FDA stated that vitamin C serves as an effective free-radical scavenger to protect cells from damage by reactive oxygen molecules (a free-radical being an atom containing an unpaired electron which tends to give the atom more reactivity, often leading to a pro-oxidative chain reaction which can damage cells). The basic biological function of vitamin E was found to be as an antioxidant where it acts as a defense against potentially harmful reactions with oxygen by deactivation of the free-radicals. In the case of beta-carotene, the agency stated that it was chosen because it is an antioxidant, and, although it is not recognized as a vitamin itself, it is a provitamin and makes important contributions to the vitamin A activity of most diets. Beta-carotene acts by trapping, deactivating, and destroying reactive oxygen molecules and preventing the damage that they can cause. FDA did not include vitamin A (retinol) and retinoic acid in its consideration because their biological functions are not achieved through an antioxidant role, and because vitamin A cannot function in a fashion similar to that of beta carotene (carotenoids) and vitamins C and E (Refs. 11 and 12).

In the final rule on antioxidant vitamins and cancer, FDA concluded that this selection of nutrients was appropriate (58 FR 2622, January 6, 1993).

In addition, a recent conference entitled ''Antioxidant Vitamins and Cancer and Cardiovascular Disease,'' initiated by FDA, supported this conclusion and affirmed that the biological role of other vitamins as direct antioxidants remains unsubstantiated (Ref. 13). Riboflavin and niacin, two of the B-vitamins, are precursors of coenzymes that are involved in large numbers of oxidation and reduction reactions. By themselves, however, these vitamins do not have direct antioxidant activities. Moreover, after conversion to their coenzyme forms, they have indirect effects that are both antioxidant and pro-oxidative in character (Refs. 14 and 15). When pro-oxidative conditions (i.e., the opposite of antioxidative) predominate, oxidative damage occurs to cells, lipids, proteins, and carbohydrates (Ref. 16). Thus, FDA tentatively concludes that these nutrients should not be classed as antioxidants.

As stated earlier, the 1990 amendments specifically required that the agency evaluate the relationship of antioxidant vitamins to cancer. Antioxidant minerals were not mentioned in the statute and were not considered by the agency. However, in this rulemaking to define ''antioxidants'' for use in nutrient content claims, FDA is not restricted in the nutrients that are to be encompassed by this term. Based on its informal survey, the agency notes that some dietary supplements, including both single nutrient and multinutrient products, use the term ''antioxidant'' on their label and in labeling to describe minerals such as copper, zinc, manganese, iron, and selenium (Ref. 9). Accordingly, FDA has reviewed the literature on the biological activities of these minerals.

As a result of its review, the agency tentatively concludes that there is no evidence that these substances have direct antioxidant properties, and that, in fact, some of them are pro-oxidative at certain levels. For example, copper, manganese, and zinc activate specific forms of the enzyme superoxide dismutase (SOD) which acts to remove the superoxide radical, and thus these minerals have indirect antioxidant effects (Refs. 17, 18, and 19). However, copper and manganese, in their free forms, are effective catalysts for oxidation reactions (i.e., pro-oxidants). Their role as an indirect antioxidant would be expected to predominate only at intakes at or below the quantities needed to saturate SOD. Higher intakes would be expected to have pro-oxidative effects (Refs. 17 and 18). Zinc does not have direct antioxidant or oxidant effects. It activates one form of SOD and thus has only indirect antioxidant activity (Ref. 19). Iron, another mineral, is an activator of catalase, which destroys peroxides, and thus has indirect antioxidant effects, but, again, iron itself catalyzes oxidative reactions (Ref. 20). Selenium is required for the activity of the enzyme glutathione peroxidase and thus has indirect antioxidant effects (Ref. 21).

The agency's tentative view is that it is appropriate to identify only those nutrients having a clear, direct antioxidant function in defining the coverage of the term ''antioxidants.'' Because none of the minerals discussed above function directly as antioxidants, the agency tentatively concludes that they should not be included in the definition of the term ''antioxidants'' for purposes of making a nutrient content claim. Accordingly, FDA is proposing in § 101.54(g)(1), in part, that ''antioxidants'' be defined as a collective term inclusive of vitamin C, vitamin E, and beta-carotene when used as a part of nutrient content claims (e.g., ''good source of antioxidants,'' ''high in antioxidants'') that describe food products. FDA also provides in the proposed regulation that the food must contain the requisite amounts of each of the three nutrients to qualify to bear the claim (e.g., for ''high in antioxidants,'' the product must contain 20 percent or more of the RDI for vitamin C and vitamin E per reference amount customarily consumed, and 20 percent or more of the RDI for vitamin A must be present as beta-carotene per reference amount customarily consumed).

Because there is a recent history of use of nutrient content claims for ''antioxidants'' on both dietary supplements and conventional foods, the agency is proposing in § 101.54(g)(1) that such claims be allowed on both types of foods. It should be noted, however, that because the agency is proposing in this document that the term ''high potency'' be limited to dietary supplements, the term ''high potency antioxidants'' could be used only on dietary supplements.

FDA notes that some herbs and other dietary ingredients use the term ''antioxidants'' in association with a nutrient content claim (e.g., ''raspberry leaf—high in antioxidants''). The agency advises that the regulations being proposed would not permit such nutrient content claims unless the product contains the nutrients identified in the proposed definition of ''antioxidants.''

4. Beta-carotene

Nutrient content claims are authorized for nutrients for which there are RDI's or DRV's. This approach has the advantage of linking nutrient content claims to established reference values, thereby providing a consistent and quantitative basis for defining terms. As a pro-vitamin, beta-carotene does not have an RDI or DRV. However, FDA stated in the final rule on nutrient content claims for dietary supplements that claims regarding beta-carotene (e.g., ''contains beta-carotene'') are claims that make implied representations about the level of vitamin A that is present in the food as beta-carotene (59 FR 378 at 384). Accordingly, the agency stated that it considers that the claim ''contains beta-carotene'' implies that there is enough beta-carotene in the food for the food to qualify as a ''good source'' of vitamin A (i.e., it contains 10 percent or more of the DV for vitamin A from beta-carotene) (59 FR 378 at 384). Such a claim is provided for in § 101.65(c).

The agency tentatively concludes that this standard should also apply to beta-carotene when it, either by itself or in association with other antioxidants, is the subject of an ''antioxidant'' claim. This standard allows beta-carotene to be tied to vitamin A, a nutrient with an RDI, as an implied claim, thereby