Vitamin A

Introduction

Vitamin A has essential actions in areas of health that include vision, cellular differentiation, organ development during embryonic and fetal growth, and membrane structure and function. Several other complex physiological processes, including growth, reproduction, and immune system functions, also depend on vitamin A (Ross 1999).

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 maintenance 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. Vitamin A deficiency is the foremost cause of preventable blindness in the world.

Safety Considerations

Vitamin A is fat-soluble and readily accumulates in the liver. Therefore, if taken at high dosages on a daily basis, the vitamin can easily accumulate to dangerous levels in the liver and other tissues. However, in nutritionally deprived populations who do not have a steady, sufficient intake of vitamin A, the same high dosages may be necessary as occasional supplements in order to prevent the severe health consequences of vitamin A deficiency. This makes the safety of vitamin A highly dependent on both the daily level of intake and the duration of consumption. The vitamin A status of the populations under study is critical to conclusions about safety, and nutritionally replete and nutritionally deficient populations must be considered separately.

The potential for adverse effects from excessive vitamin A intake in nutritionally replete populations is well documented. Conceivable risk is based on the ingestion of large amounts of preformed vitamin A in the form of retinol or retinyl esters, but not from provitamin A varieties

such as beta-carotene or other provitamin A carotenoids. There are no examples of vitamin A toxicity resulting from high intakes 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.) Vitamin A is listed on food and dietary supplement labels in international units (IU), while nutrition scientists commonly use mg or µg retinol activity equivalents (RAEs). The conversion rate between an IU and RAE are 1 IU retinol = 0.3 µg RAE. The following sections discuss the possible adverse effects of preformed vitamin A.

Liver Abnormalities

Because the liver is the principal storage site for excess vitamin A, a causal relationship between very high intakes 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 (Institute of Medicine [IOM] 2001). The human data, however, are often confounded by other factors such as alcohol intake, infectious hepatitis, hepatotoxic drugs, and pre-existing liver disease. Consumption of 25,000 to 50,000 IU of preformed vitamin A 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 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 supplement generally considered to generate any risk of birth defects is also 25,000 IU (Hathcock et al. 1990); this amount may be considered to be the LOAEL. A report 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," but how much more was not stated. The report findings are complicated by the fact that, although the average supplemental intake by these women was 21,675 IU, 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; Shaw et al. 1996; Werler et al. 1996). The finding by Rothman et al. 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 20,000 IU per day. One report to the FDA suggested a characteristic birth defect in association with maternal supplementation at 18,000 IU per day (Rosa et al. 1986). Another report found marginal indications of adverse effects on the liver in elderly subjects with chronic supplementation at levels of 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). Results of a trial in nonpregnant women documented that daily oral vitamin A supplements of 4,000, 10,000 and 30,000 IU given for 3 weeks were in the range of endogenous plasma levels of vitamin metabolites that are seen in women in early stages of pregnancy (during organogenesis). Therefore, a dose of 30,000 IU per day "should be considered as non-teratogenic in [humans]" (Wiegand et al. 1998). No other reports have indicated adverse effects from vitamin A at these supplemental levels.

Bone Fragility

Recent reports are conflicted on the issue of vitamin A's effect on bone fragility. Some 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. Other studies do not support such an effect.

In January 2001, the IOM released its review of vitamin A and other micronutrients. In assessing the safety of vitamin A, the IOM 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 the IOM 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 single-dose clinical trial by 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 IOM 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 5,000 IU per day. Other epidemiological studies available at that time, including those by Freudenheim et al. (1986) and Houtkooper et al. (1995), found no such relationship with retinol intakes of up to 6,600 IU per day.

A study from the National Health and Nutrition Examination Survey (NHANES III) by Ballew et al. (2001) examined, but could 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 small epidemiological study in Iceland also found no relationship between vitamin A and bone density (Sigurdsson et al. 2001).

The 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. In addition to the recognized inherent limitations of observational research, the NHS study reported a significantly below-average rate of total hip fracture in all postmenopausal women studied; results were limited to self-reported hip fractures with no event adjudication or identification of exact fracture site. Furthermore, multiple observations of this specific

population over time initially led to statistical associations of milk and calcium with increased risk of hip fracture, but these apparently erroneous implications disappeared with continued collection of data.

An observational study of serum retinol concentrations and bone fractures supports a relationship between retinol and increased health risk, especially for fractures 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).

Vitamin A in Nutritionally Deprived Populations

In some countries where widespread, endemic vitamin A deficiency results in large-scale occurrence of health defects—especially blindness related to xerosis and xerophthalmia—and mortality. In response, current public health programs and medical practice include the administration, once every 3 to 12 months, of 50,000 to 200,000 IU or more vitamin A as retinyl esters to children for the treatment and prevention of vitamin A deficiency (International Vitamin A Consultative Group [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 depleted liver stores of vitamin A and a large unused storage capacity. Such extremely high intakes of vitamin A would not be tolerated in populations that are nutritionally replete but are essential in populations with chronic vitamin A deficiency.

Official Reviews

IOM (2001). Based on the available data, the IOM identified a NOAEL of 15,000 IU per day and applied a UF of 1.5 to arrive at a UL of 10,000 IU per day, based on possible birth defects as the critical safety issue. The IOM 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.

European Commission's Scientific Committee on Food (EC SCF 2002). The EC SCF identified a UL of 10,000 IU of retinol per day. Like the IOM, the EC SCF based its recommendation on the risk of birth defects only, as evidence of increased risk of bone fragility is not compelling.

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM concluded that retinol intakes of 10,000 IU per day are not teratogenic but that intakes greater than 5,000 IU per day may increase bone fragility. It found no threshold for the bone fragility effects and set 5,000 IU per day as a guidance level rather than as an SUL.

CRN Recommendations

CRN considers supplements of 10,000 IU per day of preformed retinol to be safe for most people. As stated earlier, the recommendations for nutritionally replete populations must be considered separately from nutritionally deprived populations. In addition, even within nutritionally replete populations, intake from food sources can vary widely. Therefore, for people who consume high levels of vitamin-A-fortified foods or liver, a lower limit of 5,000 IU per day is recommended.

The CRN recommendations are based on evidence of birth defects risks at higher levels. The evidence for bone fragility has been conflicted, and recent studies indicate, if anything, that the preponderance of evidence may have moved away from the suggestion that vitamin A might increase the risk of hip fracture. Therefore, bone fragility is not used as a factor in CRN's recommendations.

The CRN recommendations are based on the following considerations as well:

- The LOAEL for birth defects is at least 25,000 IU of retinol per day, and there are no credible data to suggest that it is likely to be lower than 21,675 IU per day.
- The IOM selected a retinol NOAEL of 15,000 IU per day, but conservatively applied an uncertainty factor of 1.5 to derive a UL of 10,000 IU per day.

- The intake of retinol and retinyl esters from sources other than supplements is likely to be less than 3,400 IU per day (Feskanich et al. 2002).
- There is a long history of safe use of dietary supplements containing 5,000, 8,000, and 10,000 IU per day.
- The IOM NOAEL equivalent to 15,000 IU per day and the highest likely intake of 3,400 IU per day from sources other than supplements are compatible with the CRN UL of 10,000 IU per day.
- Persons with likely high intakes of retinol (e.g., those who regularly consume liver or other organ meats) should not consume supplements that contain preformed vitamin A; they may, however, safely consume vitamin A as beta-carotene.
- Some companies limit the amount of retinol in multivitamin products to 5,000 IU per day or less to avoid possible concerns about bone fragility.

Quantitative Summary for Vitamin A

CRN UL, supplemental intake	
Low consumers of fortified foods and liver	10,000 IU (3,000 µg RAE)/day
High consumers of fortified foods and liver	5,000 IU (1,500 µg RAE)/day
IOM UL, total intake	10,000 IU (3,000 µg RAE)/day
EC SCF UL, total intake	10,000 IU (3,000 µg RAE)/day
EC supplement maximum	Not determined
EVM, guidance level, total intake	5,000 IU (1,500 µg RAE)/day

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