

# MichaelMooney.net

## Research Review

Analysis of Studies from the National Library of Medicine

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### WHY I CREATE RESEARCH REVIEWS

I am frequently asked about forms and dosages of nutritional supplement ingredients.

Research Reviews provide information to answer these questions.

Scientific references are cited and text from abstracts is included to provide research details.

I evaluate ingredients by the following criteria:

- 1) Is it natural and normal to the human body?
- 2) Has it had a long history of safe use in humans?
- 3) Is it supported by science or traditional herbal wisdom?
- 4) Is it nutritionally effective?
- 5) Is it cost-effective?
- 6) Is it concentrated enough that optimal doses can be supplied in a reasonable amount of tablets?

I have no vested interest in any form of ingredient. I have no financial involvement with any raw materials manufacturer. My recommendations are based on what I believe is best for my own health and for yours, too.

### Vitamin A (Retinol) and Beta-Carotene

**Q:** Is Vitamin A (retinol) toxic and therefore should not be supplemented?

**A:** Vitamin A (retinol) is an essential nutrient and is necessary for eye health, lung health, immune health and for life itself. The lowest toxic dosage levels that have been reported were more than seven times the Recommended Daily Allowance and these high doses were taken over long periods of time.

**Q:** Can beta-carotene convert to Vitamin A in the body well enough that it is not necessary to take supplemental Vitamin A as retinol?

**A:** Studies show that millions of people do not convert beta-carotene into Vitamin A well enough to substitute for Vitamin A. This means that many people may need to supplement with Vitamin A.

**Q:** Should pregnant women avoid Vitamin A (retinol palmitate or retinol acetate), because it causes birth defects?

**A:** **The World Health Organization recommends that all pregnant women take Vitamin A as retinol.** Retinol is available as one of two safe, natural supplemental forms, retinol palmitate or acetate. U.S. Government records show no birth defects ever being caused by the amounts of Vitamin A in multi-vitamins. Vitamin A is required for a newborn baby's lung health, immune health, eye health and to bring the baby to full-term delivery.

### INSIDE

- **The Six Types Of People Most At Risk For Vitamin A Deficiency**
- **Vitamin A (Retinol) Is Required For A Healthy Pregnancy**

## Vitamin A (Retinol) And Beta-Carotene

I have asked to clarify current questions about supplemental Vitamin A (also called retinol) and beta-carotene. The most common are:

1. Is the retinol form of Vitamin A natural?
2. Is supplemental Vitamin A (retinol) toxic?
3. Are the types of Vitamin A known as retinol palmitate and retinol acetate safe?
4. Does beta-carotene substitute for Vitamin A (retinol) by converting into Vitamin A in the body as needed?
5. Does supplemental Vitamin A (retinol) cause birth defects?
6. Is Vitamin A necessary for a healthy pregnancy?
7. Is Vitamin A necessary for children's health?
8. Does Vitamin A cause bone loss?
9. Should we even supplement Vitamin A (retinol) at all?

## Vitamin A (Retinol): Is It Natural? Is It Toxic?

Vitamin A (retinol) is a vitamin and is necessary for life and overall health. Vitamin A is especially important for the health of the eyes, lungs, bones, skin, immune system, and protein formation. It is found in nature as pro-vitamin A and as pre-formed Vitamin A. Pro-vitamin A is seen as the red, orange, and yellow colored carotenes in fruits and vegetables. The most abundant and well-known carotene is beta-carotene. Pro-vitamin A (beta carotene and other carotenes) must be converted in the body into retinol (Vitamin A). Pre-formed Vitamin A is already formed as Vitamin A (retinol). It consists of various forms of retinoic acid, including the most common form, retinol. Pre-formed Vitamin A is found in nature only in animal products, such as fish and dairy products. Retinol and other natural retinoids, such as cis-retinoic acid, are metabolized in the body and stored in the liver, primarily as retinyl palmitate, another form of retinol that is made in the body.<sup>1</sup> Vitamin A in the blood stream is called serum retinol and is measured in "retinol equivalents." The word retinol is commonly used by scientists when referring to Vitamin A.

According to the US Government's nutritional advisor, the National Academy of Sciences' Institute of Medicine, the Vitamin A (retinol) found in dietary supplements is known to be safe, non-toxic and necessary for health at the recommended daily allowance (RDA) levels of 2333 IU for women and 3000 IU for men. The Institute of Medicine has stated that Vitamin A is safe at the No Observed Adverse Effect Level of 10,000 IU and safe below the Lowest Observed Adverse Effect Level, which is 21,600 IU.<sup>2</sup> (The Lowest Observed Adverse Effect Level for nutrients is a dose for which toxicity may be seen "rarely," for "some sensitive subgroups." However, several new studies have raised questions about how even lower doses of Vitamin A might affect bone loss for some people. This is investigated on page 11.

## Are Retinol Palmitate And Acetate Natural And Safe?

Vitamin A palmitate is also called retinol palmitate and Vitamin A acetate is called retinol acetate. Vitamin A palmitate is Vitamin A attached to palmitic acid, which is a more stable carrier than acetate when there are many ingredients in the supplement. Palmitic acid is manufactured naturally in the body and used to make Vitamin A water-soluble so that it can be carried in the lymph to the liver. Palmitic acid can also be obtained in nature from palm trees. Vitamin A acetate is Vitamin A attached to acetic acid, another natural carrier of Vitamin A and the same natural acid that is the primary flavor found in organic balsamic vinegar. Both Vitamin A palmitate and Vitamin A acetate are natural to the body and utilized in the body efficiently.

However, because of the high cost of extracting palmitate and acetate from foods, the palmitate in Vitamin A palmitate and acetate in Vitamin A acetate in dietary supplements are manufactured in laboratory processes. The manufactured molecules are identical to those that are found in nature and duplicate their activity in the body.

Vitamin A palmitate (retinol palmitate) and Vitamin A acetate (retinol acetate) have been investigated in thousands of published peer-reviewed studies for over forty years. They have each been shown to be safe, non-toxic and highly beneficial not only at RDA levels but also at levels up to the Tolerable Upper Limit of 10,000 IU.

Although we do not recommend taking higher doses of Vitamin A without medical monitoring, studies have shown that Vitamin A palmitate and Vitamin A acetate can be non-toxic at doses considerably higher than RDA levels. For example, one study with 292 normally healthy adults found that Vitamin A palmitate supplements did not produce toxic effects at a dose of 25,000 IU per day.<sup>5</sup>

Therapeutic individual doses of 200,00 IU of Vitamin A palmitate, given twice over a six-month period of time is safely administered by doctors to children who suffered from night blindness.<sup>6,7,8</sup> This high-dose Vitamin A therapy is recognized as a standard-of-care therapy by the World Health Organization.<sup>9</sup>

In one lung cancer study, Vitamin A palmitate supplements were therapeutically administered at 300,000 IU per day for twelve months and noted to be a *“well-tolerated and safe treatment.”*<sup>10</sup>

At the RDA levels, neither Vitamin A palmitate nor Vitamin A acetate has ever been shown to be toxic in any way. Nor can we find there any scientific evidence that there is another form of Vitamin A that is superior to either Vitamin A palmitate or Vitamin A acetate.

## **Beta-Carotene Does Not Convert Into Vitamin A Efficiently For Some People**

Most people assume that getting one's Vitamin A requirements met is easy because the body converts beta-carotene into Vitamin A as needed without any potential for toxicity. This is not true for many people. Some of the beta-carotene that we consume in foods converts into Vitamin A (retinol) in the body. If there is not enough Vitamin A (retinol) available for use in the body, a significant number of healthy people's bodies convert beta-carotene into Vitamin A to make up the difference. Increased conversion is stimulated when the body's Vitamin A (retinol) supply drops below a threshold amount. However, for many other people, the body's conversion of beta-carotene to Vitamin A is not efficient enough to produce adequate Vitamin A blood levels.<sup>3,4,18,19</sup>

## **Many American's Vitamin A Intake Is Less Than The RDA**

In the Feskenich study of 72,337 postmenopausal American women, the total daily Vitamin A (retinol) intake from food alone ranged from as low as about 800 IU to a high of about 2600 IU, with a mid-range of about 1550 IU, increasing up to 1750 to 2050 IU in the upper ranges of Vitamin A intake.<sup>4</sup>

- 1550 IU is 758 IU (33%) lower than the 2333 IU RDA for women.
- 1750 IU is 588 IU (25%) lower than the 2333 IU RDA for women.
- 2050 IU is 288 IU (12%) lower than the 2333 IU RDA for women.

This study indicated that almost half of American women may experience frank or marginal Vitamin A deficiency unless they supplement with Vitamin A. This is also likely to be true of American men, whose diets are similar to American women.

## **The Six Major Risk Groups for Vitamin A Deficiency**

Although studies show that many millions of people adequately convert dietary beta-carotene to Vitamin A in their bodies, there are also many millions of people who do not convert beta-carotene well enough to satisfy the body's need for Vitamin A. Additionally, studies show that millions of Americans do not get enough Vitamin A (retinol) from their diets. These people are at risk of Vitamin A deficiency and should consider supplementing pre-formed Vitamin A (retinol). The six major groups at risk for Vitamin A deficiency are:

1. Some healthy American women and men
2. Women with marginal or acute hypothyroidism
3. Pregnant women

4. People in third world countries
5. Children in third world countries and in the U.S.
6. Vegetarians and Vegans

## Healthy American Women And Men (45 Percent) Did Not Convert

Lin Y, et al. Variability of the conversion of beta-carotene to Vitamin A in women measured by using a double-tracer study design. American Journal of Clinical Nutrition 2000 Jun;71(6):1545-54.

**Comment:** Lin's study of 11 healthy well-fed women living in a controlled environment found that 5 out of 11 of them (45%) did not experience measurable increases in their blood Vitamin A after consuming beta-carotene. The authors said, "*The Vitamin A activity of  $\beta$ -carotene is variable and surprisingly low in women. The reasons for this are not well understood. The Vitamin A activity of  $\beta$ -carotene in men is still uncertain.*"

Hickenbottom SJ, et al. Variability in conversion of  $\beta$ -carotene to Vitamin A in men as measured by using a double-tracer study design. American Journal of Clinical Nutrition 2002 May;75(5): 900-907.

<http://www.ajcn.org/cgi/content/abstract/75/5/900>

**Comment:** This study evaluated the Vitamin A activity of beta-carotene in 11 healthy, well-fed men living in a controlled environment and found similar results as was seen in the Lin study above with 11 women. 5 of the 11 men (45%) did not experience increased Vitamin A blood levels after beta-carotene consumption. The authors concluded, "*Vitamin A activity of beta-carotene, even when measured under controlled conditions, can be surprisingly low and variable.*"

Nierenberg DW, et al. Effects of 4 y of oral supplementation with beta-carotene on serum concentrations of retinol, tocopherol, and five carotenoids. American Journal of Clinical Nutrition 1997 Aug;66(2):315-319.

**Comment:** Nierenberg's four-year study of high dose (41,000 IU per day) beta-carotene supplementation with a variety of people showed a 151% average increase in blood beta-carotene levels, but no significant increase in blood Vitamin A (retinol) levels, confirming that poor conversion of beta carotene to Vitamin A is common.

## Women: Hypothyroidism Decreases Conversion

Beta-carotene's conversion into Vitamin A (retinol) can be highly inefficient in people with certain health problems, especially people who are hypothyroid.<sup>26,27</sup> (This means that they have low [hypo] thyroid hormone production.) Undesired weight gain, especially in the hips and legs (lower body), is one of the most common symptoms of hypothyroidism in women. The incidence is lower in men, but still somewhat common over about 40 years of age.

Aktuna D, et al. Beta-carotene, Vitamin A and carrier proteins in thyroid diseases. Acta Medica Austriaca 1993;20(1-2):17-20.

**Comment:** This study stated that about 40% of women over 40 years of age have sub-clinical or overt hypothyroidism. The authors said that the conversion of beta-carotene to Vitamin A (retinol) is increased by thyroid hormone. Thus inadequate thyroid hormone production can compromise the conversion of beta-carotene to Vitamin A (retinol). Beta-carotene blood levels were shown to be significantly higher in hypothyroid people than in healthy people, because inefficient conversion allows beta-carotene to build up in the blood, which is eventually seen as an orange tint in the skin.

If you are hypothyroid and vegetarian you are especially likely to be deficient in Vitamin A, because pre-formed Vitamin A (retinol) is only contained in animal food products or dietary supplements. Plants do not contain pre-formed Vitamin A (retinol). However, the Vitamin A found in most daily formulas is manufactured, not derived from animal products.

## Third World People And Vitamin A Deficiency: An International Health Crisis

Solomons NW, et al. Plant sources of provitamin A and human nutriture. Nutrition Reviews 1993 Jul;51(7):199-204.

**Comment:** This study from scientists in Guatemala looked at Vitamin A deficiency and beta-carotene intake and stated that developing countries should not expect beta-carotene from food sources to enable the body to maintain adequate Vitamin A stores. The World Health Organization calls Vitamin A deficiency in Third World Countries an “international health crisis.”

The authors of the study said, “Evidence from feeding studies shows an almost universally poorer uptake of intact carotenoids from plant sources as opposed to pure [retinol] sources. With notable exceptions, the bioconversion of plant carotenoids to pre-formed (retinol) Vitamin A also seems to be inefficient.” The study’s authors also said, “The accepted 6:1 equivalency of beta-carotene to pre-formed Vitamin A must be challenged and reexamined in the context of dietary plants. The consequences of operating on a miscalculation could be serious indeed for public health programs designed to alleviate and eradicate hypovitaminosis A.” (Hypovitaminosis A means Vitamin A deficiency.)

Although Vitamin A deficiency occurs significantly less often in the United States, as was shown earlier, there are many people in the U.S. who experience poor beta-carotene conversion.

## Beta-Carotene Conversion: Less Than Previously Thought

Another problem with assuming that beta-carotene can substitute for Vitamin A is that the conversion factor used by the scientific community for beta-carotene conversion to Vitamin A may not be as efficient as it has been thought to be, and may vary widely in different people. For many years, beta-carotene had been assumed to convert into 1/6<sup>th</sup> as much Vitamin A (retinol) in healthy people.<sup>2,20</sup> (6,000 IU of beta-carotene would convert to 1,000 IU of Vitamin A.)

Recently, researchers have been questioning the estimate of the 6-to-1 conversion ratio of beta-carotene to Vitamin A. Their newer studies have suggested the beta-carotene conversion in many people may be as low as 21 to 1.<sup>21,22,23,24</sup> This means that 6000 IU of beta carotene would convert to only 285 IU of retinol, instead of the 1000 IU predicted by the 6 to 1 conversion rate.

## A Majority Of Americans Need Supplemental Vitamin A

When it is considered that 45% of well-fed healthy American women and men and hypothyroid women who are about 40 percent of women over 40 years of age have problems converting beta-carotene into Vitamin A, and that almost half of American women and men do not get the RDA of Vitamin A from their diets, a majority of Americans need supplemental Vitamin A (retinol) to support overall health.

## Does Vitamin A In Multivitamins Cause Birth Defects?

Mills JL, et al. Vitamin A and birth defects. American Journal of Obstetrics and Gynecology 1997 Jul;177(1):31-6.

**Comment:** This study from the National Institute of Child Health and Human Development of the National Institutes of Health said “The proportion of women consuming doses of vitamin A between 8000 and 25,000 IU was no greater in the major malformations group or the group with neural tube defects than in the normal control group.” This study also found no association between Vitamin A at 10,000 IU per day and birth defects. They also said, “If vitamin A [causes birth defects], the minimum dose [that causes birth defects] appears to be well above the level consumed by most women during [pregnancy].”

Hathcock JN, et al. Evaluation of vitamin A toxicity. American Journal of Clinical Nutrition 1990 Aug;52(2):183-202. Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC 20204.

**Comment:** This study from the United States Government Food and Drug Administration said, “*Toxicity has been associated with abuse of vitamin A supplements and with diets extremely high in preformed vitamin A.*” “*Especially vulnerable groups include...pregnant women, with birth defects being associated with maternal intakes as low as approximately 25,000 IU per day.*”

A review of the scientific literature since 1933 found no reports of birth defects caused by the amounts of Vitamin A in multivitamins, which typically is less than 10,000 IU. Additionally, the U.S. Government Centers for Disease Control, which collects and evaluates reports of toxicity for the entire United States, reported no birth defects caused by the amounts of Vitamin A found in multivitamins. However, birth defects have been observed in children whose mothers took extremely high amounts of Vitamin A during pregnancy, 25,000 IU or greater. (Doses reported ranged from 8 times the RDA to 40 times the RDA.)

## Safety And Necessity Of Vitamin A (Retinol) During Pregnancy

As an essential nutrient, Vitamin A (retinol) is required for the health of the mother and her baby during pregnancy and after.<sup>11</sup> Statistics indicate that pregnant women have approximately the same dietary habits as other women, yet they have an increased requirement for Vitamin A intake while pregnant.<sup>2</sup> The RDA of Vitamin A for non-pregnant women is 2333 IU, 2500 IU for pregnant women 18 or under and 2567 IU for pregnant women over 18 years of age. A higher RDA indicates that pregnant women are more susceptible to a Vitamin A deficiency.

Total daily Vitamin A intake during pregnancy that is below the RDA can result in a 74 percent increased chance of premature delivery and health complications for the newborn, including chronic lung disease,<sup>72</sup> blindness or vision problems,<sup>6,7,8</sup> stunted growth or compromised bone growth,<sup>12</sup> anemia,<sup>30</sup> asthma,<sup>71</sup> deficient immune function with an increased potential for neonatal infections such as diarrhea, measles and respiratory infections like pneumonia, and increased infant mortality.<sup>11</sup>

A study of 22,748 women by Rothman indicated that 10,000 IU was the threshold dose where there could be a very slight potential for birth defects that increased with dosage.<sup>13</sup> However, this study was determined to be inconclusive because of “methodological questions” when analyzed in a large review study.<sup>73</sup>

This 10,000 IU total daily intake is the amount that the American Pediatric Society says is the safe upper limit for pregnant women.<sup>14</sup> Below this intake, no significant association with increased birth defects has been seen. However, a 1989 State of California environmental law recommended an even more conservative upper daily intake of 8000 IU for pregnant women.<sup>15</sup>

Another study with pregnant women questioned the earlier study’s safe daily intake of 10,000 IU as being too conservative and calculated that Vitamin A intake up to 30,000 IU per day appeared to be safe.<sup>16</sup> Yet another study also indicated that 30,000 IU appeared to be safe.<sup>17</sup>

Prenatal multi-vitamin formulas typically contain less Vitamin A than the 10,000 IU Tolerable Upper Limit. Most contain less than the 8,000 IU recommended by the State of California. While Vitamin A doses that rise above 10,000 IU may be associated with more potential for birth defects, daily intake that is below the RDA of 2333 IU may also cause birth defects that can result in life-long chronic health problems or infant death. Pregnant women should be guided by blood tests evaluated by their doctor to help them stay within the range of best Vitamin A intake for their baby’s health. This means obtaining adequate Vitamin A through diet and supplements while avoiding excessive Vitamin A intake.

## The World Health Organization Recommends Vitamin A (Retinol) For A Health Pregnancy

Contrary to a misunderstanding that pre-formed Vitamin A (retinol palmitate and retinol acetate) in multi-vitamin supplements is toxic to the unborn child, the World Health Organization states that supplemental Vitamin A (retinol) is critically needed for a healthy pregnancy.<sup>57</sup>

Part of this misunderstanding was caused by the Rothman study, which was also reviewed by the World Health Organization. Examining all the available studies WHO stated that there have been no reports of adverse effects or toxicities for pregnancy for Vitamin A (retinol) intake of 10,000 IU (more than 4 times higher than the RDA).

In fact, the World Health Organization's paper, "Safe Vitamin A Dosage During Pregnancy And Lactation" states on page 20, "...there is no teratogenic risk [of birth defects] from preformed Vitamin A supplements of 10,000 IU given to women who habitually consume less than the RDA. However, there is no justification for daily supplements at a level above 8,000 IU for pregnant women who habitually consume vitamin A at the level of the RDA (2400 ug RE) or above."<sup>58</sup>

On page 16 of this report, it is stated that, "Recent studies strongly suggest that periconceptional supplements of vitamin A that are close to, but less than 10,000 IU/day, and that are given as a component of a multivitamin, are much more likely to be associated with reduced, rather than increased, risk of malformations."

Additionally, the International Vitamin A Consulting Group, which advises the World Health Organization, stated in a review of all available data in 1998 that, "It is safe to give fertile women, independent of their Vitamin A status, as much as 10,000 IU daily at any time during pregnancy."<sup>70</sup>

## Pregnant Women And Vitamin A Deficiency: Increased Risk of Anemia

### Vitamin A Is Critically Involved In Red Blood Cell Production And Iron Metabolism

Suharno D, et al. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993 Nov 27;342(8883):1325-8.

**Comment:** Combining Vitamin A with iron has been shown to be more effective in increasing red blood cell production than giving iron alone in girls<sup>67</sup> and in pregnant women.<sup>68, 69</sup> In this eight-week double-blind, placebo-controlled study of 251 anemic pregnant women, the combination of 8000 IU of Vitamin A (retinol palmitate) and 60 mg of iron was effective in eliminating anemia in 97% of the women compared with only 68% for those women who supplemented with 60 mg of iron alone.<sup>69</sup> Vitamin A deficiency may also impair mobilization of iron, allowing it to accumulate in the liver and spleen,<sup>62, 63</sup> so Vitamin A status should also be evaluated for anyone if there is excess iron storage. (Iron storage is tested by measuring blood ferritin).

## Vitamin A Deficient Pregnant Women: Anemia Increases The Risk Of Early (Pre-Term) Delivery

Radhika MS, et al. Effects of vitamin A deficiency during pregnancy on maternal and child health. *British Journal of Gynecology* 2002 Jun;109(6):689-93.

**Comment:** This study stated that Vitamin A (retinol) deficiency during pregnancy is associated with pre-term (early) delivery of the baby, which means that the baby may be born before full healthy development of bone, lungs, eyes, and other important body systems. As was shown, Vitamin A deficiency is also associated with a

higher incidence of anemia. Anemia during pregnancy is associated with pre-term delivery, low birth weight and certain birth defects, such as Chronic Lung Disease and visual defects. Anemia is also associated with an increased risk of maternal illness, fatigue, dyspnea, palpitations and tachycardia, vertigo, loss of appetite and even death.<sup>59</sup>

To guarantee that serum Vitamin A (retinol) is in the optimal range during the especially sensitive time of pregnancy, it is most prudent to ask your doctor for a serum retinol test. This should be done early in pregnancy.

## Vitamin A Deficient Pre-Term Babies And Chronic Lung Disease

Hustead VA, et al. Relationship of vitamin A (retinol) status to lung disease in the preterm infant. *Journal of Pediatrics* 1984 Oct;105(4):610-5.

**Comment:** This study said that “...babies who developed bronchopulmonary dysplasia had lower concentrations of blood Vitamin A at birth...than babies who did not develop bronchopulmonary dysplasia. Many preterm infants are deficient in vitamin A at birth, and failure to correct this deficiency may contribute to the development of chronic lung disease.”

Bronchopulmonary dysplasia involves poor development of lung tissue cells. Sometimes called Chronic Lung Disease, it is a disease in infants characterized by inflammation and scarring in the lungs. It develops most often in premature babies, who are born with underdeveloped lungs, make breathing difficult and causing problems with lung function.

According to the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH), between 5,000 and 10,000 cases of BPD occur every year in the United States. This birth defect is more common than folic acid deficiency-related neural tube defects (spina bifida), which affects about 1,200 babies per year.

## Children May Also Be At Risk – Around The World And In The US

Studies show that millions of children throughout the world whose only source of Vitamin A is Vitamin A's precursor, beta-carotene, do indeed have adequate levels of Vitamin A (retinol) in their blood for normal health. There is adequate beta-carotene in their diets and the conversion of beta-carotene in their bodies is efficient enough to satisfy their need for Vitamin A. But there are also millions of children who do not have adequate Vitamin A blood levels because they do not obtain enough beta-carotene or Vitamin A (retinol) from their diets or they do not convert beta-carotene to Vitamin A adequately.

Vitamin A deficiency associated health problems are more common in developing countries where overall nutrition is poor. One study stated, “*Clinical trials...indicate that young children in developing countries cannot achieve normal vitamin A status from plant diets alone.*”<sup>28</sup> This is caused by poor conversion of beta carotene to Vitamin A (retinol).

## Vitamin A Deficiency and Third World Children

Zagre NM, et al. Changes in Vitamin A intake following the social marketing of red palm oil among children and women in Burkina Faso. *Sante* 2002 Jan-Mar;12(1):38-44.

**Comment:** The 30-month study above looked at 210 mothers and their children in Burkina Faso, Africa. Because of impoverished conditions, Vitamin A deficiency is a “*major public hazard.*” The children were 1 to 3 years old when the study began. Because ninety percent of the dietary intake of Vitamin A sources came from beta-carotene from plants such as fruits and dark green leafy vegetables 64% of the mothers and 85% of the children had low blood Vitamin A (retinol) levels.

Numerous studies of children state that reliance on beta-carotene alone for the body's Vitamin A needs can compromise Vitamin A status.<sup>3,4,18,19,21,22,23,24</sup> Studies of Vitamin A deficient children show associations with many different types of health problems;

1. Hearing loss;<sup>14</sup>
2. Night blindness and eye diseases<sup>6,7,8,29</sup>
3. Increased potential to contract disease like measles;<sup>11</sup>
4. Diarrhea;<sup>11</sup>
5. Respiratory infections such as pneumonia;<sup>11</sup>
6. Anemia,<sup>30</sup>
7. Bone growth abnormalities;<sup>11</sup>
8. Stunted growth, because Vitamin A is required for growth hormone production;<sup>12</sup>
9. And even death.<sup>11</sup>

## Vitamin A Improves Infant Survival And Reduces Infections

Rahman MM, et al. Administration of 25,000 IU Vitamin A doses at routine immunization in young infants. *European Journal of Clinical Nutrition* 1995 Jun;49(6):439-445.

**Comment:** This double-blind, placebo-controlled study looked at 25,000 IU of Vitamin A (retinol) given once per month to newborns in India and determined that it was not enough to reduce infections and health problems.

Humphrey J, et al. Neonatal Vitamin A supplementation: effect on development and growth at 3 years of age. *American Journal of Clinical Nutrition* 1998;68:109-117.

**Comment:** When 50,000 IU of Vitamin A as retinol palmitate was given to infants on the first day of life and twice more during the first year, after one year there was a 64% reduction in infant mortality and an over 50% reduction in symptoms of pneumonia, a leading cause of child death. The study stated that Vitamin A deficiency is a "major public health problem throughout the developing world affecting an estimated 124 million young children and accounting for more than 1 million child deaths each year."

Ross DA. Recommendations for vitamin A supplementation. *Journal of Nutrition* 2002 Sep;132(9 Suppl):2902S-2906.

**Comment:** This study recommended that three 50,000 IU doses of Vitamin A (retinol palmitate) be given to babies during the first six months of life in communities where Vitamin A deficiency is a public health problem. While this therapy has been common used in Third World Countries, doctors in the United States have recently been administering it to babies in the United States.

**The author said,** "In all populations where vitamin A deficiency is an important public health problem, prophylactic vitamin A supplements should be given to all infants and young children (0 to 59 months), and pregnant women and postpartum women within 6 wk after delivery. The efficacy of vitamin A supplementation of young children is one of the best-proven, safest and most cost-effective interventions in international public health. The International Vitamin A Consultative Group (IVACG) also recommends that three 50,000-international unit (IU) doses of vitamin A should be given at the same time as infant vaccines during the first 6 mo of life. Recent kinetic studies have indicated that this regimen will be safe and is necessary to maintain the infant's vitamin A stores, even when the [lactating] mother is also given 400,000 IU within the first 6 wk after delivery."

## Children: Vitamin A Deficiency And Eye Diseases

Rosen DS, et al. Vitamin A deficiency and xerophthalmia in western Yemen. *European Journal of Clinical Nutrition* 1996 Jan;50(1):54-7. Helen Keller International New York.

**Comment:** Vitamin A (retinol) is critical for the health of the retina and the eye, in general. The study above detailed Vitamin A (retinol) deficiency in children in Yemen who had symptoms such as xerophthalmia (abnormal dryness of the eye due to a deficiency of tears), followed by trachoma (chronic eye infection characterized by granulations and scarring of the cornea), night blindness, ulceration of the cornea of the eye, and Bitot's spots on the cornea. Their dietary Vitamin A came mostly from food sources of beta-carotene, which did not convert to enough Vitamin A to prevent deficiency.

When babies are determined to be experiencing night blindness, the standard-of-care therapy as recommended by the World Health Organization is doctor-administered high dose Vitamin A (retinol) given in doses up to 200,000 IU twice over a six month period of time. This is known to be a safe and effective therapy.<sup>6,7,8,9</sup>

## Children: Vitamin A Deficiency And Measles

While the Vitamin A deficiency experienced by children in Third World countries is not seen as much in the United States, some children in the U.S do have problems with getting enough Vitamin A (retinol). Therefore, Vitamin A deficiency syndromes do also occur in children in the United States. The next study of 20 children in Long Beach, California who suffered from measles found that 50 percent were deficient in Vitamin A (retinol).

Arrieta AC, et al. Vitamin A levels in children with measles in Long Beach, California. *Journal of Pediatrics* 1992 Jul;121(1):75-78.

**Comment:** The authors noted: *“Studies from Africa suggest that vitamin A supplementation may reduce morbidity and mortality rates associated with measles among poorly nourished children. We studied 20 children with measles in Long Beach, Calif., and found that 50% were vitamin A deficient. This frequency among presumably well-nourished American children supports evaluation of vitamin A status as a part of acute management of measles in the United States.”*

Caballero B, et al. Low serum retinol is associated with increased severity of measles in New York City children. *Nutrition Reviews* 1992 Oct;50(10):291-292.

**Comment:** This study in New York City found an association with Vitamin A deficiency and severity of measles. The authors said, *“...decline in circulating [blood] retinol was associated with increased duration of fever, higher hospitalization rates, and decreased antibody titers.”*

While the above studies deal specifically with measles and low blood Vitamin A (serum retinol) in children in the United States, they also indicate that other health conditions in children may be associated with Vitamin A (retinol) deficiency.

## Children: Vitamin A Deficiency And Diarrhea

Usha N, et al. Assessment of preclinical vitamin A deficiency in children with persistent diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* 1991 Aug;13(2):168-75.

**Comment:** 74 percent of the children in this study who experienced persistent diarrhea were deficient in Vitamin A and had Vitamin A blood levels that were 57 percent lower than normally healthy children. Their intestinal epithelial cells were described as *“scanty and abnormal.”* Diarrhea can be a result of measles, which also is associated with Vitamin A deficiency.

## Children: Vitamin A Deficiency And Stunted Growth

Evain-Brion D, et al. Vitamin A deficiency and nocturnal growth hormone secretion in short children. *Lancet* 1994 Jan 8;343(8889):87-88.

**Comment:** This study looked at pre-pubertal short children in France who had low nighttime growth hormone secretion, which can cause the child to not grow to their full potential height. Blood measures of Vitamin A and total dietary Vitamin A were significantly lower in short children with low nighttime growth hormone secretion than in normal children or in naturally short children. Nine out of twelve of the children with low nighttime growth hormone secretion experienced increased nighttime growth hormone secretion when supplemented with 10,000 IU of Vitamin A palmitate per day for 3 months.

Khatib IM. High prevalence of subclinical vitamin A deficiency in Jordan: a forgotten risk. Food and Nutrition Bulletin 2002 Sep;23(3 Suppl):228-36.

**Comment:** This 9-month study of 1023 children between 5.5 and 9.9 years old who had a tendency towards experiencing stunted growth and anemia showed that food sources of Vitamin A (retinol) improved blood Vitamin A levels and growth scores while food sources of beta carotene and other carotenoids did not. The authors concluded, *“Vitamin A deficiency among schoolchildren as a public health problem, and that the situation is anticipated to be more profound among preschool children, who are usually at greater risk of becoming deficient.”*

Recent research has shown that the potential for postmenopausal osteoporosis can be reduced for a woman by ensuring that their bones grow properly when they are still in their mother’s womb.<sup>25</sup> Vitamin A is critically involved in healthy bone development. This is another reason that optimal Vitamin A (retinol) intake during pregnancy is important.

## Children: Vitamin A Deficiency And Anemia

Mohanram M, et al. Hematological studies in vitamin A deficient children. International Journal of Vitamin Nutrition Research 1977;47(4):389-93.

**Comment:** This study stated that children who were deficient in Vitamin A (retinol) were more likely to be anemic. Another study showed that Vitamin A (retinol) supplementation can reduce some types of anemia.<sup>60</sup> As was stated before, Vitamin A is known to be critically involved in production of red blood cells<sup>61</sup> and the mobilization of iron,<sup>62, 63</sup> and studies have shown a significant correlation between serum Vitamin A and red blood cell production.<sup>64, 65, 66</sup>

## Children And Vitamin A Deficiency: Four Times More Risk Of Asthma

Arora P, et al. Vitamin A status in children with asthma. Pediatrics and Allergy Immunology 2002 Jun;13(3):223-6.

**Comment:** This study stated that Vitamin A deficiency can cause a number of diseases in children. In this study, children 2 through 12 years of age who were deficient in Vitamin A were four times more likely to suffer from asthma than those who were not deficient.

If there are concerns with your child regarding vision or hearing problems, lung problems or asthma, intestinal health, immune function, measles, pneumonia, diarrhea, bone growth, growth problems or anemia we suggest that you work with your doctor to ensure that your child’s serum Vitamin A is in the optimal range.

## World Health Organization Vitamin A Dosing Recommendations

For populations where there is risk of Vitamin A deficiency, the World Health Organization recommends the following dosing schedule.<sup>70</sup>

### Schedule For High-Dose Vitamin A Supplementation In Vitamin A Deficient Populations

Population	Vitamin A Amount To Be Administered	Administration Time
Infants 0 to 5 months	150,000 IU as 3 doses of 50,000 IU with at least a 1-month interval between doses	6, 10, and 14 weeks

Infants 6 to 11 months	100,000 IU as a single dose every 4 to 6 months	At any opportunity
Children 12 months and older	200,000 IU as a single dose every 4 to 6 months	At any opportunity
Postpartum women (This dose is given to the lactating mother, even when infants are given the high doses in this table.)	400,000 IU as two doses of 200,000 IU at least 1 day apart and/or 10,000 IU daily or 25,000 IU weekly	As soon after delivery as possible and not more than 6 weeks later. And/or during the first 6 months after delivery

Note that these are not routine recommendations for all children and mothers. They are recommendations that apply to populations where there is known Vitamin A deficiency. For optimal health for mother and child, ask your doctor to test Vitamin A blood levels to establish whether Vitamin A supplementation is appropriate.

## Optimal Vitamin A Dosing And Bone Density: New Inconclusive Studies Create Controversy

Recently, some inconclusive questionnaire-based scientific studies<sup>3,4</sup> have created concern about Vitamin A's effects on bone density and risk of fracture in adults. These studies indicated that the best doses of Vitamin A for optimal bone density for some adults, notably senior women who were not on hormone replacement therapy, are lower than the U.S. Government's Tolerable Upper Limit of 10,000 IU.

However, these studies caused an incorrect assumption that *any* intake of Vitamin A might cause bone loss. This is not true. In the 18-year Feskenich study of 72,337 nurses, bone loss was seen for some women when there was either *too much* Vitamin A intake or *too little* Vitamin A intake. Above approximately 2800 IU per day, there was bone loss, but bone loss also occurred below about 2000 IU per day. Thus, it appeared from this data that the optimal total Vitamin A intake for some of the women in this study may be between about 2000 IU and 2800 IU per day.<sup>3</sup>

This study, which indicated that Vitamin A may reduce bone density outside of this narrow dosage range, caused significant concern about Vitamin A dosing, in general. However, as a first study in this area, it was actually lacking the solid data that would produce conclusions about how different groups of people might be affected. The study was a questionnaire-base study, known for their inaccuracy. (See box below.) The study also indicated that Vitamin A may have no negative effect on bone for a significant number of other people. For instance, women who did not use hormone replacement therapy experienced bone loss when their total Vitamin A intake was over 2800 IU or under 2000 IU, while women who used hormone replacement therapy had no significant problem. Additionally, higher calcium intake was shown to reduce the risk of bone loss by about half.<sup>3</sup>

Another study of 99 women who took 1500 mg of calcium carbonate per day showed no association with Vitamin A intake and radial bone loss.<sup>60</sup> The Feskenich study also did not evaluate the potential effects of other elements that affect bone density, such as magnesium, boron, Vitamin D, Vitamin K and zinc or weight-bearing exercise. The authors further stated, "*The study was conducted in a mostly white population of women and results may not be generalizable to other racial or ethnic groups.*"

### Major Concerns About The Accuracy Of Questionnaire-Based Studies

There are some other important concerns about the accuracy of these new studies. One major concern the authors reported is related to the calculation of total Vitamin A intake. This arises because Vitamin A intake was self-reported by the participants themselves, using food questionnaires and diaries. Food questionnaires and food diaries contain many errors and they can be inaccurate by from 20% to as great as 400%.<sup>58</sup>

The authors of these studies warn that other factors might have caused errors, such as, but not limited to, "*random error, poor reporting of personal history by study participants, long intervals between measurements,*" and "*unidentified confounders*" which can confuse the results. Furthermore, there is a concern about the

probable inaccuracy of the beta-carotene conversion to Vitamin A ratio that is used to calculate how much Vitamin A activity that dietary or supplemental beta-carotene intake can produce. When all is considered, these probable errors create serious concerns about their conclusions.

## A Newer, More Conclusive Study Shows Vitamin A Improves Bone Health

Barker, ME, et al. Serum retinoids and beta-carotene as predictors of hip and other fractures in elderly women. *J Bone Miner Res.* 2005 Jun;20(6):913-20.

This newer study looked at this issue more critically using blood measurement of Vitamin A. Blood tests yield much more credible conclusions than what can be determined by questionnaire-based studies. This study found no increased bone loss with higher Vitamin A blood levels. In fact, the authors said, *“Risk of [bone] fracture was slightly less in the [highest blood Vitamin A group] compared with the lowest.”* They also said, *“There was a tendency for increased [blood Vitamin A] to predict benefit rather than harm in terms of bone mineral density. Multivitamin or cod liver oil was associated with significantly lower risk of any fracture.”*<sup>73</sup>

Ask your doctor to measure the Vitamin A in blood tests to see if you have too much or too little Vitamin A. Optimal blood levels of Vitamin A can be a valuable part of long-term bone health.

## Vegans May Also Be At Risk

There are relatively few scientific studies on the dietary intake and the bone mineral density of vegetarians who consume some animal products like milk or eggs, and even fewer on the dietary intake and bone mineral density of vegans (vegetarians that consume no animal products).

Of the twelve studies we were able to locate in a search of the National Library of Medicine archives that compared Vitamin A intake between vegans, vegetarians and non-vegetarians,

Five were studies of vegetarians from the US, France and Great Britain that found that vegetarians and non-vegetarians in the studies both tended to have the same general range of self-reported Vitamin A intake when beta-carotene was included as a Vitamin A source.<sup>31,32,33,34,35</sup> However, including beta-carotene as a Vitamin A source can produce confusing results, because of beta carotene conversion problems.

Two other studies of vegetarians and non-vegetarians reported that the vegetarians in the studies had higher intakes of Vitamin A or beta-carotene than the non-vegetarians.<sup>36,37</sup>

Two other studies involving vegans, vegetarians and non-vegetarians, found that all had the same general range of self-reported beta carotene or Vitamin A intake, but while the vegans had intake of beta-carotene, they had no intake of Vitamin A (retinol).<sup>38,39</sup>

Two other studies involving vegans and non-vegetarians, reported that vegans had higher self-reported beta-carotene intake than non-vegetarians, but vegans have no Vitamin A intake.<sup>40,41</sup>

One study however, reported that non-vegetarians had a higher reported intake of Vitamin A than did vegans, when beta-carotene was included as a Vitamin A source.<sup>42</sup> This also produces confusing results because of beta-carotene conversion problems.

Together, these studies indicate that vegans have the same general range of Vitamin A intake as other vegetarians and non-vegetarians, but that they may tend to be slightly on the low side.

## The Concern About Bone Density For Vegans

While a recalculation of beta-carotene conversion may change some numbers and is important, it will not necessarily change how vegetarians eat. Since absorption, availability and conversion of beta-carotene to Vitamin A varies widely between individuals, generalized estimates may not tell the true story of the Vitamin A activity produced from beta-carotene intake for any one person. The more important consideration is how does vegan bone mineral density compare with the bone mineral density of non-vegetarians and other vegetarians.

Of the twelve studies on vegetarian bone mineral content, mass and densities that were located in my search of the National Library of Medicine archives,

One study reported that vegetarians between 53 and 79 years of age had better bone mineral content than non-vegetarians.<sup>43</sup>

One study reported that male vegetarians and non-vegetarians between 20 and 79 years of age had about the same bone mineral mass.<sup>44</sup>

One study reported there was no significant difference in bone mineral content between pre-menopausal vegetarians and non-vegetarians.<sup>45</sup>

Another study reported there was no significant difference in bone mineral content between older female vegetarians and non-vegetarians.<sup>46</sup>

Three other studies reported there was no significant difference in bone mineral density between post-menopausal vegetarians and non-vegetarians.<sup>47,48,49</sup>

Yet another study reported there was no significant difference in bone mineral density between pre-menopausal vegans, other vegetarians and non-vegetarians.<sup>50</sup>

Another study found that elderly female vegans and vegetarians had lower bone density at some bone sites than non-vegetarians.<sup>51</sup>

Two studies (one a 10 year follow-up of the first) found that older vegetarian women lose less bone mass than non-vegetarians.<sup>52,53</sup>

And one study found that long-term vegans had about 2½ times greater risk of fractures than non-vegetarians.<sup>54</sup>

In summary, of the 12 studies,

- 1 found that older vegetarians have higher bone density than non-vegetarians.
- 6 found no differences in either bone mineral mass, content or density between adult women or men vegetarians and non-vegetarians.
- 1 found no differences in bone density between vegans, other vegetarians and non-vegetarians.
- 1 found vegans and vegetarians have less bone mass than non-vegetarians.
- 2 found older vegetarians lose less bone mass than non-vegetarians.
- 1 found that vegans have about 2½ times the risk of fractures as non-vegetarians.

While these are relatively few studies, they do represent a small cross section of women and men from both the U.S. and around the world. Though the statistical evidence is not strong with so few studies, it does indicate that vegans tend to have slightly lower bone density than non-vegetarians and other vegetarians, but that they, like other vegetarians, tend to lose bone more slowly than non-vegetarians, and that vegans do run higher risks of fractures than non-vegetarians. Since once vegans have achieved a bone density level, they may tend to lose the bone density more slowly than non-vegetarians, the concern here is to increase bone density to a safe level.

In these cases of acceptable but slightly lower bone density, minor problems in the body with the beta-carotene conversion to Vitamin A can cause vegans to experience borderline Vitamin A deficiency problems. For vegans, moderate supplementation with pre-formed Vitamin A (retinol) can be insurance for long-term bone health.

## **Vitamin A Should Be Included In Your Daily Vitamin Formula**

While some companies are discontinuing inclusion of Vitamin A as retinol in their formulas, while substituting beta-carotene, this will leave many people with Vitamin A deficiencies. Beta-carotene does have a unique value as an antioxidant, but it is not an adequate substitute for Vitamin A and cannot be relied on to provide the benefits that real Vitamin A can. Vitamin A (retinol), as an essential nutrient, is necessary for life itself. (“Vitamins” by definition, are necessary for life.) Beta-carotene is not an essential nutrient, but has unique antioxidant properties. Beta-carotene can provide a secondary source of Vitamin A activity for some people, however, studies indicate that over half the population does not convert beta-carotene in the body into Vitamin A (retinol) well enough to support the body’s needs. Additionally, conversion of Beta-carotene is not efficient enough to be depended on as a Vitamin A source.

Except for some people with unusual health problems, Vitamin A (retinol) should be included in daily vitamin formulas, in general, as insurance for the groups of people who may be at risk for Vitamin A deficiency diseases.

Although Vitamin A deficiencies are generally not thought to be common in the US, some studies indicate that as much as half the US population is at risk of having a borderline or acute Vitamin A deficiency.

Many healthy people do not convert beta-carotene into Vitamin A in their bodies adequately no matter how much beta-carotene they get from their food.

Many people do not obtain the RDA of Vitamin A (retinol) from their diet.

Four out of ten women over 40 are hypothyroid or borderline hypothyroid and may not adequately convert beta-carotene into Vitamin A. This applies to hypothyroid men also.

Pregnant women may not obtain the RDA of pre-formed Vitamin A (retinol) from their diets, or not get enough pro-vitamin A (beta-carotene) or both. Some pregnant women may have a problem with inadequate conversion of beta-carotene into Vitamin A.

Recent research has shown that women with good bone density during their teens have less osteoporosis after menopause.<sup>55</sup> However, good bone health begins even sooner than that. Research shows that strong bone formation of the baby during pregnancy will protect bone health throughout life and after menopause.<sup>56,57</sup> Vitamin A (retinol) insurance obtained from dietary supplements will help mothers-to-be feel confident that they are doing everything possible for their baby’s future health.

Some vegans may need supplementation to get adequate levels of Vitamin A in their bodies. Supplemental pre-formed Vitamin A (retinol) can provide valuable nutritional insurance.

## **Proper Vitamin A Supplementation Is Good Nutritional Insurance**

Scientists and doctors agree that if you obtain the RDA of Vitamin A (retinol) from your diet you do not need Vitamin A supplementation. However, the above studies show that millions of Americans, including meat eaters and vegetarians are at risk for Vitamin A deficiency. Appropriately dosed pre-formed Vitamin A (retinol) in supplements is safe, effective and prudent nutritional insurance.

## **It Is Important To Know If You Are Vitamin A Deficient**

Ask your doctor to measure your Vitamin A (retinol) blood level. The lab test will tell you if your measurement is within the best range.

If your serum retinol is not optimal a dietary supplement containing Vitamin A as retinol should be considered. Additionally, a food-frequency questionnaire (also called a dietary analysis) from your doctor can help you discover where your diet can be adjusted to bring your serum retinol into normal range.

**The statements in this report have not been evaluated by the Food and Drug Administration. They are not meant to diagnose, treat, cure or prevent any disease, and are not meant to substitute for the advice of your physician.**

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