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

**Re: Docket No. 2004N-0454; Dietary Supplements; Premarket
Notification for New Dietary Ingredients; 69 Fed. Reg. 61680 (Oct. 20,
2004)**

ZeaVision LLC (ZeaVision) appreciates this opportunity to submit comments concerning Food and Drug Administration (FDA) requirements for new dietary ingredients (NDIs). Founded in 2000, ZeaVision is focused on the dietary supplement zeaxanthin, a naturally occurring carotenoid that is important to eye health. ZeaVision has a substantial interest in the development of FDA regulations and policies that ensure the availability of safe dietary supplements for consumers and create a level playing field for industry.

SUMMARY

The new dietary ingredient provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA) are powerful tools for protecting public health. We are concerned, however, that these important tools are simply not utilized at the present time. As a result, American consumers are exposed to numerous non-dietary substances that have not undergone adequate safety reviews, in clear contradiction of the FFDCA, as amended by the Dietary Supplement Health and Education Act (DSHEA).

As described more fully below, to remedy this situation, FDA is urged to take the following steps:

- Place immediate emphasis on enforcing the premarket notification requirement for NDIs, without waiting for all issues of policy to be settled;
- Prioritize action against non-dietary substances, including *meso*-zeaxanthin, a non-dietary stereoisomer of zeaxanthin;
- Ensure that premarket notifications address, as appropriate, possible adverse interactions that NDIs may have with important nutrients; and
- Continue to require that NDIs provide sufficient information on the identity and purity of NDIs.

IMMEDIATE FOCUS ON NDI ENFORCEMENT NEEDED

In the October 20 *Federal Register*, FDA posed numerous questions that speak to virtually all aspects of NDI regulation, including the classification of an ingredient as “new,” chemical identification of an NDI, and information needed to establish a reasonable expectation of safety. ZeaVision applauds FDA’s determination to commit resources to addressing these important issues of dietary supplement regulation, some of which could take several years to resolve fully. To ensure that consumers are protected in the meantime, it is imperative that FDA not wait to begin enforcing the NDI requirements until all matters of regulatory importance are settled. Protection of public health demands immediate action in many instances, particularly where non-dietary substances are concerned.

ZeaVision also urges FDA not to wait to initiate enforcement actions until tangible health concerns about an ingredient materialize. Where a dietary ingredient is “new” (i.e., was not marketed in the United States prior to October 15, 1994) and has not been present in the food supply as an article used for food in a chemically unaltered form, it is presumptively unsafe until the marketer of that ingredient establishes a reasonable expectation of safety to which FDA does not object. To enforce the law only against ingredients that pose demonstrated health risks would turn congressional intent on its head and perform a disservice to consumers. Indeed, the single most effective step FDA could take in implementing DSHEA would be to consistently enforce the premarket notification requirement for NDIs.

**PRIORITIZE ACTION AGAINST NON-DIETARY SUBSTANCES,
INCLUDING MESO-ZEAXANTHIN**

ZeaVision appreciates that numerous unlawful NDIs are presently marketed, necessitating some prioritization of agency enforcement resources. We urge FDA to prioritize actions against substances that are not in the natural human diet. In doing so, we recommend that FDA—

- Interpret a substance to be “present” in the food supply within the meaning of section 413(a)(1) only if the substance is present in food or food components consumed at greater than de minimus levels. For example, a substance found only in the eyes of certain animals is not “present in the food supply” unless it can be demonstrated that its presence in such materials has resulted in a meaningful dietary exposure to humans—one that would permit identification of any adverse health effects that might reasonably occur. The level that might constitute de minimus exposure would need to be determined on a case-by-case basis.
- Interpret a substance to be present in the “food supply” only if it is present in human food. Although the term “food” as defined in section 201(f) of the FFDCFA includes animal food, the “food supply” referenced in section 413(a)(1) is reasonably interpreted to be more narrow because DSHEA does not apply to animal feed.
- Interpret a substance to be present in the food supply “in a form in which the food has not been chemically altered” only if the substance has undergone no more than minor modifications. This interpretation is supported by the legislative history of DSHEA, which provides that “chemically altered” does not include physical modifications such as “minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry, powder, or solid in suspension.” Accordingly, by implication, chemical or other modifications that differ substantially from the physical alterations noted by Congress in enacting DSHEA will render a substance “chemically altered” within the meaning of section 413(a)(1). Among the treatments that should constitute chemical alterations are changes that may lead to the formation of non-dietary isomers of dietary substances, including stereoisomers and geometric isomers. Stereochemistry is particularly important in both normal human nutrition (e.g., in the case of sugars and amino acids) and in drugs (for which FDA has developed a policy on stereoisomers) and thus can be of substantial toxicological significance. Geometric isomers likewise can be of toxicological and/or nutritional consequence (e.g., CIS/trans fat).

- Use all available resources to examine whether a substance is “chemically altered,” including any patent literature describing how a substance is made.

A case in point is *meso*-zeaxanthin, a non-dietary stereoisomer of zeaxanthin that is presently marketed as a dietary ingredient. *Meso*-zeaxanthin preparations for commercial use are created by chemical alteration of lutein, by treating lutein with an alkaline substance to yield the *meso*-stereoisomer. *Meso*-zeaxanthin has never been shown to exist in any food source that is part of the normal human diet. Some reports have suggested that *meso*-zeaxanthin is present in the skins of certain fishes. [1/](#) These reports have subsequently been discredited, [2/](#) but even if the reports were accurate, the presence of a substance at low levels in fish skin is not reasonably interpreted to mean presence in the “food supply.”

The safety of *meso*-zeaxanthin cannot be assumed. Indeed, dietary exposure to *meso*-zeaxanthin is of toxicological concern, as *meso*-zeaxanthin presently is believed to exist only in the eye, where it has been hypothesized to result from the light-triggered or enzymatic conversion of lutein. It has not been demonstrated to be present in the blood or any other tissues of humans or other animals. Furthermore, when it was tested as a potential pigment additive for poultry, *meso*-zeaxanthin was shown to be deposited in poultry tissues in ways that differed from the deposition of the normal dietary isomer of zeaxanthin, leading to unsatisfactory pigmentation effects. [3/](#) In the absence of appropriate safety data, effects of human exposure to *meso*-zeaxanthin are unknown.

[1/](#) T. Maoka et. al, “The First Isolation of Enantiomeric and Meso-Zeaxanthin in Nature,” *Comparative Bioch. and Phys.* 83(B) No. 1: 121-124 (1986).

[2/](#) See, e.g., R.A. Bone et al., “Stereochemistry of the Human Macular Carotenoids,” *Invest. Ophthalmology and Visual Science* 34: 2033 (1993); F. Khachik et al., “Transformations of selected carotenoids in plasma, liver, and ocular tissues of humans and in nonprimate animal models,” *Invest. Ophthalmology and Visual Science* 43(11): 3383-92 (2002).

[3/](#) Perez-Vendrell AM, et al., “Influence of source and ratio of xanthophyll pigments on broiler chicken pigmentation and performance,” *J. Poult Sci.* 2001 Mar;80(3): 320-6.

Because *meso*-zeaxanthin does not exist in the normal human diet, and because *meso*-zeaxanthin preparations have been created by chemical alteration of a different compound (lutein), *meso*-zeaxanthin appears to be a “new dietary ingredient” for which a notification is required pursuant to section 413 of the FFDCa and 21 C.F.R. § 190.6. Based on publicly available information, an NDI does not appear to be in effect for *meso*-zeaxanthin. ZeaVision believes strongly that non-dietary substances such as *meso*-zeaxanthin are exactly the type of ingredients that Congress had in mind when enacting the premarket notification requirements of DSHEA.

The marketing of *meso*-zeaxanthin and other non-dietary ingredients for use in dietary supplement products is of significant concern and worthy of immediate attention and prompt action by FDA. In the case of *meso*-zeaxanthin, an imported product that is often mislabeled as “zeaxanthin,” FDA is urged to make use of its broad authority under the FFDCa to prohibit the entry into the United States of foreign products that appear to be adulterated or misbranded.

INFORMATION NEEDED TO ESTABLISH A REASONABLE EXPECTATION OF SAFETY

FDA requests comment regarding items that should be considered for purposes of establishing a reasonable expectation of safety for an NDI. ZeaVision believes strongly that in addition to appropriate toxicological studies and data, evidence that a new substance may adversely interact with established nutrients should also be considered.

Using *meso*-zeaxanthin again as an example, two recent publications shed light on the presence of this substance in primate and human eyes, and raise important questions regarding the potential effects of *meso*-zeaxanthin consumption on zeaxanthin function.

Primate eyes directly convert lutein into *meso*-zeaxanthin. ^{4/} If lutein (only) is fed, only lutein-*meso*-zeaxanthin shows up. If dietary zeaxanthin is fed, only dietary zeaxanthin shows up. A second recent paper, Bhosale, P. et al., established the binding protein responsible for selective macular (retinal uptake) of zeaxanthin. ^{5/} This human protein strongly binds zeaxanthin and *meso*-zeaxanthin but weakly binds lutein. There is some speculation that it may also convert lutein into *meso*-zeaxanthin.

^{4/} Johnson, E. et al., *Invest. Ophthalmology and Visual Science* 2004 (in press).

^{5/} Bhosale, P. et al., *J. BiolChem* (in press and online 2004).

Taken together, these two papers support the hypothesis that the human macula works hard to selectively accumulate zeaxanthin in the macula and converts lutein to *meso*-zeaxanthin when there is not enough zeaxanthin in the blood to draw from. The data may be extrapolated to suggest that—

- Dietary zeaxanthin is the more preferred structure.
- In the absence of zeaxanthin, the same special protein makes *meso*-zeaxanthin.

The results suggest either an adaptive evolutionary response or that the conversion of lutein to *meso*-zeaxanthin is an important mechanism to vision.

The introduction of *meso*-zeaxanthin into the diet raises two important safety concerns. First, if the former mechanism is in effect and it is zeaxanthin that protects the macula, then the introduction of *meso*-zeaxanthin could reduce dietary uptake and compete for retinal uptake. This effectively reduces zeaxanthin in the macula. Second, if the latter theory is correct and the lutein-*meso*-zeaxanthin conversion is in itself protective, then the end product of the reaction, *meso*-zeaxanthin, could stop the conversion by competitive or feedback inhibition, effectively stopping the reaction. Since *meso*-zeaxanthin is not found in other human tissues (including the liver), it is likely that one of these two interpretations is correct.

In either scenario, the introduction of *meso*-zeaxanthin could have detrimental effects that compromise the photoprotective effects of lutein and zeaxanthin—the nutritional significance of which is evidenced by the pending qualified health claim petition concerning their role in reducing the risk of age-related macular degeneration (AMD) and cataract formation. Because of the possible role of these two compounds in eye health, scrutiny of the safety of this new isomer in the diet deserves priority. The FDA is reminded that the *cis-trans* isomerization of rhodopsin is critical to the human visual process, suggesting that isomers are particularly important to human eye function.

ADDITIONAL ISSUES: CHEMICAL IDENTIFICATION OF AN NDI

ZeaVision also believes that the proper description of an NDI's identity and assurances as to its purity are critical to fully evaluate its safety. For example, the chemical alterations required to convert lutein into *meso*-zeaxanthin, as described above, raise serious concerns that require careful consideration. We are aware of reports indicating that the treatment of lutein with a strong alkali and alcohol solvent can create undefined and/or uncontrolled by-products, such as "cis" isomers of lutein and zeaxanthin, which do not occur in nature.^{6/} Harsh alkaline treatments may also lead to the formation of toxic substances, such as lysinoalanine. These issues similarly demonstrate the need for regulatory scrutiny of *meso*-zeaxanthin products.

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In summary, ZeaVision applauds FDA's focus on these and other important aspects of the agency's NDI requirements and policy. To protect the public health and implement DSHEA, we urge the agency to aggressively enforce the premarket notification requirements, focusing first on non-dietary ingredients such as *meso*-zeaxanthin, as progress is made on related matters.

Thank you for your consideration of these comments.

Sincerely,



Terry Hatfield
President
ZeaVision LLC

^{6/} See Bohm et al., "Trolox equivalent antioxidant capacity of different geometrical isomers of alpha-carotene, beta-carotene, lycopene, and zeaxanthin," *J. Ag. & Food Chem.* 50(1): 221-6 (2002) (describing how "cis" isomerization reduces the activity and potency of carotenoids, including zeaxanthin).