metabolism and excretion in mammals (KCA 5.1)	1. Well-defined test material. 2. *In vivo* tests in relevant test species. 3. *In vitro* tests. 4. PBPK modelling. 5. Specific endpoint can be clearly related to this data requirement.
Acute toxicity (KCA 5.2)	1. Well-defined test material. 2. Relevant test species. 3. Relevant route of exposure. 4. Specific endpoint can be clearly related to this data requirement.
Short-term toxicity (KCA 5.3)	1. Well-defined test material. 2. Relevant test species. 3. Relevant route of exposure. 4. Specific endpoint can be clearly related to this data requirement.
Genotoxicity (KCA 5.4)	1. Well-defined test material. 2. *In vitro* tests. 3. *In vivo* tests in relevant test species. 4. Specific endpoint can be clearly related to this data requirement.
Long-term toxicity and carcinogenicity (KCA 5.5)	1. Well-defined test material. 2. Relevant test species. 3. Relevant route of exposure. 4. Specific endpoint can be clearly related to this data requirement
Reproductive toxicity (KCA 5.6)	1. Well-defined test material. 2. Relevant test species. 3. Relevant route of exposure. 4. Specific endpoint can be clearly related to this data requirement.
Neurotoxicity studies (KCA 5.7)	1. Well-defined test material. 2. *In vivo* tests in relevant test species. 3. Relevant route of exposure. 4. Specific endpoint can be clearly related to this data requirement.
Other toxicological studies (KCA 5.8)	1. Well-defined test material.

	2. *In vitro* tests. 3. *In vivo* tests in relevant test species. 4. Relevant route of exposure. 5. Specific endpoint can be clearly related to this data requirement.
Medical data (KCA 5.9)	1. Well-defined test material. 2. Epidemiological studies. 3. Poisonings, clinical cases. 4. Relevant route of exposure.
Plant protection products	
Acute toxicity (KCP 7.1)	1. Well-defined test material. 2. Relevant test species. 3. Relevant route of exposure. 4. Specific endpoint can be clearly related to this data requirement.
Data on exposure (KCP 7.2)	1. Well-defined test material. 2. Field studies. 3. Calculations. 4. Specific endpoint can be clearly related to this data requirement.
Dermal absorption (KCP 7.3)	1. Well-defined test material. 2. *In vitro* tests. 3. *In vivo* tests in relevant test species. 4. Specific endpoint can be clearly related to this data requirement.

A total of 19 papers were considered not relevant (Table 13) and 5 papers were considered to be relevant or of unclear relevance (Table 14). These 5 papers were then scored for reliability. The RMS disagreed with the relevance of one of these papers, as discussed in section B.6.1.1. The RMS also identified a paper which they considered to be relevant, where the applicant had not. This paper is summarised in section B.6.8.2.5.

Table 13: Studies Excluded After Detailed Assessment

Number	Author	Year	Title	Reference	Meet relevance criteria Y or N	Meet Reliability Criteria Score	Basis for relevance/ reliability decision (title, abstract or full article)	Comments	RMS decision
1.	Amanda R. Arnold	2019	Maltodextrin, Modern Stressor of the Intestinal Environment	Cmgh 7 (2): 475–476	N	N/A	Abstract	This paper reviews the article "*The Food Additive Maltodextrin Promotes Endoplasmic Reticulum Stress-Driven Mucus Depletion and Exacerbates Intestinal Inflammation*", which is assessed itself separately within this literature review.	Acceptable
2.	Augusto RMN et al	2020	Maltodextrin in diets for weaning pigs of different weights: performance and intestinal morphometry	Animal Sciences, vol. 33, no. 1	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
3.	Coggins CR et al	2011	A comprehensive evaluation of the toxicology of cigarette ingredients: carbohydrates and natural products	Inhal Toxicol. 2011 Jun;23 Suppl 1:13-40	N	N/A	Abstract	Not relevant. Investigates whether the addition of maltodextrin to cigarettes changes smoke chemistry and its resultant toxicity. No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
4.	De Pauw K et al	2015	Effects of caffeine and maltodextrin mouth rinsing on P300, brain imaging, and cognitive performance	J Appl Physiol 15;118(6):776-82.	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable

Number	Author	Year	Title	Reference	Meet relevance criteria Y or N	Meet Reliability Criteria Score	Basis for relevance/ reliability decision (title, abstract or full article)	Comments	RMS decision
5.	Fisher-Wellman KH and, Bloomer RJ	2010	Lack of effect of a high-calorie dextrose or maltodextrin meal on postprandial oxidative stress in healthy young men	Int J Sport Nutr Exerc Metab 20(5):393-400	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
6.	Gaworski CL et al	2011	An evaluation of the toxicity of 95 ingredients added individually to experimental cigarettes: approach and methods	Inhal Toxicol. 2011 Jun;23 Suppl 1:1-12	N	N/A	Abstract	Not relevant. Investigates whether the addition of maltodextrin to cigarettes changes smoke chemistry and its resultant toxicity. No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
7.	Han R et al	2013	Iterative saturation mutagenesis of -6 subsite residues in cyclodextrin glycosyltransferase from Paenibacillus macerans to improve maltodextrin specificity for 2-O-D-glucopyranosyl-L-ascorbic acid synthesis	Applied and Environmental Microbiology 79 (24): 7562-7568	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
8.	Hauptli L et al	2016	Maltodextrin and oils in the diet of weaned piglets	Bol. Ind. Anim., Nova Odessa,v.73, n.4, p.339-346,	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable

Number	Author	Year	Title	Reference	Meet relevance criteria Y or N	Meet Reliability Criteria Score	Basis for relevance/ reliability decision (title, abstract or full article)	Comments	RMS decision
9.	Iyekhoetin MO et al	2013	Commercial processed food may have endocrine-disrupting potential: soy-based ingredients making the difference	Food Additives & Contaminants: Part A, 30:10, 1722-1727	N	N/A	Abstract	The study tested foodstuffs for potential ED potential and makes a link between those foods containing soya-based ingredients and positive results. No specificity to maltodextrin, therefore no information presented to inform EU data requirements, endpoints or risk assessments. The article is not relevant.	Acceptable
10.	Kendig MD	2014	Maltodextrin can produce similar metabolic and cognitive effects to those of sucrose in the rat	Appetite. 77:1-12	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Not Accepted – Considered relevant by RMS
11.	Kim, H T et al*	2019	The effects of maltodextrin and protein supplementation on serum metabolites in exercising competitive weight-pulling dogs	Comparative Exercise Physiology: 15 (1)- Pages: 25 - 33	N	N/A	Abstract	Study examines the metabolic changes associated with weight pulling in dogs and to investigate the effects of a dietary supplement including maltodextrin and protein supplements on serum metabolomics during recovery. No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable

Number	Author	Year	Title	Reference	Meet relevance criteria	Meet Reliability Criteria	Basis for relevance/ reliability decision (title, abstract or full article)	Comments	RMS decision
					Y or N	Score			
12.	Kong, H et al*	2020	Novel Short-Clustered Maltodextrin as a Dietary Starch Substitute Attenuates Metabolic Dysregulation and Restructures Gut Microbiota in db/db Mice	J. Agric. Food Chem. 2020, 68, 44, 12400–12412	N	N/A	Abstract	This paper is considered not relevant as it investigates a short-clustered maltodextrin as opposed to the maltodextrin subject to this dossier. Also, the paper focuses on options for diabetes therapy/management and does not examine potential maltodextrin-induced toxicities.	Acceptable
13.	Machado CA and Carvalho LSS	2015	Maltodextrin in animal feed	RPCV 110 (593-594) 14-16	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
14.	Malfatti C et al	2011	Maltodextrin's effect on the performance of elite mountain biking athletes during simulated competition and on power output at the ventilatory threshold	Human Movement 12 (3): 232-236	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
15.	Moosa RM	2014	In vivo evaluation and in-depth pharmaceutical characterization of a rapidly dissolving solid ocular matrix for the topical delivery of timolol maleate in the rabbit eye model	Int J Pharm 15;466(1-2):296-306	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable

Number	Author	Year	Title	Reference	Meet relevance criteria Y or N	Meet Reliability Criteria Score	Basis for relevance/ reliability decision (title, abstract or full article)	Comments	RMS decision
16.	Nunes Gil PC et al	2012	Influence of high levels of maltodextrin in horse diets	Livestock Science 147 (1–3): 66-71	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
17.	Poole RL et al	2016	Maltodextrin Acceptance and Preference in Eight Mouse Strains	Chem Senses; 41(1): 45–52	N	N/A	Abstract	No information presented to inform EU data requirements, endpoints or risk assessments. The article is therefore not relevant.	Acceptable
18.	Singh, P et al*	2020	Maltodextrin-induced intestinal injury in a neonatal mouse model	Dis Model Mech 27;13 (8)	N	N/A	Abstract	This paper is considered not relevant as maltodextrin exposure was applied along with induction of hypoxia. Hypoxia is well known as causing or aggravating factor in an array of pathologies including intestinal injury. These data cannot be used to assess adverse effects induced by maltodextrin in the gut of mouse neonates as it is unclear whether and to which extent maltodextrin played a role in inducing the adverse effects observed since the causing factor may have been hypoxia.	Acceptable

Number	Author	Year	Title	Reference	Meet relevance criteria	Meet Reliability Criteria	Basis for relevance/ reliability decision	Comments	RMS decision
					Y or N	Score	(title, abstract or full article)		
19.	Wu CT et al	2018	Genotoxicity and 28-day oral toxicity studies of a functional food mixture containing maltodextrin, white kidney bean extract, mulberry leaf extract, and niacin-bound chromium complex	Regul Toxicol Pharmacol Feb;92:67-74	N	N/A	Full text	Not relevant. The paper assesses a mixture and not maltodextrin alone	Acceptable

Table 14: Relevant Studies Included After Detailed Assessment

a) Relevant studies included after detailed assessment of full-text documents sorted by data requirement

Author	Year	Title	Reference	Meet relevance criteria	Meet Reliability Criteria	Basis for relevance/ reliability decision	Comments	Data point
				Y or N	Score	(title, abstract or full article)		
Hofman DL et al	2016	Nutrition, Health, and Regulatory Aspects of Digestible Maltodextrins	Crit Rev Food Sci Nutr. 2016 Sep 9;56(12):2091-100	N	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.1.1
Laudisi F et al	2019	The Food Additive Maltodextrin Promotes Endoplasmic Reticulum Stress-Driven Mucus Depletion and Exacerbates Intestinal Inflammation	Cmgh 7 (2): 457-473	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2

Author	Year	Title	Reference	Meet relevance criteria	Meet Reliability Criteria	Basis for relevance/ reliability decision (title, abstract or full article)	Comments	Data point
				Y or N	Score			
Nickerson KP and McDonald C	2012	Crohn's disease-associated adherent-invasive Escherichia coli adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin	PLoS One. 2012;7(12):e52132	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2
Nickerson KP et al	2014	The dietary polysaccharide maltodextrin promotes Salmonella survival and mucosal colonization in mice	PLoS One 7;9(7):e101789	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2
Nickerson KP et al	2015	Deregulation of intestinal anti-microbial defense by the dietary additive, maltodextrin	Gut Microbes. 2015;6(1):78-83	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2
Kendig et al.	2014	Maltodextrin can produce similar metabolic and cognitive effects to those of sucrose in the rat	Appetite 77C (2014) 1–12	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2

b) Relevant studies included after detailed assessment of full-text documents sorted by author

Author	Year	Title	Reference	Meet relevance criteria	Meet Reliability Criteria	Basis for relevance/ reliability decision (title, abstract or full article)	Comments	Data point
				Y or N	Score			
Hofman DL et al	2016	Nutrition, Health, and Regulatory Aspects of Digestible Maltodextrins	Crit Rev Food Sci Nutr. 2016 Sep 9;56(12):2091-100	N	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.1.1

Author	Year	Title	Reference	Meet relevance criteria	Meet Reliability Criteria	Basis for relevance/ reliability decision (title, abstract or full article)	Comments	Data point
				Y or N	Score			
Kendig et al.	2014	Maltodextrin can produce similar metabolic and cognitive effects to those of sucrose in the rat	Appetite 77C (2014) 1–12	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2
Laudisi F et al	2019	The Food Additive Maltodextrin Promotes Endoplasmic Reticulum Stress-Driven Mucus Depletion and Exacerbates Intestinal Inflammation	Cmgh 7 (2): 457-473	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2
Nickerson KP and McDonald C	2012	Crohn's disease-associated adherent-invasive Escherichia coli adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin	PLoS One. 2012;7(12):e52132	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2
Nickerson KP et al	2014	The dietary polysaccharide maltodextrin promotes Salmonella survival and mucosal colonization in mice	PLoS One 7;9(7):e101789	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2
Nickerson KP et al	2015	Deregulation of intestinal anti-microbial defense by the dietary additive, maltodextrin	Gut Microbes. 2015;6(1):78-83	Y	2	Full text	Refer to OECD summary provided in the dossier	MCA 5.8.2

4. Reliability criteria

Papers were assessed for reliability according to Klimisch et al. (1977)[1], which is an acceptable method for reliability scoring. All 5 papers were considered reliable after Klimisch scoring. The additional study included by the RMS was also considered reliable after Klimisch scoring. The data points they supported were:

- CA 5.1.1 Absorption, distribution, metabolism and excretion by oral exposure
- CA 5.8.2 Supplementary studies on the active substance

[1] Klimisch, H-J., Andreae, M. & Tillmann, U. (1997) A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regulatory Toxicology and Pharmacology 25 pp 1-5

B.6.10.2. Reference List

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
CA 5.0_1	Engfer, MB et al.	2000	Human milk oligosaccharides are resistant to enzymatic hydrolysis in the upper gastrointestinal tract. Am J Clin Nutr 71, 1589-96 Published		N	N/A	N/A	Y (DAR, 2011)
CA SECTION 5.	EFSA	2013	Conclusion on the peer review of the pesticide risk assessment of the active substance maltodextrin 2013; 11(1):3007 EFSA Journal Published	N	N	N/A	N/A	N/A
CA 5.0_2	Evans, R. and Hearty, A.	2020	Review of existing food and non-food uses of maltodextrins 1905806.UK0 – 4797 Exponent International Ltd The Lenz, Hornbeam Business Park Harrogate, HG2 8RE Unpublished	N	N	N/A	Certis Belchim BV	N
CA 5.0 _2	EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)	2014	Scientific Opinion on the essential composition of infant and follow-on formulae. EFSA Journal 2014;12(7):3760 Published	N	N	N/A	N/A	N
CA 5.0 _2	Scientific Committee on Food	2003	Report of the Scientific Committee on	N	N	N/A	N/A	N

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
			Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae SCF/CS/NUT/IF /65 Final European Commission Published					
CA 5.0 _2	Cosmetic Ingredient Review	2015	Safety Assessment of Polysaccharide Gums as Used in Cosmetics, Cosmetic Ingredient Review (CIR) Expert Panel Published	N/A	N	N/A	N/A	N
CA 5.0 _2	EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA)	2010	Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre. 2010; 8(3):1462, 77 pp. EFSA Journal Published	N/A	N/A	N/A	N/A	N
CA 5.0 _2	EFSA Scientific Committee	2017	Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age. 2017; 15(5):4849, 58 pp. EFSA Journal Published	N/A	N/A	N/A	N/A	N
CA 5.2.1/1	[redacted]	1991a	Hugtite: Acute oral toxicity (limit test) in the rat.	Y	N	N/A	Certis Belchim BV	Y (DAR, 2011)

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
			[redacted] Project Number: 373/1 GLP, Unpublished report					
CA 5.2.2_1	[redacted]	1991	Hugtite: Acute dermal toxicity (Limit test) in the rat Study No. 373/2 [redacted] GLP Unpublished	Y	N	N/A	Certis Belchim BV	Y (DAR, 2011)
CA 5.2.3_1	[redacted]	1991	Hugtite: Acute inhalation toxicity study, Four-hour exposure (nose only) in the rat 373/3 [redacted] GLP Unpublished	Y	N	N/A	Certis Belchim BV	Y (DAR, 2011)
CA 5.2.4_1	[redacted]	1991b	Hugtite: Acute dermal irritation test in the rabbit 373/4 [redacted] GLP Unpublished	Y	N	N/A	Certis Belchim BV	Y (DAR, 2011)
CA 5.2.6	EFSA's Panel on	2019	Safety evaluation of the food	N/A	N	N/A	N/A	N

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
	Food Contact Materials, Enzymes, Processing Aids (CEP)		enzyme alpha-amylase from non-genetically modified Aspergillus niger strain (strain DP-Azb60) EFSA Journal 2019;17(5):5680 Published					
CA 5.8.2_1	Laudisi F. et al	2019a	The Food Additive Maltodextrin Promotes Endoplasmic Reticulum Stress–Driven Mucus Depletion and Exacerbates Intestinal Inflammation Cellular and Molecular Gastroenterology and Hepatology, 7(2):457-473 Published	N	N	N/A	N/A	N
CA 5.8.2_2	European Food Safety Authority (EFSA)	2017	Guidance on dermal absorption EFSA Journal, Volume 15, Issue 6 e04873 Published	N	N	N	N/A	N
CA 5.8.2_3	Nickerson, K.P and McDonald, C.	2012	Crohn's disease-associated adherent-invasive *Escherichia coli* adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin PLoS ONE 7(12): e52132 Published	N	N	N/A	N/A	N

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
CA 5.8.2_4	Nickerson, K.P. et al.	2014	The dietary polysaccharide maltodextrin promotes *Salmonella* survival and mucosal colonization in mice PLoS ONE 9(7): e101789 Published	N	N	N/A	N/A	N
CA 5.8.2_5	Nickerson, K.P. et al.	2015	Deregulation of intestinal anti-microbial defense by the dietary additive, maltodextrin Gut Microbes 6:1, 78-83 Published	N	N	N/A	N/A	N
CA 5.8.2_6	Kendig et al.	2014	Maltodextrin can produce similar metabolic and cognitive effects to those of sucrose in the rat Appetite 77C (2014) 1–12 Published	N	N	N/A	N/A	N
CA 5.8.2_7	Laudisi et al.	2019b	Impact of Food Additives on Gut Homeostasis Nutrients 2019, 11(10), 2334; Published	N	N	N	N/A	N
CP SECTION 7 Toxicological Studies	EFSA	2013	Conclusion on the peer review of the pesticide risk assessment of the active substance maltodextrin EFSA Journal 2013;11(1):3007 Published	N	N	N/A	N/A	N/A

Safety data sheet

according to Regulation (EC) No. 1907/2006 (REACH), amended by 2020/878/EU

Maltodextrin 4,0-7,0 for biochemistry

article number: **2260**
Version: **3.1 en**
Replaces version of: 2024-03-02
Version: (3)

date of compilation: 2019-01-14
Revision: 2024-09-18

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifier

Identification of the substance	**Maltodextrin** 4,0-7,0 for biochemistry
Article number	2260
Registration number (REACH)	It is not required to list the identified uses because the substance is not subject to registration according to REACH (< 1 t/a).
EC number	232-940-4
CAS number	9050-36-6

1.2 Relevant identified uses of the substance or mixture and uses advised against

Relevant identified uses:	Laboratory and analytical use Laboratory chemical
Uses advised against:	Do not use for private purposes (household). Food, drink and animal feedingstuffs.

1.3 Details of the supplier of the safety data sheet

Carl Roth GmbH + Co. KG
Schoemperlenstr. 3-5
D-76185 Karlsruhe
Germany

Telephone:+49 (0) 721 - 56 06 0
Telefax: +49 (0) 721 - 56 06 149
e-mail: sicherheit@carlroth.de
Website: www.carlroth.de

Competent person responsible for the safety data sheet:	Department Health, Safety and Environment
e-mail (competent person):	**sicherheit@carlroth.de**

1.4 Emergency telephone number

Name	Street	Postal code/city	Telephone	Website
National Poisons Information Centre Beaumont Hospital	Beaumont Road	Dublin 9	+353 1 809 2166	https://www.poisons.ie/

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Classification according to Regulation (EC) No 1272/2008 (CLP)

This substance does not meet the criteria for classification in accordance with Regulation No 1272/2008/EC.

2.2 Label elements

Labelling according to Regulation (EC) No 1272/2008 (CLP)
not required

2.3 Other hazards

Results of PBT and vPvB assessment
According to the results of its assessment, this substance is not a PBT or a vPvB.

Endocrine disrupting properties
Does not contain an endocrine disruptor (ED) at a concentration of ≥ 0,1%.

SECTION 3: Composition/information on ingredients

3.1 Substances

Name of substance	Maltodextrin
Molecular formula	$C_6H_{10}O_5$
Molar mass	162,1 $^{g}/_{mol}$
CAS No	9050-36-6
EC No	232-940-4

SECTION 4: First aid measures

4.1 Description of first aid measures

General notes
Take off contaminated clothing.

Following inhalation
Provide fresh air.

Following skin contact
Rinse skin with water/shower.

Following eye contact
Rinse cautiously with water for several minutes.

Following ingestion
Rinse mouth. Call a doctor if you feel unwell.

4.2 Most important symptoms and effects, both acute and delayed

Symptoms and effects are not known to date.

4.3 Indication of any immediate medical attention and special treatment needed

none

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
co-ordinate firefighting measures to the fire surroundings!
water, foam, dry extinguishing powder, ABC-powder

Unsuitable extinguishing media
water jet

5.2 Special hazards arising from the substance or mixture
Combustible.

Hazardous combustion products
In case of fire may be liberated: Carbon monoxide (CO), Carbon dioxide (CO_2)

5.3 Advice for firefighters
In case of fire and/or explosion do not breathe fumes. Fight fire with normal precautions from a reasonable distance. Wear self-contained breathing apparatus.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

For non-emergency personnel
Control of dust.

6.2 Environmental precautions
Keep away from drains, surface and ground water. Retain contaminated washing water and dispose of it.

6.3 Methods and material for containment and cleaning up

Advice on how to contain a spill
Covering of drains. Take up mechanically.

Advice on how to clean up a spill
Take up mechanically.

Other information relating to spills and releases
Place in appropriate containers for disposal. Ventilate affected area.

6.4 Reference to other sections
Hazardous combustion products: see section 5. Personal protective equipment: see section 8. Incompatible materials: see section 10. Disposal considerations: see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
No special measures are necessary.

Advice on general occupational hygiene
Keep away from food, drink and animal feedingstuffs.

7.2 Conditions for safe storage, including any incompatibilities

Store in a dry place.

Incompatible substances or mixtures

Observe hints for combined storage. Incompatible materials: see section 10.

Consideration of other advice:

Ventilation requirements

Use local and general ventilation.

Specific designs for storage rooms or vessels

Recommended storage temperature: 15 – 25 °C

7.3 Specific end use(s)

No information available.

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

National limit values

Occupational exposure limit values (Workplace Exposure Limits)

Country	Name of agent	CAS No	Identifier	TWA [mg/m³]	STEL [mg/m³]	Ceiling-C [mg/m³]	Notation	Source
IE	dusts, non-specific		OELV	10			i	S.I. No. 619 of 2001
IE	dusts, non-specific		OELV	4			r	S.I. No. 619 of 2001

Notation

Ceiling-C	Ceiling value is a limit value above which exposure should not occur
i	Inhalable fraction
r	Respirable fraction
STEL	Short-term exposure limit: a limit value above which exposure should not occur and which is related to a 15-minute period (unless otherwise specified)
TWA	Time-weighted average (long-term exposure limit): measured or calculated in relation to a reference period of 8 hours time-weighted average (unless otherwise specified)

8.2 Exposure controls

Individual protection measures (personal protective equipment)

Eye/face protection

Use safety goggle with side protection.

Skin protection

• hand protection

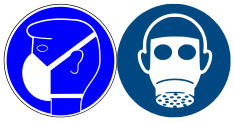
Wear suitable gloves. Chemical protection gloves are suitable, which are tested according to EN 374.

• type of material

NBR (Nitrile rubber)

- **material thickness**
  >0,11 mm
- **breakthrough times of the glove material**
  >480 minutes (permeation: level 6)
- **other protection measures**
  Take recovery periods for skin regeneration. Preventive skin protection (barrier creams/ointments) is recommended.

Respiratory protection



Respiratory protection necessary at: Dust formation. Particulate filter device (EN 143). P1 (filters at least 80 % of airborne particles, colour code: White).

Environmental exposure controls
Keep away from drains, surface and ground water.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

Physical state	solid
Colour	whitish
Odour	faintly perceptible
Melting point/freezing point	240 °C
Boiling point or initial boiling point and boiling range	not determined
Flammability	this material is combustible, but will not ignite readily
Lower and upper explosion limit	not relevant (solid)
Flash point	not applicable
Auto-ignition temperature	not determined
Decomposition temperature	>240 °C
pH (value)	not applicable
Kinematic viscosity	not relevant
<u>Solubility(ies)</u>	
Water solubility	not determined
<u>Partition coefficient</u>	
Partition coefficient n-octanol/water (log value):	this information is not available
Vapour pressure	not determined

Density and/or relative density	
Density	not determined
Relative vapour density	not relevant (solid)
Particle characteristics	No data available.
Other safety parameters	
Oxidising properties	none

9.2 Other information

Information with regard to physical hazard classes:	hazard classes acc. to GHS (physical hazards): not relevant
Other safety characteristics:	There is no additional information.

SECTION 10: Stability and reactivity

10.1 Reactivity
The product in the delivered form is not dust explosion capable; the enrichment of fine dust however leads to the danger of dust explosion.

10.2 Chemical stability
The material is stable under normal ambient and anticipated storage and handling conditions of temperature and pressure.

10.3 Possibility of hazardous reactions

Violent reaction with: strong oxidiser

10.4 Conditions to avoid
Keep away from heat. Decompostion takes place from temperatures above: >240 °C.

10.5 Incompatible materials
There is no additional information.

10.6 Hazardous decomposition products
Hazardous combustion products: see section 5.

SECTION 11: Toxicological information

11.1 Information on hazard classes as defined in Regulation (EC) No 1272/2008

Classification according to GHS (1272/2008/EC, CLP)
This substance does not meet the criteria for classification in accordance with Regulation No 1272/2008/EC.

Acute toxicity
Shall not be classified as acutely toxic.

Skin corrosion/irritation
Shall not be classified as corrosive/irritant to skin.

Serious eye damage/eye irritation
Shall not be classified as seriously damaging to the eye or eye irritant.

Respiratory or skin sensitisation
Shall not be classified as a respiratory or skin sensitiser.

Germ cell mutagenicity
Shall not be classified as germ cell mutagenic.

Carcinogenicity
Shall not be classified as carcinogenic.

Reproductive toxicity
Shall not be classified as a reproductive toxicant.

Specific target organ toxicity - single exposure
Shall not be classified as a specific target organ toxicant (single exposure).

Specific target organ toxicity - repeated exposure
Shall not be classified as a specific target organ toxicant (repeated exposure).

Aspiration hazard
Shall not be classified as presenting an aspiration hazard.

Symptoms related to the physical, chemical and toxicological characteristics

- **If swallowed**
Data are not available.
- **If in eyes**
Data are not available.
- **If inhaled**
Data are not available.
- **If on skin**
Data are not available.
- **Other information**
Health effects are not known.

11.2 Endocrine disrupting properties
Does not contain an endocrine disruptor (ED) at a concentration of ≥ 0,1%.

11.3 Information on other hazards
There is no additional information.

SECTION 12: Ecological information

12.1 Toxicity
Shall not be classified as hazardous to the aquatic environment.

12.2 Persistence and degradability
Theoretical Oxygen Demand: 1,184 $^{mg}/_{mg}$
Theoretical Carbon Dioxide: 1,629 $^{mg}/_{mg}$

12.3 Bioaccumulative potential
Data are not available.

12.4 Mobility in soil
Data are not available.

12.5 Results of PBT and vPvB assessment
Data are not available.

12.6 Endocrine disrupting properties
Does not contain an endocrine disruptor (ED) at a concentration of ≥ 0,1%.

12.7 Other adverse effects
Data are not available.

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Consult the appropriate local waste disposal expert about waste disposal.

Sewage disposal-relevant information

Do not empty into drains.

Waste treatment of containers/packagings

Handle contaminated packages in the same way as the substance itself. Completely emptied packages can be recycled.

13.2 Relevant provisions relating to waste

The allocation of waste identity numbers/waste descriptions must be carried out according to the EEC, specific to the industry and process.

13.3 Remarks

Waste shall be separated into the categories that can be handled separately by the local or national waste management facilities. Please consider the relevant national or regional provisions. Non-contaminated packages may be recycled.

SECTION 14: Transport information

14.1	**UN number or ID number**	not subject to transport regulations
14.2	**UN proper shipping name**	not assigned
14.3	**Transport hazard class(es)**	none
14.4	**Packing group**	not assigned
14.5	**Environmental hazards**	non-environmentally hazardous acc. to the dangerous goods regulations

14.6 Special precautions for user

There is no additional information.

14.7 Maritime transport in bulk according to IMO instruments

The cargo is not intended to be carried in bulk.

14.8 Information for each of the UN Model Regulations

International Maritime Dangerous Goods Code (IMDG) - Additional information

Not subject to IMDG.

International Civil Aviation Organization (ICAO-IATA/DGR) - Additional information

Not subject to ICAO-IATA.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

Relevant provisions of the European Union (EU)

Restrictions according to REACH, Annex XVII

not listed

List of substances subject to authorisation (REACH, Annex XIV)/SVHC - candidate list

not listed

Seveso Directive

2012/18/EU (Seveso III)			
No	**Dangerous substance/hazard categories**	**Qualifying quantity (tonnes) for the application of lower and upper-tier requirements**	**Notes**
	not assigned		

Deco-Paint Directive

VOC content	0 %

Industrial Emissions Directive (IED)

VOC content	0 %

Directive on the restriction of the use of certain hazardous substances in electrical and electronic equipment (RoHS)
not listed

Regulation concerning the establishment of a European Pollutant Release and Transfer Register (PRTR)
not listed

Water Framework Directive (WFD)
not listed

Regulation on the marketing and use of explosives precursors
not listed

Regulation on drug precursors
not listed

Regulation on substances that deplete the ozone layer (ODS)
not listed

Regulation concerning the export and import of hazardous chemicals (PIC)
not listed

Regulation on persistent organic pollutants (POP)
not listed

Other information
Directive 94/33/EC on the protection of young people at work. Observe employment restrictions under the Maternity Protection Directive (92/85/EEC) for expectant or nursing mothers.

National inventories

Country	Inventory	Status
AU	AIIC	substance is listed
CA	DSL	substance is listed
CN	IECSC	substance is listed
EU	ECSI	substance is listed
KR	KECI	substance is listed
MX	INSQ	substance is listed
NZ	NZIoC	substance is listed
PH	PICCS	substance is listed

Country	Inventory	Status
TR	CICR	substance is listed
TW	TCSI	substance is listed
US	TSCA	substance is listed (ACTIVE)
VN	NCI	substance is listed

Legend

AIIC	Australian Inventory of Industrial Chemicals
CICR	Chemical Inventory and Control Regulation
DSL	Domestic Substances List (DSL)
ECSI	EC Substance Inventory (EINECS, ELINCS, NLP)
IECSC	Inventory of Existing Chemical Substances Produced or Imported in China
INSQ	National Inventory of Chemical Substances
KECI	Korea Existing Chemicals Inventory
NCI	National Chemical Inventory
NZIoC	New Zealand Inventory of Chemicals
PICCS	Philippine Inventory of Chemicals and Chemical Substances (PICCS)
TCSI	Taiwan Chemical Substance Inventory
TSCA	Toxic Substance Control Act

15.2 Chemical safety assessment

No Chemical Safety Assessment has been carried out for this substance.

SECTION 16: Other information

Indication of changes (revised safety data sheet)

Section	Former entry (text/value)	Actual entry (text/value)	Safety-relevant
2.3		Endocrine disrupting properties: Does not contain an endocrine disruptor (ED) at a concentration of ≥ 0,1%.	yes
14.8	Transport of dangerous goods by road, rail and inland waterway (ADR/RID/ADN) - Additional information: Not subject to ADR, RID and ADN.		yes
15.1		National inventories: change in the listing (table)	yes

Abbreviations and acronyms

Abbr.	Descriptions of used abbreviations
ADR	Accord relatif au transport international des marchandises dangereuses par route (Agreement concerning the International Carriage of Dangerous Goods by Road)
CAS	Chemical Abstracts Service (service that maintains the most comprehensive list of chemical substances)
Ceiling-C	Ceiling value
CLP	Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures
DGR	Dangerous Goods Regulations (see IATA/DGR)
EC No	The EC Inventory (EINECS, ELINCS and the NLP-list) is the source for the seven-digit EC number, an identifier of substances commercially available within the EU (European Union)
ED	Endocrine disruptor
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of Notified Chemical Substances
GHS	"Globally Harmonized System of Classification and Labelling of Chemicals" developed by the United Nations

Abbr.	Descriptions of used abbreviations
IATA	International Air Transport Association
IATA/DGR	Dangerous Goods Regulations (DGR) for the air transport (IATA)
ICAO	International Civil Aviation Organization
IMDG	International Maritime Dangerous Goods Code
NLP	No-Longer Polymer
PBT	Persistent, Bioaccumulative and Toxic
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RID	Règlement concernant le transport International ferroviaire des marchandises Dangereuses (Regulations concerning the International carriage of Dangerous goods by Rail)
S.I. No. 619 of 2001	Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001
STEL	Short-term exposure limit
SVHC	Substance of Very High Concern
TWA	Time-weighted average
VOC	Volatile Organic Compounds
vPvB	Very Persistent and very Bioaccumulative

Key literature references and sources for data

Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. Regulation (EC) No. 1907/2006 (REACH), amended by 2020/878/EU.
Agreement concerning the International Carriage of Dangerous Goods by Road (ADR). Regulations concerning the International Carriage of Dangerous Goods by Rail (RID). International Maritime Dangerous Goods Code (IMDG). Dangerous Goods Regulations (DGR) for the air transport (IATA).

Disclaimer

This information is based upon the present state of our knowledge. This SDS has been compiled and is solely intended for this product.