

### 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.
Peroxy, alkoxy	$RO_2^\cdot, RO^\cdot$	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 <i>in vivo</i> 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 ( $O_2^-$ ) and its protonated form, hydroperoxyl ( $HO_2$ ), hydroxyl ( $OH$ ), peroxy ( $RO_2$ ), alkoxy ( $RO$ )—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 ( $NO$ ), 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