Water-Soluble Vitamins

Vitamin C

Function

The classic disease of vitamin C deficiency is scurvy. This condition is produced by inadequate ascorbic acid, which plays an important role in the hydroxylation of lysine and proline residues in the collagen protein of connective tissue and joints (Jacob 1994). In addition to collagen formation, ascorbic acid has other important biological functions, including copper and iron reduction (which facilitates iron absorption), carnitine biosynthesis, neurotransmitter biosynthesis, reductive protection of folic acid, and reductive regeneration of vitamin E. Much of the current interest in vitamin C is focused on its ability, as a reducing agent, to quench free radicals. All of these effects may promote optimal health through support for the immune system and defense of tissues against the oxidative challenges associated with chronic disease, including cardiovascular disease and cancer (Frei 1991; Niki 1991; Stadtman 1991; Sevanian et al. 1991; Sies and Stahl 1995).

Vitamin C inhibits chemical synthesis of nitrosamines (most of which are animal carcinogens) in gastric contents, but inhibition is not complete until dietary intake reaches about 1,000 mg per day (Tannenbaum et al. 1991; Schorah et al. 1991; Correa 1992; Food and Drug Administration 1993). Ascorbic acid also serves as a reducing agent in mixed-function oxygenase activities for the oxidation of some drugs (Hathcock 1985).

Recommended intakes for vitamin C—90 mg for men and 75 mg for women—are based on pharmacokinetic data. These values include substantial margins above the minimum 10 to 15 mg per day needed to prevent clinically evident scurvy (Food and Nutrition Board 2000). For smokers, the recommended values are increased by an additional 35 mg.

Safety Evidence

Very large doses of vitamin C have been taken daily over the course of many years, and only minor undesirable effects have been attributed with any certainty to the vitamin's use. Owing to a widespread belief that vitamin C may provide a wide range of health benefits and is virtually nontoxic, it is often taken in large quantities (Hathcock and Rader 1990). Clearly, vitamin C has a low order of toxicity, or adverse effects would be common. The most convincing evidence for the safety of high intakes of vitamin C comes from placebo-controlled clinical trials that utilized doses of up to 10,000 mg per day for more than a year, with no

adverse effects reported (Bendich and Langseth 1995). A placebo-controlled clinical trial in 100 cancer patients used doses of 10,000 mg per day for up to 468 days without adverse effect (Moertel et al. 1985).

Although large intakes of ascorbic acid may cause transient gastroenteritis or diarrhea in some individuals, several of the purported adverse effects that have been referred to in books and review articles have little apparent basis in fact. Evaluation of the evidence for and against these effects has shown them to be unsupported in regard to risk from oral consumption (Food and Nutrition Board 2000; Hathcock and Rader 1990).

The hypothesized adverse effects of ascorbic acid are discussed below:

1. **Conditioned scurvy.** This bogus phenomenon has been so widely cited in review articles that it has become conventional wisdom. It is said to result from a conditioning of adults who have had large intakes of vitamin C and of infants whose mothers consumed large amounts during pregnancy, such that blood levels are rapidly depleted to scorbutic levels after discontinuation of ascorbic acid. Detailed review, including bibliographic tracing, does not substantiate any such phenomenon (Food and Nutrition Board 2000). High intake results in accelerated clearance, but this does not result in blood levels that are lower than normal (Schrauzer and Rhead 1973; Tsao and Leung 1988). A paper commonly cited in support of conditioned scurvy in infants whose mothers took vitamin C was speculative, and did not provide data that supported such a relationship (Cochrane 1965). Oral scurvy due to withdrawal from high vitamin C intake was reported in another paper (Siegel et al. 1982), but the diagnosis was not confirmed, the time to onset was suspiciously short, and no plasma vitamin C determinations were made. In summary, conditioned scurvy has not been substantiated, despite very large numbers of people taking vitamin C quantities of a gram or more over the last thirty years.

2. **Oxalate kidney stones.** Reported large increases in urinary oxalate levels following high intakes of vitamin C are an artifact of analysis, owing to oxalate production from ascorbic acid in an analytical procedure that involves heat (Hoffer 1985). More recent reports based on better assay procedures have indicated a small but significant increase in oxalate excretion (still within the normal range) by persons consuming 1,000 mg of ascorbic acid daily (Levine et al. 1996). It is not clear whether this increase of 10 to 15 mg of oxalate excretion per day might be caused by the instability of ascorbic acid in the urine during collection, storage, or analysis. Some reports assert that ascorbic acid is a risk factor for calcium oxalate kidney stones (Urivetzky et al. 1992). Other research involving alternative sample handling procedures found no increase with a different preparation of ascorbic acid at intakes of up to 8 g per day (Fituri et al. 1983). One study found that oxalate production occurred

only in the urine sample *in vitro* with oral ascorbic acid intakes of up to 10 g (Wandzilak et al. 1994). A significant contribution of high ascorbic acid intake to urinary oxalate is not established (Costello 1993), and the association of oxalate kidney stones with higher ascorbic acid intake remains speculative (Gerster 1986). Indeed, the available epidemiological evidence suggests a decreased risk of oxalate kidney stones with increased intake of vitamin C. For example, a prospective epidemiological study found the relative risk of oxalate renal stones to be decreased for men consuming 1,500 mg or more of vitamin C, in comparison with those men consuming less than 250 mg (Curhan et al. 1996). These data provide further support for an earlier retrospective study (Fellstrom et al. 1989) that produced similar results. An authoritative review found no risk of oxalate kidney stones in relation to vitamin C intake (Food and Nutrition Board 2000).

3. **Increased uric acid excretion.** Similar to the increased oxalate concern, it has been theorized that a large increase in urate excretion could increase the risk of urate renal stones. A significant increase in uric acid excretion has been reported with vitamin C intakes at 1,000 mg and higher (Levine et al. 1996). A single dose of 4 g of ascorbic acid has been reported to increase fractional clearance of uric acid (Stein et al. 1976). Five other studies, however, showed no effect of vitamin C intakes of up to 12 g per day on uric acid excretion (Food and Nutrition Board 2000). The clinical effects, if any, of the increased uric acid production have not been identified.

4. **Prooxidant effects, excessive iron absorption, or excessive iron release.** A potential for harm by high intake of ascorbic acid through prooxidant effects has been widely discussed (Herbert 1993; Herbert 1994; Herbert et al. 1996), but an authoritative review discredited such claims (Food and Nutrition Board 2000). Some research (Kondo et al. 1988) has been cited (Herbert et al. 1996) as demonstrating that an ascorbate-driven free radical reaction damages cells. This research, which used *in vitro* studies with phagocytes, found increased release of iron from senescent erythrocytes by the phagocytes only at abnormally high ascorbic acid concentrations. The concentrations used were more than tenfold above the highest plasma ascorbic acid levels of subjects consuming 1,000 mg to 2,500 mg of ascorbic acid per day (Levine et al. 1996). The hypothesis that high intake of ascorbic acid will produce direct prooxidant effects is not consistent with the data on iron release, and contrasts with the antioxidant effects of vitamin C observed under a wide variety of conditions (Frei 1991).

   The concept that the enhancement of iron absorption by ascorbic acid leads to excess iron-related disease has also been suggested (Herbert et al. 1996) based on the iron-heart disease hypothesis (Sullivan 1981; Salonen et al. 1992). This hypothesis, that high iron status produces an increased risk of heart disease, is

not supported by subsequent evidence and evaluation (Sempos et al. 1996; Liao et al. 1994; Aronow 1993; Moore et al. 1995; Baer et al. 1994; Morrison et al. 1994). Ascorbic acid intakes of 2,000 mg per day for two years did not cause excessive iron uptake (Cook et al. 1994). This finding provides additional evidence that high ascorbic acid intake is unlikely to produce any iron-related increase in heart disease. Intakes of up to 10,000 mg per day for up to three years have been evaluated in clinical trials without side effects (Bendich and Langseth 1995). Moreover, endogenous ascorbate prevented, rather than promoted, lipid peroxidation in iron-overloaded plasma (Berger et al. 1997).

5. **Vitamin B_{12} destruction.** The *in vitro* observation of the apparent destruction of vitamin B_{12} by ascorbic acid (Herbert and Jacob 1974) has been erroneously interpreted as an adverse effect of vitamin C. Vitamin C intakes of up to 4 g per day have no effect on vitamin B_{12} status (Afroz et al. 1975; Ekvall et al. 1981). A major review found no evidence that vitamin B_{12} antagonism is a credible adverse effect of vitamin C (Food and Nutrition Board 2000).

6. **Erosion of dental enamel.** Chewable vitamin C tablets, used daily, have been reported to lead to severe erosion of dental enamel because of the acidity and abrasiveness of these products (Guinta 1983), but the practical clinical significance of this effect has not been established. The dental enamel erosion is brought about by the high acidity of ascorbic acid (pH of 2.8); therefore, if chewable tablets of vitamin C are properly formulated to a pH of approximately 4 to 5 using sodium ascorbate or another buffering agent, erosion of dental enamel should not be a problem. Chewable vitamin C should not be formulated and marketed without a buffering formulation. As marketed in the U.S., millions of consumers use chewable vitamin C without dental problems.

7. **Gastrointestinal distress.** The only concretely documented adverse effects of high vitamin C intake are gastrointestinal symptoms such as nausea, abdominal cramps, and diarrhea of osmotic origin (Miller and Hayes 1982). When these effects occur, the vitamin C dosage is usually 3,000 mg per day or higher, taken at once; but a few individuals respond at single doses as low as 1,000 mg. This effect results from a direct osmotic effect of unabsorbed ascorbic acid and can usually be avoided by taking the vitamin as a buffered salt rather than as a free acid. The symptoms usually disappear within a week or two with no further consequences.

Published Official Reviews of Vitamin C Safety

The FNB found no credible reports of adverse effects other than gastrointestinal distress related to irritation and osmotic diarrhea from large doses (Food and Nutrition Board 2000). For these effects, FNB identified a LOAEL of 3,000 mg per day and because of the mild and transient nature of the effects, selected a UF of 1.5, thus deriving a UL of 2,000 mg per day.

The UK EVM also found no credible reports of adverse effects other than mild gastrointestinal distress and diarrhea (Expert Group on Vitamins and Minerals 2003). That body elected to apply a standard toxicological default uncertainty factor of 3, setting a GL at 1,000 mg per day.

CRN ULS for Vitamin C

Vitamin C has an extremely low potential for toxicity. Despite decades of widespread use at multigram levels, the only established adverse effects are gastrointestinal impacts such as irritation, bloating, and diarrhea. These effects are usually mild, transient, and self-limiting through discontinuation or lowering of the adverse dosage.

CRN recognizes that very high intake of vitamin C can cause diarrhea and related gastrointestinal adverse effects and concludes that these are a sufficient basis to set a ULS. CRN also identifies a LOAEL of approximately 3,000 mg. Given the mild, transient, and self-correcting nature of the adverse effects, CRN considers a UF of 1.5, as identified by FNB, to be ample. The FNB and UK EVM set their UL in relation to total daily intake, but neither considered in detail whether the UL could be higher if the intake were evenly spread out over a day or whether it should be lower for a single dose. CRN identifies a ULS of 2,000 mg per day, but recommends limiting any single dose to 1,000 mg, in order to ensure avoidance of undesirable gastrointestinal effects.

Comparison of Safety Values for Vitamin C

CRN ULS	2,000 mg (1,000 mg per single dose)
US FNB UL	2,000 mg
EFSA* UL	Reviewed but not established (1,000 mg as guidance)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	1,000 mg

* EFSA (European Food Safety Authority) assumed this assessment function in place of EC SCF in January 2004

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