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August 26, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

VIA FAX: (301) 827 6870

Re: Docket No. 2004Q-0201

A petition for the following health claims was submitted to your office on July 1, 2004 on behalf of the Lycopene Health Claim Coalition. ("Petition"):

1. Although the evidence is not conclusive, tomato lycopene may reduce the risk of prostate cancer.
2. Although the evidence is not conclusive, tomato lycopene may reduce the risk of prostate cancer when consumed as part of a healthy diet.
3. Although the evidence is not conclusive, tomato products, which contain lycopene, may reduce the risk of prostate cancer.
4. Although the evidence is not conclusive, tomatoes and tomato products, which contain lycopene, may reduce the risk of prostate cancer.
5. Although the evidence is not conclusive, tomato products, which contain lycopene, may reduce the risk of prostate cancer when consumed as part of a healthy diet.
6. Although the evidence is not conclusive, tomatoes and tomato products, which contain lycopene, may reduce the risk of prostate cancer when consumed as part of a healthy diet.
7. Although the evidence is not conclusive, lycopene in tomato products may reduce the risk of prostate cancer.

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8. Although the evidence is not conclusive, lycopene in tomatoes and tomato products may reduce the risk of prostate cancer.
9. Although the evidence is not conclusive, lycopene in tomato products may reduce the risk of prostate cancer when consumed as part of a healthy diet.
10. Although the evidence is not conclusive, lycopene in tomatoes and tomato products may reduce the risk of prostate cancer when consumed as part of a healthy diet.
11. Although the evidence is not conclusive, lycopene in fruits and vegetables, including tomatoes and tomato products, may reduce the risk of prostate cancer.

Our comments filed on or about July 8, 2004 in response to the petition of American Longevity, Inc., are attached for incorporation as a comment with respect to the Petition.

We would like to point out that the above claims, taken as a whole, by including a reference to lycopene in all claims for tomatoes and tomato products, are misleading in that they imply that lycopene is the reason for the reduction in risk. As is more fully explained in the attachment, the scientific evidence strongly supports a link between tomatoes and tomato-based products and a reduction in risk for certain cancers. Whether lycopene or one or more of the diverse array of other tomato components may explain this relationship is a matter for continuing investigation.

Sincerely,



Chor San Khoo, Ph.D.

Attachment



Chor San Khoo, Ph.D.
Vice President – Global Nutrition & Health

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July 8, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

VIA FAX: (301) 827 6870

Re: Docket No. 2004Q-0201

A petition for the following health claims was submitted to your office on January 21, 2004 on behalf of Petitioner American Longevity, Inc. ("Petition"):

- Lycopene may reduce the risk of certain forms of cancer.
- Lycopene may reduce the risk of prostate cancer.
- Lycopene may reduce the risk of lung cancer.
- Lycopene may reduce the risk of gastric cancer.
- Lycopene may reduce the risk of colorectal cancer.
- Lycopene may reduce the risk of breast cancer.
- Lycopene may reduce the risk of cervical cancer.
- Lycopene may reduce the risk of endometrial cancer.
- Lycopene may reduce the risk of ovarian cancer.
- Lycopene may reduce the risk of pancreatic cancer.
- Tomatoes may reduce the risk of certain forms of cancer.
- Tomatoes may reduce the risk of prostate cancer.
- Tomatoes may reduce the risk of lung cancer.
- Tomatoes may reduce the risk of gastric cancer.
- Tomatoes may reduce the risk of colorectal cancer.
- Tomatoes may reduce the risk of breast cancer.
- Tomatoes may reduce the risk of cervical cancer.
- Tomatoes may reduce the risk of endometrial cancer.

- Tomatoes may reduce the risk of ovarian cancer.
- Tomatoes may reduce the risk of pancreatic cancer.
- Lycopene-containing tomato-based foods may reduce the risk of certain forms of cancer.
- Lycopene-containing tomato-based foods may reduce the risk of prostate cancer.
- Lycopene-containing tomato-based foods may reduce the risk of lung cancer.
- Lycopene-containing tomato-based foods may reduce the risk of gastric cancer.
- Lycopene-containing tomato-based foods may reduce the risk of colorectal cancer.
- Lycopene-containing tomato-based foods may reduce the risk of breast cancer.
- Lycopene-containing tomato-based foods may reduce the risk of cervical cancer.
- Lycopene-containing tomato-based foods may reduce the risk of endometrial cancer.
- Lycopene-containing tomato-based foods may reduce the risk of ovarian cancer.
- Lycopene-containing tomato-based foods may reduce the risk of pancreatic cancer.

On behalf of Campbell Soup Company, I would like to offer our comments on the Petition, for your consideration.

The proposed model claims, as stated above, do not conform to the scientific evidence.

As elaborated below, a strong body of scientific evidence, including high quality prospective observational cohort studies, supports claims for tomatoes and tomato-based products and a reduced risk of certain forms of cancer and of prostate cancer. The weight of scientific evidence supporting a potential claim for tomatoes and tomato-based products is, however, of a different magnitude than that supporting the claims proposed by the Petition for lycopene or for “lycopene-containing tomato-based foods.”¹

With few exceptions, the evidence cited in support of the lycopene hypothesis has been derived from data investigating the effects of ingestion of tomatoes and tomato-based food products. This is true with respect not only to epidemiologic studies, but also with respect to clinical studies and laboratory animal studies. Given the dramatic differences in the weight of scientific evidence in support of a claim for tomatoes and tomato-based food products and a claim for lycopene or for some “lycopene-containing” tomato derivative, there should be a clearly understandable difference in the language that may be communicated to consumers on label.²

Campbell Soup Company supports the authorization of unqualified health claims stating:

- Diets rich in tomatoes and tomato-based products may reduce the risk of certain forms of cancer.
- Diets rich in tomatoes and tomato-based products may reduce the risk of prostate cancer.

¹ We would understand the unusual wording of this proposed claim to contemplate products which may not contain all portions of the tomato which are traditionally incorporated in tomato based foods.

² Unfortunately, of course, the overwhelming majority of consumer food products the consumption of which has contributed to the data in support of these claims, cannot bear a label health claim due to disqualifying levels of sodium.

- Tomatoes and tomato-based products may reduce the risk of certain forms of cancer.
- Tomatoes and tomato-based products may reduce the risk of prostate cancer.

We do not support the authorization of unqualified health claims for lycopene or the authorization of any unqualified health claims for any of the other cancers listed in the Petition.

A useful starting point in evaluating the state of scientific knowledge concerning the relationship between consumption of tomato based products and cancer risk is a 1999 review by Dr. Edward Giovannucci published in the *Journal of the National Cancer Institute* (“Giovannucci Review”).³ This review was not cited in the Petition and, consequently, is attached for your reference.

Dr. Giovannucci described the impetus of his 1999 review as follows:

Until recently, the health aspects of tomatoes had received relatively little attention. The antioxidant properties of lycopene, a carotenoid consumed largely from tomatoes, have raised interest in the tomato as a food with potential anticancer properties. Higher consumption of tomatoes is in fact compatible with current general recommendations aimed at increasing intake of fruits and vegetables. Nonetheless, whether unique benefits derive from tomatoes is important to establish because tomatoes are used in many processed items that are not necessarily identified with fruit or vegetable consumption. These items include tomato and spaghetti sauce, tomato soup, salsa, ketchup, and tomato paste. Moreover, many of these processed foods are better sources of bioavailable lycopene than are fresh tomatoes.⁴

The Giovannucci Review analyzed all scientifically sound studies published in English that examined the intake of tomatoes or lycopene in relation to the risk of any cancer in humans. This was done to discern whether or not a unique benefit or association could be established from a review of the scientific literature. As Dr. Giovannucci reported:

Among 72 studies identified, 57 reported inverse associations between tomato intake or blood lycopene level and the risk of cancer at a defined anatomic site; 35 of these inverse associations were statistically significant. No study indicated that higher tomato consumption or blood lycopene level statistically significantly increased the risk of cancer at any of the investigated sites. About half of the relative risks for comparisons of high with low intakes or levels for tomatoes or lycopene were approximately 0.6 or lower. . . . Because the data are from observational studies, a cause-effect relationship cannot be established definitively. However, the consistency of the results across numerous studies in diverse populations, for case-control and prospective studies, and for dietary-based and blood-based investigations argues against bias or confounding as the explanation for these findings. Lycopene

³ Giovannucci, “Tomatoes, Tomato-Based Products, Lycopene, and Cancer: Review of the Epidemiologic Literature,” *Journal of the National Cancer Institute*, Vol. 91, No. 4, pp. 317-331, February 17, 1999.

⁴ *Ibid.* p. 317. References omitted from quotations throughout.

may account for or contribute to these benefits, but this possibility is not yet proven and requires further study.⁵

According to Dr. Giovannucci, “. . . the epidemiologic data indicate that high consumers of tomatoes and tomato products are at a substantially decreased risk of numerous cancers, although not all cancers. The results are consistent for a variety of cancers across numerous diverse populations and with the use of different study designs.”⁶

Although it cannot be said that data with respect to consumption of tomatoes and tomato products and cancer risk *necessarily* support claims concerning lycopene, it can be said that lycopene data necessarily supports claims concerning tomatoes and tomato products. In fact,

Tomatoes and tomato products, including juices, pastas, soups, and ketchup, are the single most important source of lycopene in the diet, providing >85% of dietary lycopene. Heat processing increases the bioavailability of lycopene by breaking down cell walls and allowing extraction of the lycopene from the chromoplasts, where it is found in raw tomatoes.⁷

Indeed, further confirmation of the association between the intake of tomatoes and tomato products (or the lycopene contained in them) and a reduction in the risk for various cancers has continued to evolve since the publication of the meta-analysis in the Giovannucci Review, as is clearly set forth in Dr. Glade’s review of the evidence submitted with the Petition.

The likelihood that an association exists between consumption of diets rich in tomato-based foods and reduced cancer risk has been established by considering the totality of the scientific evidence and considering (a) the strength of the observed association, (b) the consistency of results of studies of the association, and (c) the biological plausibility of the association (namely, the hypothesized role of lycopene).

There is, in fact, significant scientific agreement concerning the existence of an association between diets rich in tomato products and a reduced risk of certain types of cancers. Although causality with respect to the inverse association between the consumption of tomatoes and tomato products has not been proven, proof of causality is not required for an unqualified health claim. The strength of the inverse association between the intake of tomatoes and tomato products and the incidence of certain cancers, the consistency of that inverse association across an impressive number of high quality studies, including prospective observational cohort studies, and the biological credibility of the inverse association provide a sufficient basis on which to inform the public about the protective role tomatoes and tomato products may play, as compared to the role that lycopene may play in explaining that protective role. It would be unreasonable to insist that causality be

⁵ Ibid. p. 317.

⁶ Ibid. p. 326.

⁷ David Heber, “Colorful cancer prevention: α -carotene, lycopene, and lung cancer,” American Journal of Clinical Nutrition 2000; 72:901-2. Dr. Heber’s article is attached for your reference.

understood and definitively proven before consumers may benefit from a clear and unambiguous communication of this knowledge about tomato based products as to which there is a high level of comfort among qualified scientists.

According to lycopene the same status as tomatoes and tomato based foods is, however, not justified by the current state of scientific knowledge. Definitive evidence that lycopene mediates the observed cancer preventive properties of tomatoes and tomato based foods *in vivo* will only be obtainable by further clinical trials.

That lycopene may significantly inhibit the rates of proliferation of various human prostate carcinoma cell lines in culture is not, for example, definitive evidence that it will have the same effect *in vivo*. Because of the lack of stability of lycopene, we do not know whether it may be lycopene or the break down products of lycopene that have the observed effect in cell culture and even whether the same break down products exist *in vivo*. The inhibition may be an artifact of cell culture.

Whether or not lycopene, either alone or in combination with other components⁸ of tomatoes, accounts for the epidemiologic data has not been proven. What has been proven is that lycopene is a bio-marker that correlates with tomato consumption and that may be one of several components in tomato products that mediate the observed health benefits. Polyphenols from tomatoes, have, for example, been shown to reduce insulin-like growth factor-I stimulated rat prostate cancer cell proliferation *in vitro* and it is hypothesized that several polyphenols commonly found in foods alter the apoptotic threshold of prostate cancer cells, thereby slowing the progression of human prostate cancer.⁹ Indeed, the implications of current research are “that tomato and soy products provide a diverse array of compounds that together, over a long period of dietary exposure, may provide an important opportunity to slow prostate carcinogenesis.”¹⁰ Consequently, we do not know definitively that the effects attributed to lycopene by the Petition are properly attributed to lycopene alone, to lycopene in combination with other tomato components, or to tomato components other than lycopene.

For these reasons, we recommend that unqualified health claims be authorized stating:

- Diets rich in tomatoes and tomato-based products may reduce the risk of certain forms of cancer.
- Diets rich in tomatoes and tomato-based products may reduce the risk of prostate cancer.
- Tomatoes and tomato-based products may reduce the risk of certain forms of cancer.
- Tomatoes and tomato-based products may reduce the risk of prostate cancer.


⁸ Lycopene is a component of tomatoes and certain other foods, but is not properly characterized as a “nutrient” because no deficiency has been identified.

⁹ Wang, S, DeGroff VL, Clinton, SK. “Tomato and Soy Polyphenols Reduce Insulin-Like Growth Factor-I-Stimulated Rat Prostate Cancer Cell Proliferation and Apoptotic Resistance In Vitro via Inhibition of Intracellular Signaling Pathways Involving Tyrosine Kinase” *J. Nutr.* 133:2367-2376, July 2003 (A copy of this article is attached for your reference)

¹⁰ *Ibid.*

We also recommend that the health claims submitted by the Petitioner be allowed with appropriate qualifying language that makes clear that, at present, the role of lycopene in reducing the risk of cancer is a hypothesis with considerable support, but remains the subject of on-going debate and research.

Sincerely,

A handwritten signature in black ink, appearing to read "Chor San Khoo". The signature is fluid and cursive, with the first letter of each name being capitalized and prominent.

Chor San Khoo, Ph.D.

Attachments