# Dietary Reference Intakes

## Proposed Definition and Plan for Review of Dietary Antioxidants and Related Compounds

A Report of the
Standing Committee on the Scientific Evaluation of
Dietary Reference Intakes and Its Panel on
Dietary Antioxidants and Related Compounds

Food and Nutrition Board

INSTITUTE OF MEDICINE


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## REVIEWERS

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the Institute of Medicine in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The content of the final report is the responsibility of the Institute of Medicine and the study committee and not the responsibility of the reviewers. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. The committee wishes to thank the following individuals, who are neither officials nor employees of the Institute of Medicine, for their participation in the review of this report:

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While the individuals listed above have provided many constructive comments and suggestions, responsibility for the final content of this report rests solely with the authoring committee and the Institute of Medicine.

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# Contents





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# Dietary Reference Intakes: Proposed Definition and Plan for Review of Dietary Antioxidants and Related Compounds

## INTRODUCTION

There has been intense interest recently among the public and the media in the possibility that increased intakes of "dietary antioxidants" may protect against chronic disease. Many research programs are underway in this area. Epidemiological evidence suggests that the consumption of fruits and vegetables may reduce the risk of both cancer and cardiovascular disease, and it has been hypothesized that this is due in part to the presence of antioxidant compounds in fruits and vegetables. As a result, these compounds have been considered together by many people and loosely termed *dietary antioxidants*.

Closer examination, however, reveals that compounds typically grouped together as dietary antioxidants can differ quite considerably from one another, both in terms of their chemical behavior and in terms of their biological properties. This report from the Institute of Medicine's Food and Nutrition Board provides a proposed definition of dietary antioxidants so as to characterize the biological properties of these compounds.* In this first of two reports, the Panel on

*This study was requested by the federal steering committee for Dietary Reference Intakes and coordinated by the Office of Disease Prevention and Health Promotion of the U.S. Department of Health and Human Services and the U.S. Army Medical Research and Materiel Command of the U.S. Department of Defense. The overall DRI project, of which this is a part, is a comprehensive effort undertaken by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee) of the Food and

Dietary Antioxidants and Related Compounds also identifies the nutrients and food components that it will evaluate in detail, assuming adequate scientific data are available, to establish Dietary Reference Intakes (DRIs) for these selected substances.

DRIs are reference values that are quantitative estimates of nutrient intakes to be used for planning and assessing diets for healthy people. They include Recommended Dietary Allowances (RDAs) as goals for intake by individuals, but also include three other reference values. These include the Estimated Average Requirement (EAR), Adequate Intake (AI), and the Tolerable Upper Level (UL).

In its second report, the panel will provide a comprehensive set of DRIs for those nutrients and food components selected, in the current report, for detailed examination. This selection is not based on the panel's definition of a dietary antioxidant. Beta-carotene, vitamin C, and vitamin E are included as requested by the federal steering committee for Dietary Reference Intakes. Similarly, other dietary compounds will be included in the review that may be related in function, but may not necessarily act as antioxidants. Therefore, the nutritional recommendations that will be presented in the second report for some of these dietary components may not be determined by or related to their possible action as antioxidants.

## TOWARD A DEFINITION OF *DIETARY ANTIOXIDANT*

In order to elicit other perspectives about the attributes of dietary antioxidants, the Panel on Dietary Antioxidants and Related Compounds held an open meeting and workshop. A broad range of definitions from experts in the field was presented (see the Appendix for Acknowledgments), however, there was no firm agreement among the presenters. The situation is complicated as some compounds, at least *in vitro,* can be antioxidants under one condition and prooxidants under others. Adding to the complexity is the fact that antioxidants contained in foods are not interchangeable and may differ from one another both in their sites and mechanisms of action. For example, vitamin E is a most effective chain-breaking antioxidant, whereas beta-carotene is a most effective singlet oxygen quencher. In contrast to these fat-soluble antioxidants that function in cell membranes, lipoproteins, and lipid droplets, water-soluble vitamin C directly quenches a variety of reactive oxygen and nitrogen species in the aqueous portion of cells and extracellular fluids. Selenium, not present in high enough quantities to be a direct antioxidant, participates as an essential constituent of glutathione peroxidases and thioredoxin reductase in the breakdown of peroxides, thus preventing the potentially damaging generation of reactive oxygen species.

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Nutrition Board, Institute of Medicine, National Academy of Sciences, with active involvement of Health Canada.

### Possible Health Benefits

There is a considerable body of biological evidence that, at high levels, reactive oxygen and nitrogen species, hereafter referred to as ROS and RNS respectively, can be damaging to cells and thus might contribute to cellular dysfunction and disease. ROS and RNS are also damaging to other body components that do not reside in cells, such as are found in blood and other body fluids, for example, synovial and cerebrospinal fluids. To the extent that this theory is substantiated by future research, the panel considered whether or not the definition of a dietary antioxidant should rest on demonstrated health benefits.

Antioxidant compounds in the diet may or may not confer health benefits. Some questions and controversy remain regarding the linkage of antioxidants with decreased risk of chronic disease. For example, some clinical intervention trials have shown that in long-term current smokers, high doses of beta-carotene supplements did not decrease, and may have actually increased, their risk of lung cancer. Because antioxidants work via different mechanisms, it is unlikely that a common health benefit could be produced by each of them. Therefore, the panel decided to base its definition on the functional or physiological parameters of antioxidants. In the second report, the panel will review the available scientific evidence regarding all of the compounds selected to determine if they demonstrate potential health benefits.

## PROPOSED DEFINITION

This proposed definition is based on several criteria: (1) the substance is found in human diets; (2) the content of the substance has been measured in foods commonly consumed; and (3) in humans, the substance decreases the adverse effects of reactive oxygen and nitrogen species *in vivo*. Thus, the panel developed the following proposed definition of a dietary antioxidant:

> *A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiological function in humans.*

### Presence in Human Diets

In order to meet the definition of a dietary antioxidant proposed here, nutrients and food components must be found in typical human diets.

**TABLE 1** Examples of Reactive Oxygen and Nitrogen Species

| Name | Formula | Comments |
|---|---|---|
| Superoxide | $O_2^-$ | An oxygen-centered radical. Has limited reactivity. |
| Hydroxyl | $OH^\cdot$ | A highly reactive oxygen-centered radical. Very reactive indeed: Attacks all molecules in the human body. |
| Peroxyl, alkoxyl | $RO_2^\cdot$, $RO^\cdot$ | Oxygen-centered radicals formed (among other routes) during the breakdown of organic peroxides. |
| Oxides of nitrogen | $NO^\cdot$, $NO_2^\cdot$ | Nitric oxide ($NO^\cdot$) is formed *in vivo* from the amino acid L-arginine. Nitrogen dioxide ($NO_2^\cdot$) is made when NO reacts with $O_2$ and is found in polluted air and smoke from burning organic materials (e.g., cigarette smoke). |

SOURCE: Adapted from Halliwell, 1996, with permission; © International Life Sciences Institute, Washington, D.C.

## Measurement of Quantities in Foods

In order to meet the definition of a dietary antioxidant proposed here, the dietary intakes of the nutrient or food component must be able to be calculated from available national databases. These databases include the U.S. Department of Agriculture's National Nutrient Databank, the Canadian Nutrient File, and other databases that contain a nationally representative sample of foods commonly eaten in the United States or Canada and that report concentrations for the antioxidant of interest and others. It is recognized that limitations exist in the use of food composition databases to accurately estimate intakes.

## Decreased Adverse Effects of Some ROS and RNS

In order to meet the definition of a dietary antioxidant proposed here, the nutrient or food component must decrease the adverse effects of some ROS and RNS (see Table 1 for examples of ROS and RNS). An explanation of the biochemical and physiological mechanisms of these adverse effects follows.

### *Role of ROS and RNS in Health and Disease*

ROS and RNS are produced metabolically by the body. It has been estimated that about 1 to 3 percent of the oxygen we utilize goes to make ROS. In

addition, exposure to UV radiation or to air pollutants such as cigarette smoke (which contains oxidants) or ozone can cause the body to increase the levels of reactive radical species.

ROS is a collective term that includes several oxygen radicals—superoxide ($O_2^{\cdot-}$) and its protonated form, hydroperoxyl ($HO_2^{\cdot}$), hydroxyl ($OH^{\cdot}$), peroxyl ($RO_2^{\cdot}$), alkoxyl ($RO^{\cdot}$)—and nonradicals—hydrogen peroxide ($H_2O_2$), hypochlorous acid (HOCl), ozone ($O_3$), and singlet oxygen ($^1O_2$)—that are oxidizing agents or are easily converted into radicals. RNS includes nitric oxide ($NO^{\cdot}$), peroxynitrite ($ONOO^-$), and peroxynitrous acid (ONOOH). Various compounds in the human body generate free radicals in their metabolism. Examples are catecholamines and compounds found in the mitochondrial electron-transport chain.

In addition, activated phagocytes produce ROS as one of the defense mechanisms they use to kill microbes. Thus, in this situation, ROS are used by the body as a defense mechanism against infection.

An imbalance of oxidants and antioxidants resulting in increased levels of ROS, RNS, or both can result in damage to lipids, proteins, carbohydrates, and DNA. A considerable body of biological evidence shows that ROS and RNS can damage cells and other body components and could in theory contribute to dysfunction and disease states. It has been postulated that oxidative damage caused by increased levels of production of ROS or RNS may contribute to the development of many chronic diseases, including age-related eye disease, atherosclerosis, cancer, coronary heart disease, diabetes, inflammatory bowel disease, neurodegenerative diseases, respiratory disease, and rheumatoid arthritis.

### *Antioxidant Mechanisms*

The mechanisms of antioxidant action for decreasing the adverse effects of ROS or RNS are varied. They include (1) decreasing ROS or RNS formation; (2) binding metal ions needed for catalysis of ROS generation; (3) scavenging ROS, RNS, or their precursors; (4) up-regulating endogenous antioxidant enzyme defenses; (5) repairing oxidative damage to biomolecules, such as glutathione peroxidases or specific DNA glycosylases; and (6) influencing and up-regulating repair enzymes. Some antioxidants remove free radicals by reacting directly with them in a noncatalytic manner before the radicals react with other cell components. For example, vitamin E inhibits lipid peroxidation by scavenging radical intermediates in the radical chain reaction with polyunsaturated fatty acids. The effectiveness of each dietary antioxidant depends on which ROS or RNS is being scavenged, how and where they are generated, the accessibility of the antioxidants to this site, and what target of damage, or oxidizable substrate, is involved.

Antioxidant defense mechanisms include not only low-molecular-weight compounds, but also some antioxidant defense systems in the human body that

are enzymatic, such as: (1) superoxide dismutase enzymes, which remove superoxide ($O_2^{\cdot -}$) by accelerating its conversion to $H_2O_2$ and $O_2$; (2) glutathione peroxidases, which convert $H_2O_2$ to water and $O_2$ and which convert various hydroperoxides to harmless compounds; and (3) catalase, which converts $H_2O_2$ to water and $O_2$ but only functions at relatively high concentrations of the ROS.

*Evidence for Antioxidant Activity*

Many substances have been shown to have antioxidant activity *in vitro*. However, *in vitro* findings are of uncertain relevance to the *in vivo* situation in healthy humans. The definition of a dietary antioxidant focuses on antioxidant effects of substances when consumed by humans. Therefore, dietary antioxidants are substances that have been shown to decrease the effects of ROS and RNS in humans.

A battery of markers of *in vivo* oxidative damage/oxidative stress are now available. Potential biomarkers include (1) lipid peroxidation products, such as lipid hydroperoxides, malondialdehyde or other aldehydic decomposition products of lipid hydroperoxides, exhaled pentane and ethane, and $F_2$-isoprostanes; (2) several DNA oxidation products such as 8-oxo-deoxyguanosine, 8-oxydeoxyadenosine, and thymine glycol; (3) protein carbonyls; and (4) nitrated protein derivatives.

## FOOD COMPONENTS THAT WILL BE REVIEWED BY THE PANEL

This section contains a description of the scope of the second report of the Panel on Dietary Antioxidants and Related Compounds. The panel has focused on nutrients and food components found in North American diets because the objective of the second report of this panel is to present a set of DRIs for promotion and maintenance of health in Americans and Canadians. The inclusion of substances is not based upon the requirement that they meet the proposed definition of a dietary antioxidant. Although there may be some functional relationship to their proposed roles as antioxidants, their inclusion in the second report is not based upon their meeting this criterion. The panel plans to review beta-carotene and other carotenoids, vitamin C, vitamin E, and selenium. The rationale for including these food components but not other potential substances follows.

### Beta-Carotene and Other Carotenoids

Beta-carotene and other carotenoids—such as alpha-carotene, lycopene, lutein and zeaxanthin, and cryptoxanthin—are widely consumed in human diets, and adequate food composition data exist to estimate their consumption in

healthy people. Studies demonstrating the possible antioxidant effects of carotenoids in humans are available, at least with regard to beta-carotene, as are a large number of observational studies associating carotenoid intake or carotenoid status with a variety of health effects. In addition, some experimental studies of beta-carotene in humans are also available. Thus, an examination of the scientific evidence regarding beta-carotene and other carotenoids is warranted. The panel will review the available scientific evidence and, if it is adequate, will recommend DRIs for beta-carotene and possibly other carotenoids.

## Vitamin C

Vitamin C is found in abundance in fruits and vegetables. It is a cofactor in the biosynthesis of a number of different compounds including collagen, carnitine, and neurotransmitters. In addition, because it can donate electrons, it effectively quenches a variety of ROS and RNS in aqueous body compartments, and it has been shown in some cases to prevent oxidative damage *in vivo* to lipids and DNA. Under certain circumstances, vitamin C can promote the formation of ROS or RNS *in vitro*. Vitamin C is found widely throughout the body and is concentrated in tissues susceptible to oxidative damage including leukocytes, the lung, eye, brain, and heart. It is readily regenerated *in vitro,* and because of its high reductive capacity, has the potential ability to regenerate other body antioxidants. Vitamin C's role in preventing scurvy is relatively well defined and is distinct from its role in oxidant defense. A great deal of observational and experimental evidence is available regarding vitamin C's health effects. Thus, the panel will review the available scientific data and, if it is adequate, will establish DRIs for vitamin C.

## Vitamin E

Vitamin E is composed of a group of fat-soluble molecules that occur naturally in eight different forms (four tocopherols and four tocotrienols) that have similar chromanol structures. It occurs widely in the diet from both plant and animal sources, and adequate food composition data are available. Vitamin E has been demonstrated to possess antioxidant activity *in vivo* and can protect unsaturated lipids throughout the body. Under certain circumstances, vitamin E can act as a prooxidant *in vitro*. In addition, there is epidemiological and experimental evidence regarding the health-promoting effects of vitamin E. Thus, the panel will review the available scientific data and, if it is adequate, will establish DRIs for vitamin E.

### Selenium

Selenium is a required constituent of several enzymes that remove ROS *in vivo*. Moreover, selenium is present in human diets, and its consumption has been quantitated in a number of different populations. Biomarkers for selenium and data for selenium intake exist and have been reported in studies of populations that vary with respect to selenium status. Some intervention studies have been performed that demonstrate effects of selenium supplementation on biomarkers and on the development of disease. Thus, the panel will review the available scientific data and, if it is adequate, will establish DRIs for selenium.

## FOOD COMPONENTS THAT WILL NOT BE REVIEWED BY THE PANEL

### Phenols and Polyphenols

Phenols and polyphenols are widely distributed in plant foods. They have been shown to have antioxidant activity *in vitro* and may possibly elicit biological effects consistent with sustained and improved human health in several observational studies. Nonetheless, comprehensive food composition data, which are required to assess dietary intakes in a population, are unavailable. In addition, only extremely limited data are available on the absorption and metabolism of these food components. Although phenols and polyphenols may be important dietary constituents, insufficient data are available at this time to warrant their inclusion in this evaluation.

### Other Proposed Dietary Antioxidants

The overall DRI framework includes a planned review, by another expert panel, of food components grouped as "other food components." That review, when it is initiated, may include other related compounds not addressed by this panel, such as flavonoids, phenols and polyphenols, phytoestrogens, lipoic acid, and food additives. Because the published literature on some of these potentially important dietary substances is scant at this time, other data may emerge in the future that could allow a consideration of setting DRIs for these compounds as well.

## SUMMARY

The panel's proposed definition of a dietary antioxidant follows:

*A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiological function in humans.*

This proposed definition is based on several criteria: (1) the substance is found in human diets; (2) the content of the substance has been measured in foods commonly consumed; and (3) in humans, the substance decreases the formation of adverse effects of reactive oxygen and nitrogen species *in vivo*.

Additionally, based on its review of the scientific literature on dietary antioxidants and related compounds, and on the availability of data relating the intake of these substances to potential benefits to human health, in its second report the panel will evaluate the extent to which beta-carotene and other selected carotenoids, vitamin C, vitamin E, and selenium play a role in health. DRIs will be set for these food components if adequate data are available and if their role in health can be established and quantified. Therefore, for some of these nutrients and food components, their DRIs may not be determined by or related to their possible action as an antioxidant.

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APPENDIX

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