

Response Panel on the Impact of Nutrient and Nonnutrient Antioxidants on Cancer and Cardiovascular Disease

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Dr. John Milner (Pennsylvania State University):

I will start by asking some questions. How many of you are concerned about your antioxidant intake? A large number. How many of you select foods based on antioxidant content? A smaller number.

How many of you take supplements that are considered antioxidants?

Will people actually start selecting foods based on antioxidants, or will they still resort to taking pills? These are some of the questions that I think we need to address, along with some of the associated safety issues.

But right now, let's start by reviewing what occurred yesterday at this meeting.

Dr. Jeffrey Blumberg (U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University):

I thought all the presentations yesterday were both thoughtful and thought provoking. I noted particularly Dr. Janero's assertion that we need to document the presence of free radical species and their association with the condition that people are looking at, in his case the heart, as well as document the action of free radicals on metabolic or histologic or functional injury. Then we need to demonstrate a positive manipulation by antioxidants. I think these kinds of criteria are quite useful as we consider the effect of antioxidants on health. Dr. Janero also emphasized the need for scientific judgment of the clinical significance of these kinds of interactions.

While these are important criteria, we also need to recognize that this approach forces our dependence on the assumption that the mechanism of action is an antioxidant mechanism of action. Yet we also heard discussions about a number of other possible mechanisms unrelated to the antioxidant effect of these nutrients, for example, effects on eicosanoid and cytokine metabolism and on immune function. And although I did not hear it discussed, we also know, for example, that some of the antioxidants can affect parameters like platelet adhesion and aggregation, protein kinase activity, and their effects on endothelial cell proliferation and so on. So I think we need to remember that we are interested in the role of these nutrients on health and disease prevention, and we may detract a bit from this relationship if we focus too much on demonstrating an antioxidant mechanism as the only possible underlying cause.

During the discussions yesterday, we also heard other criteria for assessing the scientific evidence, beyond that of biologic plausibility, of the antioxidant mechanism. We also heard that we need to look at the totality of the scientific evidence — from cell culture models, animal models, clinical trials, and epidemiologic surveys. We heard the need to consider things like the strength of the data, the quality of the data, and the consistency of the data. Indeed, these are also important criteria.

Regarding health claims for these substances, it is important to recognize that we are not just talking about scientific theory; we are here to discuss today's public health needs and demands. I think we need to broaden the discussion beyond a strict view of just benefit and risk to consider, for example, the prevalence of the diseases we are concerned about. Cardiovascular disease and cancer are the leading causes of morbidity and mortality today. We need to remember the significance of this.

We also need to think about the probability of the correctness of the data. I think we all recognize that it is unlikely we will ever have enough scientific evidence to be 100% convinced that the data are unequivocal. We need to make a decision before we reach that point, which could be decades away.

We also need to think about the costs involved. There are two kinds of costs. One is the financial costs. When we consider the roles of foods and even supplements, the cost of intervention to prevent these diseases is small compared to drug-type or other kinds of interventions. We also need to consider the cost of delaying these kinds of health claims. The impact of delaying a potentially beneficial recommendation can be quite dramatic. What are the costs, in terms of cancer and heart disease, for example, if we wait another 10 years before these recommendations are communicated in an effective way to the public?

We heard Mr. Taylor say that the FDA has already defined antioxidants as vitamins C and E and beta carotene. Calling them antioxidants, I suppose, also defines their mechanism of action. But I think we heard

yesterday from a number of speakers about the promising role of the nonnutrient antioxidants, which are also included in the title of this workshop. I think these nonnutrient antioxidant phytochemicals hold great promise, both individually and in terms of their synergy with each other and with the antioxidant vitamins.

We also heard that the FDA has proposed to consider an antioxidant health claim only for cancer, and yet we heard some very compelling evidence for its effects in cardiovascular disease and in cataracts.

We heard an interesting discussion on the potential benefits of antioxidants in people who exercise, although the conclusions in that area await further research. But we did not hear of some other potential benefits of these antioxidants, for example, their ability to reduce the incidence of infectious diseases, to boost immune responses, and perhaps even to reduce the effects of noninfectious inflammatory diseases like arthritis.

We did hear a bit about the degenerative central nervous system disorders like Lou Gehrig's disease and Parkinson's disease and about diabetes. We need to look at them as well when we look at the clinical studies, epidemiologic surveys, and animal data, and consider the potential role of antioxidants in promoting health and preventing these diseases.

Ms. Nancy Ernst (National Heart, Lung, and Blood Institute):

I will confine my remarks to heart disease, since that is the area in which I have specialized for my entire career at the National Institutes of Health. During my early clinical research days at NIH, many people felt that polyunsaturated fats were the answer to heart disease. The physicians — clinical associates — at NIH, among the brightest people in the world, were taking polyunsaturated fats by the tablespoon. Today's best advice is to limit fat intake. Therefore, being out in front with your prescriptions, self-prescriptions, does not necessarily mean you have the wisdom of the future.

Dr. Frances Coletta, in her opening remarks yesterday, identified our objectives. One of those was to evaluate the strength of the evidence with which we were presented, and another was to identify the research steps from which to move forward. This has been one of the most interesting workshops I have attended recently. We really have a lot of information, and we know a lot of answers. But we have so many questions too.

I would like to see Dr. Halliwell's work continued, also Dr. Thomas', and additional basic research initiated. We find associations in epidemiology, but we have to pursue explanations through basic research. Yesterday's presentations on heart disease concerned cell culture research, small animal research, and epidemiologic research. But how much clinical research did we hear about yesterday? Very little. When I look over the portfolio of work that we are supporting in the institute (National Heart, Lung, and Blood Institute), there are not very many clinical studies.

Even though we are at the "second wave" of health claims, in my view we are in the first wave of antioxidant research. I think we have gone so far with our decision making about health claims that we have stymied the breadth of research that is under way. Let me give you an example of my concern.

We held a workshop in our institute on what we should do in antioxidant research. We called in leaders in this area, and we had great minds deliberating. A decision of those researchers was to determine whether vitamins would cause regression in lesions in coronary arteries. One suggested approach was to use angiographic trials to determine, in about two years, whether a combination of several antioxidants is associated with lesion regression. That is very exciting.

However, if a mixture of antioxidants leads to regression we will not know whether the vitamin combination was responsible or whether one or more of the vitamins provided the effect. If we do not find regression, we will not know whether it was particular to the selection (which) of vitamins in the mixture and or the dosage (how much) of the vitamins in the combination.

Another concern is insufficient recognition of the importance of other compounds in the diet and of nonnutrient constituents. We are doing almost no research to determine interrelationships and synergism. I think the people at this meeting can come away with some good hypotheses. We need to know so much more.

Dr. John Hathcock (U.S. Food and Drug Administration):

Yesterday's presentations provided evidence of two things. One, there is easily sufficient biological plausibility from *in vitro* and animal studies to justify continuation of human studies on the effects of antioxidants in health. I think that practically everybody would agree to that. Two, there is sufficient epidemiologic data associating higher intakes of foods containing antioxidant nutrients and other substances with decreased risk of several types of cancer, and also heart disease to justify further mechanistic and animal-type research.

The question is, how do we put this together and decide whether we have sufficient or insufficient data to reach any practical conclusions? Several speakers discussed the effects of antioxidants that provide biological plausibility, I have summarized these into five categories, although I recognize, as several speakers did, that they can be divided into many more areas.

One is direct chemical antioxidant activity, that is, the destruction of free radicals, proximate carcinogens, or perhaps even ultimate electrophilic carcinogens. Two is the activation of antioxidant enzymes, for example, selenium in glutathione peroxidase. Three is induction of detoxification enzymes such as phase 1 and phase 2, phase 1 being principally the cytochromes P450 and other types fitting phase 1, and phase 2 being the conjugations or transferences. Four is "immune system support" and whether this occurs through an antioxidant or not. Five is the function of precursors of antioxidant nutrients that may be anticarcinogenic, beta carotene and other carotenoids serving as precursors for vitamin A.

Mr. Taylor, the FDA's deputy commissioner for policy, was asked, in the context of the nutritional labeling act, "What is significant scientific agreement?" This is a somewhat narrower question than this symposium is designed to address — antioxidants and health, but nutritional labeling is a major public policy agenda item that we at FDA have to come to grips with and that I think all of you are interested in.

Mr. Taylor responded by giving example of what the significant scientific agreement is not. He said that it is not the FDA's drug standard, that is, there is no categorical requirement for clinical trials, although certainly clinical trials are available. We are eager to use them. It is not a consensus standard, that is, not everybody has to agree. But he also noted that you have to have a basic core of agreement, that is, you cannot have scientific agreement if almost everything you find is in disagreement. He also concluded that there is no "bright line" way out of this. There is no clear line of demarcation that any of us at the FDA have been able to see, or that anybody who has commented on in the docket has been able to point out in a way that has been understandable by us.

He also said that FDA is both constrained by and empowered by the science — that we ultimately have to practice good science. But we are compelled by law to look for significant scientific agreement.

Yesterday's presentations revealed certain strengths and weaknesses in the data from one nutrient-disease pair to another. These strengths and weaknesses reside in all the areas and all the criteria for inferring causality that have been described in a number of publications, including the National Academy of Sciences' book *Diet and Health*.

With regard to the strength of the association — that is, the magnitude of the effect — and the consistency of the association, I would say they are high for fruits and vegetables and several cancers, but less so for some other and diseases, although there is some consistency there — temporally correct association. This usually works when there are data to define the temporal relationships, but often I see studies that are not adequately designed to address that issue. I would categorize the dose-response relationship from one study to another as being from poor to excellent. You see strong dose-response relationships in some studies done in some particular ways, for example, those that look for intakes of some particular substances in certain populations with certain outcomes. In others, it disappears.

In my opinion, specificity of the association is the major weakness of the standard epidemiologic approach to the world. The question is, Can we solve this problem without imposing the drug standard? Your scientific opinions on that issue are valid and interesting to us. With regard to biological plausibility, perhaps beta-carotene is the weakest if we are looking for antioxidant-based plausibility. When these criteria have been met, the question of safety becomes relevant.

In my opinion, the data on the antioxidants are weakest in the areas of specificity and the validity of the surrogate and intermediate markers. And then this is the safety question. We are in the midst of a rulemaking process, so please let us know your opinions.

Dr. Regina Ziegler (National Cancer Institute):

Last spring I, and a number of my colleagues at NCI, were asked to comment on the guidelines that the FDA was talking about in terms of labeling and health claims with respect to cancer. What we suggested was that we would be comfortable with a health claim saying that vegetables and fruits, particularly those vegetables and fruits rich in vitamin A (but we could have said beta-carotene) and rich in vitamin C, may reduce your risk of cancer. We also felt comfortable with the health claim that vegetables, fruits, and grains rich in fiber may reduce your risk of cancer.

Something similar to that, I believe, got approved the last time around. That is what we felt comfortable with, and the Center for Disease Control offered a similar opinion.

We specifically did want the word "antioxidants" in there. We specifically wanted to refer to those micronutrients that are historically involved in nutrition, basically beta-carotene and vitamin A and vitamin C. We specifically wanted to talk about food groups rich in these nutrients — in other words, fruits and vegetables — rather than about the particular substituent.

People have mentioned a large number of studies, 200, that possibly support the role of beta-carotene and vitamin C and cancer etiology. One thing I would like to emphasize is that even though one can pull in 200 studies, a lot of them are pretty awful. I think we are beyond the point where we should just be counting studies. We should look at those good studies and see what they say, and maybe not mention the poor ones. There are certainly not 200 good ones. Often, the more studies you bring in as evidence, the weaker your criteria are for saying that a study does provide evidence for the hypotheses.

When we look at the studies — and right now I am thinking of the good ones, not necessarily the weaker ones — the reason that a number of us at NCI do not feel that they implicate beta-carotene or vitamin C per se as the only constituents is, again, that we think they only show that fruits and vegetables are protective. Unfortunately, in only a very few studies have people tried to see whether vegetables and fruits or an estimate of beta-carotene or an estimate of vitamin C is more predictive of reduced risks.

In every one of the situations, simple frequency of intake of a food group, either vegetables or fruits, is more predictive of reduced risk. This is true if one looks at the studies of lung cancer and beta-carotene and fruits and vegetables. It is also true of a number of the major studies of stomach cancer and vitamin C and fruits and vegetables. It does not mean that beta-carotene and vitamin C do not play a role, but there may well be other things going on.

What we think may be going on, in addition to roles for beta-carotene and vitamin C, is that increased fruit and vegetable intake may reduce the intake of total fat, subclasses of fat, percent of calories from fat. We think this is probably good. We think there may be other carotenoids involved. We just do not know. We think there may be other constituents of vegetables and fruits. Phytoestrogens are popular now. Someone mentioned the plant phenols. All of these may be involved.

The other thing we are concerned about is that increased fruit and vegetable intake goes along with a number of life-style factors that reduce the risk of cancer: more physical activity, less smoking, less alcohol consumption, more frequent visits to the doctor. No matter how many variables you put into an analysis, you cannot adequately control for confounding by those. We can move toward getting those out of the analysis, but we are sure that they accompany vegetable and fruit intake, which probably means that our estimates of reduced risk are somewhat overestimated.

I think we are all aware that vitamin E does not come into our diet through vegetables and fruits. NCI does not feel comfortable saying anything about vitamin E at the present time in terms of guidelines for labeling. When you look at the evidence for vitamin E, there are a very few studies, maybe 10 or fewer, on vitamin E. It is still an area in development.

What type of evidence would we like to see? We are not saying that you can't make any guidelines until everything is figured out.

In the cancer area, we are very conscious of the fact that interepidemiologic studies are not incorporating measures of oxidative damage or integrated measures of antioxidant levels to see whether they are stronger predictors of reduced risk than just our simple fruit and vegetable intake. This can be done, but it has not been done.

This is why we shy away from the word "antioxidant." I do not know what such studies would find. Also, we are aware that there are a variety of mechanisms, as have been discussed for beta-carotene and vitamin C.

We would like to see — although I do not think we are going to see — a common mechanism for cancer etiology, in the same way a common mechanism seems to be developing for heart disease. What we do know is that as you look at the different cancers, especially those for which reduced risk is associated with increased vegetable and fruit intake, we see very different patterns. We do not think that there is that common etiology. Esophageal cancer is associated with multiple deficiencies — possibly vitamin C, and maybe beta-carotene. Vitamin C deficiency seems to be related to stomach cancer; for lung cancer it is beta-carotene.

Hormone-related cancers are a whole different question. Phytoestrogens — which occur in fruits and vegetables-possibly may play a role here. We also do not have the Ames mechanism of base degradation by oxidative damage to fit in with a lot of our mechanisms for cancer right now. The mechanism that Dr. Correa presented for stomach cancer, where he introduced beta-carotene and vitamin C into his model, differs from the Ames model. We do not have a clear mechanism yet that is neatly tied to oxidative damage.

We are very aware that clinical trials are finally producing results. I mentioned that one big chemoprevention trial is going to be published September 15 in the *Journal of the National Cancer Institute*. Another one, a big Finnish study, is going to be coming out late in the year.

I agree with what Dr. Correa said. If we get a clear, protective effect of these single or group supplements that we are administering that is terrific. A negative result or an ambiguous result may be hard to interpret. We really need to see what these studies are going to say and then move from there.

Dr. John Milner (Pennsylvania State University):

We have heard four very thought-provoking presentations. Are there any questions?

Dr. George Blackburn (Harvard Medical School, Deaconess Hospital):

Rather than looking at the global studies, suppose we take the 10 least ambiguous and best studies and try to determine whether we can isolate the nutrients to continue this discussion on whether we are ready to go to specific antioxidants. If so, do we use the FDA standard of significant scientific agreement, or get into the NCI question?

Dr. Regina Ziegler (National Cancer Institute):

The scientists at NCI are talking about vegetables and fruits rich in vitamin A or beta-carotene, however you want to put it, and vitamin C. That is why we have our five-a-day fruit and vegetable program. We thought about this before we implemented it.

What confuses me is where this emphasis on antioxidant micronutrients has come from. Antioxidant micronutrients or antioxidant nutrients seem to have developed a life of their own.

Dr. John Hathcock (U.S. Food and Drug Administration):

The reason we chose the antioxidant nutrients, literally, was because Congress handed that to us. We were mandated in the Nutrition Labeling and Education Act of 1990 to address 10 topic areas. One of them was antioxidant nutrients and cancer. We had to decide what to include in that. We have been asked since then why we didn't include selenium.

First, selenium is not a vitamin. It would have been nice to expand the scope to encompass everything that we think is even peripherally relevant. But we did not have the resources or time to do that with.

Dr. John Milner (Pennsylvania State University):

I might add that selenium is also not an antioxidant. It is an antioxidant only by virtue of being part of glutathione peroxidase.

Can we recommend the increased consumption of fruits and vegetables and talk about at least one antioxidant? Do the two have to be mutually exclusive? I do not care if it is vitamin A or if it is vitamin C, or sulfhydryls and other active compounds in various foods, but can we pick one and then add others as we go along?

Dr. John Hathcock (U.S. Food and Drug Administration):

In terms of either authorizing or not authorizing a health claim, while the law instructed FDA to address a particular issue of antioxidant vitamins to begin with, if we find a valid disease-nutrient relationship and there is significant scientific agreement, the mechanism really does not have to be antioxidant or any other particular thing. Any mechanism will do as long as there is a sufficient database to conclude that there is significant scientific agreement, however that might be defined.

Dr. Regina Ziegler (National Cancer Institute):

Given what you said, if you do not need to put the word "antioxidant" in, let's not. The problem with the word "antioxidant" is that we are not sure there is a common mechanism. Once we use the word "antioxidant", it opens the door to other antioxidants that may not naturally occur in the food supply that can be packaged at who knows what levels. Unless we really want to suggest that any antioxidant might be protective, we should not use the word "antioxidant", but instead talk about the compounds or the food groups that we think are protective.

Dr. John Milner (Pennsylvania State University):

We heard about BHA and BHT yesterday and their efficacy. They clearly are antioxidants, but they may not be working by that mechanism. If we do not use a general, nonspecific term, we really could have lots of confusion.

Dr. John Hathcock (U.S. Food and Drug Administration):

BHA and BHT are clearly enzyme inducers as well as antioxidants. When we use the term "antioxidant", we are indeed trying to attribute the effect to a particular category of activity and perhaps mechanism. Is that a good idea?

Dr. John Milner (Pennsylvania State University):

It is important to get a range of opinions. We must make sure that we find significant scientific agreement that is truly scientific agreement, not just pressure.

Ms. Nancy Ernst (National Heart, Lung, and Blood Institute):

If I could draw an analogy here, when we labeled saturated fats and included all saturated fats, we did not do so because of one common mechanism. I think stearic fatty acid is there because it may have an association with heart disease, but it is not through the cholesterol-raising effect. Do you want to clarify that?

Dr. John Hathcock (U.S. Food and Drug Administration):

I firmly believe that there are enough mechanistic and animal studies available on one category of antioxidant vs. another; that is easily an attractive hypothesis. But it may not be the only category of action of the effects of vitamin E on the immune system, for example. If these effects are disease protective, I do not know whether they are through an antioxidant mechanism or some other mechanism. In terms of the public health, if there is an effect, we would not need to know the mechanism. It would be nice to know it, but it would not be necessary.

Unidentified:

Dr. Ziegler mentioned that there were two trials being published, one in September and one later. If the results of those trials are negative, what would the views of the panel be then? In the Finnish trial they are studying beta-

carotene and vitamin E in men who might have cancer of the lung. They are all smokers. Ten thousand men are involved, and the trial is lasting 5 years.

The man who is conducting this study did not look very happy the last time I saw him. When I asked him "Would you recommend the supplementation of antioxidants to diet?", he answered "For what purpose?"

If those results are negative, maybe we should think about it a little bit before actually going public and saying, "Yes, we ought to use antioxidants." What is your view on this?

Dr. Regina Ziegler (National Cancer Institute):

The Linxian, China, trial, which will appear on September 15 in *JNCI*, is two studies back to back. One was a multivitamin supplementation involving a wide variety of vitamins and minerals plus beta-carotene. That was one intervention. The other intervention was set up so that it could distinguish small groups of micronutrients. In other words, it could see what goes together. I think vitamin A is paired with zinc, and they are tested together. I think vitamin C is tested with molybdenum, and I think beta-carotene with vitamin E.

The Finnish trial tried to separate the effects of beta-carotene and vitamin E. The trials are complicated and you have susceptible groups. It would be amazing to me if the study produced a totally negative result.

Dr. John Milner (Pennsylvania State University):

I think we need to go back and talk about these 10 studies, or 100 studies, that may give us some consensus. Can we make some kind of blanket statement?

Dr. Jeffrey Blumberg (U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University):

The question that was asked was a good one: What are we going to learn from these clinical studies that are about to be published, or that are under way, or that are being planned? We have to be very careful about extrapolating the results of clinical trials using high doses of antioxidants in populations at high risk. We are talking about heavy smokers. We learned yesterday about a study in Colombia of a population with a lot of *H. pylori* colonization of the gut. How do we translate these findings into what we are really focusing on, which is health claims for disease prevention in the general population? Many of these clinical studies involve populations that are at very high risk or already have the disease. We need to distinguish between disease prevention and the treatment of disease.

I think many of these clinical trials are of great interest, but do not necessarily bear direct relevance to the issue of health promotion and disease prevention in the general public.

Dr. John Milner (Pennsylvania State University): Assessment is a critical issue that we have not figured out how to handle. Should we be making blanket recommendations?

Dr. Jeffrey Blumberg (U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University):

Even if a trial comes out positive and says that 50 or 100 mg of beta-carotene a day is effective in preventing some diseases, how do we translate that into a recommendation for food, even fortified to RDA-type levels? We are talking about superdietary intakes.

Dr. John Milner (Pennsylvania State University):

What is the cost of not acting now? It would be a minimal cost compared to some of the health care cost issues

Dr. Lenore Kohlmeier (University of North Carolina, Chapel Hill):

I have a question for Dr. Ziegler, who told us that the National Cancer Institute recommended foods rich in vitamin E, C, or beta-carotene. How much confidence was there in the evaluation that beta-carotene is really what we should be looking at? As I understand it, most of these epidemiologic studies are what I would call "vegetable epidemiology," where we are asking people, "How often do you eat food X?" Food frequency is a notoriously poor method for estimating things like beta-carotene intake. There are many other substances in the same food sources that may be responsible for the very promising protective effects that are there.

Why are we focusing on beta-carotene in light of what we have heard here that it does not seem to have *in vitro* antioxidant properties?

Dr. Regina Ziegler (National Cancer Institute):

To clarify, what we have talked about were fruits and vegetables rich in vitamin A, which would be beta-carotene, and vitamin C. We did not include vitamin E.

I am worried that nobody seems to think there is a downside risk. Let's say lycopene has received some attention. There has been some unpublished USDA work recently that clearly shows that any one carotenoid interferes with the absorption of another carotenoid. We have a wide variety of carotenoids, and some may be important in addition to just beta-carotene. One thing we are worried about is if we put a lot of beta-carotene into the diet, is it going to prevent absorption and utilization of another carotenoid which may be helpful?

The reason the focus is on beta-carotene is because we started off with vitamin A and cellular differentiation. Then people said maybe it is beta-carotene, which we know is a precursor of vitamin A. We leapt on beta-carotene. A lot of these early studies which people keep quoting really look only at carotenoid-rich vegetables and fruits. They do not look at other vegetables and fruits. So we have very few studies at the present time that really disentangle all vegetables and fruits from carotenoid-rich vegetables and fruits, because the questions are all about the same.

Similarly, people often cite serum or plasma beta-carotene studies as indicative of a beta-carotene effect. While I agree that this is the simplest explanation, we are also aware, those of us in the field, that serum beta-carotene levels are a very good measure of elevated vegetable and food intake.

Dr. Nomura at Hawaii and I, and probably other groups also, are now starting to look systematically at the range of carotenoids to see whether this protective effect associated with elevated beta-carotene is seen with elevated levels for all the carotenoids. Beta-carotene was lucky because it goes to vitamin A, and that is why it got attention first.

Dr. Lenore Kohlmeier (University of North Carolina, Chapel Hill):

So you would say that maybe it is not beta-carotene. Would you say that maybe it is not even one of the carotenoids?

Dr. Regina Ziegler (National Cancer Institute):

That could be. We do not know. NCI is not a regulatory agency. We are scientists, and we struggle to come up with our best estimate of science, and then we leave it to FDA to come up with real spreads.

We want to talk about vegetables and fruits rich in vitamin A and vitamin C, and I think one reason we felt comfortable putting those in was, again, that they are nutrients that have a history, that precedes any of this recent interest in the antioxidant vitamins. Maybe we should have just said a variety of vegetables and fruits. We considered that also.

Unidentified:

Should we be fortifying foods that might be appropriate vehicles with these different antioxidant vitamins? I do not see that people are going to eat that much, or they are not going to buy a supplement or remember to take it, so we have to change the food supply. Are there thoughts about that?

Dr. John Hathcock (U.S. Food and Drug Administration):

Supplementation vs. fortification is very much a freedom-of-choice kind of issue, as well as a scientifically based kind of issue. That is, a person can choose to take a supplement or not, but the general food supply is fortified over a broad base, then everyone is apt to be getting a particular nutrient at some level, whether they consciously intended to or not.

The recent deliberations on folic acid and neural tube defects are a wonderful example of this kind of dilemma. There was significant scientific agreement that there is a likely benefit to be had, or reduction in risk to be had, if a woman takes an appropriate amount of folic acid at the right time. But agreeing on the vehicle for delivering that benefit was another question altogether. Clearly, taking a supplement is something that could deliver that probable benefit. Eliciting that behavior over a broad base of the right population at the right time is difficult. On the other hand, putting it into the food supply generates higher intakes in people with already high intakes. It generates nonintended exposures, so that the question of safety arises. It is a very complicated issue of how to get the lower percentiles up to a protective level without pushing the upper percentiles of intake off the top end.

Ms. Nancy Ernst (National Heart, Lung, and Blood Institute):

I would also like to add a comment about the cost of not making a decision. Making a decision in the absence of sufficient evidence — saying that it is costly not to make the decision — means that research in the area is likely to decline. With constrained federal research funding, people may stop extensive studying in a research area where FDA allows a health claim — because the relationship is established. The cost issue is complex.

Dr. Jeffrey Blumberg (U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University):

I beg to differ. In a somewhat analogous situation, almost 30 years ago a public health effort involving another type of health claim was initiated, that is, warning labels on cigarette packages. Even after that public health action was made an enormous amount of research continued to be funded regarding the relationship between cigarette smoking and health. I think the cigarette labeling campaign has been partly effective. It certainly did not shut off research in 1966 because they decided then that smoking was not good for your health. In fact, we have learned a lot more in terms of refining and expanding our knowledge about the relationship between smoking and health, based on research that has been done after the labeling was implemented.

Dr. Regina Ziegler (National Cancer Institute):

I agree with what you are saying, but I think there is also a cost in terms of the American public's credibility, not to mention the credibility of people in Washington. Maybe that is less important.

Certainly in the area of cancer, there have been so many hypotheses that have been generated in the last decade. First we told the American public that if they eat this or that, cancer is going to kill them, as we see in any of the newspapers.

I would rather talk about protection than risk. I think we have to be very careful to be reasonably certain of what we communicate to the American public. For example, if a few years from now the thinking changes on antioxidants, the American public is going to say that scientists do not know what they are doing. In terms of guidelines and fortification schemes, we need to be careful.

Dr. Carole Dichter (Campbell Soup Company):

I wanted to pursue a question related to Dr. Blumberg's comment regarding evaluating the data in terms of the general population and health promotion effects. Dr. Blumberg and the other members of the panel, do you think some of the large-scale prospective epidemiologic studies might have a bit more meaning in this area than clinical trials or some of the traditional ways of evaluating these scientific data because you are looking at a larger group of the population? I am thinking about some of the results from the Nurses' Health Study and the health professionals' follow-up study.

Dr. Jeffrey Blumberg (U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University):

That is a very good point. Dr. Machlin talked about the usual reference to epidemiologic studies as provoking new hypotheses but not being able to determine cause and effect. Yet I think epidemiology is really where some of the most compelling evidence lies, along with the biological plausibility we get from experimental studies. I think the epidemiology is reflective of the general population and the public health effort that we are talking about.

I think too much reliance on clinical trials, for some of the reasons I mentioned, could mislead us. Clinical trials must be restricted to utilizing but one or two doses of usually one or two nutrients for a limited time in a very selective and often small population of people at high risk. If the results of a study are negative, questions always remain about the selection of the dose, duration, subjects, and the interactions with other nutrients — and more trials are proposed.

Many of these studies, particularly the kinds that many scientists in the medical community demand — the double-blind, placebo-controlled clinical trials with a disease as an end point — are most relevant to therapeutic drug criteria. Nutrients and foods are not drugs, and I do not think we should try to regulate them like they are. We are dealing with different kinds of issues in terms of both efficacy and safety.

When we talk about these studies, we must not overpromise the potential benefits. What we are talking about is the ability of these antioxidant nutrients to reduce the risk for several chronic diseases. They are not going to cure the diseases. They are not going to prevent them in everyone. But if we have some compelling evidence with substantial scientific agreement that we can reduce cancer or heart disease morbidity and mortality by only 10% or 20% with antioxidant interventions, then we have an overwhelmingly important public health contribution to make.

There are multifactorial risks for these diseases involving environmental and genetic factors. What we are talking about is being able to inform the public that they can empower themselves by choosing appropriate foods, dietary patterns, and nutritional supplements to create a proactive health benefit. I think we can get that kind of information from appropriate epidemiologic studies if those studies are consistent with other scientific evidence. I do not think we have to await the final results of ongoing clinical trials, which in fact may not give us all the relevant information we need.

Ms. Nancy Ernst (National Heart, Lung, and Blood Institute):

I think that we need, from the heart perspective, research to establish cause and effect. We know that heart disease has been declining since the mid-1960s. Survey data show that intakes of fruits and vegetables has increased — and saturated fat intakes have declined. Many life-style factors have changed. We have questions yet to answer and many research steps from which to move forward.

Dr. John Hathcock (U.S. Food and Drug Administration):

I think that the way to decide these issues, from a public health viewpoint and from a food labeling viewpoint for FDA, is through a composite of the different scientific approaches. I pointed out some weaknesses as I saw them in epidemiologic studies — that is, the specificity issues — but there are also weaknesses in the clinical trials approach. Perhaps we are looking for a tree and missing the forest around it.

Having pointed out that I like the composite approach, we are in the midst of rule making, and I am not going to pronounce that I do or do not think that the totality of the evidence is sufficient at this point.

Dr. Regina Ziegler (National Cancer Institute):

I agree with Dr. Blumberg that chemoprevention trials are not going to provide all the answers, nor are they the only piece of evidence. But let's imagine that someone wanted to do a trial of beta-carotene supplementation in healthy U.S. physicians for a 5- or 10-year period. The physicians took their beta-carotene but the study failed to find any striking — any 10% — reduction of risk. There may have been a small effect, but it was indistinguishable from the control group. These findings would have to be integrated into our view about the effectiveness of beta-carotene. If you want us to fall back on the prospective studies and retrospective studies, case-control and cohort studies — I do them and I believe in them — that is fine, but then let's look and see what they say.

These studies are looking at natural dietary patterns within a population. That is why we are talking about vegetables and fruits and grains, because that is what we see in these studies. If you want to go beyond these studies to nail specific things, maybe we are going to have to come up with some type of scientific evidence that identifies those particular compounds. This is in the area of cancer, not heart disease.

Dr. John Milner (Pennsylvania State University):

I would like to express my appreciation for the excellent presentations of all of our panel members and the insight they have given us into this complex issue, as well as the many thoughtful questions we have heard.