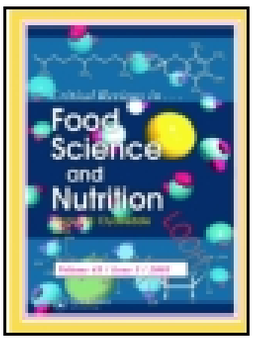

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Archaic RDA Methodology for Vitamin C

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Archaic RDA methodology for vitamin C

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The 2012 review by Frei *et al.*, entitled *Authors' Perspective: What is the Optimum Intake of Vitamin C in Humans* is both flawed and misleading. Their assertion that there is a tradition for basing the RDA for vitamin C on prevention of acute scurvy, true as it may be, is irrelevant unless it is also based on scientific data. The reviewers provide numerous illustrations to suggest that vitamin C "may exert additional health benefits" with respect to chronic disease. However, their claim that studies "have not found consistent benefit with respect to chronic disease prevention" stems from a lack of understanding of the dosing and pharmacokinetics of vitamin C, as has been explained previously, in detail (Hickey *et al.*, 2008; Duconge *et al.*, 2008).

The reported belief of Frei *et al.* that there is a "lack of apparent proof of benefit" from RCTs might be considered in terms of the irrationality of a requirement for scientific proof. Refutation, not proof, is core to the scientific method (Popper, 2002). Nevertheless, Frei *et al.* are aware that RCTs are ill suited to determining an RDA. A more appropriate scientific methodology would employ a Bayesian interpretation of all the available data (Gelman *et al.*, 2003).

We do not agree that the currently available scientific evidence is sufficient to determine the optimum intake of vitamin C in humans while omitting relevant information, including the epigenetic, genetic, and evolutionary data. We do agree with Frei *et al.* that vitamin C supplementation lowers hypertension, endothelial dysfunction, chronic inflammation, *Helicobacter pylori* infection, and acts as a biological antioxidant lowering oxidative stress, which contributes to chronic disease prevention. In addition, biologically plausible data and mechanisms of action suggest that shortage of vitamin C is a key feature in coronary heart disease, stroke, and cancer.

The idea that the data from human metabolic, pharmacokinetic, and observational studies supports an optimal intake of 200 mg per day of vitamin C is demonstrably incorrect. Frei *et al.* have ignored decades of observations and results reported for high dose supplementation. In particular, the ascorbate requirement variation reported by Cathcart (1985) and others (Pauling, 1987; Hickey *et al.*, 2005, 2008) are disregarded. Cathcart (1981) reported that, during periods of stress or illness, the body's tolerance to oral doses increases in proportion to the disease severity. The magnitude of this increase is large and obvious—two to three orders of magnitude (from, say, 2 grams to 300 grams). This is consistent with the body requiring increased intakes. Such reports also suggest a definitive clinical response, with a clear pharmacokinetic explanation. These data imply that people require a reserve daily intake (Hickey *et al.*, 2008). Importantly, they also invalidate the Frei *et al.* claims concerning limited "bioavailability."

Frei *et al.* claim, wrongly, that blood plasma is "saturated" at 60-80 μM/L following a low dose of vitamin C. The graph presented to support this contention (Frei *et al.* Fig 1) has been shown conclusively to be incorrect, since the measurements were taken 12 hours after the dose, and vitamin C has a dual phase elimination process (Hickey *et al.*, 2005). The half-life of plasma ascorbate above this level is approximately 30 minutes. Disconcertingly, this graph shows plasma levels of vitamin C measured *after the vast majority of the dose had been excreted*. The reviewers' physiological conclusions are therefore invalid.

In healthy humans, graphs of concentration against time, after a single large oral dose of ascorbic acid, peak some hours later at about 250 μM/L. The NIH's misleading "saturation" concept has been discredited, though it was used to determine the current RDA. Even the NIH's own research suggests that plasma "saturation" does not occur below at least 18 grams a day, leading

to a sustained plasma level of at least 220 μM/L (Padayatty et al, 2004). We should not need to point out that this level is well above the reviewers' claimed 60-80 μM/L saturation point. Independent studies suggest that some oral forms of vitamin C, other than standard ascorbic acid tablets, can achieve far higher plasma levels than this (Hickey *et al.*, 2008). Such reports suggest that plasma levels of 400-800 μM/L can be achieved, and thus sustained levels approaching a millimole (1000 μM/L), may be attained using oral intakes. It has been noted elsewhere that long term supplementers may have baseline plasma levels of about 150 μM/L after 12 hours depletion, suggesting a modified distribution within the body (Hickey *et al.*, 2008).

Frei *et al.* quote figures for the absorption of vitamin C by lymphocytes, platelets, monocytes, and neutrophils. These are specialised cells, known to absorb millimolar concentrations of vitamin C (U.S. Institute of Medicine, 2000). Indeed, at low intakes, most of the body stores of vitamin C are contained in such sensitive tissues, including brain, adrenal, and white blood cells. Even a proverbial back-of-the-envelope calculation shows that the majority of other body cells must contain far less than this else the adult body pool would be 8-26 grams (1-3 mM/L in a 70Kg human allowing for extracellular fluid and a molecular weight of ascorbate of 176 g/mol); the total body pool is only about 1,500 mg for people taking RDA levels (Kallner, 1979) or an order of magnitude lower. Thus, the claim of Frei *et al.* that results from these cells are typical and suggest "saturation of all tissues at this dose" is demonstrably inaccurate.

Frei *et al*. assert that the current RDA approach has left 40-50% of people in developed countries severely (<11μM/L) or marginally deficient (<28μM/L), illustrating the failure of the RDA methodology. Specifying a micronutrient based RDA has not provided the population with an

adequate intake. The reviewers provide an account of how such low plasma levels are associated with the major chronic diseases, including cardiovascular disease, stroke, and cancer. However, observations on the benefits of megadose intakes are excluded. Contrary to popular belief, a gram of vitamin C is considered a low dose for both disease prevention and therapy by many experts in the field, such as Linus Pauling who consumed 18 grams per day (Pauling, 1987). The hypotheses that these chronic diseases are a primarily a result of chronic shortage of vitamin C is entirely consistent with the data presented, but is not even mentioned. This is particularly disturbing, as the first author is head of research at the Linus Pauling Institute, an organisation formed to investigate these ideas.

In presenting an author's perspective, it is important to not exclude internationally accepted interpretations, particularly when they present a direct challenge to the authors' hypothesis. This is especially the case when proposing a case for an RDA that is substantially that of the NIH (Levine et al, 1996; 2001), uses controversial NIH data, and the lead author's main source of funding is an NIH organisation. Critically, the essential research to establish an optimal intake has not been performed particularly in respect of claims for chronic vitamin C deficiency being a primary driver of chronic disease. Until we can recognise the limitations of current knowledge it is unwise to set limits on intake.

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