

# FAQ #1

## What are the risks of adverse effects from periodic vitamin A supplementation?

The risks are small. The high levels of retinol present after a single dose are cleared quickly from the blood; and, once stored, vitamin A is harmless. For children, a single large dose, appropriate for age, will not harm anyone and may help many. Side effects sometimes occur, but these are mild and transient. Pregnant women, and women who might be pregnant, should avoid large doses of vitamin A, particularly very early in pregnancy. For pregnant women, daily doses of 10,000 IU, or weekly doses of 25,000 IU, are safe and recommended by some in areas where vitamin A deficiency is common.

This question is frequently asked because

- Large-dose supplements of vitamin A are now commonly distributed to preschool-aged children in many countries (they are a proven, cost-effective strategy to reduce childhood mortality in areas where vitamin A deficiency is common);
- Vitamin A is stored by the body, and toxicity will result if “too much” of the vitamin is consumed;
- For pregnant women, very large doses can be teratogenic (that is, can cause harm to the developing fetus).

The question is generally asked with two groups in mind: pregnant women or young children. Penny Nestel and Jim Olson have addressed the issue with regard to pregnant women in more detail in the paper *Safety of Vitamin A for Pregnant and Postpartum Women*. This paper also defines some general concepts related to biology and toxicity of vitamin A. MOST staff have prepared a brief statement on safety for young children, entitled *Safety of Vitamin A for Children*. These papers are on the following pages.

### Summary Guidelines

Age appropriate doses for the prevention of vitamin A deficiency:

Infants < 6 months	50,000 IU orally
Infants 6–12 months	100,000 IU orally
Children > 12 months	200,000 IU orally
Mothers	200,000 IU, within eight weeks of delivery

Frequency of dosing of children:

Dosing at four- to six-month intervals should be sufficient to prevent serious consequences of vitamin A deficiency. Those known to have received a large-dose vitamin A supplement within the last 30 days should not receive an additional dose (unless clinical vitamin A deficiency or measles is present).



# SAFETY OF VITAMIN A FOR PREGNANT AND POSTPARTUM WOMEN

by

Penelope Nestel and Jim Olson<sup>1</sup>

## Physiological Role

Vitamin A functions in vision, cell differentiation, embryonic development, spermatogenesis, the immune response, taste, hearing, appetite, and growth. Except for vision, these processes largely depend directly or indirectly on cell differentiation.

## Consequence of Deficiency

Vitamin A deficiency can cause eye signs, blindness, reduced resistance to infection, and an increased risk of mortality.

## Dietary Sources

Vitamin A is naturally found in the diet in two forms:

- 1) *preformed vitamin A* (mostly as retinyl esters or retinol) from foods of animal origin such as liver, milk and milk products, fish and meat; and,
- 2) *provitamin A carotenoids*, generally from plant foods, which can be biologically transformed to vitamin A.

Globally, about 60 percent of dietary vitamin A comes from provitamins A. The conversion of provitamin A to vitamin A is increased when the vitamin A status is poor. Many factors influence the absorption and utilization of provitamin A such as the amount, type, and physical form of the carotenoids in the diet; intake of fat, vitamin A, and fiber; protein and zinc status; existence of certain diseases; and parasitic infections.

## Recommended Dietary Intakes

The WHO *safe recommended dietary intake* (RDI) of vitamin A is 350 Fg/day for infants, 400 Fg/day for children 1 to 6 years, 600 Fg/day for pregnant women, and 850 Fg/day for lactating women. These values are expressed in total Fg retinol equivalents, in which 6 Fg of the most common provitamin A (beta-carotene) in food is equivalent nutritionally to 1 Fg retinol.<sup>2</sup>

## Toxicity

Vitamin A toxicity can be classified into three categories: acute, chronic, and teratogenic. *Acute toxicity* results from one or several closely spaced very large doses of vitamin A, usually more than 100 times the safe RDI. The signs are usually transient and disappear after a few days. *Chronic toxicity* occurs with recurrent intakes over a period of months to years of excessive doses of vitamin A that are usually at least 10 times the safe RDI. Most people recover fully from chronic toxicity. *Teratogenic toxicity*, in pregnant women, is known to result from substantial doses (more than 7,500 Fg or 25,000 IU) of vitamin A injected daily, from larger doses (more than 30,000 Fg or 100,000 IU) taken for several days or weeks, or from a single large dose (150,000 Fg or 500,000 IU). Daily doses of 4,500 Fg or 15,000 IU, however, have

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<sup>2</sup> One IU of preformed vitamin A is equivalent to 0.3 Fg all-trans retinol, thus 600 Fg retinol Fg per day for a pregnant women is equivalent to 2,000 IU.

been taken by pregnant women for significant periods without apparent harm to their offspring. Safe levels of intake for periodic low doses and for single large doses have not been defined. The most sensitive period for toxic effects at all doses is the first trimester of pregnancy. Beyond the first trimester, the risk to the fetus is much less. Teratogenic toxicity results in fetal resorption, abortion, birth defects, and permanent learning disabilities in the offspring as well as toxic effects on the mother.

### **Available Supplements**

Most oral vitamin A supplements contain retinyl palmitate in oil together with a small amount of vitamin E. The upper safe level of vitamin A from supplements for pregnant women in regions of the world where vitamin A deficiency is common is accepted as being 3,000 Fg or 10,000 IU/day.

### **Post-Partum Supplementation**

Following the birth of a child, women are highly unlikely to become pregnant for a period of 6 to 8 weeks: thus, current IVACG guideline of administering a single oral dose of up to 60,000 Fg (200,000 IU) within 6 to 8 weeks postpartum is considered to be safe. Furthermore, there is no evidence that the fetus of a woman who becomes pregnant 2 to 3 months after taking a postpartum mega dose is adversely affected. The reason is that retinyl ester concentrations rise rapidly in the plasma in response to an oral mega dose but they are quickly cleared, usually returning to low normal values within 24 hours. Much of a dose of vitamin A is stored in the stellate cells of the liver and, to a much lesser degree, in other tissues. Stored vitamin A is innocuous. Thus, the teratogenic toxic period for a single mega dose is limited to the first 6 to 48 hours after oral administration. No disastrous short-term outcomes have been reported in mothers of young infants where the dose and timing of post-partum vitamin A have been controlled.

### **Supplementation during Pregnancy**

In pregnant women, whose estimated daily dietary intake of retinol equivalents is below 400 Fg/day or in geographic areas where vitamin A deficiency is common, daily supplements of 3,000 Fg preformed vitamin A (10,000 IU) or 7,500 Fg (25,000 IU) at weekly intervals is recommended. Care must be taken to avoid giving supplements of vitamin A to pregnant women who frequently ingest liver and other foods rich in preformed vitamin A. Dietary carotenoids are not teratogenic. Supplementation at the recommended levels of preformed vitamin A during one pregnancy should not adversely affect, and might well benefit, the outcome of subsequent pregnancies.

### **Fortified Foods**

Fortified sugar generally contains 15 Fg/g (50 IU) retinol. A preschool child eating 20 g sugar/day (about 3 teaspoons) would get 300 Fg (1,000 IU) retinol/day from sugar. An adult eating 150 g sugar/day would get 2,250 Fg (7,500 IU) retinol/day. Given that the upper safe level of intake from supplemental vitamin A for pregnant women is 3,000 Fg (10,000 IU)/day, the safety margin would be 750 Fg (2,500 IU), which is more than the equivalent of a RDI.

There have been no reports of toxicity in countries that fortify sugar. A daily intake of 200 to 300 Fg (670 to 1,000 IU) retinol along with periodic mega dosing will not predispose children to toxicity.

## SAFETY OF VITAMIN A FOR CHILDREN

Oral administration of periodic high doses of retinyl palmitate in oil (60,000 Fg retinol or 200,000 IU) is now commonly used to reduce vitamin A deficiency in developing countries. Minor and transient side effects (bulging fontanelles, vomiting) have been noted in a few children even at this dose and so safety is an obvious concern. Concern about toxicity is also an important issue for supplementation programs because it may reduce public acceptance of the program.

### Summary Guidelines

Age appropriate doses for the prevention of vitamin A deficiency:

Infants < 6 months	50,000 IU orally
Infants 6–12 months	100,000 IU orally
Children > 12 months	200,000 IU orally

Frequency of dosing:

The dosing at 4-6 month intervals should be sufficient to prevent serious consequences of vitamin A deficiency.

### Risks of overdosing

The 1997 guidelines of WHO/UNICEF/IVACG state that

"...if a high-dose supplement has been administered more than 1 month previously, an additional dose is not harmful. In contrast, a child who has received a routine high-dose supplement within the past month should not receive an additional targeted dose."

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### Toxicity of vitamin A

The exact level of consumption at which individuals exhibit toxicity symptoms is difficult to determine as several factors influence the toxicity threshold. Among these are the size and age of the individual, the duration of consumption, and the quantity and form of vitamin A consumed. Olson (1996) determined that for children the threshold for acute toxicity was a single dose of >330,000 IU.

## Signs and symptoms of vitamin A toxicity in children

Acute toxicity	Chronic toxicity
Loss of appetite	Loss of appetite
Bulging fontanelles	Bulging fontanelles
Drowsiness	Loss of hair
Increased intracranial pressure	Bone pain and tenderness
Irritability	Hyperostosis
Vomiting	Photophobia
	Skin desquamation
	Hepatomegaly

Adapted from Hathcock et al. 1990 and Olson 1996.

### National Immunization Days

Much of the concern about overdosing with vitamin A comes from distributing high-dose vitamin A supplements in conjunction with National Immunization Days (NID) campaigns. In such campaigns, all children 6–59 months are given high-dose supplements. This “piggy-backing” of interventions offers children and health services great benefits in areas where vitamin A is deficient. Children receive the proven health benefit of improved vitamin A status at the same time as receiving an immunization. The vitamin A does not reduce the efficacy of the immunization. The health services benefit by saving greatly on resources—the additional cost of distributing vitamin A supplements in conjunction with delivering the immunization is very small. Further, immunization coverage is likely to be enhanced when mothers are adequately informed about the benefits of vitamin A supplementation.

The success of NIDs campaigns depends upon moving large numbers of children through the immunizations and vitamin A distribution processes. The operation must be time-efficient and at the same time ensure that children are not put at any risk from receiving too much vitamin A.

The WHO guidelines for the Distribution of Vitamin A during National Immunization Days (WHO, 1998) suggest that

“To avoid delays, during NIDs the screening should be limited to asking the age of the child to ensure the correct dose is given. It is *not* necessary to screen for previous dose of vitamin A. The minimum interval between doses of vitamin A is one month.

Exceptionally, the interval between doses is reduced for the treatment of measles or clinical VAD.” Page 3.

The risk of serious harm to a child from receiving a high-dose capsule of vitamin A is low. The high levels of retinol esters present after dosing are cleared quickly from the blood to storage in the liver; and, once stored, vitamin A is harmless. A single massive dose for children, appropriate for age, will not harm anyone and may help many. Side effects sometimes occur, but these are mild and transient.

## **MOST recommendations for screening children in NIDs**

1. All children should be screened to determine the child's age (for correct dosage), and an effort should be made to screen for previous dose of vitamin A. In preparing for the NID, the team should ascertain whether or not vitamin A has been, in fact, delivered in the communities over the previous month. Where screening individuals for previous dosage is not possible or reliable, all children 6–59 months can be supplemented with vitamin A.
2. When asking about the timing of receiving previous vitamin A supplementation, teams should make sure that mothers are *not* referring to a polio vaccine possibly received in a previous round of NID. Health workers could show a capsule to the mother and ask, “Has your child received a capsule like this in the past month?” Alternatively, if they have a list of the children given a routine dose within the previous month (Note: not therapeutic doses for xerophthalmia or measles), these children should be excluded from vitamin A supplementation during the NID.

For a review of the physiological role, consequence of deficiency, dietary sources, and recommended intakes, see the paper *Safety of Vitamin A for Pregnant and Postpartum Women*.

### References:

Hathcock, J.N.; Hattan, D.G.; Jenkins, M.Y.; and McDonald, J.T. Evaluation of vitamin A toxicity. *Am J Clin Nutr* 1990; 52:183–202.

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WHO/UNICEF/IVACG Task Force. *Vitamin A Supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*, 2nd edition. WHO, Geneva, 1997.

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