

## Editorial

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## Toxicity of Antioxidants

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The fundament of toxicology is the risk-benefit analysis. This means that the positive as well as the negative health effects of all compounds, including antioxidants, have to be assessed and related to each other. Only in this way the rationale for the use of a compound can be evaluated.

The beneficial effects of antioxidants are due to their ability to protect against free radical damage. In the diseases and other pathological conditions where free radicals are implicated, the biochemistry may greatly vary, i.e. the radicals involved, their flux, the site where they are generated and the target they attack can differ.<sup>1</sup> Thus for each type of radical damage specific criteria need to be fulfilled by an antioxidant in order to be active. Free radicals of biological interest are often divided into oxygen centred and nitrogen centred radicals. Reactive Oxygen Species (ROS) is a collective term that includes both oxygen centred radicals and certain oxygen containing non-radicals that are oxidizing agents or easily converted into radicals. In the Reactive Nitrogen Species (RNS) the reactivity of the species is located on or near a nitrogen atom. The adjective “reactive” is not always appropriate; H<sub>2</sub>O<sub>2</sub>, O<sub>2</sub>•<sup>-</sup> and NO• quickly react only with very few molecules. OH• reacts instantaneously with almost everything. RO<sub>2</sub>•, RO•, HOCl, NO<sub>2</sub>•, ONOOH, and O<sub>3</sub> have a reactivity that lies in between these extremes.

Regarding safety, in the 16<sup>th</sup> century Paracelsus already stated that all compounds are toxic, provided the dose is high enough. There is no reason to assume that antioxidants should be an exception to this rule. On the contrary, the mega-dosages sometimes recommended make safety a very relevant issue for antioxidants. The biological origin of most antioxidants helps to increase the acceptance of antioxidant supplementation by the general public. The perception is that the biological origin guarantees that antioxidants are not harmful; biological and natural is incorrectly thought to be synonymous to safe.<sup>2</sup>

The adage on the use of antioxidant supplementation seems to be: The more, the better. Indeed, antioxidant supplements are taken frequently by a great part of the public at a relatively high dose despite our limited knowledge on their beneficial health effect and safety. From a toxicological point of view, the free radical processes as well as the profiles of antioxidants have to be elucidated to a greater extent to be able to further rationalize and optimize antioxidant therapy.<sup>3</sup>

An important issue in the use of antioxidants is metabolism.<sup>4</sup> Like other bioactive compounds, metabolites formed by phase 1 and phase 2 enzymes can contribute to the beneficial and toxic effect of an antioxidant. More importantly, during the actual antioxidant activity of a free radical scavenging antioxidant, it is converted into a metabolite.<sup>1</sup> The effect of such a metabolite on a biological system is relevant since the metabolite usually contains some residual reactivity of the radical that has been scavenged.

According to 2013, Annual Report of the American Association of Poison Control Centers (AAPCC): National Poison Data System (NPDS), more than 65,000 instances of vitamin toxicity are reported annually to US poison control centers.<sup>5</sup> Unintentional and intentional exposures continue to be a significant cause of morbidity and mortality in the United States.<sup>4</sup> It

is of importance to identify groups that are at risk. In spite of the focus on the adverse effects of antioxidants and vitamins, priority should be given to identify groups that are likely to benefit.<sup>6</sup>

The bottom line is that in the appraisal of antioxidants, their benefits must first be identified and substantiated by elucidating the molecular mechanism. The risks must then be identified the molecular mechanism. The optimal benefit-risk ratio has to be determined for each antioxidant and each individual separately, also taking into account, the dose.<sup>7</sup>

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.

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