Carrageenan

Toxicology

Natasha Fallahi &
Justin Jobelius

Research Question

What is the effect of carrageenan in human consumption and personal use?

Carrageenan - Defined

Indigestible polysaccharide that is extracted from red algae.

Undegraded carrageenan is approved for use in food products, while degraded carrageenan (aka poligeenan) is not approved.

Chemical Structure

High-molecular-weight polysaccharides made up of repeating galactose units and 3,6 anhydrogalactose (3,6-AG), both sulfated and nonsulfated. The units are joined by alternating α-1,3 and β-1,4 glycosidic linkages.

(Necas & Bartosikova, 2013)

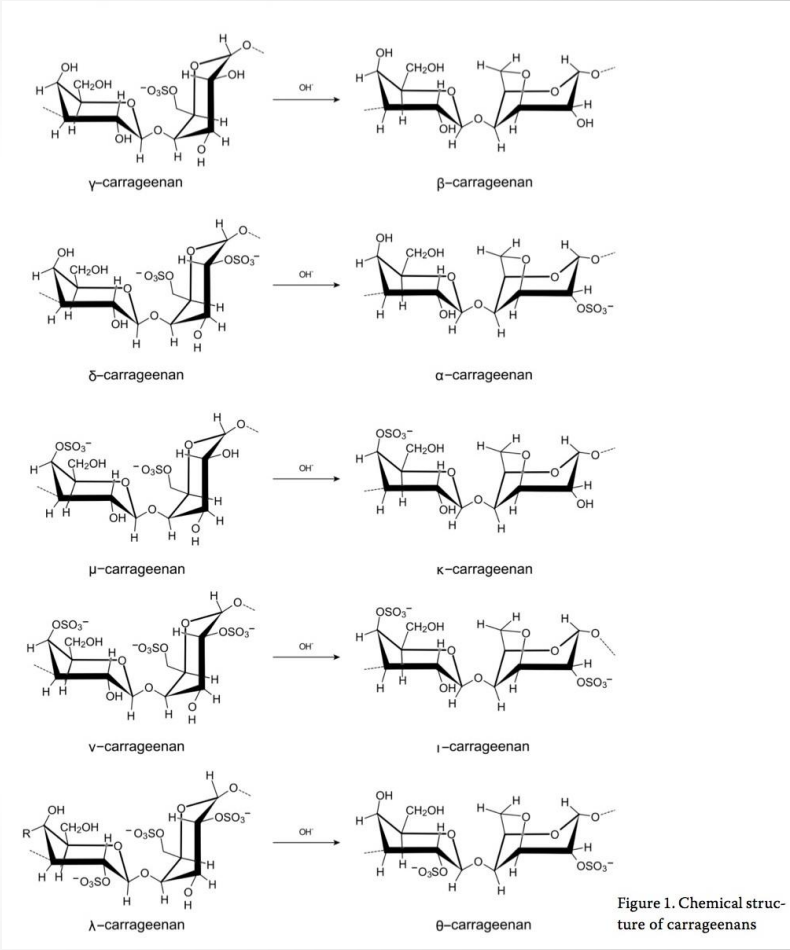


Figure 1. Chemical structure of carrageenans

Natural Compounds Mimicked

Gelatinous extracts of the Chondrus crispus (Irish Moss) seaweed have been used as **food additives since approximately the 1400s**.

About 600 years ago, people living along the coast of Carragheen County on the southern coast of Ireland started using the plant, known as **Irish moss**, a common name for Chondrus, **in foods, medicines, and as fertilizer**. They subsequently noted its **milk reactivity**. Irish moss has also been known as carrageen from the same Irish word which means “rock moss”. Irish settlers to America in the 1700's brought with them a taste for Irish moss, and it was soon recognized as a component of the natural flora off the coast of Massachusetts.

(FAO, 2014)

Use & Exposure

Thickener

Stabilizer

Gelling Agent / Binder

Individual exposure:

- Foods
- Drinks
- Personal Care Products
- Pet Food
- Pharmaceuticals

In the USA, it is permitted in organic and non-organic foods, including juices, chocolate milk, and organic infant formula.

The use of carrageenan in infant formula, organic or otherwise, is prohibited in the EU for precautionary reasons, but is permitted in other foodstuffs.

(FAO, 2014)

Examples of Use (FAO, 2014)

Soy milk and other plant milks: used to thicken, in an attempt to emulate the consistency of whole milk

Desserts, ice cream, cream, milkshakes, salad dressings, sweetened condensed milks, and sauces: gel to increase viscosity

Toothpaste: stabilizer to prevent constituents separating

Fruit Gushers: ingredient in the encapsulated gel

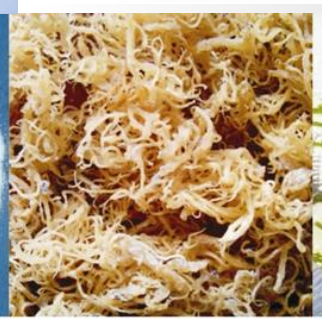
Personal lubricants

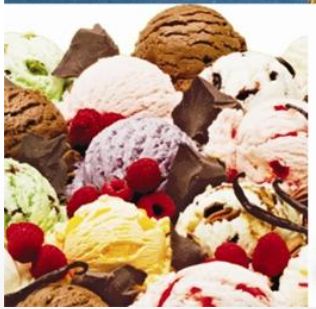
Toothpastes

Lotions & Creams

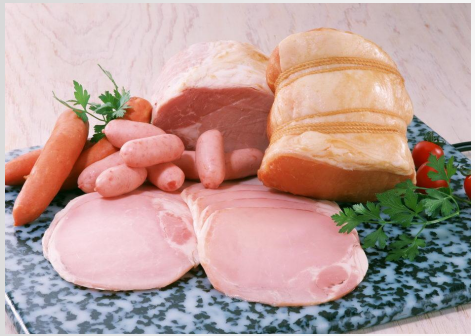
Shampoo and cosmetic creams: thickener

Air freshener gels





Examples of Use (FAO, 2014)



Beer: clarifier to remove haze-causing proteins

Pâtés and processed meats (ham, e.g.) and Vegetarian hot dogs: substitute for fat, increase water retention, and increase volume, or improve sliceability

Marbling: the ancient art of paper and fabric marbling uses a carrageenan mixture on which to float paints or inks; the paper or fabric is then laid on it, absorbing the colours

Shoe polish: gel to increase viscosity

Biotechnology: gel to immobilize cells/enzymes

Pharmaceuticals: used as an inactive excipient in pills/tablets

Diet sodas: to enhance texture and suspend flavours

Pet food

Fire fighting foam: thickener to cause foam to become sticky

Mechanism of Gel Action

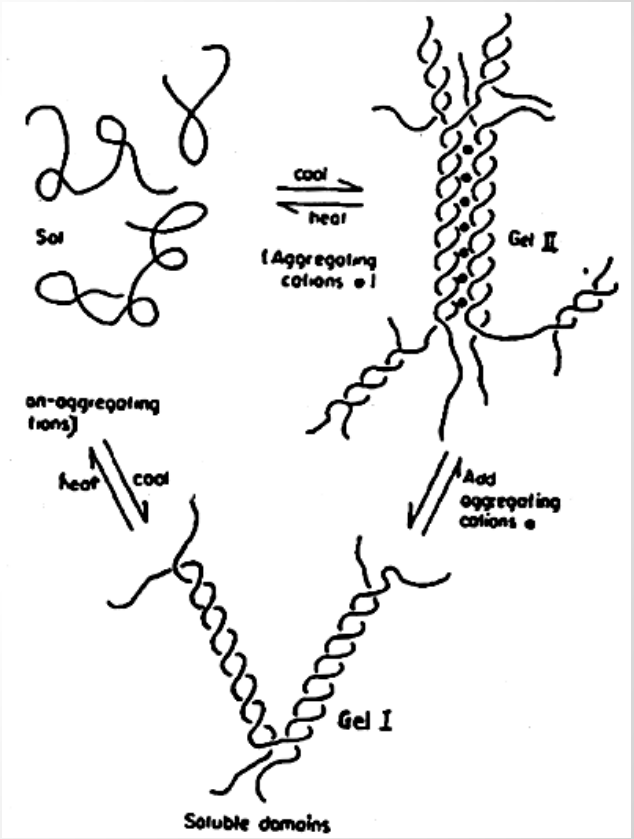
- Gel formation is attributed to the formation of double helices bundles.

- Upon cooling a three-dimensional network is crosslinked through coaxial double helices, forming small soluble clusters or “domains” consisting typically of about 10 chains without causing gelation (Gel I).

- Further crosslinking of these “domains” into a cohesive gel structure forming the junction zones in the gel (Gel II) involve side-by-side association of double helices from different domains.

- Helix-helix aggregation occurs only in the presence of cations (typically K+ for K- and Ca2+ for ι-carrageenans) which can suppress electrostatic repulsion between the highly charged participating chains by packing within the aggregate structure (Gel II)”

(Morris, Rees & Robinson, 1980)



Mechanism of Gel Action

- The effect of sulfation on gelling properties correlate with the formation of double helices.

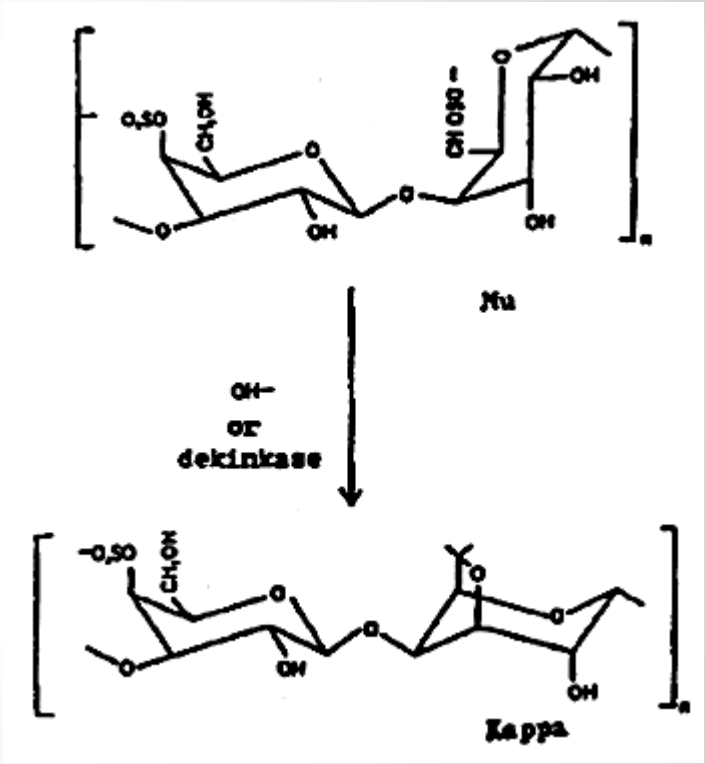
- Gel strength is more sensitive to the presence of 6-sulfate groups than to 2-sulfate or 4-sulfate groups, as the former exert a much greater effect on the conformational regularity of the polysaccharide. -

- As 1, 4-linked unit is sulfated at C-6 as in μ-carrageenan it exists in Cl chair conformation, as do all the 1,3-linked units. This introduces a kink into the polymer chain.

- 1, 4-linked unit transforms to IC form resulting in the removal of the kink (Fig. 16) increasing the degree of conformation regularity and exhibiting high gelling ability.

- The presence of even one kink in 200 residues has a distinct effect in lowering gel strength”

(Morris, Rees & Robinson, 1980)



The change from Cl to IC conformation as 3,6-AG ring is formed

Target Organs

Intestinal epithelial tissue

Colon - ulcerations & cancerous lesions

Proposed Mechanisms of Injury

(Tobacman, 2001)

Site	Effect
Intestinal lumen	Ingested carrageenan can undergo acid hydrolysis in stomach, possible breakdown by intestinal bacteria.
Intestinal epithelial cells	Take up degraded carrageenan, as indicated by metachromatic staining from cecum to rectum. Vacuoles observed to contain metachromatic material. Epithelial cells may undergo lysis from effect of lysosomal disruption producing erosions.
Inflammatory infiltrate	PMN cells and macrophages infiltrate to site of intestinal inflammation. Macrophages have metachromatic staining associated with uptake of degraded carrageenan. Lysosomal vacuolation occurs as well as lysosomal disruption with release of intracellular enzymes from macrophage destruction, leading to intestinal ulcerations. Process of chronic inflammation, as with ulcerative colitis.
Macrophage circulation	Macrophages may circulate and may lead to extraintestinal effects related to carrageenan.

Mechanism of Injury cont.

One of the particular immune pathways activated by carrageenan is similar to those activated by other “natural” poisons, such as pathogenic bacteria (including Salmonella). (Bhattacharyya et al., 2010)

Some Effects:

Epithelial cell loss, macrophage infiltration, loss of crypts. (Tobacman, 2001)

Multiple pinpoint cecal and colonic ulcerations. (Tobacman, 2001)

Increase incidence in benign mammary tumors and testicular neoplasms (Tobacman, 2001)

Target Organs & Dose-Response

Colon

Macrophages

Liver

Stomach

Small Intestine

- 5% in the diet for 21-45 days resulted in the accumulation of 36-400 pg/g of colonic tissue. The carrageenan was contained in macrophages (Grasso et al., 1973)

- Also found in liver, stomach, and small intestine (Udall et al., 1981)

Injury Dose

- Poligeenan at 0.5-2% resulted in diarrhea, hemorrhage, and ulcerations. Carrageenan at 1-3% resulted in no colonic changes (Benitz, Golberg & Coulston, 1973)

- In guinea pigs, carrageenan at a 5% concentration in the diet caused ulcers in the colon. In pigs, concentrations of carrageenan between .05 and .5% administered for 83 days resulted in abnormalities in the intestinal lining, but no ulceration (Tobacman, 2001)

- Very low concentrations (1–10 mg/L) of undegraded, high-molecular weight CGN cell death, reduced cell proliferation, and cell cycle arrest (Bhattacharyya et al., 2008)

Acute Toxicity (Weiner, 1991)

In acute oral toxicity study, there were no deaths at the highest dose tested.

Therefore, the LD_{50} is greater than 5000 mg/kg carrageenan in rats.

Table 2
Acute toxicity of food-grade carrageenan [6].

Test	Species	Result
Acute oral toxicity	Rat	$LD_{50} > 5000$ mg/kg
Acute dermal toxicity	Rabbit	$LD_{50} > 2000$ mg/kg
Acute inhalation toxicity	Rat	4-hr $LC_{50} > 930.8 \pm 74.4$ mg/m^3 (maximum attainable dust)
Primary eye irritation	Rabbit	Non-irritating (unwashed eyes) Minimally irritating (washed eyes)
Primary skin irritation	Rabbit	Non-irritating to intact skin Minimally irritating to abraded skin
Skin sensitization	Guinea pig	Non-sensitizing

Metabolization & Elimination

Metabolized by the *hydrolysis of glycosidic linkages at lower pH*, especially pH ≤ 3.0; also desulfation by sulfatases (Necas & Bartosikova, 2013)

In the one study, rats quantitatively excreted the carrageenan *in the feces*, and it had the *same gel filtration distribution pattern* as that of the administered material (Necas & Bartosikova, 2013)

In another study, in male rats given radiolabelled carrageenan, there appeared to have been *some uptake* into the intestinal wall, Peyer's patches, mesenteric and cecal lymph nodes, and serum. (Necas & Bartosikova, 2013)

Risk & Prevalence

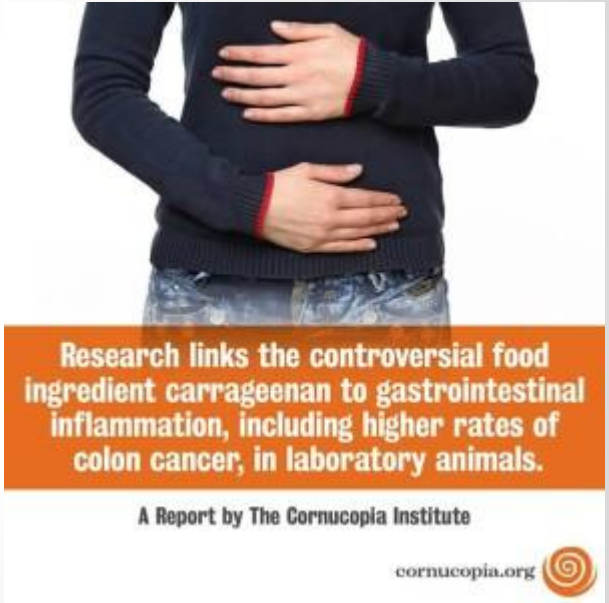
Risks:

Inflammatory bowel disease, ulcerations & neoplasms of the GI tract. (Tobacman, 2001)

Prevalence:

Public health effects of carrageenan in human consumption are unknown.

The rising incidence and prevalence of inflammatory GI conditions such as Crohn's disease and ulcerative colitis tell a precautionary tale, as does the litany of research elucidating the harmful effects of long-term, low-level inflammation.



Care Management

Reduce or eliminate ingestion / exposure of carrageenan - read the ingredients on your food labels!

Following ingestion, cut down intake of known inflammatory mediators to minimize inflammation of the gut.

When gut is inflamed, limit rough fibrous foods and hard foods.

Follow anti-inflammatory diet to curb chronic, low level inflammation.

Eat gut soothing food, drink plenty of water, eat smaller portions to allow gut to heal, and take probiotics.

Because acute toxicity is non-lethal, there is no emergency management protocol following ingestion of carrageenan.

Market Alternatives

- Locust bean gum
- Gum arabic
- Alginate
- Guar gum
- Xanthan gum

HomemadeDIY

Moving Forward

- The FDA must do a substantive review of carrageenan, and the literature about its effects on physiology.
- If deemed toxic by the FDA, action steps must be taken to remove carrageenan from the marketplace of consumable products.
- More research is needed on the carcinogenic properties of the substance.
- How do genetic characteristics influence how carrageenan is metabolized?

In Closing

"Because of the acknowledged carcinogenic properties of degraded carrageenan in animal models and the cancer-promoting effects of undegraded carrageenan in experimental models, the widespread use of carrageenan in the Western diet should be reconsidered." (Tobacman, 2001)

Bibliography

Benitz, K. F., Golberg, L., & Coulston, F. (1973). Intestinal effects of carrageenans in the rhesus monkey. *Food and Cosmetics Toxicology, 11*(4), 565–575.

Bhattacharyya, S., Alip, B., Pradeep, K., Dudeja, & Tobacman, J. K. (2008). Carrageenan Induces Cell Cycle Arrest in Human Intestinal Epithelial Cells in Vitro 1–3. *Journal of Nutrition, 138*(3), 469-475.

Bhattacharyya, S., Liu, H., Zhang, F., Jam, M., Dudeja, P. K., Michel, G., Linhardt, R. J., & Tobacman, J. K. (2010). Carrageenan-induced innate immune response is modified by enzymes that hydrolyze distinct galactosidic bonds. *Journal of Nutritional Biochemistry, 21*(10), 906-13.

FAO Agar and Carrageenan Manual. “Chapter III: Properties, Manufacture and Application of Seaweed Polysaccharides - Agar, Carrageenan and Algin.“ Fao.org (1965-01-01).

Grasso, P., Sharratt, M., Carpanini, F. M. B., & Gangolli, S. D. (1973). Studies on carrageenan and large-bowel ulceration in mammals. *Food and Cosmetics Toxicology, 11*, 555-564.

Morris, E. R., Rees, D. A., & Robinson, G. (1980). Cation-specific aggregation of carrageenan helices: Domain model of polymer gel structure. *Journal of Molecular Biology, 138*(2), 349–362.

Bibliography

Necas, J., & Bartosikova, L. (2013). Carrageenan: A review. *Veterinarni Medicina*, *58*(4), 187–205.

Tobacman, J. K. (2001). Review of harmful gastrointestinal effects of carrageenan in animal experiments. *Environmental Health Perspectives, 109*(10), 983–994.

Udall, J. N., Harmatz, P., Vachino, G., Galdabini, J., & Walker, W. A. (1981). Intestinal transport and liver uptake of a food additive present in infant formulas (Abstract). *Pediatric Research, 15*, 549.

Weiner, M. L. (1991) Toxicological properties of carrageenan. *Agents and Actions*, *32*,(1-2), 46-51.