A DEEPER UNDERSTANDING OF THE SAFETY OF VITAMIN A

In Australia all supplements containing Vitamin A will automatically display this warning on the label:
'Warning: If you are pregnant, or considering becoming pregnant, do not take Vitamin A supplements without consulting your doctor or pharmacist. When taken in excess of 3000 micrograms retinol equivalents (RE), Vitamin A can cause birth defects. The recommended daily amount of Vitamin A from all sources is 700 micrograms retinol equivalents for women and 900 micrograms retinol equivalents for men.'
The TGA requires this warning to appear on the label of all Australian therapeutic products containing Vitamin A in order to ensure consumer safety.[1]

THE ROLE OF VITAMIN A

Vitamin A is a fat-soluble vitamin that is **not synthesised by the body** and must be obtained through the diet.[2] Vitamin A is required for:[3]

- the integrity of epithelial cells throughout the body
- regulating the expression of various genes that encode structural proteins, enzymes, extracellular matrix proteins and receptors
- **embryonic development, particularly the development of the spinal cord and vertebrae, limbs, heart, eyes and ears**
- maintaining differentiation of parts of the eye and to change light to neural signs for vision cornea and conjunctiva as well as for photoreceptor rod and cone cells in the retina
- the maintenance of immune function; an adequate supply also plays a role in preventing morbidity and mortality from infectious disease, particularly in children

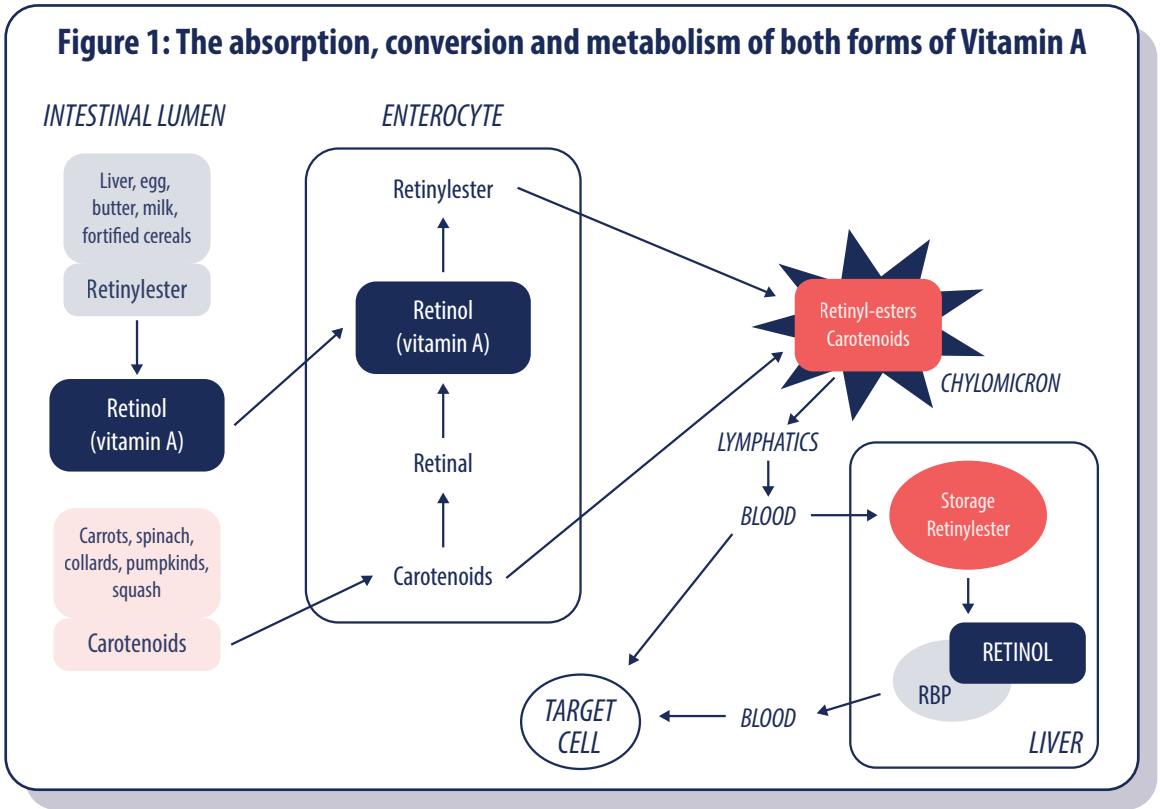
FORMS

There are two main forms of Vitamin A:

1. **Preformed Vitamin A (retinol and retinyl ester)** is found in meat, poultry, fish and dairy products and 70-90% of dietary or supplemental sources are absorbed from the intestinal lumen into intestinal cells (enterocytes). The absorption rate is driven by the individual's systemic Vitamin A concentration, as well as zinc and iron status.[4]
2. **Provitamin A (carotenoids)**, the most common form being **betacarotene**, is found in oils, fruits, vegetables, and other plant-based products and requires conversion to retinol in the enterocytes.[4]

Vitamin A concentrations are maintained largely by the liver where it is stored as retinol and can provide up to a 2-year supply.[4]

Figure 1: The absorption, conversion and metabolism of both forms of Vitamin A



VITAMIN A SAFETY IN PRECONCEPTION, PREGNANCY AND LACTATION

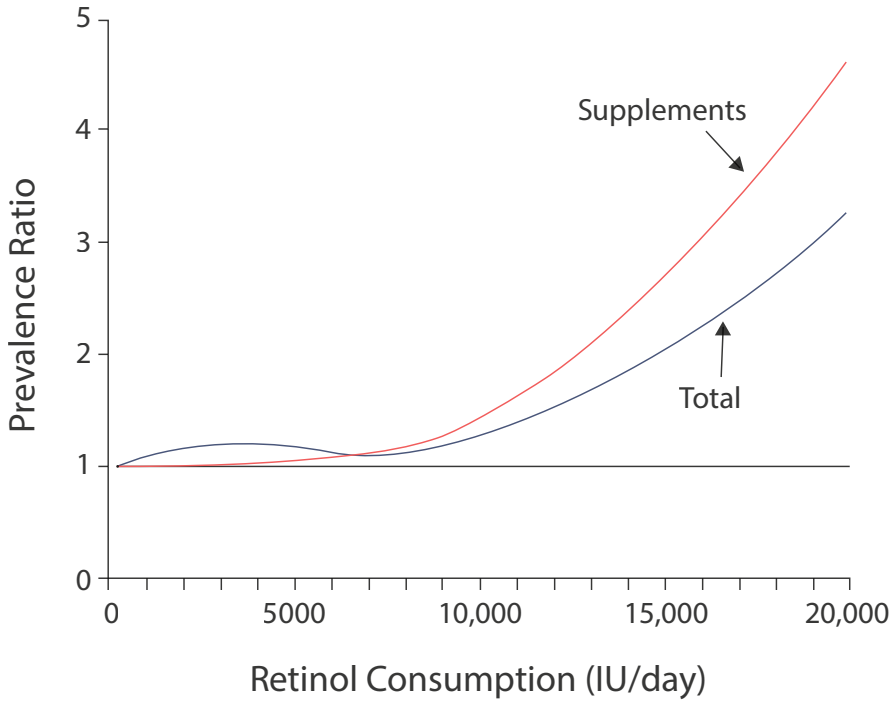
The concern regarding the teratogenicity of Vitamin A in humans began with the study conducted by Rothman et al. in 1996 which concluded that supplemental doses of more than 10,000IU (3000µg RE) of preformed Vitamin A may increase the risk of abnormalities in the developmental neural crest tissues.[5] The relationship between increasing dose and increased risk is relative for both food and supplemental sources (See Figure 2) so the upper level of intake (UL) includes the total daily intake of preformed Vitamin A.

Research confirms that doses of 3000µg RE (10,000IU) daily or below show no Vitamin A-related birth defects or teratogenicity.[4] This is in line with current TGA guidelines and label warnings for Vitamin A supplementation.[1] Interestingly, the negative effects of Vitamin A in pregnancy were associated with high doses consumed before the 7th week of gestation, but not beyond this point.[4]

To minimise the negative effects associated with maternal intake of Vitamin A, do not exceed the UL of 3000µg RE (10,000IU) daily in preconception, pregnancy and lactation. It is also important to note that Vitamin A is a crucial inclusion for early embryonic and foetal development.[2] Both the deficiency and excess of Vitamin A during embryonic development can result in congenital malformations.[5]

Vitamin A is a crucial micronutrient for pregnancy, developing babies and lactation and the metabolic demand for this vitamin and risk of deficiency is greater during these times.[2,4]

Figure 2: The prevalence of Vitamin A-related birth defects in relation to retinol consumption per day



THE GENERAL POPULATION

The UL set by the National Health & Medical Research Council (NHMRC) for Vitamin A is related to age, pregnancy status and abnormal liver pathology and is based on infant and adult research and extrapolated for relative body weight.[3]

Figure 3: Daily upper level of intake (UL) for the general population in micrograms (µg) and international units (IU)

Age	µg RE/day	IU/day
Infants 0-12 months	600ug RE	2,000IU
Children 1-3 years	600ug RE	2,000IU
4-8 years	900ug RE	3,000IU
9-13 years	1,700ug RE	5,667IU
14-18 years	2,800ug RE	9,333IU
Adults	3,000ug RE	10,000IU
Pregnancy and Lactation	3,000ug RE	10,000IU

ASSESS AND MONITOR

Those who consume high levels of alcohol, have pre-existing liver disease, hyperlipidaemia or severe protein malnutrition may be particularly susceptible to excess intake of Vitamin A and may not be afforded the protection of the UL set for the general population.[3]

Prolonged use of doses over 25,000IU or more may cause side effects such as hypervitaminosis A which is related to the cumulative effect rather than a specific daily dose.[3] Monitor patients' liver function and fat-soluble vitamin levels (especially Vitamins D, E and K) which directly compete for absorption in the small intestine.[6]

SHOULD I BE CONCERNED ABOUT BETACAROTENE?

Betacarotene is an important dietary source of Vitamin A, often recommended as a safer alternative to Vitamin A for children and during pregnancy.[3] However, the bioavailability and Vitamin A equivalency of betacarotene is regulated by dose and is highly variable.[7] For example, absorption of betacarotene from plant sources ranges from 5-65% in humans and the higher the betacarotene intake, the lower the conversion to Vitamin A.

Factors beyond dosage affecting the conversion and absorption of betacarotene include, but are not limited to:[7]

- dietary factors such as fat content, cooking method, fibre content, and vegetarian or vegan diets
- current health and Vitamin A status
- age and nutrient deficiencies
- gastrointestinal integrity
- genetic polymorphisms associated with betacarotene metabolism, such as BCM01 which account for 32-69% of some population groups and result in impaired betacarotene conversion

Based on the absence of adverse effects, the UL for betacarotene cannot be established for supplemental use or dietary consumption. Although betacarotene is a precursor of Vitamin A, excess intake has not been associated with Vitamin A toxicity in humans as the metabolic conversion is regulated by Vitamin A status. High intake may cause yellowing of the skin.[3]

VITAMIN A SAFETY CHECKLIST

- ✓ Does the product contain an AUSTL or AUSTR number to confirm it is a listed or registered product in Australia? Some imported products may contain Vitamin A and not display the warning
- ✓ Clarify what form of Vitamin A the product contains
- ✓ Determine the appropriate UL for Vitamin A intake for the age of the patient and health status when formulating your prescription (Figure 3)
- ✓ For all adults, pregnant women, or women planning a pregnancy, confirm the total of preformed Vitamin A from all supplements falls below 10,000IU or 3000µg daily
- ✓ Assess medical history thoroughly for pre-existing liver disease and alcohol consumption
- ✓ Periodically monitor liver function and other fat-soluble vitamin status if using Vitamin A supplementation for more than 3 months
- ✓ **Do not give Vitamin A supplementation if a patient is taking retinoid medications**

REFERENCES

1. Australian Government. Therapeutic Goods (Permissible Ingredients) Determination (No.2) Item 4268. Federal Register of Legislation. https://www.legislation.gov.au/Details/F2019L00834/Html/Volume_5. Published 2019. Accessed October 3, 2019.
2. Maia SB, Souza ASR, Caminha MDFC, et al. Vitamin a and pregnancy: A narrative review. Nutrients. 2019;11(3):1-18. doi:10.3390/nu11030681
3. Australian Government. National Health & Medical Research Council. Vitamin A. Nutrient Refernce Values for Australia and New Zealand. https://www.nrv.gov.au/nutrients/vitamin-a. Published 2014. Accessed October 3, 2019.
4. Natural Medicines Database. Vitamin A. Professional Monograph. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=964. Published 2019. Accessed October 3, 2019.
5. Rothman KJ, Moore LL, Singer MR, Nguyen U-SDT, Mannino S, Milunsky A. Teratogenicity of High Vitamin A Intake. Obstet Gynecol Surv. 1996;51(5):275-276. doi:10.1097/00006254-199605000-00007
6. Goncalves A, Roi S, Nowicki M, et al. Fat-soluble vitamin intestinal absorption: Absorption sites in the intestine and interactions for absorption. Food Chem. 2015;172:155-160. doi:10.1016/j.foodchem.2014.09.021
7. Haskell MJ. The challenge to reach nutritional adequacy for vitamin A: b-carotene bioavailability and conversion—evidence in humans. Am J Clin Nutr. 2012;96(5):1193-1203. doi:10.3945/ajcn.112.034850.1