

Part 2: Vitamins

Fat-soluble vitamins and beta-carotene

Vitamin A (Retinol and Its Esters)

Function

Vitamin A has essential impacts on areas of health that include vision, cellular differentiation, organ development during embryonic and fetal development, and membrane structure and function. In regard to eye health and function, the vitamin plays at least two distinct roles: (1) as a retinal-opsin complex that serves as a phototransducer, and (2) in the health and function of the various eye membranes. In the first case, deficiency of vitamin A in the retina leads to night blindness. In the second, deficiency can lead to xerophthalmia, with a loss of the basic integrity of the eye structure and possible total blindness. Several other complex physiological processes, including growth, reproduction and immune system functions, also depend on vitamin A (Ross 1999). Vitamin A deficiency is the foremost cause of preventable blindness in the world.

Valid and Safe Uses of High-Dose Vitamin A in Nutritionally Deprived Populations

In some countries where widespread, endemic vitamin A deficiency results in large-scale occurrence of health problems—especially blindness related to xerosis and xerophthalmia—and mortality, current public health programs and medical practice include the administration, once every three to twelve months, of 15 to 60 mg (50,000 to 200,000 IU) or more of vitamin A as retinyl esters to children for the treatment and prevention of vitamin A deficiency (IVACG 1984; Ross 1999). Even though the dosage (which varies according to the age of the child) appears high, it must be noted that this is not a daily dose but rather a periodic dose, administered to a target population with very depleted liver stores of vitamin A and a large unused storage capacity. Such extremely high intakes of vitamin A are not tolerated on a daily basis or in populations that are nutritionally replete.

Safety Evidence

Vitamin A is fat-soluble and readily accumulates in the liver. Its absorption is not linear, but is dependent on the vitamin A status of the individual. At very high intakes, the vitamin can accumulate in the liver and other tissues. Thus, both the daily level of intake and the duration of consumption at that level are important influences on the safety of vitamin A.

The potential for adverse effects from excessive vitamin A intake is well documented. Potential risk is based on the ingestion of excessive amounts of preformed vitamin A in the forms of retinol or retinyl esters, but not from provitamin A forms such as beta-carotene or other provitamin A carotenoids. There are no examples of vitamin A toxicity resulting from high intake of beta-carotene or other carotenoids. The safety of beta-carotene itself is a separate question and will be addressed in the section on that nutrient.

Liver abnormalities Because liver is the principal storage site for excess vitamin A, a causal relationship between very high intake and liver toxicity is well established in both animals and humans. The adverse effects can include reversibly elevated liver enzymes as well as other conditions with greater persistence, such as fibrosis, cirrhosis, and even death (Food and Nutrition Board 2001). The human data, however, are often confounded by other factors such as alcohol intake, infectious hepatitis, hepatotoxic drugs, and preexisting liver disease. Consumption of 7,500 to 15,000 µg RE (25,000 to 50,000 IU) of preformed retinol equivalents per day for periods of several months or more can produce multiple adverse effects, including liver toxicity (Hathcock et al. 1990), but the effects in this intake range may be dependent on compromised liver health or function. A supplemental intake of approximately 7,500 µg RE (25,000 IU) is the lowest dose at which such effect can be confidently attributed to vitamin A in persons with mildly or moderately compromised liver health (Geubel et al. 1991).

Birth Defects The smallest daily vitamin A supplement generally considered to generate any risk of birth defects is also 7,500 µg RE (25,000 IU) (Hathcock et al. 1990); this amount may be considered to be the LOAEL. One report, however, by Rothman et al. (1995) concluded that there was a significantly increased risk of neural crest birth defects at maternal daily supplemental levels of “more than 10,000 IU” (i.e., more than 3,000 µg RE). The average supplemental intake by these women was actually 6,500 µg RE (21,675 IU), but the authors did not identify individual supplemental intakes in the seven cases involving birth defects. All seven cases involved intakes at levels greater than 10,000 IU, but how much greater is not known. Several issues have been raised about the validity of the defect classification scheme used and the resulting likelihood that the study overestimated the risk associated with vitamin A at the levels identified in this study (Oakley and Erickson 1995; Werler et al. 1996; Shaw et al. 1996). The finding by Rothman and colleagues was not confirmed by a more recent study (Lammer et al. 1996).

A few reports suggest the possibility that there may be some risk of vitamin A toxicity at supplementation levels below 6,000 µg RE (20,000 IU) per day. One report to the FDA suggested a characteristic birth defect in association with maternal supplementation at 5,400 µg RE (18,000 IU) per day (Rosa et al. 1986).

Another report found marginal indications in elderly subjects of adverse effects on the liver with chronic supplementation at levels of 1,500 to 3,000 µg RE (5,000 to 10,000 IU) per day (Krasinski et al. 1989). This observation has not been confirmed (Stauber et al. 1991), and the same laboratory was unable to repeat this finding in later research (Johnson et al. 1992). No other reports have indicated adverse effects from vitamin A at these supplemental levels.

Based on the available data, FNB identified a NOAEL of 4,500 µg per day (15,000 IU) and applied an uncertainty factor of 1.5 to arrive at a UL of 3,000 µg (10,000 IU), based on possible birth defects as the critical safety issue.

Bone fragility Some recent reports have suggested that relatively low intakes of preformed vitamin A (that is, retinol and retinyl esters) could increase bone fragility and risk of hip fracture, but other relevant studies do not support such an effect.

In January 2001, FNB released its review of vitamin A and other micronutrients. In assessing the safety of vitamin A, FNB considered possible adverse effects in relation to bone mineral density and hip fracture, concluding that the studies are “provocative but conflicting, and therefore they are not useful for setting a UL for vitamin A.”

The evidence that FNB reviewed relating vitamin A to potential adverse effects on bone included animal studies, human mechanistic studies, and epidemiological evidence. Animal and human biochemical data indicate a mechanism for possible adverse effects of retinol on bones, but this research does not establish the occurrence of these effects in humans consuming practical levels of vitamin A. A new, single-dose clinical trial by Melhus and coworkers (Johansson and Melhus 2001) confirms the mechanistic effect in humans—but with a single dose of over 27,000 IU of retinol (as 15 mg of retinyl palmitate). This clinical study confirms and refines previous knowledge about interactions of vitamin A and vitamin D.

At the time of the FNB review, the only epidemiological study suggesting an adverse relation between high levels of vitamin A intake and bone health was the 1998 Swedish population study by Melhus and coworkers (Melhus et al. 1998). Melhus and coworkers interpreted those data as showing a significant increase in the risk of hip fracture when retinol intakes reached 1.5 mg (5,000 IU) per day. Other epidemiological studies available at that time, including those by Freudenheim and coworkers (Freudenheim et al. 1986), and Houtkooper and coworkers (Houtkooper et al. 1995), found no such relationship with retinol intakes of up to 2.0 mg (6,600 IU) per day.

A recent study from the National Health and Nutrition Examination Survey (NHANES III) by Ballew and coworkers (Ballew et al. 2001) examined but could

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not detect any relationship between plasma retinyl esters and bone density. Plasma retinyl esters are good indicators of excessive vitamin A intake, and bone density is an excellent indicator of the resistance of bones to fracturing. The NHANES III study is a large survey of a cross section of the entire U.S. population. A new, small epidemiological study in Iceland agrees with the NHANES III data in finding no relationship between vitamin A and bone density (Sigurdsson et al. 2001).

The recent publication of results from the Nurses' Health Study (NHS) (Feskanich et al. 2002) measured the risk of hip fracture in comparison with vitamin A intakes estimated from food frequency recalls. This NHS study reported a significantly below-average rate of hip fracture in this cohort of postmenopausal women (who were younger than the median age for postmenopausal women) but reported a relationship between vitamin A intake and risk of hip fracture.

A recent observational study of serum retinol concentrations and bone fractures supports a relationship between retinol and increased health risk, especially for fracture of the hip (Michaelsson et al. 2003). The level of dietary intake associated with the increased risk is not apparent from this study. The ability of retinol to induce the resorption of bone may be ameliorated by adequate intake of vitamin D (Boucher 2003).

Considering the totality of available evidence, CRN believes that the overall database remains at least as conflicted and unresolved as it was at the time FNB reached its conclusion in 2001. If anything, the preponderance of evidence may have moved away from the suggestion that vitamin A might increase the risk of hip fracture. Thus, the bone fragility evidence is not used as the basis for CRN's conclusions on vitamin A safety.

Published Official Reviews of Vitamin A Safety

The FNB concluded that a suitable UL in relation to birth defect risk is 3,000 µg per day (Food and Nutrition Board 2001). Additionally, FNB evaluated the evidence for vitamin A increasing bone fragility and concluded that those data were insufficient to serve as the basis for a UL value.

The EC SCF concluded that while evidence of possible increased risk of bone fragility is not compelling, that of the risk of birth defects is convincing (Scientific Committee on Food 2002). Thus, EC SCF identified a UL for total intake of 3,000 µg of retinol.

The UK EVM concluded (Expert Group on Vitamins and Minerals 2003) that retinol intakes of 3,000 µg are not teratogenic, but that intakes greater than 1,500

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µg may increase bone fragility. The UK EVM found no threshold for the bone fragility effects and set 1,500 µg as a GL rather than as an SUL.

CRN ULS for Vitamin A (Retinol and Its Esters)

CRN considers supplements of 3,000 µg (10,000 IU) of preformed retinol to be safe for most people, as judged on the following basis:

- The LOAEL for birth defects is at least 7,500 µg (25,000 IU) of retinol, and there are no credible data to suggest that it is likely to be lower than 6,500 µg (21,675 IU).
- The FNB selected a retinol NOAEL of 4,500 µg (15,000 IU), but conservatively applied a UF of 1.5 to derive a UL of 3,000 µg (10,000 IU).
- The intake of retinol and retinyl esters from sources other than supplements is likely to be less than 1,014 µg (3,400 IU) (Feskanich et al. 2002).
- There is a long history of safe use of dietary supplements containing 5,000 IU, 8,000 IU and 10,000 IU.
- The FNB NOAEL equivalent to 15,000 IU and the highest likely intake of 3,400 IU from sources other than supplements are compatible with ULS of 3,000 µg (10,000 IU).
- The possible effects of retinol on bone fragility are based on epidemiological evidence and remain speculative and unconfirmed.
- Persons with likely high intakes of retinol, for example those who regularly consume liver or other organ meats, should not consume supplements that contain preformed vitamin A, but may safely consume vitamin A as beta-carotene.
- A large number of companies are voluntarily decreasing the amount of retinol in multivitamin products to 1,500 µg RE (5,000 IU) or less to avoid concerns about bone fragility.

CRN considers that its current policy position of limiting vitamin A products to 3,000 µg (10,000 IU) is fully justified by the totality of currently available scientific evidence.

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Comparison of Safety Values for vitamin A (retinol and its esters)	
CRN ULS	
Low consumers of fortified foods and liver	3,000 µg (10,000 IU)
High consumers of fortified foods and liver	1,500 µg (5,000 IU)
US FNB UL	3,000 µg (10,000 IU)
EC SCF UL	3,000 µg (10,000 IU)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	1,500 µg

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