

# The Safety of the Vitamins: An Overview

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On the basis of the reviewed information it is considered that the vitamins can be divided into two broad categories (Table 1).

- a) Those with a safety level at least 50—100 times the RDA and no clear indication of serious adverse reactions above that level. This level should be adequate to match any required pharmacological dose, and these vitamins should be regarded as safe for elevated dose use, not necessarily controlled by doctors.
- b) Those with a safety ratio of about 10 times, often influenced by the health status of the individual or those with serious irreversible adverse reactions. These vitamins (retinoid, calciferol, pyridoxine) can be used safely at an RDA level but should only be administered at higher dosage under medical supervision to avoid dose escalation.

	Safe for non-medical use	Safe at RDA, therapeutic use under medical control
Water soluble	Thiamine Niacin Riboflavin Pantothenic acid Biotin Folic acid Cobalamins Ascorbic acid	Pyridoxine
Fat soluble	Tocopherols	Retinol Calciferols Phylloquinone

Table 1: Categorisation of the safety of the vitamins. For details of the reasoning see the text.

The early definition of a vitamin was relatively clear (Marks, 1985): a natural, organic substance essential for normal cellular function and absorbed from the food. But as more has been learned about the nature, function, and source of some of these substances, it has become clear that some could better be termed prohormones (e.g., calciferol), and that for others most of the requirement can be met other than through food intake (e.g., ergocalciferol, phylloquinone). And other essential dietary items required in only relatively small amounts have not been designated vitamins. For this review the pragmatic approach has been adopted, by including those substances that have traditionally been classified as vitamins by the majority of nutritionists.

From the above it follows that at levels of intake approximately equivalent to those found each day in a good mixed diet, vitamins are beneficial and with only very rare exceptions (e.g., vitamin D in sarcoidosis) show no adverse reactions. Hence, in reviewing the safety of the vitamins, we are not primarily concerned with dietary levels of intake but with high dosage. These have been called variously, therapeutic, pharmacolog-

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ical, or megadoses. I shall not deal with the rationale of the use of these doses; others at this symposium will do so. In this review I accept that they are used in this way and therefore consider the safety implications of such use.

### **Factors Influencing Safety**

We can divide the considerations of safety of any ingested substance according to the following aspects:

- a) *The number of doses to be given and the time interval between doses.* With only very rare exceptions (e.g., phylloquinone), the vitamins are usually given for therapeutic purposes on a daily basis for many days or weeks. It is indeed rare to find a vitamin that is toxic after a single dose, the only real examples lying in some of the fat-soluble vitamins in which steady release from large tissue stores after a single dose may give rise to toxic manifestations. Accordingly, I have given maximum consideration to the safe daily level for chronic administration.
- b) *The mode of administration.* Administration of the vitamins by the parenteral route is unusual in most countries. Such a route may involve additional toxicity, for it may bypass intestinal absorption dynamics and avoid liver first-pass metabolism, while the development of a parenteral formulation may feature adverse reactions to excipients rather than to the vitamin. Accordingly, I am mainly concerned with the oral route of administration, but refer as necessary to other routes for specific vitamins.
- c) *The health of person.* The main physiological factors influencing safety are pregnancy, youth and old age, and I refer to these where appropriate. The present review is concerned largely with safety in adults. Pathology may also considerably affect vitamin safety. I have commented on the influence of disease states where they adversely affect safety. On the other hand, disorders leading to increased safety (e.g., malabsorption syndromes) have been largely ignored.
- d) *Interference by food or drugs.* Almost without exception, such interactions reduce the toxicity rather than increase it and hence have been largely ignored.

### **Methods for Determining a Safe Level**

The accent in this review is on a safe level and not on the adverse effects. Accordingly, I have attempted to determine the safe level for each of the vitamins by a) A literature search, broadly of the world literature from the 1950s onwards. Clearly the level at which side effects arise depends upon the definition accepted for "adverse effects"—and the credence accorded to individual anecdotal reports. The policy I have adopted is to ignore mild or temporary side effects that are characteristic of a nuisance rather than a danger. This is particularly true for side effect. That are clearly predictable on the basis of the pharmacological effects (e.g., flushing from nicotinic acid). On the other hand, I have tended to be overcautious about accepting anecdotal evidence of more serious effects without full proof of a causal relationship.

- b) Evidence of chronic administration of the vitamin for a sufficient period for a low toxicity to have a chance of appearing and at a level at least as high as the safety margin which is quoted. For most of the vitamins the level of administration is high enough to define a reliable safety margin, for a few, high doses have not been given, or given for too short a time, and it has been necessary to define a safe level which is probably below that which might justifiably be claimed (e.g., folic acid).

### **Expressing the Safety Margin**

Since the basis of my appraisal has been chronic daily administration, I have felt that the best method by which the safety margin could be expressed was a ratio of the RDA. For this purpose I have taken the United States RDA for adult males as the basis. The US value is probably more widely accepted internationally than any other figure and has been revised more recently than most, though a further revision is now long overdue.

### **Individual Vitamins**

In this review, emphasis has been put on the key references relating to the individual vitamins. A recent monograph (Marks, 1986) details the individual papers.

### *Water-Soluble Vitamins*

It is relevant to note that the ad hoc committee of the National Nutritional Consortium of the USA which considered vitamin toxicity in 1979 (Fed. Reg., 1979) noted that thiamine, riboflavin, niacin, biotin, pantothenic acid, pyridoxine, and cyanocobalamin possessed "such low toxicity" that they were not reviewed. A current similar review would probably consider one or two (but not more) worthy of consideration. Hence, it is clear that views on safety may change as new information becomes available.

### Ascorbic Acid

With the very extensive use made of ascorbic acid in therapy and the food trade, it is scarcely surprising that the level for safety has been the subject of extensive review over the past few years (Korner & Weber, 1972; Barness, 1977; Hornig & Moser, 1981). A large number of adverse reactions have been alleged to occur with the use of large doses of ascorbic acid, but almost without exception further study has demonstrated that the allegations are without foundation, viz.:

- that oxalate stones can occur: The conversion of ascorbic acid to oxalate does not reach critical levels even at an ascorbic acid intake of 10 g per day (Schmidt et al., 1981) in normal persons; however, caution should be exercised when there is severe renal insufficiency (Pru et al., 1985).
- that it could lead to cyanocobalamin depletion: This finding resulted from a faulty extraction method for cyanocobalamin (Herbert & Jacob, 1974; Ekvall et al., 1981).

- that rebound ascorbic acid depletion could occur: not confirmed in reliable studies (Hornig & Moser, 1981).
- that it is mutagenic: This has not been confirmed when physiological conditions are applied (Norkus et al., 1983).
- that it decreases immunological tolerance: not confirmed (Prinz et al., 1977).
- that it causes a dangerous elevation of iron absorption: In normal persons this is not true, but in disorders associated with enhanced iron absorption, high doses of ascorbic acid are contraindicated (Nienhuis, 1981), although the evidence for a significant further undesirable uptake is not very convincing.

Some of the other alleged problems (e.g., glucose, uric acid, occult blood analysis) are directly attributable to the chemical reactivity of ascorbic acid.

An overview of all the information shows that the safe daily level is at least 100 times the RDA.

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