

cancer risk,<sup>15</sup> and CSPI does not identify any other potential health benefit of carotenoids established by this article. Similarly, the second publication (Bertram, J. S. and H. Bortkiewicz, "Dietary Carotenoids Inhibit Neoplastic Transformation and Modulate Gene Expression in Mouse and Human Cells," *American Journal of Clinical Nutrition*, 62:1327S-1336S, 1995, at 1328S.), notes that the investigators' results simply provide "a possible mechanistic basis for the activity of carotenoids as chemopreventive agents (emphasis added)." Moreover, citing this second publication, CSPI asserts that "carotenoids affect intercellular communications" (CSPI obj. at p. 20, footnote 19). However, CSPI does not demonstrate how the effect of carotenoids on intercellular communications supports its assertion that carotenoids are beneficial to health.<sup>16</sup> Accordingly, FDA is denying CSPI's hearing request on this issue (§ 12.24(b)(3)).<sup>17</sup>

CSPI's second argument to support its position that FDA erroneously concluded that there is no demonstrated health benefit of carotenoids, except the provitamin A function of beta-carotene, is that the agency wrongly insisted on randomized trials to establish the role of carotenoids in health. CSPI bases this allegation on the fact that FDA quoted Dr. Alvan Feinstein in the preamble to the 1996 final rule. CSPI implies that FDA relied on Dr. Feinstein and thus, ignored evidence in the record that establishes a beneficial role of carotenoids in human health. In addition, CSPI claims that Dr. Feinstein

is a "debunker" and he, and his views, lack credibility.

These allegations are not adequate to justify a hearing on this issue for three reasons. First, CSPI quotes Dr. Feinstein out of context. Contrary to CSPI's claim, Dr. Feinstein did not "insist" on randomized trials. Instead, Dr. Feinstein described certain limitations of epidemiologic studies (studies such as those cited by another witness, Dr. Meir Stampfer), including the fact that it is difficult to draw conclusions about cause and effect relationships from such studies (61 FR 3118 at 3147 to 3148), a conclusion not directly challenged by CSPI. Thus, FDA is denying CSPI's hearing request on this point because a hearing will not be granted where the information to support the factual conclusion urged is unreliable (§ 12.24(b)(2)). Second, CSPI asserts that Dr. Feinstein failed to acknowledge that the test methods he advocated might not be meaningful for dietary carotenoids. Because CSPI offers no evidence to suggest that these methods are not appropriate and does not show how, if at all, prevailing on this factual issue would change the outcome of the rulemaking, FDA is denying a hearing on this issue (§ 12.24(b)(2) and (b)(4)). Finally, in reaching its position on carotenoids, FDA considered all the comments, data, and information that the agency had received on carotenoids, including information from epidemiological studies (61 FR 3118 at 3149). FDA's position on the carotenoids issue is not inconsistent with the findings of the epidemiological studies relied upon by CSPI (61 FR 3118 at 3149). Thus, even if Dr. Feinstein's views were shown to be incorrect and CSPI prevailed on this issue, the outcome of the ruling would not be altered. Therefore, FDA is denying CSPI's request for a hearing on this issue (§ 12.24(b)(4)).

## 2. Does Consumption of Olestra Cause a Harmful Depletion of Carotenoids?

In its second objection and request for a hearing, CSPI asserts that consumption of olestra likely would cause major depletions of serum levels of carotenoids and that this depletion could be harmful because carotenoids have beneficial properties.<sup>18</sup> CSPI also asserts that even a 5 to 10 percent

reduction in serum levels of carotenoids could be harmful. CSPI offers several arguments to support this portion of its objection.<sup>19</sup>

First, CSPI asserts generally that the amounts of olestra consumed are sufficient to cause major depletions of carotenoids, referring to "the section [above] on consumption estimates." (CSPI obj. at p. 24.) However, there is no such section in CSPI's submission.<sup>20</sup> Moreover, CSPI's objection did not offer any facts to contradict FDA's conclusion in the final rule that the magnitude of olestra's effects on carotenoid absorption are likely to be within the range of normal variation (61 FR 3118 at 3149). Accordingly, FDA is denying CSPI's challenge to the agency's determination that any depletion of carotenoids by olestra consumption would be minor because a hearing on a factual issue will not be granted in the absence of specifically identified, available evidence to support the requestor's position (§ 12.24(b)(2)).

CSPI also challenges FDA's conclusion on the magnitude of carotenoid depletion by asserting that patterns of consumption of olestra will not prevent such depletion. In particular, CSPI asserts that P&G's depletion studies only measured the status of beta-carotene and thus, the full impact of olestra consumption on carotenoids was not assessed. However, CSPI did not submit or otherwise specifically identify evidence to establish that olestra's effect on beta-carotene was not representative of the additive's effect on carotenoids generally. Moreover, CSPI does not demonstrate how resolving this particular issue in its favor will alter the outcome of this proceeding. Accordingly, FDA is denying CSPI's objection and hearing request (§ 12.24(b)(2) and (b)(4)).

CSPI also claims that FDA erroneously relied on data presented by P&G on patterns of consumption when the agency concluded that olestra's effects on carotenoid absorption would not be harmful. CSPI did not present

<sup>15</sup> CSPI states that "carotenoids reverse oral leukoplakia in rats." (CSPI obj. at p. 20, footnote 19.) However, the Garewal article cited by CSPI in support of this statement presents no data on the reversal of oral leukoplakia in rats.

<sup>16</sup> As noted previously, in the 1996 final rule, FDA concluded that the variation in serum levels of carotenoids associated with olestra consumption is within the normal range, given diet variations and the bioavailability of carotenoids, a conclusion not addressed directly by CSPI. In view of this unchallenged conclusion, the Bertram and Bortkiewicz paper, id. at 1333S-1334S, appears to support a finding of no harm from olestra's effects on carotenoid levels of consumers of olestra-containing food. "Our demonstration that dietary carotenoids can inhibit neoplastic transformation and modulate the expression of gene products in both human and mouse cells implies that these ubiquitous compounds have hitherto unknown properties. Moreover, these effects were produced at micromolar concentrations that are within the physiologic range \* \* \*"

<sup>17</sup> Indeed, the paper by Bertram and Bortkiewicz is consistent with FDA's conclusion that the available evidence demonstrates an association between a diet rich in fruits and vegetables and reduction in the risk of certain diseases. "Many epidemiologic studies have shown a consistent inverse correlation between consumption of foods rich in carotenoids \* \* \* and future risk of cancer." (Id. at 1327S.)

<sup>18</sup> To the extent that CSPI contends that there is a lack of reasonable certainty of no harm from olestra's depletion effect on carotenoids, CSPI's hearing request is denied because whether a food additive is safe for its intended use (i.e., whether there is a reasonable certainty of no harm) is a question of law to be decided based on the facts established in the record. Under § 12.24(b)(1), a hearing will not be granted on issues of policy or law.

<sup>19</sup> It is important to note that depletion of serum carotenoid levels is relevant only if carotenoids themselves are shown to have human health benefits. As discussed in the previous section, CSPI's objection and hearing request fails to establish any genuine issue of material fact regarding FDA's conclusion that there is no demonstrated health benefit of any carotenoid except the provitamin A function of beta-carotene. Thus, this portion of CSPI's objection and hearing request is also denied because resolution of this issue in CSPI's favor would not alter the outcome of this proceeding (§ 12.24(b)(4)).

<sup>20</sup> It is possible that CSPI intended to reference the discussion in its White Paper (CSPI exh. 1) on consumption estimates, but no such reference was given (§ 12.24(b)(2)).