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CRN ANALYSIS

"Antioxidant Supplements for Prevention of Mortality in Healthy Participants and Patients with Various Diseases"

Bjelakovic G., et al., Cochrane Database of Systematic Reviews 2008, Issue 2

Background:

An updated meta-analysis examining the efficacy of antioxidant supplements in primary or secondary prevention of mortality was published in *The Cochrane Database of Systematic Reviews 2008, Issue 2,* in April 2008. The authors of the meta-analysis conclude that "there is no evidence to support antioxidant supplements for primary or secondary prevention of mortality and that vitamin A, beta-carotene, and vitamin E may in fact increase mortality. Future randomized trials could evaluate the potential effects of vitamin C and selenium for primary and secondary prevention. Such trials should be closely monitored for potential harmful effects. Antioxidant supplements need to be considered medicinal products and should undergo sufficient evaluation before marketing."

These are the same authors that published similar meta-analyses in the *Journal of the American Medical Association* (*JAMA*) in February 2007 and in the *Lancet* in September 2004. Although they have updated their meta-analysis, by handpicking additional studies and correcting a litany of minor mistakes made in previous versions, it is for all intents and purposes not a new study, nor is it truly new information. In fact, it appears to be a systematic attempt by the authors to publish work that supports their own pre-determined conclusions about antioxidants and the way they should be regulated.

The Council for Responsible Nutrition (CRN) believes this latest attempt to discredit antioxidants does nothing to change the practical implications for consumers, specifically a generally healthy population, that uses antioxidant supplements as part of their proactive wellness regimen in an attempt to fill nutrient gaps or help reduce the risk of chronic disease. Healthy consumers can feel confident in continuing to take antioxidant supplements for the benefits they provide. Consumers with serious illnesses, such as cancer, heart disease, liver disease, etc., should consult with their physician on anything they put into their body. This updated meta-analysis does nothing to change those facts.

There are a number of serious flaws with the meta-analysis, several of which were previously pointed out in response to the *JAMA* publication. These flaws have not been addressed with this updated meta-analysis and include the following points:

- This meta-analysis only evaluated randomized, controlled trials (RCTs); there is an equally vast, if not more so, body of observational data involving antioxidants, which was not considered in this analysis. Thus, this covers only a portion of the evidence base, so it cannot be considered comprehensive.

- The researchers identified 748 studies that could be included in this analysis; however, then determined that there were only 409 "eligible" RCTs. Of those, they excluded all but 67 studies. Thus, their conclusions are based on less than nine percent of the totality of available RCT evidence on

antioxidant supplementation, and do not look at any research other than RCTs, which are in essence treatment trials.

- In selecting which RCTs to use, the researchers excluded any RCT in which no deaths were reported (405 articles), which begs the question of how one can properly evaluate whether a substance can prevent mortality when studies that demonstrate no harm are automatically excluded.

- The selected studies included studies examining different antioxidants (and in some cases, not even antioxidants), different doses, different populations with different health statuses, for different durations—in short, the authors combined heterogeneous studies and tried to make one generalized conclusion. As the saying goes, it's like comparing apples to oranges.

- The authors relied on their own self-selected, and far from agreed upon, criteria for assessing bias (identical to that used in the last *JAMA* meta-analysis and criticized at that time by some highly respected researchers in the form of letters to the editor) where they established specific inclusion criteria. If any of the inclusion criteria from a scientific trial was deemed "inadequate", in the researchers' opinions, then the study was deemed "high risk bias." Not surprisingly, the studies that are considered "high risk bias" in this meta-analysis tend to be those that show a benefit to antioxidant supplementation, while those labeled as "low risk bias" tended to show harm.

- Only all-cause mortality was assessed in the review. As a result, the authors didn't seek to eliminate deaths that may have been caused by accident, homicide, suicide, medical conditions that have nothing to do with supplementation or other circumstances. The authors intimated that all deaths were attributable to antioxidant supplements, ignoring other potential factors and did not offer any biological plausibility for their conclusions.

- These authors included vitamin A studies in their meta-analysis, despite the fact that experts within the scientific community universally agree that vitamin A does not function as an antioxidant and should not be characterized as one. The vitamin A RCTs that were included used extremely high doses of vitamin A, in some cases well above the established Tolerable Upper Limit (UL) established by the Dietary Reference Intakes (DRI), which may have significantly skewed the overall results of this analysis.

- Given the researchers' own conclusion that antioxidant supplements should undergo pre-market approval, they betray their scientific duty and display their personal bias. The researchers do not explore the regulatory practices anywhere in this 191-page paper and it is not clear that the researchers possess any expertise in the field of policy and public health. The entire paper, therefore, seems designed to support this regulatory agenda.

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