Safety of Carrageenan in Foods

A recent review of the toxicology of carrageenan by Tobacman (*1*) raised questions about the safety of carageenan-containing foods. Intact carageenan is a high molecular weight hydrocolloid (molecular weight 1.5–20 × 10^6). One concern has focused on the potential for degraded (low molecular weight) carageenan to be formed by acid hydrolysis in the stomach and the possibility that this material could promote cancer of the colon (*1*). Rats fed degraded carrageenan have been shown to develop colorectal tumors (*2*). Studies involving initiation with the genotoxic carcinogen azoxymethane, followed by quantitation of the number of aberrant intestinal crypts formed in response to subsequent carrageenan exposure, have also suggested that degraded carageenan has the potential to promote colon cancer in rats (*3*).

These findings have led to degraded carrageenan being classified by the International Agency for Research on Cancer (IARC) as 2B, a possible human carcinogen, based on animal study data. Native carrageenan has been classified by IARC as 3, unclassifiable with respect to carcinogenicity in humans.

In a recent paper, Taché et al (*4*) used a well-established and highly sensitive aberrant crypt assay to examined the potential for carrageenan to promote azoxymethane-induced colonic cancer; they found no promoting effect when a humanized gut flora was used. Because the carrageenan was administered in the drinking water, it was available for degradation in the acidic environment of the stomach. The use of normal rodent microbiologic flora produced a promoting effect of carrageenan in this model system (*4*), confirming positive results of previous studies, in contrast with the negative effect that occurred using humanized intestinal flora in the rat. Thus, the conclusion must be that this colon cancer-promoting effect is a rodent-specific phenomenon, requiring a rodent intestinal microbiologic flora, and that carrageenan would not promote colon cancer in humans.

The concerns with regard to the induction of ulcerative colitis expressed by Tobacman (*1*) are also inappropriately extrapolated from animal data with regard to human risk. There have been many studies carried out with carrageenan in animals, and carrageenan has been used to induce inflammation in susceptible species and to test the anti-inflammatory properties of new candidate drugs. Although guinea pigs are very sensitive to the induction of colitis by carrageenan, primates—a more appropriate species for comparison to humans—are resistant to the induction of colitis by carrageenan.

The safety of carrageenan for use in foods was confirmed at the 57th meeting of the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) in Rome in June 2001 (*5*). The JECFA recommended an acceptable daily intake (ADI) of "not specified," the most favorable ADI for a food additive. This recommendation was made after a review of all of the current toxicology and carcinogenicity studies on carrageenan by two world experts in this field, S. Cohen (University of Nebraska Medical Center, Omaha, NE, USA) and N. Ito (Nagoya City University Medical School, Nagoya, Japan). It included consideration of studies not cited by Tobacman (*1*) in her evaluation.

Phil Carthew
Unilever Safety and Environmental Assurance Centre
Sharnbrook, Bedfordshire, United Kingdom
E-mail: Philip.Carthew@unilever.com

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Carrageenan in Foods: Response

Carrageenan has been the subject of significant investigation for several decades, and the complexity pertaining to it may have impeded our ability to form a clear impression about its harmful effects. In rodent models, there is clear evidence that degraded carrageenan can induce ulcerations and neoplasms. Also, there is clear evidence that food-grade carrageenan can be broken down to degraded carrageenan by acid hydrolysis and by bacteria, and degraded carrageenan is likely to contaminate food-grade carrageenan. Although most of our concerns about carcinogenic exposures arise in relation to the unmetabolized product, the situation with carrageenan requires some extension of our perspective to recognize that exposure to undegraded carrageenan is inevitably accompanied by exposure to degraded carrageenan. If we accept the Delaney standard of no known carcinogens in food or the pesticide standard of no more than one in part in a million (*1*), the use of carrageenan in food is clearly in excess.

Carthew has raised issues pertaining to the role of human intestinal flora on the effects related to carrageenan and the possibility of interspecies variation in the toxicity of carrageenan. The paper by Taché et al. (*2*) referred to by Carthew actually supports concerns about the availability of degraded carrageenan after exposure to food-grade carrageenan and human microflora. The authors report data on the average molecular weight of carrageenan recovered from stool samples in feeding experiments with rats in which human intestinal microflora had been introduced. The average molecular weight of the carrageenan extracted from feces was 346,000 ± 18,000 in the rats with the conventional intestinal flora and was slightly lower (307,000 ± 37,000) in the rats exposed to human intestinal microflora. This strongly suggests that metabolism of dietary carrageenan does not depend on the presence of rodent microflora.

Interpretation of Taché et al.'s (*2*) data on the number of crypt foci and the numbers of aberrant crypts is confounded by lack of a comparable control group, as noted by the authors. When they sought to expose a control population to similar conditions (life in an isolator, sawdust bedding), they found that the rats developed only 20 aberrant crypt foci per colon; this was far less than the previously reported controls that developed 86 ± 23 aberrant crypt foci per colon or the experimental animals with human intestinal microflora that developed 55 ± 18 aberrant crypt foci per colon (*3*), suggesting unresolved experimental issues pertaining to initiation. This confounds interpretation of the data about promotion. Also, Taché et al. (*2*) did not provide details about the actual composition of the microflora in their experimental rats, and we do not know if it was consistent throughout the experiment. Hence, these data cannot be used to declare that the colon cancer-promoting effect of food-grade carrageenan is a "rodent-specific phenomenon" and that it requires a rodent intestinal microbiologic flora.

When the Food and Drug Administration (FDA) considered the status of carrageenan in the early 1970s, their review included a

study of 24 rhesus monkeys with appropriate controls (*4,5*). Investigators observed that monkeys fed 2% degraded carrageenan did not gain weight, had an immediate change in stool consistency, and consistently had blood in their stools, which was associated with a decline in hemoglobin, until approximately 10 weeks after the withdrawal of the carrageenan. In addition, they developed mucosal erosions and ulceration and multiple crypt abscesses. Pathologic changes were dose and duration dependent. Thus, these data indicate that degraded carrageenan can induce colitis in primates.

It is unfortunate that the June 2001 meeting of the FAO/WHO Expert Committee on Food Additives (JECFA) (*6*) rated the acceptable daily intake (ADI) of carrageenan as "not specified," as they had done previously, including at the 28th meeting in 1984 (*7*), rather than establishing a different position. In the 1999 report on carrageenan prepared as part of the World Health Organization Food Additives Series, Greig (*8*) stated that the JECFA ADI of "not specified" for carrageenan was temporary, pending review in 2001. Also, Greig (*8*) pointed out that degraded carrageenans and processed *Eucheuma* seaweed were not included by the JECFA in the specifications of food-grade carrageenan in 1984. Subsequently, a review of carrageenan was undertaken for the 2001 meeting. Greig (*8*; p. 16) noted that

> Maintenance of a restriction on the relative mass distribution in the specifications of carrageenan for food use provides protection against the adverse effects of carageenans (sp) of low relative molecular mass.

However, in 2001 the JECFA apparently did not endorse any specific restriction on the molecular weight of food-grade carrageenan. The report of Cohen and Ito to which Carthew refers and the full report of JECFA 2001 are not yet published.

I hope that the recommendations pertaining to carrageenan will be revised by regulatory groups. Clearly, there are significant economic issues and interests for the food industry and for populations involved in farming red seaweeds. In the United States, the FDA has ignored the harmful potential of carrageenan for over 20 years, but now is the time to reevaluate carrageenan and its potential harmful effects.

Joanne Tobacman
University of Iowa Health Care
Iowa City, Iowa
E-mail: joanne-tobacman@uiowa.edu

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Time for a Change in Philosophy

As people are becoming aware, there are signs that Earth is demonstrating finite capabilities to support the continued existence of life. The atmosphere appears to be heating, the oceans appear to be declining in their ability to support life, and many species of wildlife are becoming extinct.

The prevailing thought in the social sciences seems to be that the planet has infinite capacity to support the continued existence of life. All theology and all philosophy related to governments and cultural habits were developed on the basis of the belief that the planet had infinite capacity to support life, but this was ages ago, when the planet's resources truly appeared to be endless.

The philosophies now being followed largely determine how people judge right from wrong and, although most people may not realize it, motivate couples to have large families. As a consequence, the world population is growing exponentially larger. The world population grows in number similarly to the way bacteria grows under favorable conditions. Every generation is larger than the generation preceding it.

Without a major change in the philosophies of the world population, which motivate people as a whole to behave very destructively toward their own survival interests, life on this planet will have a limited future.

Joe Kinney
Engineering graduate
Plainfield, Indiana
E-mail: JCK17@yahoo.com

Mercury and the Central Nervous System

The toxicity of mercury described in the table in "Environmental Aftermath" (*1*) in *EHP* [109:A530 (2001)] needs clarification.

In the table, mercury is cited as damaging only the peripheral nervous system. Of much greater public health concern, however, are the toxic effects of mercury to the central nervous system (CNS). Organic mercurials, particularly methyl mercury, preferentially accumulate within cerebellar neurons of the CNS and, in significant concentrations, can thereby affect motor function and coordination, particularly in the fetus. Elemental mercury, the form found in thermometers and precision instruments, as cited in the table, is preferentially distributed as mercury vapor to centers of the CNS that affect cognitive function (personality and behavior) rather than those that control motor function. These are the effects of predominant public health concern associated with mercury exposure from environmental sources. This clarification may be of interest to those concerned about mercury exposure associated with the World Trade Center site.

James S. Woods
School of Public Health and
Community Medicine
University of Washington
Seattle, Washington
E-mail: jwoods@u.washington.edu

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