Handling Subcommittee

# Carrageenan 2018 Sunset

*Comments*

Comments submitted in advance of the

## *National Organic Standards Board*

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CORNUCOPIA

INSTITUTE

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# HANDLING SUBCOMMITTEE

# Carrageenan – 2018 Sunset

**SUMMARY**

The Cornucopia Institute **opposes** the relisting of carrageenan at 205.605(a) Nonagricultural (Nonorganic) substances allowed as ingredients in or on processed products labeled as ''organic'' or ''made with organic (specified ingredients or food group(s))" because **of decades of public scientific research showing biological reactivity in human cells causing harm to human health**. Carrageenan also lacks essentiality.

***Rationale:***

- Carrageenan is non-essential. **Every organic product containing carrageenan has an organic alternative, being produced by one or more competitors.**

- **The 2016 TR fails to discuss the undisputed fact that degraded carrageenan is present within food-grade carrageenan.** At the request of European regulators, the Marinalg Working Group attempted to reliably measure the amount of degraded carrageenan in food-grade carrageenan. The lab results were posted online and proved that bioactive, low molecular weight carrageenans (poligeenan) were present in all samples of food-grade carrageenan. Fortunately, The Cornucopia Institute downloaded these documents before they were subsequently removed from the internet by the industry lobby.[1]

- As a result, the 2005 European Commission's recommendation that no more than 5% of foodgrade carrageenan fractions should have molecular weight below 50 kDa[2] has not been met by the industry.[3,4]

- The statement made by the NOSB handling subcommittee that they are "troubled that the research showing inflammation and glucose intolerance is all from one research team and has not been replicated," is **simply not true**.

[1] Marinalg International (2006) Technical Position on Measurements Related to Meeting the EC Molecular Weight
[2] European Committee Scientific Committee on Food. Opinion on Carrageenan. Expressed on 5 March 2003. Available online: http://ec.europa.eu/food/fs/sc/scf/out164_en.pdf. Last accessed March 23, 2016.
[3] www.coruncopia.org (reports tab)
[4] Marinalg International (2006) Technical Position on Measurements Related to Meeting the EC Molecular Weight distribution Specification for Carrageenan and PES. (Formally available online, but later removed by the company. Appendix B in Cornucopia's carrageenan report www.cornucopia.org).

- There are a number of labs around the world that have studied the inflammatory effects of carrageenan. **Approximately 10,000 references in PubMed occur when "inflammation and carrageenan"** is searched. In the European Commission review from 2003, hundreds of studies that discussed the effects of carrageenan on intestinal inflammation were reviewed. **A few important references that are missing from the TR include:**

  1. The clinical impact of carrageenan and diabetes, currently being studied in Germany (University of Tuebingen, Dr. Robert Wagner and Dr. Norbert Stefan).[5]
  2. The effects of carrageenan on insulin resistance and inhibition of insulin signaling, currently being studied by T.W. Jung, S.Y. Lee, and H.C. Hong.[6]
  3. The induction of diabetes by carrageenan in an animal model, studied by H.S. Baek and J.W. Yoon (1991).[7]
  4. NIH-supported Mouse Metabolic Phenotyping Center at Vanderbilt has demonstrated the impact of carrageenan exposure on responses to insulin in hyperinsulinemic-euglycemic mouse studies.[8]

- **The positions taken by regulatory agencies have been influenced by aggressive lobbying and industry-funded reports about carrageenan — <u>by law the NOSB needs to take a more critical approach</u>.** The positions taken by the regulatory agencies are often based on a single study in which critical points are obfuscated.

  As an example, the recent infant pig feeding study[9], on which the Joint FAO/WHO Expert Committee on Food Additives (JECFA) partially based its decision, contained several critical flaws including (this questionable, industry-funded research was heavily relied upon by the HS):

  1) Use of infant pigs in which the innate immune response to carrageenan is expected to be less than in humans.

  2) Onset of the pig study was <u>after</u> ingestion of maternal colostrum and maternal

[5] https://clinicaltrials.gov/ct2/show/NCT02629705. Last accessed on March 23, 2016.
[6] Jung TW, Lee SY, Hong HC, Choi HY, Yoo JH, Baik SH, and Choi KM (2014) AMPK activator-mediated inhibition of endoplasmic reticulum stress ameliorates carrageenan-induced insulin resistance through the suppression of selenoprotein P in HepG2 hepatocytes. *Molecular and Cellular Endocrinology* 382(1):66-73.
[7] Baek HS and Yoon Jw (1991) Direct involvement of macrophages in destruction of beta-cells leading to development of diabetes in virus-infected mice. *Diabetes* 40(12):1586-97.
[8] Bhattacharyya S, Feferman L, Unterman T, Tobacman JK. (2015) Exposure to common food additive carrageenan alone leads to fasting hyperglycemia and in combination with high fat diet exacerbates glucose intolerance and hyperlipidemia without effect on weight. *Journal of Diabetes Research*:513429. doi: 10.1155/2015/513429.
[9] Weiner ML et al (2015) An infant formula toxicity and toxicokinetic feeding study on carrageenan in preweaning piglets with special attention to the immune system and gastrointestinal tract. *Food and Chemical Toxicology* 77:120-131.

feeding for an unspecified, and variable number of days, unlike the common use in human infant formula feeding at birth.

3) Several "incidental" deaths occurred during the study with no explanation.

4) Watery feces were increased in the carrageenan-treated animals.

5) Glycosuria (the excretion of excessive water in urine) occurred in 4 out of 12 animals.

6) Rectal weight was significantly reduced in males that received carrageenan.

7) Weights were reported without ranges or standard deviations.

8) Animals entered the study close to the age of weaning, rather than immediately after birth.

9) Histopathology images demonstrate differences between control and carrageenan-treated tissues that were not included in the text.

10) There was an absence of any long-term data. [Tobacman, personal communication]

There were many similar flaws including prolonged recovery periods following exposure to carrageenan in the Benitz feeding studies also used by the World Health Organization to determine that carrageenan is safe[10]. Even with this prolonged recovery, there were significant changes in the endothelial cells of the livers of the monkeys treated with carrageenan. [Tobacman, personal communication]

- The 2016 TR states that "carrageenan can be avoided by sensitive individuals as it is included in the label, thereby making it easy to avoid." This is incorrect. With this logic, all "sensitive" consumers would have to be knowledgeable about carrageenan's inflammatory characteristics. Furthermore, when carrageenan is a "secondary" ingredient, as in condensed milk, beer, and cream, it is not listed on the label.

- The statement made by the NOSB subcommittee that "only some people are sensitive" is inaccurate. **Carrageenan is bioactive and inflammatory (and a potential carcinogen due to long-term exposure) in all individuals, not just those who exhibit acute symptoms.**

  It might be true that only a subset of the population exhibit acute symptoms. However, the specific chemical composition of carrageenan is immunogenic due to

[10] Benitz KF, Golberg L, and Coulston F. (1973) Intestinal effects of carrageenans in the Rhesus monkey (*Macaca mulatta*). *Food and Cosmetics Toxicology* 11:565-575.

the presence of the galactose-alpha-1,3-galactose bond, which humans do not make. Therefore, the effects of carrageenan occur in all individuals and are independent of the molecular weight, although more harmful effects are observed with lower molecular weight carrageenans (which are present in all food-grade carrageenan).

- Industry has also tried to discount studies in human colonic epithelial cell line NCM460, which is routinely used in many cell culture studies (not just investigating carrageenan) because it enables survival in culture. This is not an issue, because all of the studies had controls that were **not** exposed to carrageenan for comparison, and data were analyzed by appropriate statistics.

- Studies have also shown inflammation in normal human colonic epithelial cells from colon surgery specimens, from other established rodent and human intestinal cell lines, and in mouse models.[11]

- It's widely accepted that degraded carrageenan is dangerous to human health. **Several studies, have demonstrated that food grade carrageenan, when exposed to stomach acid, degrades in the digestive track** posing significant, potential risk.[12,13]

- Studies that look at the average molecular weight of carrageenan, many of which are discussed in the TR, are not useful because they **obscure the presence of lower molecular weight forms that contaminate all food grade carrageenan**.

- The lack of more "dose-response" studies has been erroneously criticized in reports funded by industry, but several dose-response studies have been performed. **The amount of carrageenan exposure in many of the experiments that demonstrate inflammation is less than what is consumed in the typical diet** (average carrageenan consumption of 250 mg/day. Levels of daily consumption of carrageenan in the diet may be much higher, on the order of 18-40 mg/kg/d).

[11] Borthakur A, Bhattacharyya S, Dudeja PK, and Tobacman JK (2007) Carrageenan induces interleukin-8 production through distinct Bc110 pathway in normal human colonic epithelial cells. *American Journal of Gastrointestinal Liver Physiology* 292: G829-G838.

[12] Uno Y, Omoto T, Goto Y, Asai I, Nakamura M, and Maitani T (2001) Molecular weight distribution of carrageenans studies by a combined gel permeation/inductively coupled plasma (GPC/ICP) method. *Food Additives and Contaminants* 18: 763-772.

[13] Pittman KA, Goldberg L, and Coulston F (1976) Carrageenan: the effect of molecular weight and polymer type on its uptake, excretion and degradation in animals. *Food and Cosmetics Toxicology* 14(2):85-93.

## DISCUSSION

Carrageenan functions as a bulking agent, carrier, emulsifier, gelling agent, glazing agent, humectant, stabilizer, or thickener. It is typically used at a rate ranging from 0.03% to 0.75%, and its most common uses are in dairy products, non-dairy "milk" analogs, processed meats, yogurts, chewable vitamins, pizza crusts, toothpastes, wet pet foods and drink mixes.

It is a direct food additive with an **average** molecular weight of 200-800 kDa, and may be referred to as "undegraded" or "native" carrageenan in the literature, however **this misrepresents the substance because all carrageenan contains some detectable percentage of degraded carrageenan (used to induce cancer to study anti-inflammatory drugs)**. The kappa, iota or lambda formation of carrageenan is defined by the number and position of sulfate groups, but all types are used in foods.

The European Commission's recommendation that no more than 5% of carrageenan fractions should have molecular weight below 50 kDa[14] has been impossible for the industry to comply with, based on their own reports.[15] Carrageenan with molecular weight less than 50kDa are thought to cause the most severe health problems.

### Human Health Concerns Referenced in the 2016 Technical Review

A number of studies by multiple researchers have identified potential human health concerns, including:

- "The literature is in agreement that poligeenan **causes ulcerations of the cecus and proximal colon in experimental animals**, leading to its classification by the International Agency for Research on Cancer as a **possible human carcinogen**" (line 27-29).

- "In an early in vivo study by Pittman, Golberg and Coulston (1975)[16], carrageenan was given to guinea pigs, monkeys and rats via drinking water or in the diet. Fecal and liver samples were examined quantitatively by gel electrophoresis to determine changes in molecular weight of carrageenans after passing through the digestive tract. The **study demonstrated that high molecular weight carrageenans are degraded to some extent as a result of their passage through the intestinal tract**.

[14] European Committee Scientific Committee on Food. Opinion on Carrageenan. Expressed on 5 March 2003. Available online: http://ec.europa.eu/food/fs/sc/scf/out164_en.pdf. Last accessed March 23, 2016.
[15] Marinalg International (2006) Technical Position on Measurements Related to Meeting the EC Molecular Weight distribution Specification for Carrageenan and PES. (Formally available online, but later removed by the company. Appendix B in Cornucopia's carrageenan report www.cornucopia.org).
[16] Pittman KA, Goldberg L, and Coulston F (1976) Carrageenan: the effect of molecular weight and polymer type on its uptake, excretion and degradation in animals. *Food and Cosmetics Toxicology* 14(2):85-93.

- Polysaccharides such as carrageenan are depolymerized (degraded) in acid solution, and the rate of polymerization depends on pH and temperature (Capron, Yvon and Muller 1996)[17]. The findings showed that **after 2 hours in simulated gastric juice at pH 1.2, almost 90% of the carrageenan had a mass of less than 100 kDa and 25% had a mass of less than 20 kDa**.

- "Grasso et al. (1973)[18] identified multiple pin-point caecal and colonic ulcerations in guinea pigs after being fed 5% diet of carrageenan for 45 days" (line 116-117).

- "A series of studies has shown that carrageenan **can induce a complex inflammatory cascade in human intestinal epithelial cells through an immune-mediated mechanism** (Borthakur et al. 2012)[19] and a reactive oxygen species (ROS)-mediated mechanism (Bhattacharyya, Dudeja and Tobacman 2008)[20], which contribute to an inflammatory response. **A feedback loop leads to extended inflammation…** (Bhattacharya et al. 2010a[21], Borthakur et al. 2007[22]; Bhattacharyya et al. 2010b[23]; Bhattacharyya, Feferman, and Tobacman 2015[24])" (lines 147-155).

- "A review article by Tobacman (2001) of animal studies on the effects of carrageenan and poligeenan on gastrointestinal health concluded that **undegraded carrageenan is associated with intestinal ulcerations and neoplasms**. The article attributed these issues to the **contamination of undegraded carrageenan by components of low molecular weight**, the spontaneous metabolism to lower molecular weight by acid hydrolysis under conditions of normal digestion, or the interactions with intestinal bacteria. (Nicklin and Miller 1984[25]; Rustia, Shubik and Patil 1980[26]; Pittman, Golberg

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[17] Capron IM, Yvon, and Muller G (1996) In-vitro gastric stability of carrageenan. *Food Hydrocolloids* 10(2):345.

[18] Grasso PM, Sharrat MB, Carpanini, and Gangolli SD (1973). "Studies on Carrageenan and Large-bowel Ulceration in Mammals." *Food Cosmetic Toxicology* 11:555-564.

[19] Borthakur A, Bhattacharyya S, Anbazhagan AN, Kumar A, Dudeja PK, Tobacman JK. (2012) Prolongation of carrageenan-induced inflammation in human colonic epithelial cells by activation of an NFκB-BCL10 loop. *Biochimica Biophysica Acta* 1822(8):1300-7.

[20] Bhattacharyya S, Dudeja PK, Tobacman JK. (2008) Carrageenan-induced NFkappaB activation depends on distinct pathways mediated by reactive oxygen species and Hsp27 or by Bcl10.
*Biochimica Biophysica Acta* 1780(7-8):973-82.

[21] Bhattacharya, Sumit, et al. (2010) B-cell CLL/Lymphoma 10 (BCL10) Is Required for NF-kB Production by Both 316 Canonicl and Noncanonical Pathways and for Nf-kB-inducing Kinase (NIK) Phosphorylation. *Journal of Biological Chemistry* 285(1): 522-530.

[22] Borthakur A, Bhattacharyya S, Dudeja PK, and Tobacman JK (2007) Carrageenan induces interleukin-8 production through distinct Bc110 pathway in normal human colonic epithelial cells. *American Journal of Gastrointestinal Liver Physiology* 292:G829-G838.

[23] Bhattacharya S et al. (2010) Carrageenan-induced innate immune response is modified by enzymes that hydrolyze distinct galactosidic bonds. *Journal of Nutritional Biochemistry* 21: 906-913.

[24] Bhattachayra S, Feferman L, and Tobacman JK. (2015) Carrageenan Inhibits Insulin Signaling through GRB10-mediated Decrease in Tyr(p)-ISR1 and through Inflammation-induced Increase in Ser(P)$^{307}$-IRS1. *Journal of Biological Chemistry* 290(17): 10764-10774.

[25] Nicklin S and Miller K (1984) Effect of orally administered food-grade carrageenans on antibody-mediated and cell-mediated immunity in the inbred rat. *Food Chemical Toxicology* 22(8): 615-621.

[26] Rustia M, Shubik P, and Patil K (1980) Lifespan carcinogenicity tests with native carrageenan in rats and hamsters. *Cancer Letters* 11:1-10.

and Coulston 1975[27]; Engster and Abraham 1976[28]; Poulsen 1973[29]; Benitz, Golberg and Coulston 1973[30]; Grasso et al. 1973[31])" (lines 161-165).

- "Since different animal species, different animals within the same species, and different human intestinal cell lines have produced different experimental results, **it is reasonable to expect that humans may also experience varying degrees of sensitivity to carrageenan in the diet**" (lines 177-180).

**Inaccuracies in the 2016 Technical Review**

- "Poligeenan, also called "degraded carrageenan" or "C16" in the literature, is a distinctly different substance from foodgrade carrageenan…" (line 19-20). **Correction: Poligeenan(degraded carrageenan) is found in food-grade carrageenan.**

- "Poligeenan (CAS# 53973-98-1) is an artificially formed polymer produced by subjecting carrageenan to extensive acid hydrolysis at low pH (0.9-1.3) and high temperatures (>80º C) for an extended period of time." (line 19-22) **Correction: poligeenan is found naturally in all red seaweeds and in food-grade carrageenan**.

- "Its [poligeenan] only application today is as a 25 component of x-ray imaging diagnostic products" (line 24-25). **Correction: carrageenan is used in research to induce inflammation and study the effect of anti-inflammatory drugs.**

- "It is possible that food-grade carrageenan may contain some low molecular weight fractions that are equivalent to poligeenan, although validated analytical methods to accurately measure the low molecular weight distributions of carrageenan are not fully developed or available to the industry" (lines 31-33). **Correction: reports from both academia and industry show that food-grade carrageenan is well documented to contain poligeenan.**

[27] Pittman KA, Goldberg L, and Coulston F (1976) Carrageenan: the effect of molecular weight and polymer type on its uptake, excretion and degradation in animals. *Food and Cosmetics Toxicology* 14(2):85-93.
[28] Engster M and Abraham R (1976) Cecal response to different molecular weights and types of carrageenan in the guinea pig. *Toxicology and Applied Pharmacology* 38(2):265-282.
[29] Poulsen E (1973) Short-term Peroral Toxicity of Undegraded Carrageenan in Pigs. *Food Cosmetic Toxicology* 11:219-227.
[30] Benitz KF, Golberg L, and Coulston F (1973) Intestinal Effects of Carrageenans in the Rhesus Monkey (Macaca mulatta). *Food Cosmetic Toxicology* 11:565-575.
[31] Grasso P, Sharrat M, Carpanini MB, and Gangolli SD (1973) Studies on Carrageenan and Large-bowel Ulceration in Mammals." *Food Cosmetic Toxicology* 11:555-564.

**Missing Studies in the 2016 Technical Review**

- Marinalg International (2006) Technical Position on Measurements Related to Meeting the EC Molecular Weight distribution Specification for Carrageenan and PES. (Formally available online, but **later removed by the company**. Appendix B in Cornucopia's carrageenan report www.cornucopia.org). **Summary of findings**: **Degraded carrageenan was found in all food-grade carrageenan samples, but the percentage could not be replicated across different labs.**

- Tobacman JK (2015) The Common Food Additive Carrageenan and the alpha-gal epitope. *Journal of Allergy and Clinical Immunology* 136(6): 1708-9. **Summary of findings**: The specific chemical composition of carrageenan is immunogenic due to the presence of the galactose-alpha-1,3-galactose bond, which humans do not make. Therefore, the effects of carrageenan occur in all individuals and are independent of the molecular weight of the carrageenan ingested, although more harmful effects occur from low molecular weight carrageenan.

- Coleman MR and Coleman MT (2015) "Dairy-free" dietary substitute, abdominal pain, and weight loss. *Clinical Medical Reviews and Case Reports* 2:8. **Summary of findings**: Elimination of carrageenan-containing almond milk from the diet of a patient that had substituted it for cow's milk several months prior resulted in stabilization of weight and resolution of abdominal pain.

- Jung TW, Lee SY, Hong HC, Choi HY, Yoo JH, Baik SH, and Choi KM (2014) AMPK activator-mediated inhibition of endoplasmic reticulum stress ameliorates carrageenan-induced insulin resistance through the suppression of selenoprotein P in HepG2 hepatocytes. *Molecular and Cellular Endocrinology* 382(1):66-73. **Summary of findings**:Carrageenan causes inflammation through toll-like receptor 4, which plays an important role in insulin resistance and type 2 diabetes mellitus. Carrageenan induces endoplasmic reticulum (ER) stress in a time- and dose-dependent manner.

- Bhattacharyya S, Feferman L, and Tobacman JK (2014) Regulation of Chondroitin-4-Sulfotransferase (CHST11) Expression by Opposing Effects of Arylsulfatase Bon BMP4 and Wnt9A. *Biochim Biophys Acta* 1849(3): 342-352. **Summary of findings**: Exposure to the common food additive carrageenan, which reduces ARSB activity, reduced expression of bone morphogenetic protein (BMP)-4 in colonic epithelium and increased Wnt9A expression and Wnt/β-catenin signaling.

- Bhattacharyya S, Feferman L, and Tobacman JK (2014) Increased Expression of Colonic Wnt9A through Sp1-mediated Transcriptional Effects involving Arylsulfatase B, Chondroitin 4-Sulfate, and Galectin-3 *The Journal of Biological Chemistry* 289(25): 17564-17575. **Summary of findings**: Mechanism by which Wnt expression was increased by carrageenan exposure was unknown. Extracellular events can regulate transcription through changes in arylsulfatase B and chondroitin 4-sulfation.

- Yang B, Bhattacharyya S, Linhardt R and Tobacman JK (2012) Exposure to common food additive carrageenan leads to reduced sulfatase activity and increase in sulfated glycosaminoglycans in human epithelial cells. *Biochimie* 94(6): 1309-16. **Summary of findings**: Exposure to small amounts of food-grade carrageenan reduces the activity of sulfatase enzymes, which are critical for many vital cellular processes.

- Bhattacharyya S, Dudeja PK and Tobacman JK (2010) Tumor necrosis factor alpha-induced inflammation is increased but apoptosis is inhibited by common food additive carrageenan. *Journal of Biological Chemistry* 285(50): 39511-22. **Summary of findings**: This study examines the particular mechanisms by which food-grade carrageenan cause inflammation.

- Bhattacharyya S, Gill R, Chen ML, Zhang F, Linhardt RJ, Dudeja PK and Tobacman JK (2008) Toll-like receptor 4 mediates induction of the Bcl10- NFkappaB-interleukin-8 inflammatory pathway by carrageenan in human intestinal epithelial cells. *Journal of Biological Chemistry* 283(16): 10550-8. **Summary of findings**: Exposure of human colonic epithelial cells in tissue culture to small quantities of food-grade carrageenan was associated with changes in molecular signaling pathways that resemble the changes found in human colonic polyps. Untreated polyps can develop into colon cancer.

- Bhattacharyya S, Borthakur A, Dudeja PK and Tobacman JK (2008) Carrageenan induces cell cycle arrest in human intestinal epithelial cells in vitro. *Journal of Nutrition* 138(3): 469-75. **Summary of findings**: Exposure of human colonic epithelial cells in tissue culture to small quantities of undegraded (food-grade) carrageenan produced an increase in cell death with cell cycle arrest, effects that can contribute to ulcerations.

- Bhattacharyya S, Borthakus A, Dudeja PK and Tobacman JK (2007) Carrageenan reduces bone morphogenetic protein-4 (BMP4) and activates the Wnt/ beta-catenin pathway in normal human colonocytes. *Digestive Diseases and Sciences* 52(10): 2766-74. **Summary of findings**: This study identified mechanisms by which food-grade carrageenan influences the development of human intestinal polyps. Untreated intestinal polyps can develop into colon cancer.

- Suzuki J, Na HK, Upham BL, Chang CC and Trosko JE (2000) Lambda-carrageenan-induced inhibition of gap-junctional intercellular communication in rat liver epithelial cells. *Nutrition and Cancer* 36(1): 122-8. **Summary of findings**: Carrageenan functions as a tumor-promoting chemical by inhibiting GJIC (Gap-junctional intercellular communication is believed to help healthy cells fight cancer). The data revealed inhibition of GJIC by carrageenan similar to that by the well-documented tumor promoter phorbol ester.

- Corpet DE, Taché S, and Préclaire M (1997) Carrageenan given as a jelly does not initiate, but promotes the growth of aberrant crypt foci in the rat colon. *Cancer Letters*

114:53–55. **Summary of findings**: Consumption of food-grade carrageenan promotes the growth of aberrant crypt foci in the rat colon. Aberrant crypt foci are abnormal glands in the colon that are precursors to polyps and are one of the earliest changes seen in the colon that may lead to cancer.

- Calvert RJ and Reicks M (1988) Alterations in colonic thymidine kinase enzyme activity induced by consumption of various dietary fibers. Proceedings of the Society for Experimental Biology and Medicine 189:45–51. **Summary of findings**: Researchers examined the reported effects of various dietary fibers on chemically induced colon carcinogenesis in rats. This study found a four-fold increase in thymidine kinase activity (a measure for malignant disease) in colonic mucosa following exposure to food-grade carrageenan. No differences were found following exposure to guar gum, a food additive used as an alternative to carrageenan.

- Arakawe S, Okumua M, Yamada S, Ito M, Tejima S (1986) Enhancing effect of carrageenan on the induction of rat colonic tumors by 1,2-dimethylhydrazine and its relation to ß-glucuronidase activities in feces and other tissues. *Journal of Nutritional Science and Vitaminology* 32:481–485. **Summary of findings**: Higher rates of tumors were found in rats fed undegraded carrageenan in the diet.
- Watt J and Marcus R (1981) Danger of carrageenan in foods and slimming recipes. *The Lancet* 317(8215): 338. **Letter to The Lancet**: Scientists repeat their concern with the use of carrageenan in food in a letter to The Lancet.

- Watt J and Marcus R (1980) Potential hazards of carrageenan. *The Lancet* 315(8168): 602-603. **Letter to The Lancet**: The authors of published research showing increased rates of ulcerative colitis-like disease in laboratory animals given food-grade carrageenan wrote the letter to The Lancet. Highly respected, The Lancet is one of the world's leading medical journals. The scientists express their concern with the safety of carrageenan in food.

- Watanabe K, Reddy BS, Wong CQ, Weisburger JH (1978) Effect of dietary undegraded carrageenan on colon carcinogenesis in F344 rats treated with azoxymethane or methylnitrosourea. *Cancer Research* 38:4427–4430. **Summary of findings**: This study found higher rates of tumors in rats fed undegraded carrageenan in the diet.

**Past NOSB Actions and Deliberations**

During the last Sunset Review in 2012, the NOSB received comments from both the scientific community and the public concerning carrageenan's impact on human health. Industry critiqued research methodology used in publically funded studies and claimed that results were not always consistent with how carrageenan behaves when ingested in food. The NOSB stated they could not thoroughly investigate these issues within the short period of time between the Sunset announcement and the vote to renew.

Since this time, **all of industry's criticisms of publically funded research have been addressed and, based on industry talking points, the handling subcommittee has attempted to discredit the public research/researchers.**

The Handling Subcommittee commissioned a Limited Scope Technical Report, completed by OMRI and released to the public in March 2016, **however the authors were not disclosed. The scientific community's preeminent public researcher on carrageenan was not consulted for any information in researching the TR** [Tobacman, personal communication].

Even after the TR was released the Handling Subcommittee incorrectly stated "We are troubled that the research showing inflammation and glucose intolerance is all from one research team and has not been replicated. We hope that in the next few months before we vote more conclusive research replication or rebuttal will help inform our decision."

**This statement is woefully inaccurate. Even the TR (which is missing some published research) sites dozens of scientists and articles showing harm from food-grade carrageenan**. Yes, Dr. Tobacman's group was the first to evaluate how the inflammatory effects of carrageenan inhibit insulin signaling and cause insulin resistance. However, other investigators have published effects of carrageenan on inhibition of insulin signaling (Jung et al, Molecular Cell Endocrinology 2014[32]), and investigators in the NIH-supported Mouse Metabolic Phenotyping Center at Vanderbilt demonstrated the impact of carrageenan exposure on responses to insulin in hyperinsulinemic-euglycemic mouse studies (Bhattacharyya, Journal of Diabetes Research, 2015.)[33]

[32] Jung TW, Lee SY, Hong HC, Choi HY, Yoo JH, Baik SH, and Choi KM (2014) AMPK activator-mediated inhibition of endoplasmic reticulum stress ameliorates carrageenan-induced insulin resistance through the suppression of selenoprotein P in HepG2 hepatocytes. *Molecular and Cellular Endocrinology* 382(1):66-73.

[33] Bhattacharyya S, Feferman L, Unterman T, Tobacman JK. (2015) Exposure to common food additive carrageenan alone leads to fasting hyperglycemia and in combination with high fat diet exacerbates glucose intolerance and hyperlipidemia without effect on weight. *Journal of Diabetes Research*:513429. doi: 10.1155/2015/513429.

**The Handling Subcommittee is Repeating Industry Propaganda**

In addition, studies of carrageenan feeding in infant pigs conducted by industry researchers detected glycosuria in 4 out of 12 of the animals (Weiner et al, Food and Chemical Toxicology, 2015).[34] Studies conducted decades ago by industry scientists at Albany Medical College showed elevated blood sugars and reduced hepatic glycogen stores, consistent with diabetes.[35] Investigators in Germany (Drs. Wagner and Stefan University of Tuebingen) are currently examining the impact of carrageenan on glucose tolerance and insulin resistance in an ongoing clinical study.[36] **Tobacman's group has been funded by the American Diabetes Association** to detect the impact of the no-carrageenan diet on glucose tolerance in prediabetic patients. Other investigators have reported induction of diabetes by carrageenan in an animal model (Baek, Diabetes, 1991).[37]

The Handling Subcommittee also stated "It is also worth noting that in the time since the last review the World Health Organization JECFA committee re-evaluated carrageenan for use in infant formula and changed their opinion on restricting its use to have an unrestricted status." **This determination was based largely on the *flawed* industry study of carrageenan intake in infant pigs** (Weiner et al, Food Chemical Toxicology, 2015.)[38]

**Flaws in this study include**: 1) use of infant pigs in which the innate immune response to carrageenan is expected to be less than in humans, since pigs make the alpha-1,3-galactosyltransferase enzyme and the galactose-alpha-1,3-galactose bond of carrageenan is not immunogenic in the pig; 2) onset of the study was after ingestion of maternal colostrum and maternal feeding for an unspecified, and variable number of days in the study animals; 3) antibiotics and iron supplements were given prior to and throughout the 28-day carrageenan feeding; 4) several "incidental" deaths occurred with no explanation; 5) soft and/or watery feces were increased in the carrageenan-treated animals; 6) glycosuria occurred in 4/12 animals; 7) rectal weight was significantly reduced in males; 8) weights, which were reported without ranges or standard deviations, were unusually high (all over 10 kg) at Study Day 28, suggesting that the animals were at least 5 weeks old, and therefore had entered the study closer to the age of weaning, expected to be at day 19.4 after birth; 9) histopathology demonstrates differences between control and carrageenan-treated tissues, including increased inflammatory infiltrate in the lamina propria and reduced colonic

[34] Weiner ML et al (2015) An infant formula toxicity and toxicokinetic feeding study on carrageenan in preweaning piglets with special attention to the immune system and gastrointestinal tract. *Food and Chemical Toxicology* 77:120-131.

[35] Abraham R, Benitz KF, Mankes R, and Rosenblum I (1985) Chronic and Subchronic Effects of Various Forms of Carrageenan in Rats. *Ecotoxicology and Environmental Safety* 10: 173-183.

[36] https://clinicaltrials.gov/ct2/show/NCT02629705. Last accessed on March 23, 2016.

[37] Baek HS and Yoon Jw (1991) Direct involvement of macrophages in destruction of beta-cells leading to development of diabetes in virus-infected mice. *Diabetes* 40(12):1586-97.

[38] Weiner ML et al (2015) An infant formula toxicity and toxicokinetic feeding study on carrageenan in preweaning piglets with special attention to the immune system and gastrointestinal tract. *Food and Chemical Toxicology* 77:120-131.

haustrations, and 10) absence of any long-term data. The essential chemical structure of carrageenan contains the immune epitope galactose-alpha-1,3,-galactose which is not made by human cells and stimulates immune responses, including rejection of transplanted tissue from other mammals, except Old World apes.

**Hence, the feeding studies performed in pigs by industry are irrelevant in this regard, since carrageenan is not anticipated to stimulate the innate immune response in the pigs.**

The 28-day pig feeding study was not conducted rigorously, and **the report obfuscates differences between the carrageenan-exposed and control groups.** This 28-day study is inadequate to justify prolonged feeding of carrageenan-containing formula to millions of babies. Finally, a previous, industry-supported study in infant baboons did not examine long-term effects or effects on immunity (McGill, Gastroenterology, 1977).[39] Increased colonic pathology was identified in the carrageenan-treated animals, including increases in crypt abscesses and hyperemia of the colonic mucosa after 112 days.

**In Reference to Specific Questions Posed by the Handling Subcommittee**

1) If humans have varying degrees of sensitivity to carrageenan in the diet, is that enough reason to prohibit it in all organic foods? Humans are also sensitive to gluten, dairy, legumes, and many other foods; is that a reason to keep them out?

- The effects of carrageenan on human health have been studied in depth over the past several decades. The chemical structure of carrageenan and the interaction with the TLR4 receptor indicate the likelihood that carrageenan's effects are attributable to fundamental biological characteristics of [all] humans.

- **Industry has tried for decades to differentiate between harmful effects attributable to low molecular weight poligeenan** vs. high molecular weight carrageenan. Now, there is an attempt by industry to distinguish a low molecular weight tail of carrageenan from poligeenan. **These distinctions are absurd.** Carrageenan is composed of disaccharide units, similar to the structure of chondroitin sulfate or heparin. Molecular weight may vary for these sulfated glycosaminoglycans depending on the number of disaccharide units. The disaccharide units of poligeenan, or carrageenan, or the low molecular weight tail of carrageenan are the same.

- **Food-grade carrageenan contains some lower molecular weight forms naturally, and the amount increases due to processing, heat, acid, intestinal bacteria, and mechanical processing, such as chewing.**

[39] McGill HC Jr., McMahan CA, Wigodsky HS, *et al*. (1977) Carrageenan in formula and infant baboon development. *Gastroenterology* 73:512-517.

**Carrageenan is Not Essential**

Many brands are now using the lack of carrageenan in their formulations as a marketing tool. **Over the past five years, a number of prominent companies have announced they have or will soon remove carrageenan from their product lines.** These companies include WhiteWave, one of the largest marketers of organic/natural foods in the country. However, as of April 2016, Whitewave's Horizon organic low-fat sour cream and cottage cheese still have carrageenan. They have removed it from many of their other products, including Tuberz yogurt for children, chocolate milk, and whipping cream.

In response to growing marketplace concern, the following companies have completely removed carrageenan from their product lines: Almond Breeze®, Amazing Grass Kidz Superfood®, Annie's®, Califia Farms®, and Good Karma®. So Delicious® (also owned by WhiteWave) has removed it from their refrigerated coconut milk, but not their shelf-stable selections.

In other cases, companies continue to defend its safety, frequently posting biased information, supplied by lobbyists to the carrageenan industry, on their websites.

Organic Valley is working to remove it from their product lines. In November 2012, they reformulated their eggnog to be carrageenan-free. They also removed it from there chocolate milk. As of April, 2016, the only remaining Organic Valley product with carrageenan is heavy whipping cream that is "ultra-pasteurized", whereas its heavy whipping cream that is labeled "pasteurized" (standard high temperature short time pasteurization — HTST) does not.

The Cornucopia Institute's webpage (www.cornucopia.org), on the "Reports" tab, has the latest resources on carrageenan in products, including a buyers guide to help families choose products without carrageenan.

**CONCLUSION**

The Cornucopia Institute **opposes** the relisting of carrageenan at 205.605(a) because of harm to human health and lack of essentiality. The carrageenan industry has tried for decades to retain the use of carrageenan in food products, because of its cost-effective biological reactivity with ingredients. **This same biological reactivity is what makes carrageenan harmful**.

Efforts by industry to cover up the harmful effects of carrageenan resemble similar efforts by those with other vested interests (tobacco, climate change, fracking, etc.). **These cover-ups must not go unchallenged. The Organic sector expects better.**

The reason Congress established the power of the NOSB, to review synthetic and non-organic food ingredients and other inputs, was that the body assumed that there would be a higher, more rigorous standard set for organic foods in comparison to conventional protocols.

Since all independently funded public research illustrates the danger to human health, in ingesting food-grade carrageenan, and most, but not all, industry funded research suggests the opposite, it would be generous to suggest that the current scientific literature is "mixed."

It is incumbent upon the NOSB to err on the side of caution, operating under the *Precautionary Principle*, by excluding carrageenan from use in organic foods.