Safety of vitamin A[1,2]

Adrianne Bendich and Lillian Langseth

ABSTRACT Vitamin A adequacy is discussed in terms of the recommended allowances appropriate for the needs of the majority of individuals. Deficiency can result in xerophthalmia and permanent blindness and in increased mortality rates among children. Toxicity has been associated with the overconsumption of vitamin A supplements. Acute hypervitaminosis A may occur after ingestion of ≥ 500 000 IU (over 100 times the RDA) by adults or proportionately less by children. Symptoms are usually reversible on cessation of overdosing. Factors influencing chronic hypervitaminosis A include dosing regimen, physical form of the vitamin, general health status, dietary factors such as ethanol and protein intake, and interactions with vitamins C, D, E, and K. Both excess and deficiency of vitamin A in pregnant animals was shown to be teratogenic. In humans, congenital malformations associated with maternal overuse of high doses of vitamin A were reported but no cause-and-effect relationship has been established. Deficiency of the vitamin during pregnancy has also been associated with congenital abnormalities. Reported incidences of vitamin A toxicity are rare and have averaged fewer than 10 cases per year from 1976 to 1987. *Am J Clin Nutr* 1989;49:358–71.

KEY WORDS Vitamin A, vitamin deficiency, hypervitaminosis A, toxicity, birth defects

Introduction

Vitamin A is an essential nutrient for humans because it cannot be synthesized de novo within the body. It is provided by the diet in two forms: preformed vitamin A, found naturally only in animal products; and carotenoid vitamin A precursors (provitamin A), found primarily in foods of plant origin.

The term *vitamin A* is used generically for all β-ionone derivatives (other than carotenoids) that have the biological activity of all-*trans* retinol. Forms of vitamin A include retinol, retinal (also called retinaldehyde), and various retinyl esters (1). Retinoic acid can perform some but not all of the biological functions of vitamin A. The focus of this report will be the safety of oral intake of naturally occurring compounds with vitamin A activity. In this regard, many of the levels of vitamin A cited in this paper have been given in IU rather than retinol equivalents. In many instances the authors of the original papers did not indicate the vitamin A ester consumed by their subjects. Thus, it would not be accurate to calculate retinol equivalents or milligrams of retinol based solely upon information given in IU.

Vitamin A function and metabolism

Vitamin A is necessary for vision, reproduction, the integrity of membrane structures, the normal functioning of body cells, growth, and development.

Storage

Vitamin A, a fat-soluble vitamin, is stored in the body to a much greater extent than the water-soluble vitamins. The storage capacity of the human body for this vitamin is generally large enough to satisfy the normal requirement for 1–2 y (2). The vitamin is stored primarily in the liver: > 90% of total body stores are found in this organ (3).

Transport

Vitamin A is normally transported in plasma bound to a specific transport protein called retinol-binding protein (RBP). The vitamin is mobilized from the liver and delivered to the tissues in the form of the retinol-RBP complex. The mobilization and delivery of retinol are controlled in part by processes that regulate the rates of synthesis and secretion of RBP by the liver (4).

Formation from carotenoids

Carotenoid precursors are converted to vitamin A mainly in the small intestine during absorption. The rate of conversion is relatively slow and the efficiency of ca-

[1] From the Department of Clinical Nutrition, Hoffmann-La Roche Inc, Nutley, NJ and the Nutrition Research Newsletter, Palisades, NY.
[2] Address reprint requests to A Bendich, Hoffmann-La Roche Inc, 76/412-N, 340 Kingsland Street, Nutley, NJ 07110-1199.
Received September 21, 1987.
Accepted for publication March 15, 1988.

Am J Clin Nutr 1989;49:358–71. Printed in USA.

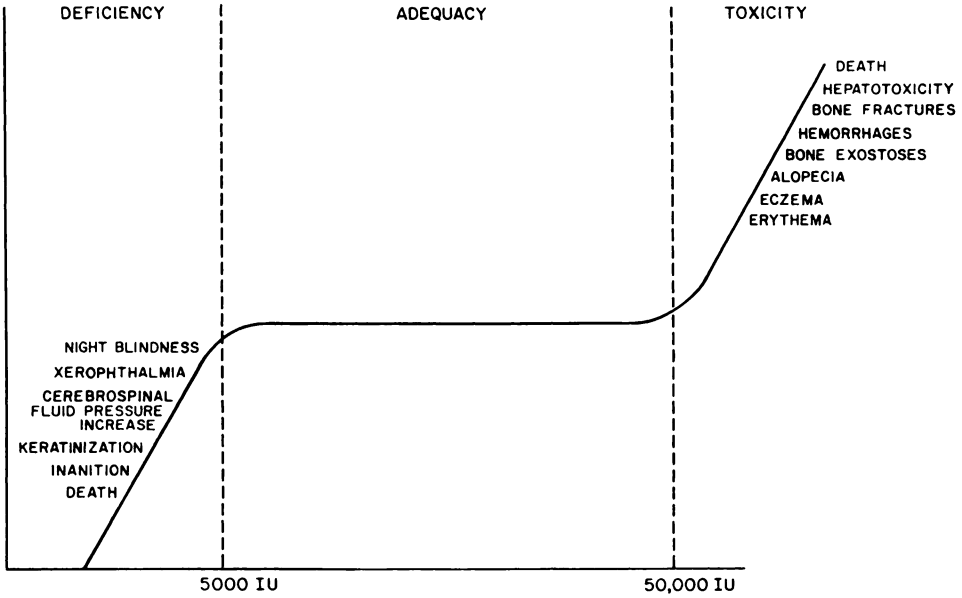

FIG 1. Range of vitamin A intake for adults. Adapted from reference 8.

rotenoid absorption in the intestine decreases as carotenoid intake increases (5). The efficiency of carotenoid conversion varies among individuals (3). There are more than 400 known carotenoids but only an estimated 50–60 of these have provitamin A activity. β-Carotene has the greatest provitamin A activity of all known carotenoids. Other carotenoids with provitamin A activity include α-carotene, γ-carotene, and cryptoxanthin (6). The conversion of β-carotene to vitamin A is regulated so that excess vitamin A is not absorbed from carotene sources (7).

Vitamin A deficiency

In humans the most obvious and clinically important manifestation of vitamin A deficiency is the eye disease xerophthalmia, which can lead to permanent blindness (**Fig 1**) (8). The early stages of xerophthalmia, including the characteristic symptom of night blindness, are reversible but the condition becomes irreversible upon ulceration of the eye tissue (5). The clinical aspects were recently reviewed by Wittpenn and Sommer (9).

Deficiency in industrially underdeveloped countries

Vitamin A deficiency is a major public health problem particularly in industrially underdeveloped countries. Worldwide it is the second most prevalent nutritional disease after protein-calorie malnutrition. Vitamin A deficiency is especially common in tropical and subtropical regions (10). Each year an estimated 1–5 million people throughout the world, usually infants and preschool children, develop vitamin A deficiency and 100 000–250 000 become permanently blind (11).

The deficiency of vitamin A has also been identified as a major killer of children in developing countries. Children suffering from this deficiency were found to have substantially increased overall morbidity and mortality rates, mainly from increased rates of respiratory disease and diarrhea (12). Recently, supplementation was shown to decrease mortality and morbidity associated with measles infections in marginally vitamin A-deficient children (13).

Administration in underdeveloped countries

In industrially underdeveloped countries where regular supplementation is generally impractical, high supplementary oral doses of vitamin A are given to children two to four times yearly preferably spaced at even intervals. In these instances each dose would be 100 000 IU for infants aged < 1 y and 200 000 IU for children aged > 1 y. This type of vitamin A supplementation is of great benefit in preventing vitamin A-deficiency blindness and reducing mortality in children (11). Intermittent supplementation of this kind occasionally produces transient symptoms of hypervitaminosis A in susceptible individuals; however, this is medically acceptable under such circumstances because there are no serious or long-lasting effects (14). Other prophylactic intervention measures are vitamin A fortification of food and increased consumption of fruits and yellow and green vegetables.

Deficiency in industrially developed countries

The habitual vitamin A intake of most people in North America and Western Europe is sufficient to result in a rise in liver vitamin A concentrations with each decade of life (15). Nevertheless, some individuals are deficient in vitamin A and the problem may go unrecognized. In two major nutrition surveys—the First Health and Nutrition Examination Survey (NHANES I, 1971–74) (16) and the US Department of Agriculture (USDA) Nation-

TABLE 1
IU and RE equivalents

1 IU	= 0.3 μg preformed retinol
	= 0.6 μg β-carotene
	= 1.2 μg other mixed carotenoids
1 RE	= 1.0 μg retinol
	= 6.0 μg β-carotene
	= 12 μg other mixed carotenoids
	= 3.3 IU activity from retinol
	= 10 IU activity from β-carotene

wide Food Consumption Survey (1977–78) (17)—vitamin A was found to be a problem nutrient, ie, one in which ≥ 20% of the population surveyed was obtaining < 70% of the Recommended Dietary Allowance (18) (RDA). These data were confirmed more recently in NHANES II data, which were extended to include black and Hispanic populations (10). It is obvious, therefore, that a significant proportion of the US population is receiving lower than recommended levels of vitamin A.

Vitamin A adequacy

Vitamin A adequacy is usually discussed in terms of recommended allowances designed to meet or exceed the needs of the majority of individuals. Adequacy is based on maintenance of the normal range of vitamin A in serum or plasma (0.70–2.79 μmol/L).

Vitamin A in expressed either as international units (IU) or retinol equivalents (RE). In the United States the RDA for vitamin A is now given in RE (18). Because food composition tables still employ the more widely used IU, however, this unit is still used in applied nutrition. **Table 1** shows the IU and RE equivalents. To evaluate diets, the following formula is applicable:

$$\text{RE} = \mu\text{g retinol} + \mu\text{g } \beta\text{-carotene} \times 0.167 + \mu\text{g other mixed carotenoids} \times 0.083 \quad (1)$$

For comparison, the equivalent IU values can be calculated by multiplying the RE values by 3.33 (6). Because each system employs different assumptions about the efficiency of conversion of carotene to vitamin A in the body, conversion from IU to RE is not straightforward. The ambiguity lies in the fact that the term vitamin A is used both for preformed vitamin A and for dietary vitamin A, which consists of a mixture of provitamin A carotenoids and vitamin A. Thus, the RDA of 1000 RE for adult males is equivalent to 5000 IU of dietary vitamin A when the intake consists of 2500 IU of preformed vitamin A and 2500 IU of β-carotene equivalents. In terms of preformed vitamin A alone, the RDA is 3333 IU. When considering supplements of preformed vitamin A, the latter value should be used. The 1980 RDAs for vitamin A for the different age and sex groups, including pregnant and lactating women, are listed in **Table 2** (18). The allowances are intended to provide for individual variation among most normal persons as they live in the United States under usual environmental stresses.

In the 1974 tables (19) vitamin A activity is given as REs and IUs. In the 1980 edition (18) only REs are given. The differences between the RE and IU values are based on the assumption that the RE for infants aged < 6 mo is all as retinol in milk during the first 6 mo of life. All subsequent intakes are assumed to be half as retinol and half as β-carotene when calculated from IUs. As REs, three-fourths are as retinol and one-fourth as β-carotene.

Vitamin A Toxicity

Perspective

Worldwide the incidence of vitamin A excess, or hypervitaminosis A, is a very minor problem compared with the incidence of vitamin A deficiency. An estimated 200 cases of hypervitaminosis A occur annually whereas an estimated 1 million people develop vitamin A deficiency each year (5).

Over the last 50 y the number of reported cases of hypervitaminosis A has remained relatively constant despite the significant growth in production and use of vitamin A supplements. As indicated in **Figure 2,** higher incidences occurred in 1952–55 and again in 1970–72 (5, 20–38). The earlier rise coincided with the use in Europe of two very potent vitamin A-vitamin D supplement preparations administered by prescription to infants primarily in France and Spain. The second involved many cases in which high doses of vitamin A were taken for dermatological disorders either by prescription or by self-medication.

The potential for high intake of vitamin A does exist. The vitamin is available without prescription in concentrations of 25 000 IU per capsule: four of these capsules taken every day would provide approximately 20 times the RDA, which over a period of months might eventu-

TABLE 2
Recommended daily dietary allowances of vitamin A*

Sex-age group	RDA	
	RE	IU
Infants aged < 6 mo	420	1400
Infants aged 6 mo–1 y	400	2000
Children aged 1–3 y	400	2000
Children aged 4–6 y	500	2500
Children aged 7–10 y	700	3300
Boys and men aged ≥ 11 y	1000	5000
Girls and women aged ≥ 11 y	800	4000
Additional allowance for pregnancy	+200	+1000
Additional allowance for lactation	+400	+2000

* From reference 18.

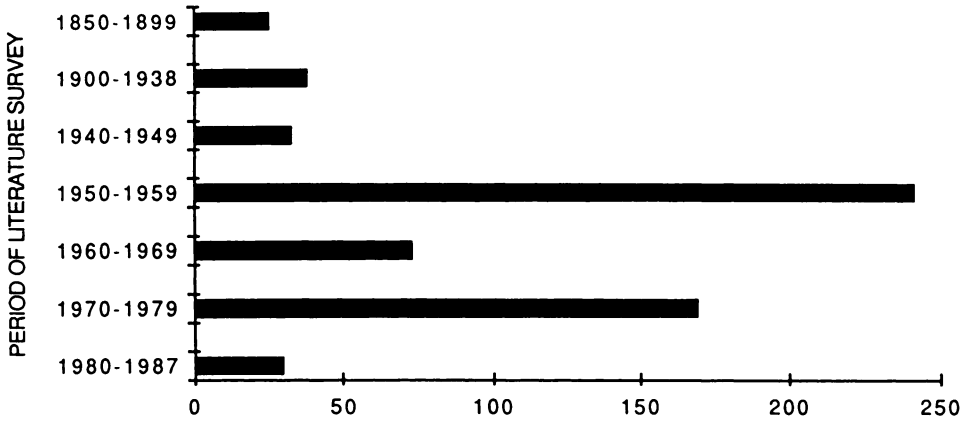

FIG 2. Cases of overt signs of hypervitaminosis A reported in the literature resulting from food and/or supplements. Cases reported between 1850 and 1979 were cited in Bauernfeind (5). Cases reported between 1980 and 1987 are taken from data of Farris and Erdman (20) (n = 1), Ramachandran et al (21) (n = 11), Misbah et al (22) (n = 1), Bush and Dahms (23) (n = 1), LaMantia and Andrews (24) (n = 1), James et al (25) (n = 1), Wason and Lovejoy (26) (n = 1), Fumich and Essig (27) (n = 1), Baadsgaard and Thomsen (28) (n = 1), Forouhar et al (29) (n = 1), White (30) (n = 1), Rosenberg et al (31) (n = 1), Schurr et al (32) (n = 1), Bürgi et al (33) (n = 1), Silverman and Lecks (34) (n = 1), Weber et al (35) (n = 1), Hatoff et al (36) (n = 1), Ellis et al (37) (n = 1), and Inkeles et al (38) (n = 2).

ally cause toxicity symptoms in some individuals. Several scientists (6, 20, 39) expressed concern over the possibility that publicity about the use of vitamin A and its synthetic analogues in the treatment of acne and other dermatological problems and certain cancers as well as its possible role in cancer prevention might lead to inappropriate self-medication with vitamin A supplements.

In 1980 the Food and Drug Administration conducted a national telephone survey of an age-stratified random sample of 2991 adults to determine total usage of vitamin-mineral supplements as well as intake of specific nutrients. With the exception of pregnant and lactating women, 40% of the population consumed one or more vitamins and/or mineral supplements. Data on intake of specific nutrients by supplement users showed that median vitamin A intake in all groups was between 100 and 200% of the RDA. Maximum intakes (395–500% of the RDA) were recorded in ~5% of all supplement users (40). Even with 5% of the supplement users consuming three to five times the RDA, symptoms of hypervitaminosis A were not reported at these levels.

Hypervitaminosis A can be divided into two categories: acute, resulting from ingestion of a very high dose over a short period of time, and chronic, resulting from continued ingestion of high doses for months or even years.

Acute hypervitaminosis A

Biochemical basis

High intakes (over five times the RDA) of vitamin A over short periods of time (2–3 wk) raise steady-state serum vitamin A values from a normal range of between 0.70 and 2.79 μmol/L to levels > 2.79 μmol/L. Levels > 62.8 μmol/L have been reported. When vitamin A intake is discontinued, levels rapidly return to normal.

Excess retinol causes changes in biological membranes, an effect believed to be due to retinol's surface-active properties. Retinol, however, does not show surface-active effects when it is bound to RBP (4). Therefore, toxicity appears to occur only when the amount of vitamin A present exceeds the capacity of RBP to bind to it. Vitamin A that is not bound to RBP binds to lipoproteins, and in this form it has toxic effects when it comes into contact with membranes and body cells (5). In other words, in vitamin A toxicity, plasma RBP levels are normal but concentrations of vitamin A not bound to the specific RBP are increased (41).

Symptoms of acute hypervitaminosis A

Table 3 lists the most common symptoms of hypervitaminosis A as identified by Bauernfeind (5) in a survey of 200 literature reports. Each symptom listed in the table was mentioned in at least 25 reports. Typical symptoms of acute hypervitaminosis A include bulging fontanels in infants and headache in adults (both presumably resulting from increased intracranial pressure), nausea, vomiting, and occasionally fever, vertigo, and visual disorientation (6). Peeling of the skin may also occur (42). The symptoms are generally transient and do not lead to permanent adverse effects (6). The symptoms of hypervitaminosis A may differ depending on the age of the victim and on whether the condition is acute or chronic.

Natural food causes

Cases of acute hypervitaminosis A caused by natural food sources are rare but they have a very long history. It has been hypothesized that pathological changes found in a *Homo erectus* skeleton (prehuman ancestor) from

TABLE 3
The most commonly reported symptoms of hypervitaminosis A*

Symptom	Number of mentions in 200 case reports
Nausea, vomiting	68
Fatigue, malaise, lethargy, somnolence, weakness, asthenia	64
Headache	56
Bulging fontanel	51
Elevated serum vitamin A	50
Anorexia	46
Mouth or lip fissures or chapping	41
Irritability	37
Ataxia (vertigo, dizziness, giddiness, equilibrium or walking problems)	34
Dry or dry scaly skin	34
Elevated CSF pressure, cranial hypertension, pseudotumor cerebri	33
Alopecia	32
Hepatomegaly, palpable or tender liver	32
Tenderness, aching, or swelling of the extremities	31
Pruritis	29
Double, distorted, or blurred vision	27
Hemorrhages, petechia (bleeding gums, membrane, nose, skin)	25
Joint pains	25

* Adapted from Bauernfeind (5).

1.5 million years ago were caused by hypervitaminosis A attributable to the consumption of carnivore livers. Because carnivores derive and store large amounts of preformed vitamin A from livers of their prey, their own livers may contain > 3.41 μmol/g (43). Normal levels of vitamin A in carnivores are difficult to establish. The range observed over time and in different species varies from a low of 0.92 μmol/g in the livers of antarctic huskies (44) to 36.14 μmol/g in halibut liver (45). Consumption of the livers of carnivorous animals or large fish has caused severe acute illness in more recent times (21, 22, 44–46).

The livers of herbivores (plant-eating animals, such as chickens, cows, and lambs) contain ~0.17 μmol vitamin A/g. These are generally safe when consumed in moderation as part of a mixed diet; however, regular consumption of large quantities of liver might contribute to excess vitamin A intakes (43).

Supplement overdose

Most cases of acute hypervitaminosis A result from overuse of supplements rather than from ingestion of food sources: of the 579 cases reported from 1850 until 1980, only 129 resulted from consumption of unusual types of animal liver. The majority resulted either from misuse of vitamin A supplements by the consumer or from overprescribing of supplements by a physician. Overdosing of children by parents or grandparents was the primary example of hypervitaminosis A caused by the consumer, accounting for 25% of cases (5).

Bush and Dahms (23) described a fatal case of hypercalcemia, hyperphosphatemia, bleeding disorders, and pulmonary insufficiency in a newborn baby who had received more than 60 times the recommended amount of vitamin A per day for 11 d. The baby's parents had administered an incorrect amount of a prescribed supplement of vitamin A in an aqueous solution.

Some of the preconceptions or misunderstandings that led to overdosing by the public in these reports may have included the belief that if a little is good, more should be better; confusion about product potency; confusion over instructions (eg, drops vs droppersful); and self-medication for dermatological conditions or other miscellaneous reasons.

Prescription-related hypervitaminosis A occurred when physicians failed to stress to patients or parents the dangers of excessive vitamin A levels (for appropriate levels, see Table 2), chose to accept some hypervitaminosis A symptoms in exchange for therapeutic benefits, or failed to warn dermatological patients not to exceed the recommended time period for taking high doses of vitamin A. Circumstances causing hypervitaminosis A in case reports published since 1980 are described in **Table 4.** Representative or recent cases of acute hypervitaminosis A resulting from abnormal vitamin consumption patterns in adults and children are described in **Table 5.**

Chronic hypervitaminosis A

Chronic hypervitaminosis A is more common than acute hypervitaminosis A. Its symptoms (Fig 1) are highly variable but anorexia, dry itchy skin, loss of hair (more prominent in adults), increased intracranial pressure, hepatomegaly (more prominent in children), and fatigue are among the most common manifestations. Women may show menstrual disturbances and children often show bone changes (subperiosteal new bone growth and cortical thickenings, especially of the small bones of the hands and feet and the long bones) that do not occur in adults (5). Elevated blood lipid levels are sometimes observed in patients with chronic hypervitaminosis A (51, 52).

Chronic hypervitaminosis A often goes unrecognized unless a careful history is taken and serum vitamin A is determined (23). Serum levels of vitamin A are generally > 3.49 μmol/L and there are increased levels of the unbound retinol resulting in a change in the ratio of free retinol to retinol bound to RBP as well as increases in retinyl esters (6).

A review of the literature suggests that among adults vitamin A toxicity is uncommon at doses < 100 000 IU/d (5). Most of the literature deals with reported cases of hypervitaminosis A in which dose is not totally reliable. However, there are several reports of controlled studies: Wald et al (53), 36 000 IU/d for 6 mo; Kinley and Krause (54), 36 000 IU/d for ≤ 6 mo; Dubin and Hazen (55), 100 000 IU/d for ≤ 23 mo; and Van Bruggen and Straumfjord (56), 100 000 IU/d for ≤ 36 mo. Minor symptomatic and physical changes affecting the skin and mucous membranes, all of which are known to be revers-

TABLE 4
Causes of vitamin A overdose in cases reported since 1980

Reference	Patient	Dose	Circumstances leading to overdose
LaMantia and Andrews, 1981 (24)	62-y-old man	4 000 000 IU vitamin A and 10 mg vitamin D	Patient ingested a veterinary vitamin preparation on impulse.
Farris and Erdman, 1982 (20)	16-y-old boy	50 000 IU/d	Self-medication for acne.
James et al, 1982 (25)	5-y-old girl	Capsules containing 25 000 IU vitamin A and 250 μg vitamin D	Supplements given by mother in attempt to improve eyesight. Child later took more of the vitamin without supervision.
Silverman and Lecks, 1982 (34)	6-y-old boy	20 000 IU vitamin A	Supplements given by nonmedical practitioners to patient on very restricted protein diet in an effort to treat allergies.
Wason and Lovejoy, 1982 (26)	7-y-old boy	25 000–50 000 IU vitamin A/d for 1 y plus unspecified multivitamins	Supplements administered by parents who customarily took large doses of vitamins themselves.
Fumich and Essig, 1983 (27)	15-y-old boy	≥100 000 IU/d	Patient hoped to improve athletic performance.
Baadsgaard and Thomsen, 1983 (28)	35-y-old woman	60 000–100 000 IU/d for 6 y	Self-treatment of psoriasis
Forouhar et al, 1984 (29)	37-y-old woman	75 000 IU for 4 y and 150 000 IU for 2 y	Self-prescribed supplements for self-diagnosed problems with night vision.
Bush and Dahms, 1984 (23)	Newborn	90 000 IU/d for 11 d	Parents accidentally administered excess doses of prescribed supplement.
White, 1984 (30)	44-y-old man	150 000 IU/d	Prescribed for skin lesions. Patient permitted to continue treatment indefinitely.
Bürgi et al, 1985 (33)	62-y-old woman	≤250 000 IU/d for 5 y	Over-the-counter preparation taken to gain vitality.

ible, were reported in the low-dose study by Wald (53). No toxic effects were reported in the other three studies.

Fatal toxicity in adults was only reported in two cases and both were complicated by extenuating circumstances and concurrent illnesses. These cases associated with chronic hypervitaminosis A are discussed later in this paper under the section entitled General Health Status.

Among children, chronic hypervitaminosis A appears to occur at dosages in the range of 12 000 to > 500 000

TABLE 5
Representative cases of acute hypervitaminosis A

Age range of subjects	Number of subjects	Dose	Major adverse effects	Reference
Infants to 7 y	23	300 000–750 000 IU	Bulging fontanel, headache, nausea, vomiting	Marie and Sée, 1953 (47) Marinoni and Panizon, 1954 (48)
9–10 y	2	5 000 IU and 300 000 IU	Pleural effusion, ascites, EEG abnormalities, seizure, bone changes	Rosenberg et al, 1982 (31) Schurr et al, 1983 (32)
Females 25–37 y	3	75 000 IU, 1 000 000 IU, and 1 300 000 IU	Headache, vomiting, splenomegaly, ascites, dermatitis, visual disturbances	Furman, 1973 (49) Misbah et al, 1984 (22) Forouhar et al, 1984 (29)
Males 30–62 y	3	150 000 IU, 4 000 000 IU, and 51 000 000 IU	Headache, vomiting, visual disturbances, anemia, dermatitis, hyperglycemia, hepatomegaly, hypercalcemia, high serum vitamin A	Goeckenjan et al, 1972 (50) LaMantia and Andrews, 1981 (24) White, 1984 (30)

TABLE 6
Factors influencing vitamin A toxicity

Factor	Effect	Reference
Vehicle of administration	Toxicity more rapid when vitamin administered in aqueous rather than oily solution.	Koerner and Voellm, 1975 (57)
Liver disease	Excess stores of vitamin A in liver increase risk of hypervitaminosis A during liver disease.	Hatoff et al, 1982 (36)
Hemodialysis therapy	Patients may have elevated vitamin A levels and anemia; hypercalcemic subjects have higher serum vitamin A levels than do normocalcemic subjects.	Farrington et al, 1981 (58) Blumberg et al, 1983 (59) Ono, 1984 (60)
Ethanol	Animal studies suggest interaction between ethanol and vitamin A causing liver damage; no such data available on humans.	Leo and Lieber, 1983 (61)
Vitamin C	High doses of vitamin A reduce tissue storage of ascorbic acid.	Bauernfeind, 1980 (5)
Protein malnutrition	Vitamin A linked with protein metabolism; protein malnutrition increases risk of hypervitaminosis.	Weber et al, 1982 (35) Silverman and Lecks, 1982 (34)
Vitamin D toxicity	Vitamin A reduces hypercalcemia and other adverse effects of vitamin D toxicity in experimental animals.	Arnrich, 1978 (62) Bauernfeind, 1980 (5)
Vitamin E	Vitamin E protects against disruption of membrane lipoprotein structure (in animals) and reduced number of congenital anomalies produced by vitamin A in rats; no data in humans.	Glauert et al, 1963 (63) Lucy and Dingle, 1964 (64) Soliman, 1972 (65) Bauernfeind, 1980 (5)
Vitamin K	Possible antagonism between vitamins A and K; animals and humans with hypervitaminosis A manifest hypoprothrombinemia (a sign of vitamin K deficiency).	Bauernfeind, 1980 (5)

IU/d, depending upon the size and weight of the child (5).

Many reports of hypervitaminosis A depend on patients' estimates of the doses taken, which may not be accurate. Toxic manifestations are unlikely to occur at some of the lower vitamin A intakes reported. In the instances where vitamin A was administered under the supervision of a physician (thus resulting in a more accurate estimate of intake), manifestations of hypervitaminosis A were abstract or slight, indicating a higher tolerated dose and duration (5).

There are great variations in response between individuals and, in addition, a wide range of health and dietary factors can influence susceptibility to chronic hypervitaminosis A. Among these factors (shown in **Table 6**) are dosing regimen and form in which the vitamin is given, age and body weight of the consumer, general health status and concurrent health problems (such as anemia, malnutrition, liver, and kidney disease) that can compromise response patterns, and dietary factors, such as ethanol intake, nutrient interactions (eg, with vitamins D, E, C, and K), and protective nutrient factors.

Dosing regimens associated with chronic hypervitaminosis A

An examination of 75 cases of chronic hypervitaminosis A in adults showed that symptoms develop in a shorter period of time when higher levels of the vitamin are consumed (5). For a dose of 100 000 IU, the response time was 6–108 mo; for 150 000–200 000 IU, 6–85 mo; for 400 000–700 000 IU, 1–36 mo; and for 1 000 000 IU, days to weeks.

Form of the vitamin

Aqueous dispersions of vitamin A cause higher plasma vitamin A values than do oily solutions (5) and at comparable doses symptoms of toxicity appear sooner after the administration of vitamin A in the aqueous form (57).

Age and body weight

Hypervitaminosis A in children corresponds to basic toxicologic principles: lower body weight results in toxicity at lower doses than those observed in adults with higher body weights. In children, however, hypervitaminosis A develops quickly and usually resolves quickly. Farris and Erdman (20) reported a severe and prolonged case of vitamin A toxicity in a 16-y-old boy who had consumed 50 000 IU vitamin A/d for 2 y (chronic usage).

General health status

Anemia. One of the two fatalities in adults that has been in part attributed to chronic hypervitaminosis A occurred in a 62-y-old woman with hemolytic anemia (33). The patient had taken up to 17 capsules of a multivitamin preparation daily (each containing 15 000 IU vitamin A) for 5 y, corresponding to an intake of 250 000 IU vitamin A/d or 300 million IU over 5 y. The multivita-

min preparation had been taken by the woman because she thought it would increase vitality.

Protein malnutrition. There is a close link between vitamin A metabolism and protein metabolism because an adequate protein intake is necessary for normal synthesis and functioning of all proteins, including RBP (5). There are two recent reports of cases in which low doses of vitamin A led to hypervitaminosis A in protein-deficient patients. Silverman and Lecks (34) described a case of vitamin A toxicity and protein-calorie deficiency in a 6-y-old boy; 20 000 IU vitamin A and 800 IU vitamin D were administered daily for 1 y before hospitalization. Weber et al (35) described a 62-y-old man who developed hypervitaminosis A that presented as liver dysfunction after ingesting 40 000–50 000 IU/d for 7 y. The patient also suffered from protein deficiency because of an abnormal diet. When he was placed on a normal diet and ingestion of 40 000–50 000 IU of vitamin A was stopped, the vitamin A toxicity symptoms gradually disappeared.

Liver disease. Individuals with excess stores of vitamin A in the liver are at higher risk of developing hypervitaminosis A. A 79-y-old man who had consumed 50 000 IU vitamin A/d for 17 y but showed no signs of hypervitaminosis A had vitamin A levels in his liver 40 times higher than normal (66). Hatoff et al (36) described a 42-y-old male vegetarian who developed hypervitaminosis A after an infection from viral hepatitis. Upon questioning, it was revealed that he had consumed 25 000 IU of vitamin A/d for 10 y as well as an additional 25 000 IU/d from food. He had discontinued use of vitamin A at the time of being diagnosed with hepatitis. It is assumed that the patient probably had mild, unrecognized chronic hypervitaminosis A before his acute illness; he had noted dry skin, cracked lips, and fatigue for the year preceding hospital admission. It is known that the level of RBP is reduced during viral hepatitis. Because vitamin A is more toxic when not bound to RBP, it has been hypothesized that the viral hepatitis was responsible for the unmasking of hypervitaminosis A in this patient. Of the two fatal cases associated with chronic hypervitaminosis A in adults, the second was associated with liver disease. Leitner et al (67) described a fatal case of cirrhosis in a 48-y-old man who had consumed large but variable quantities of carrot juice over a long period of time and who intermittently took retinol supplements as well. Starting with 3000 IU/d as retinyl acetate he gradually increased this amount to 5 000 000 IU/d. Hypervitaminosis A may therefore have played a part in his death (68). However, it was suggested by Sinclair (69) that falcarinol or some other toxic substance found in carrots, might have been responsible. In fact, death was attributed by the coroner to carrot juice addiction (70).

Kidney disease. Patients undergoing hemodialysis for renal failure appear to be at increased risk of hypervitaminosis A. Investigators (58–60) found higher than normal serum vitamin A levels in patients undergoing hemodialysis and recommend monitoring of serum vitamin A in this population group.

Hyperlipoproteinemia. It is possible that hyperlipoproteinemia may be associated with high serum vitamin A levels. In a study by Ellis et al (37) it was found that eight out of nine type V hyperlipoproteinemic subjects had retinol present in the chylomicron–very-low-density lipoprotein (VLDL) fraction whereas the nine control subjects did not. None of the subjects was using vitamin A supplements and none had any clinical symptoms of hypervitaminosis A. This observation could be explained by the fact that hyperlipoproteinemia type V is defined as a mixed hyperlipoproteinemia of the two lipoproteins that deliver fat and fat-soluble vitamins to the body. Individuals with this condition may therefore have a higher vitamin A content in this lipoprotein fraction.

Dietary factors

Ethanol intake. In rats, amounts of vitamin A that were innocuous when administered alone caused severe liver damage when the animals were also given ethanol on a chronic basis (61). The liver lesions included types of damage that are not produced in rats by ethanol alone: necrosis, inflammation, and fibrosis. Whether a similar interaction occurs in humans is unknown.

Nutrient interactions. 1) Interactions between vitamins A and D. Because vitamins A and D are often consumed together, it can be difficult to separate the symptoms of the two hypervitaminoses. Some symptoms listed for hypervitaminosis A may actually be caused by hypervitaminosis D (for example, hypercalcemia). Symptoms common to both hypervitaminoses include, among others, weakness, fatigue, lassitude, headache, nausea, vomiting, diarrhea, polydipsia, anorexia, weight loss, and conjunctivitis (5).

2) Interactions between vitamins A and E. Although many symptoms of hypervitaminosis A may be mitigated by vitamin E, interactions between these two vitamins are not without unfavorable effects as well. Animal studies over a wide range of dosages showed that vitamin A can reduce vitamin E activity by as much as 30% and can also decrease plasma and liver vitamin E levels (71). In a human study, however, 25 000 IU/d of vitamin A given for 16 wk (as a retinyl palmitate supplement) did not affect plasma vitamin E levels (72).

3) Interactions between vitamins A and C. There may be an interaction between hypervitaminosis A and vitamin C deficiency in species requiring vitamin C (ascorbic acid). In guinea pigs hypervitaminosis A is associated with reduced liver and serum vitamin C levels and administration of ascorbic acid reduces hypervitaminosis A symptoms. In humans high intakes of vitamin A appear to reduce tissue storage of ascorbic acid (5).

4) Vitamin K. There may be an antagonism between vitamin A and K as is indicated by the appearance of hypoprothrombinemia, a sign of vitamin K deficiency, in both animals and humans with hypervitaminosis A (5).

Protective nutrient factors. 1) Vitamin D. When vitamins A and D are both taken in excess, they appear to protect against some of the other's adverse effects. Large doses of vitamin A have reduced hypercalcemia and

other adverse effects of vitamin D toxicity in experimental animals (5, 62). Experimental animals dosed with large quantities of both vitamins showed less disruption of bone metabolism than expected.

2) Vitamin E. In animal models vitamin E protects against the disruption of membranes caused by hypervitaminosis A (63, 64). In experimental animals administration of vitamin E eliminated some toxic effects of vitamin A; in one experiment it reduced the number of congenital anomalies produced by vitamin A in rats (65). The addition of a small amount of vitamin E to the vitamin A preparations used in intermittent high-level dosing in developing countries has been judged to be a justifiable practice (5).

Reversal of hypervitaminosis A. In most cases, when vitamin A intake is discontinued, many symptoms of hypervitaminosis A are relieved within a few days or a week. Full recovery usually follows within weeks or months (5) although there appear to be individual differences in the recovery time from hypervitaminosis A even when patients have all consumed similar doses (19, 22).

Long-term or irreversible effects of hypervitaminosis A include bone changes and cirrhosis. Of all the chronic hypervitaminosis A symptoms, bone changes are among the most lasting although permanent bone malformations appear to be relatively rare (5). There is also some evidence that hypervitaminosis A can cause irreversible damage to the liver (73). Long-term follow-up studies have documented the appearance of cirrhosis that was histologically similar to alcohol-induced cirrhosis in patients who took very high levels of vitamin A for very long periods of time (74). Inkeles et al (38) reported cirrhosis in a nondrinking subject who had consumed large amounts of beef liver over a period of 8 or 9 y. After initiation of a low-vitamin A diet, the patient's liver function returned to normal.

Teratogenesis

Animals

Hypervitaminosis A. Very high doses of vitamin A have been shown to produce more than 70 types of congenital anomalies in experimental animals. The dosage varies among species.

In rats 25 000 IU/d during critical periods of organogenesis produced malformations. Correcting for the interspecies difference in body weight, this dose of vitamin A is equivalent to > 25 million IU for a human. The recommended intake of vitamin A in rats is 100 IU/d (75). The offspring of rats given a single large dose of vitamin A in early pregnancy (75 000–150 000 IU on days 9, 10, and 11) had abnormalities including absence of the brain, absence or abnormality of the eyes, cleft palate, malformations of the extremities, labial fissures, dental anomalies, and cataracts (2).

In a 1973 study by Hutchings et al (76), pregnant rats were given 60 000 IU vitamin A (~230 000 IU/kg) on days 14 and 15 of gestation. In a 1974 study Hutchings and Gaston (77) gave pregnant rats 90 000 IU vitamin A (~280 000 IU/kg) on days 17 and 18. No congenital malformations were observed in either study; however, behavioral deficits (including delay in learning time) were observed, especially among offspring of animals dosed at days 14 and 15. The behavioral teratogenesis was attributed to damage to the hippocampal and cerebellar areas in the brain (77). The behavioral effects of prenatal hypervitaminosis A on rats have been reviewed by Arnrich (62). Vorhees and Butcher (78), and Hutchings (79).

Teratogenicity was demonstrated in mice, hamsters, guinea pigs, rabbits, and pigs (80). In a dose-response study in hamsters, it was found that the lowest dose of vitamin A that produced gross malformations was 100 times the requirement for the vitamin in this species (81).

In a study by Cohlan (82) the dosage of vitamin A that was required to cause teratogenicity in rats and mice was equivalent on a weight basis to 4.6 million IU vitamin A given to an adult female (55 kg). If the dosage comparison utilized surface area equivalents, the dosage of vitamin A would be equivalent to 3.7 million IU in the adult female. The correlation from animal studies to humans would therefore result in a potential teratogenic dosage of vitamin A that would be 462 times the current US RDA for vitamin A for pregnant women, which is 1000 RE/d. Although it is not possible to make direct extrapolations from animal to human data, such studies can serve as a point of reference providing an idea of the probable expected level at which equivalent dose ranges might prove teratogenic in humans because there are no data that define a teratogenic level of vitamin A.

Vitamin A deficiency. Vitamin A deficiency can also cause birth defects in animals. Carefully controlled animal studies using vitamin A-deficient diets have resulted in incomplete pregnancies. If the animals were given diets marginally deficient in vitamin A, severe congenital malformations were found in the offspring (14).

Humans

Excessive intake during pregnancy. Five cases of birth defects were reported where unusually large doses of vitamin A had been taken during pregnancy. It should be emphasized, however, that no clear cause-and-effect relationship was demonstrated in any of these cases. Pilotti and Scorta (83) described a case in which a physician prescribed a daily regimen of 40 000 IU vitamin A and 15 mg vitamin D to a woman from about day 40 to day 70 of the pregnancy. The woman gave birth to a child with urinary tract abnormalities. Bernhardt and Dorsey (84) reported a case in which a woman who had taken a fish-oil product daily that contained 25 000 IU of vitamin A during the first trimester of pregnancy and 50 000 IU from months four through nine gave birth to a child with congenital abnormalities of the urinary tract. Stånge et al (85) reported a case of malformations of the central nervous system, hypoplastic kidneys, and small adrenal glands in a neonate born in the 42nd week who died

shortly after delivery. The mother had taken 150 000 IU vitamin A/d from gestation day 19 to day 40 for treatment of acne. No symptoms of hypervitaminosis had been reported during the pregnancy. Von Lennep et al (86) described a fetus with partial sirenomelia detected by prenatal diagnostic techniques in a mother who had taken large doses of vitamin A and vitamin E daily (150 000 IU vitamin A and 210 mg vitamin E) from 2 wk before until 2 wk after the presumed date of conception. Sirenomelia is a congenital anomaly characterized by fusion of the legs. Mounoud et al (87) described a 2-y-old boy with Goldenhar's syndrome (oculoauriculovertebral dysplasia) whose mother, a laboratory assistant, had accidentally swallowed 10 mL of an oily solution of vitamin A—IUs not specified but estimated at 500 000 by Rosa et al (88)—in her second month of pregnancy.

In a recent review of teratogenicity of vitamin A congeners, Rosa et al (88) listed 12 unpublished cases of birth defects associated with use of high levels of vitamin A during pregnancy. Two of the cases occurred before 1984 and involved excessive maternal vitamin A exposure (40 000 IU and 60 000 IU/d). Nine of the 10 additional unpublished cases that occurred since 1984 were associated with high doses of vitamin A with long-term exposure before and after conception often in combination with high dosages of other vitamins.

Safe doses of vitamin A during pregnancy and lactation. The overall evidence suggests but does not prove that excessive intake of vitamin A could be teratogenic in humans. In view of the potential for possible adverse effects, Bauernfeind (5) made a cautionary recommendation that pregnant women should not be included in massive-dose supplementation programs used as a public health measure in some developing countries unless future research shows that there is no risk to the fetus. He recommended that vitamin A doses given during pregnancy should not exceed 10 000 IU/d. The safety of this dosage level is supported by the work of Pereira and Begum (89), who reported that vitamin A supplements of 10 000 IU/d maintained blood vitamin A levels in the mother without increasing blood levels in the newborn infant.

Hrubetz et al (90) administered vitamin A to women in the last 3 mo of pregnancy and throughout lactation in doses of 50 000, 100 000, and 200 000 IU/d. Although these dosages far exceed current recommendations, there was no evidence of any deleterious effects to the mothers or the offspring. A statistically significant increase in the vitamin A content of breast milk was observed at the two higher dosages; however, at 50 000 IU the increase was only observed in the first 10 d of lactation and just reached statistical significance. The authors concluded that administration of supplemental vitamin A to nursing mothers affects the vitamin A content of their milk only if the dose exceeds a certain threshold. That threshold appears to be ~50 000 IU/d. Nursing mothers unknowingly may become pregnant before weaning the current nursling and hence high vitamin A levels should not be given beyond the first prenatal month as a precautionary measure (14).

The safety of the near-universal practice of giving multivitamin supplements to pregnant women was debated in a series of letters to the British Medical Journal in which some authors contended that this might increase the risk of malformations because of vitamin A toxicity (91–93). In a prospective case-control study (94) fewer birth defects were observed in a group of mothers who used a daily vitamin supplement containing 4000 IU vitamin A before conception and during early pregnancy than in a control group not receiving vitamins. Both cases and controls were mothers who had previously given birth to offspring with neural-tube defects.

In an earlier 12-y study of 87 mothers who had given birth to offspring with cleft lip and/or cleft palate, Conway (95) reported no abnormalities in 59 subsequent pregnancies among 39 mothers who received vitamin-mineral supplementation (including 12 500 IU vitamin A) during the first trimester. Four abnormalities occurred in 78 pregnancies of 48 mothers who did not receive vitamin therapy. Whether vitamin A played a role in these beneficial effects is not known; however, at the level of vitamin A intake reported in this study, no teratogenic effects were observed.

The present review suggests that prenatal use of a daily multivitamin supplement containing vitamin A may result in fewer birth defects. There has never been a single reported case worldwide of teratogenicity associated with the level of vitamin A present in the prenatal vitamin supplements given to pregnant women in the United States. The supplements usually contain 4000–8000 IU vitamin A. In 1980 the National Academy of Sciences (NAS)–National Research Council (NRC) Recommended Daily Dietary Allowance for pregnant women was set at 1000 RE (3300 IU retinol/d) (18). In 1986 the International Vitamin A Consultative Group recommended an intake of 650 RE/d during pregnancy (96).

Many women of childbearing age do not consume the recommended amount of vitamin A. The National Center for Health Statistics showed that the 50th percentile level of consumption is only 2369–2698 IU (97). The same survey also showed that the female, income-below-poverty-level group had an even lower vitamin A status. This survey data indicating a low maternal vitamin A status may, in part, be an explanation for the number of preterm infants born with very low plasma vitamin A levels. A strong association was found between vitamin A deficiency in preterm infants and the incidence and severity of bronchopulmonary dysplasia (98–100).

Vitamin A deficiency and human birth defects. There is also a possibility that vitamin A deficiency during pregnancy may be associated with human teratogenesis (101). Sarma (102) described a baby with microcephaly and anophthalmia who survived for only 24 h. The mother herself was vitamin A deficient and was blinded by xerophthalmia. Another case involved a child born with eye defects, including microphthalmia and coloboma (103).

Summary. On the basis of all of the current evidence, it is recommended that information about the possible hazards of both deficient and excessive levels of vitamin A be communicated as widely as possible to women of childbearing age. There appears to be little risk of teratogenicity associated with the correct use of the vitamin supplements prescribed for pregnant women. In many cases these supplements may be of significant benefit to both mother and child.

Carotenoids

Overconsumption of carotenoids does not result in hypervitaminosis A presumably because the body converts carotene to retinol in a regulated manner (68). Carotene supplements, when taken in quantities large enough to triple plasma carotenoid levels, did not increase plasma retinol levels (72). Consumption of 30 mg/d of carotenoid supplements may cause hypercarotenemia, a condition characterized by high serum carotenoid levels, large amounts of carotenoids in the liver, and carotenoid deposits in the skin that cause yellow-orange pigmentation particularly in the palms and soles (6). The pigmentation of hypercarotenemia differs from that of jaundice in that the whites of the eyes remain white in carotenemia (2).

Hypercarotenemia is of medical significance because it sometimes results from conditions other than carotene overconsumption and these conditions may require treatment. It may occur in patients with an inherited inability to convert carotene to retinol; such patients may develop vitamin A deficiencies while eating normal diets (68). Hypercarotenemia may also occur as a result of diabetes mellitus, hypothyroidism, and anorexia nervosa (42).

Hypercarotenemia has not been shown to have any adverse systemic effects. There was a single report associating carotenemia with amenorrhea in some nonanorectic women (104). However, in women taking high levels of β-carotene (> 180 mg/d) for long periods of time, no disruption in menstrual function was observed (105) and it was suggested that substances other than carotene in vegetables might be responsible. Carrots, in particular, contain several substances that might be toxic in high doses (69). The hypercarotenemia reported in the amenorrhic women (104) was due to overconsumption of carotene-containing vegetables not to the use of pure carotene supplements; this is also true for most other reported cases of hypercarotenemia.

Summary

Vitamin A is an essential nutrient necessary for vision, reproduction, the integrity of membrane structures, the normal functioning of body cells, growth, and development. Deficiency is a major public health problem in some areas of the world and results in xerophthalmia, permanent blindness, and excess mortality rates among children. On a global basis reports of vitamin A toxicity are rare and there are few reported fatalities.

Vitamin A adequacy is discussed in terms of recommended allowances appropriate for the needs of the majority of individuals: RDAs established in 1980 are 1000 RE for men and 800 RE for women with extra allowances for women during periods of pregnancy and lactation.

Acute hypervitaminosis A may result from natural food sources (excessive consumption of livers of carnivorous animals or large fish) or more frequently from overconsumption of vitamin A supplements. Acute hypervitaminosis A may occur after ingestion of 500 000 IU (100 times the RDA) or more by an adult (or proportionately smaller doses by children) over a short period of time. The most common symptoms include nausea and vomiting, fatigue, headaches, bulging fontanel (in infants), elevated serum vitamin A, and anorexia. All of these symptoms are usually reversible on cessation of overdosing.

Chronic hypervitaminosis A may occur when excessive amounts of vitamin A are consumed over long periods of time. Many cases of hypervitaminosis go unnoticed so that the levels and duration of intake that may result in chronic hypervitaminosis are controversial: in adults it is doubtful whether symptoms can occur at doses < 100 000 IU/d; in children the range is from 12 000 to > 500 000 IU/d depending on body size and weight. Factors influencing chronic hypervitaminosis A include dosing regimen, physical form of the vitamin, general health status (anemia, malnutrition, liver and kidney diseases, and hyperlipoproteinemia), dietary factors (such as ethanol and protein intake), and interactions with vitamins C, D, E, and K.

Vitamin A given at very high levels (100 times NRC levels) is teratogenic in animals and a deficiency of the vitamin during pregnancy can also cause birth defects. Several cases of human congenital malformations associated with maternal overuse of high doses of vitamin A have been reported but no cause-and-effect relationship has been established. It is recommended that vitamin A doses given during pregnancy should not exceed the US RDA level of 2424 RE/d. Nursing mothers should not receive > 15 152 RE/d to avoid excess vitamin A content of their milk. Deficiency of vitamin A in pregnancy has also been associated with human congenital abnormalities.

Overdosing by the general public may result from confusion over product potency or dosing instructions or from inappropriate self-medication. Prescribed supplements may lead to hypervitaminosis A if physicians do not communicate the dangers of excess consumption to patients.

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