Dr. Margaret Hamburg
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

March 15, 2013

RE: FDA-2008-P-0347

Dear Dr. Hamburg

The FDA is responsible for protecting public health by assuring the safety of our nation's food supply. When a body of publicly funded scientific literature points to harm from consuming a common, widely used yet unnecessary food ingredient, the FDA should act in the interest of public health.

Dr. Joanne Tobacman, a physician-scientist who has studied food-grade carrageenan for the past decade with her colleagues at the University of Illinois – Chicago, filed a citizen petition in 2008 requesting to revoke the regulations that permit the use of carrageenan in food. After nearly four years, your office denied her request on June 11, 2012.

The denial letter, written by Ted Elkin (Acting Deputy Director for Operations, Center for Food Safety and Applied Nutrition), appears based on an incomplete review of the scientific literature.

Every claim made in the denial letter to support the FDA's decision to deny the request (i.e. every claim that supports the safety of carrageenan in foods and beverages) can be refuted, based on strong scientific evidence. In some cases, even the carrageenan industry's own data refutes claims that carrageenan is safe to consume. In addition, some of the studies cited to back the FDA position came from industry associated or industry funded research.

Carrageenan contributes no nutritional value, nor does it improve the flavor, safety or shelf-life of foods and beverages. It is added solely to affect the texture ("mouthfeel") of foods and beverages, and for the convenience of the customer who

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does not have to shake beverages like chocolate milk before consumption. In terms of a cost-benefit analysis, the scientific evidence of harm far outweighs negligible benefits.

We would like to formally take this opportunity to urge the FDA to reconsider its decision to deny the citizen petition that was filed in 2008 by the country's preeminent independent researcher on the issue, which requested the revocation of regulations permitting the use of carrageenan.

We urge you to consider the following:

1. The FDA claim that food-grade carrageenan is not contaminated with degraded carrageenan has been refuted by several studies, including by the carrageenan industry's own laboratory test results.[1]

In 2003, the European Commission's Scientific Committee on Food reviewed safety data on carrageenan, and concluded that food-grade carrageenan is not safe unless the amount of degraded carrageenan is kept to a minimum.

The Committee declared that levels of degraded carrageenan in food-grade carrageenan should be kept at levels below 5%.[i] This decision prompted carrageenan manufacturers to perform laboratory testing of food-grade carrageenan.

Test results shared by Marinalg International, the trade group for carrageenan manufacturers, showed that eight of twelve samples of food-grade carrageenan contained higher than 5% degraded carrageenan according to at least one of the six laboratories (in many cases, according to multiple laboratories). The highest level of degraded carrageenan found in a sample was 25%. All samples contained at least some degraded carrageenan according to the majority of laboratories.[ii]

2. Your claim that food-grade carrageenan does not degrade in the digestive system has been refuted by several studies, including one of the studies you cited in your defense of carrageenan.

You cite Capron et al. (1996)[iii] to support your claim that food-grade carrageenan does not degrade; however, this study found:

> *"In simulated gastric juice the degradation of kappa-carrageenan is very limited; only 10% of the carrageenan exposed is reduced to a molecular weight <100 kDa."*

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[1] The International Agency for Research on Cancer of the World Health Organization classifies degraded carrageenan as a List 2B "possible human carcinogen"

This industry-funded study aims to defend the safety of carrageenan, and therefore uses terms such as "very limited" and "only 10%." Clearly, the study shows that degradation *does occur*, and that consumption of food-grade carrageenan leads to exposure to degraded carrageenan in the intestinal tract.

Other studies that suggest degradation occurs in the acid environment of the digestive tract include Ekstrom and Kuivinen (1983)[iv] and Ekstrom (1985).[v]

3. You claim that the five studies supplied by Dr. Tobacman in the 2008 petition, which were *in vitro* studies, are "not relevant to routes of exposure" from food. We ask that the FDA consider the totality of scientific evidence, which includes animal studies and *in vitro* studies.

The *in vitro* studies presented by Dr. Tobacman in 2008 have identified the biological mechanisms by which carrageenan causes harm. Researchers used food-grade (undegraded) carrageenan. These studies are important and should not be dismissed. They show that small amounts of food-grade carrageenan trigger an innate immune response in the body, similar to the biological pathways that are activated by pathogenic bacteria such as *Salmonella*.

Another study found that exposure of human colonic epithelial cells in tissue culture to small quantities of undegraded carrageenan produced inflammation by a second pathway of reactive oxygen species, as well as by the innate immune pathway.[vi]

Animal studies have shown that food-grade carrageenan causes gastrointestinal disease in laboratory animals. The *in vitro* studies answer the questions of *how* the damage occurs. For example, one *in vitro* study identified a specific pathway activated by food-grade carrageenan, which is significant since the pathway influences the development of human intestinal polyps, which can develop into cancer if left untreated.[vii]

The FDA must consider the entire body of scientific literature pointing to harm from food-grade carrageenan. This includes both animal studies and *in vitro* studies. No single study can prove or disprove the safety of carrageenan; rather, the totality of research, including funding sources, must be considered. The body of scientific literature pointing to harm cannot be ignored.

Moreover, on page 3, you state that *in vitro* studies pointing to harm are irrelevant, and then point to an *in vitro* study on page 4 to defend the safety of carrageenan.

4. You claim that the FDA "considers the administration of undegraded carrageenan as a part of the diet of animals to be a more appropriate experimental model for evaluating the safety of exposure to carrageenan through consumption in humans," yet many of the animal studies that point to potential harm from exposure to food-grade carrageenan were not identified and reviewed in the analysis that led to your 2012 denial letter.

We urge you to reconsider your analysis, ensuring that all studies in the attached appendix are considered. These studies use food-grade carrageenan in animal model studies, and point to harm.

5. You wrote that some studies pointing to harm were "refuted," without specifying a credible source for this criticism or its basis.

On page 4, you attempt to refute studies showing food-grade carrageenan promotes the growth of aberrant crypt foci and tumors in laboratory animals. You wrote that "the findings of these studies have been disputed," based on a paper by Duika Burges Watson (Reference 11). Dr. Burges Watson is a social scientist at Durham University in the UK, with no medical degree or Ph.D in a scientific or medical field (she holds a Ph.D. in geography). She has no background in oncology, gastroenterology, or any other field of medical research. You cited her work to refute studies performed by medical researchers funded by the National Institutes of Health.

These studies may have been refuted by Dr. Burges Watson, but they have been accepted by medical researchers. For example, Dr. Joanne Tobacman reviewed the same studies and did not attempt to refute them. Dr. Tobacman is a physician-scientist with a medical degree. She has worked as a practicing physician and researcher at several universities and hospitals, and worked for several years at the National Cancer Institute.

Why does the FDA consider the opinion of a social scientist with a Ph.D. in geography to be more valid than the scientific review of a medical researcher, published in the official journal of the National Institutes of Environmental Health Sciences of the National Institutes of Health?[viii]

Conclusion

The FDA did not include many important studies in its analysis, and did not consider the totality of scientific evidence before reaching its decision to deny the 2008 citizen petition requesting to revoke the regulations that allow carrageenan in foods and beverages.

We urge you to revisit your conclusion after conducting a thorough and rigorous analysis of the scientific evidence presented in this petition. We specifically ask that you eliminate the bias with which you performed your initial analysis.

For example, in your initial analysis, you stated that *in vitro* studies are not relevant, and then used an *in vitro* study to defend the safety of carrageenan. You rejected well-conducted studies by medical researchers based on a paper by a social scientist with no scientific expertise. You conducted your own literature review and unearthed several studies defending carrageenan while failing to cite numerous

studies using food-grade carrageenan in the diet of laboratory animals that found higher rates of gastrointestinal disease, including tumors.

Moreover, you did not consider additional studies that have been published between 2008, when the citizen's petition was filed, and 2012, when you issued your denial letter. If the FDA waits nearly four years to issue a response, it is incumbent upon the agency to either perform a literature review of recent publications, and include those in its analysis, or to invite the petitioner to submit any relevant studies that were published since the initial filing.

Given the profits at stake, this is a controversial topic, with criticism on both sides. If the FDA's responsibility truly is to protect public health and ensure the safety of our food supply, then study funding and the corporate affiliations of study authors must be considered as well.

We note that the vast majority of carrageenan research funded by the National Institutes of Health points to harm,[ix] and a review study in the journal of the National Institute of Environmental Health Sciences states, "the use of carrageenan in the Western diet should be reconsidered," while studies defending carrageenan are overwhelmingly conducted by scientists with financial ties to the carrageenan industry.[x]

Finally, there are no benefits to society or public health from adding carrageenan to foods or beverages. It is added solely to change the texture of food. Already, some food manufacturers are replacing carrageenan with other thickeners and stabilizers, or eliminating thickeners altogether and asking their customers to shake the product before consumption. If carrageenan is prohibited, the food industry will quickly adapt.

We ask that the FDA reconsider the 2008 citizen petition requesting to remove carrageenan and carrageenan salts, and the related furcelleran and furcelleran salts from the list of food additives that can be safely used in food.

Sincerely,

Charlotte Vallaeys
Director, Farm and Food Policy
The Cornucopia Institute

CC:

Ted Elkin

Acting Deputy Director for Operations
Center for Food Safety and Applied Nutrition
Food and Drug Administration
College Park, MD 20740

Appendix

Note: We have included studies that are unfavorable to the petition, and urge the FDA to consider the funding source and author affiliations of these studies. We note that every study that supports this petition has been funded either by public institutions, such as the National Institutes of Health, or private foundations without a financial interest in the study's outcomes.

Meanwhile, studies unfavorable to the petition are almost exclusively funded by the industry that profits from the continued use of carrageenan in food.

The studies are listed in chronological order of publication.

1960s:

Watt J, Marcus R (1969) Ulcerative colitis in the guinea-pig caused by seaweed extract. *Journal of Pharmacy and Pharmacology* 21:187S–188S.

> **Summary of findings**: This study was one of the first to show that food-grade carrageenan contributes to ulcerative colitis-like disease in laboratory animals (guinea pigs).
>
> **Author affiliations**: University of Liverpool, United Kingdom

1970s:

Grasso P, Sharratt M, Carpanini FMB, Gangolli SD (1973) Studies on carrageenan and large-bowel ulceration in mammals. *Food and Cosmetics Toxicology* 11:555–564.

> **Summary of findings**: The researchers administered both degraded and undegraded/food-grade carrageenan in the diet of several species of laboratory animals. Guinea pigs and rabbits experienced ulcerations in the large intestine, symptoms which were not detected in rats, squirrel monkeys, hamsters and ferrets.
>
> **Author affiliations**: The British Industrial Biological Research Association, a privately owned consulting firm.

Engster M and Abraham R (1976) Cecal response to different molecular weights and types of carrageenan in the guinea pig. *Toxicology and Applied Pharmacology* 38:265–282.

> **Summary of findings**: In this short-term study, researchers administered different types of carrageenan in the diet and drinking water of guinea pigs for two weeks. They found ulceration of the intestines in guinea pigs given

undegraded iota-carrageenan in the drinking water. No changes were observed in the other groups, and it is unclear what effects would have been seen if the experiment had been continued for longer than two weeks.

Funding: National Institute of Environmental Health Sciences, National Institutes of Health

Author affiliation: Albany Medical College

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.

Funding: National Cancer Institute (National Institutes of Health)

Author affiliations: Naylor Dana Institute for Disease Prevention, American Health Foundation

1980s:

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.

Watt J and Marcus R (1981) Harmful effects of carrageenan fed to animals. *Cancer Detection and Prevention* 4(1-4): 129-34.

Review article: The authors reviewed the scientific literature and found "an increased number of reports … describing harmful effects of degraded and undegraded carrageenan supplied to several animal species in their diet or drinking fluid.

"Harmful effects [of food-grade carrageenan] are almost certainly associated with its degradation during passage through the gastrointestinal tract. There is need for extreme caution in the use of carrageenan or carrageenan-like products as food additives in our 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*.

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: This study found higher rates of tumors in rats fed undegraded carrageenan in the diet.

Author affiliations: Nagoya City University, Japan

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 and Chemical Toxicology* 22:615–621.

Summary of findings: Researchers using undegraded carrageenan administered in the drinking water of rats showed that carrageenan penetrates the intestinal barrier.

Author affiliations: The British Industrial Biological Research Association, a privately-owned consulting firm.

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.

Funding: Food and Drug Administration

Author affiliations: Food and Drug Administration

1990s:

Weiner ML (1991) Toxicological properties of carrageenan. *Agents and Actions* 32(1-2): 46-51.

> **Summary of findings**: Based on a review of animal feeding studies, carrageenan is safe.
>
> **Author affiliation**: FMC Corporation (multibillion dollar chemical corporation and leading carrageenan manufacturer)

Wilcox DK, Higgins J, Bertram TA (1992) Colonic epithelial cell proliferation in a rat model of nongenotoxin-induced colonic neoplasia. *Laboratory Investigation* 67:405–411.

> **Summary of findings**: This study shows an association between loss of epithelial cells (the cell membranes in the intestine) and the consumption of both undegraded and degraded carrageenan.
>
> **Funding**: Proctor & Gamble Company
>
> **Author affiliations**: Proctor & Gamble Company

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.
>
> **Author affiliations**: French National Institute of Agronomic Research, Toulouse, France

Since 2000:

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**: This study aimed to better understand the role of food-grade carrageenan in carcinogenesis. The experiments in this study were designed to test the hypothesis that carrageenan might function 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.

Author affiliations: Michigan State University

Tobacman JK (2001) Review of Harmful Gastrointestinal Effects of Carrageenan in Animal Experiments. *Environmental Health Perspectives* 109(10).

Review study: This study examined existing research done to date (2001). The author concluded: "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."[xi]

Author affiliation: University of Iowa

Hagiwara A, Miyashita K, Nakanishi T, Sano M, Tamano S, Asai I, Nakamura M, Imaida K, Ito N and Shirai T (2001) Lack of Tumor Promoting Effects of Carrageenan on 1,2-Dimethylhydrazine-induced Colorectal Carcinogenesis in Male F344 Rats. *Journal of Toxicologic Pathology* Vol. 14; 37.

Summary of findings: This study found no statistically significant increases in malignant tumors in rats given food-grade carrageenan in the diet.

Author affiliations: Nagoya City University, Daiyu-kai Institute for Medical Science and San-Ei Gen FFI, Inc.
(San-Ei Gen FFI, Inc is a Japanese carrageenan manufacturer)

<u>Cornucopia Note</u>: The study has been criticized by publicly funded scientists, primarily because the study was terminated as higher rates of tumors in the carrageenan group were detected. The rats were killed after 90 days (a rat's natural lifespan is 2 years). When the study was terminated, tumor rates were higher, but not yet high enough to be statistically significant.

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.

Summary of findings: The study measured the molecular weight of 29 samples of food-grade carrageenan and concluded that no sample had a significant level of degraded carrageenan. The detection limit was 5%.

Author affiliations: San-Ei Gen FFI, Inc, a Japanese food additive manufacturer. In addition to carrageenan, San-Ei Gen FFI manufactures flavors, colors, preservatives and the artificial sweetener sucralose.

Cohen SM and Ito N (2002) A critical review of the toxicological effects of carrageenan and processed euchema seaweed on the gastrointestinal tract. *Critical Reviews in Toxicology* 32(5): 413-44.

Summary: The authors of this review criticized research studies pointing to gastrointestinal harm from consuming carrageenan. The authors conclude that "there is no credible evidence supporting a carcinogenic effect or a tumor-promoting effect on the colon in rodents."

<u>Cornucopia Note</u>: The authors were commissioned by the carrageenan industry to criticize the studies that have found higher rates of gastrointestinal disease in laboratory animals. The authors reviewed 23 studies, and found fault with every one.

Weiner M, Nuber D, Blakemore WR, Harriman JF and Cohen SM (2007) A 90-day dietary study on kappa-carrageenan with emphasis on the gastrointestinal tract. Food and Chemical Toxicology 45(1): 98-106.

Summary of findings: The study found no clinical signs in rats fed high doses of food-grade carrageenan with up to 12% degraded carrageenan, other than soft stool. The authors reported that the gastrointestinal tract "appeared normal" even in the rats given high doses of carrageenan in the diet.

Author affiliations: FMC Corporation, a leading manufacturer of carrageenan. In addition to manufacturing carrageenan, FMC Corporation (a $3.4 billion conglomerate) produces pesticides and industrial chemicals.[xii]

Borthakur A, Bhattacharyya S, Dudeja PK and Tobacman JK (2007) Carrageenan induces interleukin-8 production through distinct Bcl10 pathway in normal human colonic epithelial cells. *American Journal of Physiology, Gastrointestinal and Liver Physiology* 292(3): G829-38.

Summary of findings: Exposure of human colonic epithelial cells in tissue culture to small quantities of undegraded (food-grade) carrageenan produced inflammation by a second pathway of reactive oxygen species, as well as by the innate immune pathway.

Funding: Department of Veterans Affairs; National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

Author affiliations: University of Illinois at Chicago and Jesse Brown Veterans Affairs Medical Center

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.

Funding: National Institutes of Health

Author affiliations: University of Illinois at Chicago

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

Summary of findings: Exposure to human colonic epithelial cells in tissue culture to small quantities of food-grade carrageenan produced inflammatory responses.

Funding: National Institutes of Health

Author affiliations: University of Illinois at Chicago

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.

Funding: National Institutes of Health

Author affiliations: University of Illinois at Chicago and Jesse Brown Veterans Affairs Medical Center

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 carrageenanin 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.

Funding: National Institutes of Health; Veterans Administration

Author affiliations: University of Illinois at Chicago; Jesse Brown Veterans Affairs Medical Center; Rensselaer Polytechnic Institute

Bhattacharyya S, Borthakur A, Tyagi S, Gill R, Chen ML, Dudeja PK, Tobacman JK (2010) B-cell CLL/lymphoma 10 (BCL10) is required for NF-kappaB production by both canonical and noncanonical pathways and for NF-kappaB-inducing kinase (NIK) phosphorylation. *Journal of Biological Chemistry*. 1;285(1):522-30

Summary of findings: Carrageenan stimulates innate immune-mediated pathways of inflammation.

Funding: National Institutes of Health; Veterans Administration

Author affiliations: University of Illinois at Chicago

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

Summary of findings: This study examines the immune response by which food-grade carrageenan causes inflammation.

Funding: Veterans Administration

Author affiliations: University of Illinois at Chicago; Jesse Brown Veterans Affairs Medical Center; Rensselaer Polytechnic Institute; University Pierre and Marie Currie/Sorbonne University, Paris, France

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 causes inflammation.

Funding: Veterans Administration

Author affiliations: University of Illinois at Chicago; Jesse Brown Veterans Affairs Medical Center

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

Summary of findings: Inflammation of the colon caused by exposure to low levels of food-grade carrageenan persists beyond the initial period of exposure.

Funding: National Institutes of Health

Author affiliations: University of Illinois at Chicago

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.

Funding: National Institute of General Medical Sciences, National Institutes of Health

Author affiliations: University of Illinois at Chicago; Jesse Brown Veterans Affairs Medical Center; Rensselaer Polytechnic Institute

Bhattacharyya S, O-Sullivan I, Katyal S, Unterman T and Tobacman JK (2012) Exposure to the common food additive carrageenan leads to glucose intolerance, insulin resistance and inhibition of insulin signalling in HepG2 cells and C57BL/6J mice. *Diabetologia* 55(1): 194-203.

Summary of findings: Carrageenan in the diet may contribute to diabetes. Carrageenan impairs glucose tolerance, increases insulin resistance and inhibits insulin signalling in vivo in mouse liver and human HepG2 cells. These effects may result from carrageenan-induced inflammation.

Funding: National Institutes of Health; American Diabetes Association

Author affiliations: University of Illinois at Chicago

[i] 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 January 14, 2013.
[ii] Marinalg International. 2005. Technical position on measurements related to meeting the EC molecular weight distribution specification for carrageenan and PES. Attached.
[iii] Capron I, Yvon M and Muller G (1996) In-vitro gastric stability of carrageenan. Food Hydrocolloids 10(2): 239-244
[iv] Ekström, L.G. (1985) Molecular-weight-distribution and the behaviour of kappa-carrageenan on hydrolysis. Part II. *Carbohydrate Research* 135: 283-289.
[v] Ekström L.G. and Kuivinen J (1983) Molecular weight distribution and hydrolysis behaviour of carrageenans. Carbohydrate Research 116: 89-94.
[vi] Borthakur A, Bhattacharyya S, Dudeja PK and Tobacman JK (2007) Carrageenan induces interleukin-8 production through distinct Bcl10 pathway in normal human colonic epithelial cells. *American Journal of Physiology, Gastrointestinal and Liver Physiology* 292(3): G829-38
[vii] 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
[viii] Tobacman JK (2001) Review of Harmful Gastrointestinal Effects of Carrageenan in Animal Experiments. *Environmental Health Perspectives* 109(10)
[ix] The following studies have been conducted with grants from the National Institutes of Health:

1. Borthakur A, Bhattacharyya S, Dudeja PK and Tobacman JK (2007) Carrageenan induces interleukin-8 production through distinct Bcl10 pathway in normal human colonic epithelial cells. *American Journal of Physiology, Gastrointestinal and Liver Physiology* 292(3): G829-38
2. 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
3. Bhattacharyya S, Dudeja PK and Tobacman JK (2008) Carrageenan-induced NFkappaB activation depends on distinct pathways mediated by reactive oxygen species and Hsp27 or by Bcl10. *Biochimica and Biophysica Acta* 1780(7-8): 973-82
4. Bhattacharyya S, Borthakus 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
5. 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 carrageenanin human intestinal epithelial cells. *Journal of Biological Chemistry* 283(16): 10550-8
6. Borthakur A, Bhattacharyya S, Anbazhagan AN, Kumar A, Dudeja PK and Tobacman JK (2012) Prolongation of carrageenan-induced inflammation in

human colonic epithelial cells by activation of an NFκB-BCL10 loop. *Biochimica and Biophysica Acta* 1822(8): 1300-7

[x] For example, one of the authors of Hagiwara et al 2001 is employed by San-Ei Gen FFI, Inc, a Japanese carrageenan manufacturer. Hagiwara A, Miyashita K, Nakanishi T, Sano M, Tamano S, Asai I, Nakamura M, Imaida K, Ito N and Shirai T (2001) Lack of Tumor Promoting Effects of Carrageenan on 1,2-Dimethylhydrazine-induced Colorectal Carcinogenesis in Male F344 Rats. *Journal of Toxicologic Pathology* Vol. 14; 37.

The primary authors of a study that concludes carrageenan is safe are employed by FMC Corporation, a carrageenan manufacturer. Weiner M, Nuber D, Blakemore WR, Harriman JF and Cohen SM (2007) A 90-day dietary study on kappa-carrageenan with emphasis on the gastrointestinal tract. Food and Chemical Toxicology 45(1): 98-106.

[xi] Tobacman JK (2001) Review of Harmful Gastrointestinal Effects of Carrageenan in Animal Experiments. *Environmental Health Perspectives* 109(10)

[xii] FMC Corporation investor relations page. Available online at http://phx.corporate-ir.net/phoenix.zhtml?c=117919&p=irol-homeProfile&t=&id=&. Last accessed on January 24, 2013