Review

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Vitamin A in pediatrics: An update from the Nutrition Committee of the French Society of Pediatrics

Vitamine A chez l'enfant : mise au point du Comité de nutrition de la Société française de pédiatrie

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Summary

Vitamin A (retinol) fulfills multiple functions in vision, cell growth and differentiation, embryogenesis, the maintenance of epithelial barriers and immunity. A large number of enzymes, binding proteins and receptors facilitate its intestinal absorption, hepatic storage, secretion, and distribution to target cells. In addition to the preformed retinol of animal origin, some fruits and vegetables are rich in carotenoids with provitamin A precursors such as β-carotene: 6 μg of β-carotene corresponds to 1 μg retinol equivalent (RE). Carotenoids never cause hypervitaminosis A. Determination of liver retinol concentration, the most reliable marker of vitamin A status, cannot be used in practice. Despite its lack of sensitivity and specificity, the concentration of retinol in blood is used to assess vitamin A status. A blood vitamin A concentration below 0.70 μmol/L (200 μg/L) indicates insufficient intake. Levels above 1.05 μmol/L (300 μg/L) indicate an adequate vitamin A status. The recommended dietary intake increases from 250 μg RE/day between 7 and 36 months of age to 750 μg RE/day between 15 and 17 years of age, which is usually adequate in industrialized countries. However, intakes often exceed the recommended intake, or even the upper limit (600 μg/day), in some non-breastfed infants. The new European regulation on

Résumé

La vitamine A (rétinol) a de multiples fonctions dans la vision, la croissance et la différenciation cellulaires, l'embryogenèse, l'entretien des barrières épithéliales, l'immunité, etc. De nombreux enzymes, protéines de liaison et récepteurs facilitent l'absorption digestive, le stockage hépatique, la sécrétion hépatocytaire et la distribution du rétinol aux cellules cibles. Hors le rétinol préformé d'origine animale, certains légumes et fruits sont riches en caroténoïdes à activité provitaminique A, comme le ß-carotène, dont 6 μg correspondent à 1 équivalent rétinol (ER). Les caroténoïdes n'entraînent jamais d'hypervitaminose A. La concentration hépatique, marqueur fiable du statut, étant, en pratique, inaccessible, on a recours, malgré son manque de sensibilité et de spécificité, à la rétinolémie. Une concentration inférieure à 0,7 μmole/L (200 μg/L) est un indicateur d'apports insuffisants. Une rétinolémie supérieure à 1,05 μmole/L (300 μg/L) reflète un statut satisfaisant. Les apports journaliers conseillés en ER vont de 250 μg à 7–36 mois jusqu'à 750 μg à 15–17 ans et sont satisfaits dans les pays industrialisés. Les apports dépassent les apports conseillés, voire les limites de sécurité (600 μg/j) chez certains nourrissons non allaités. La nouvelle réglementation européenne (2015) sur les préparations pour nourrissons

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infant and follow-on formulas (2015) will likely limit this excessive intake. In some developing countries, vitamin A deficiency is one of the main causes of blindness and remains a major public health problem. The impact of vitamin A deficiency on mortality was not confirmed by the most recent studies. Periodic supplementation with high doses of vitamin A is currently questioned and food diversification, fortification or low-dose regular supplementation seem preferable.
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et de suite, et la suppression des suppléments en rétinol non justifiés devraient en principe limiter cet excès d'apport. Dans certains pays en développement, la carence vitaminique A, cause majeure de cécité, reste d'actualité. Son impact sur la mortalité préscolaire n'apparaît plus dans des études récentes ; le recours aux charges semestrielles jusque-là recommandées est controversé, au profit d'une meilleure diversification alimentaire, voire d'aliments enrichis ou d'une supplémentation régulière à faible dose.
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1. Introduction

Vitamin A (retinol) is a fat-soluble vitamin that plays a key role in vision, growth, cellular differentiation, embryonic and fetal development, immunity, and preservation of skin and mucosal barriers. This vitamin is provided as preformed vitamin A in foods of animal origin and as carotenoids (provitamin A), mainly β-carotene, in some fruits and vegetables. Vitamin A deficiency remains a public health problem in developing countries, mainly in Africa and in the Indian subcontinent, with a high prevalence in young children (in association with protein-energy malnutrition) and in pregnant women [1,2]. This deficiency is rare in developed countries, occurring in some diseases that induce lipid maldigestion (e.g., cystic fibrosis [3], cholestasis), lipid malabsorption (e.g., short-bowel syndrome, hypobetalipoproteinemia), or any liver disease associated with low liver vitamin A concentration and decreased synthesis of retinol-binding protein 4 (RBP4). A mutation in the RBP4 gene induces early and severe retinitis pigmentosa with undetectable plasma RBP and severe depletion of blood retinol [4]. Vitamin A in acute or chronic excess can produce various disorders, including cranial hypertension [5–7].

2. History

The therapeutic efficacy of animal liver (via local application or oral ingestion) against blindness and keratomalacia has been known since antiquity. In 1913, McCollum and Davis, and Osborne and Mandel isolated a fat-soluble factor A, which was found in cod liver oil, animal liver, butter and egg yolk. This factor was efficient against keratomalacia in deficient rats. In 1930, Capper and Moore showed that β-carotene can also correct the consequences of vitamin A deficiency and concluded that this molecule could be converted into vitamin A. The first descriptions of human deficiencies were reported in Denmark, where an outbreak of keratomalacia from 1911 to 1917 was linked to the replacement of butter with cheaper margarine. This issue was solved when the blockade of the Danish harbors by the German Navy forced the Danish population to go back to butter. The chemical structure of vitamin A was identified by Karrer in 1931 and it was synthesized by Isler in 1947 [8,9].

3. Physiology

3.1. Chemical structure

3.1.1. Vitamin A or retinol

Retinol is only found in animal organisms. It is a 20-carbon molecule belonging to the retinoid family. The molecule has a cyclohexenyl (β-ionone) core and a lateral chain with a polar terminal radical that can be hydroxyl (retinol), aldehyde (retinal) or carboxyl (retinoic acid). Retinal and retinoic acid are the two active forms of vitamin A. There are many isomers, two of which have physiological functions: 11-*cis*-retinal and 9-*cis*-retinoic acid [10]. In foods, vitamin A is found as retinyl-ester (mainly retinyl-palmitate).

3.1.2. Carotenoids

Carotenoids, which are pigments present in some fruits and vegetables, mainly yellow and orange vegetables and those with dark-green leaves, have provitamin A properties. These molecules are symmetrical and can be split into two retinol molecules by an enzyme closely regulated to avoid any risk of hypervitaminosis A. The vitamin A activity of β-carotene is lower than expected from its chemical composition. Roughly, 6 mg of β-carotene generate one retinol equivalent (RE) and 12 mg of the other provitamin A carotenoids (such as α-carotene of β-cryptoxanthin) are needed to yield one RE *(table I)* [11].

3.2. Gut absorption

3.2.1. Retinol

After micellar solubilization, retinol esters are hydrolyzed by nonspecific pancreatic lipases and by a retinyl-ester hydrolase in the brush border membrane of enterocytes. The absorption rate of free retinol is high (between 75% and 90%). At physiological concentrations, absorption occurs through a diffusion process facilitated by several transporters. At pharmacological dosages, free retinol is also absorbed via a passive

Table I
Units, equivalents and retinol conversion factors.

1 µg of retinol = 1 µg of retinol equivalent (RE)
1 µg of retinol = 3.33 IU of retinol
1 IU of retinol = 0.30 µg of retinol[a]
1 RE corresponds to 6 µg[a] *of β-carotene or 12 µg*[b] *of another carotenoid with provitamin A properties*
Conversion of µg retinol to nanomolar values and vice versa (MW = 286)
µg of retinol × 3.5 = nmol of retinol
nmol of retinol × 0.286 = µg of retinol

IU: international unit; nmol: nanomole; MW: molecular weight.
[a] *http://apps.who.int/iris/bitstream/10665/42716/1/9241546123.pdf, p. 26.*
[b] *The Institute of Medicine (IOM) recommends conversion coefficients to be double these values, respectively 12 and 24 µg of carotene for 1 µg RE [6].*

diffusion process. Within the enterocyte, retinol is linked to two cell proteins, re-esterified, incorporated into chylomicrons and finally transported to the liver via the lymphatic system and then the blood [6,7,12,13].

3.2.2. Carotenoids

After micellar solubilization, carotenoids are absorbed via a passive diffusion process for which some cholesterol and fatty acid transporters could play a facilitating role. The absorption rate varies from 9% to 60% depending on the type and the amount of carotenoids, the food matrix and cooking. Lipids increase carotenoid absorption. The conversion factor ranges from 28/1 for the β-carotene contained in some vegetables to 2/1 for the same β-carotene in oil solution. Before absorption, a carotenoid must be separated from the alimentary matrix, which is facilitated by homogenization and mild heating. For instance, 65% of β-carotene is absorbed from carrot puree whereas only 41% is absorbed from raw carrots [11,12].

3.3. Hepatic storage

Hepatocytes capture 75% of the retinyl-esters contained in chylomicrons and their residual particles. Peripheral tissues, mainly adipose tissue, capture the remaining 25%. After postprandial hepatic uptake, retinol is secreted into the bloodstream following linkage to RBP4, a protein synthesized by the liver, or is stored in specific hepatic stellar cells (Ito cells), accounting for 8% of liver cells and in which 90% of hepatic retinol is found. Retinol is stored as retinyl-ester in large lipid-containing vacuoles. When the body is in need of retinol, the retinyl-esters are transferred into the hepatocytes, hydrolyzed, and the retinol is released from the liver linked to RBP4 [12–14]. The signal informing the liver of vitamin A shortage in peripheral tissue is still unknown.

3.4. Retinol plasma transport

The retinol stored in the liver needs to be linked to apoRBP4 to be secreted into the bloodstream. The retinol/apoRBP4 complex constitutes the holoRBP4, which is secondarily associated with the transthyretin (TTR); this process stabilizes holoRBP4 and prevents renal loss of this complex [6,7]. Zinc is necessary for the synthesis of RBP4 and TTR. In animal models, zinc deficiency induces a decrease in the RBP4 plasma level without a depletion of retinol liver stores. In cystic fibrosis, decreased blood retinol and RBP4 levels have been associated with low plasma zinc levels, which are restored to normal after zinc supplementation [3]. However, the impact of zinc on retinol status seems minor since vitamin A supplementation improves plasma retinol status even in populations with a high prevalence of zinc deficiency [15]. Iron deficiency is also associated with a low plasma retinol level associated with an increase of hepatic retinol and retinyl-esters. This is probably due to impaired hepatic retinol mobilization related to a lower activity of retinyl-ester hydrolases [16].

3.5. Distribution and physiological roles in tissues

HoloRBP4 is reversibly linked to cell membranes of target tissues by a transmembrane receptor, stimulated by retinoic acid 6 (STRA6). This protein allows a specific transport mode, which differs from the three classical mechanisms: primary active, secondary active and channel-facilitated transport [17]. STRA6 is found in many tissues, e.g., retina, brain, muscles, testes and placental epithelial cells. This transporter is not found in the liver nor the gut [17]. Once inside the cell and linked to specific proteins, retinol is partially metabolized to its active forms, retinaldehyde (retinal) and retinoic acid, while the remaining retinol is stored as retinyl-esters [18].

3.5.1. Biological activity

3.5.1.1. In retina

In retina, retinol is oxidized to retinaldehyde (retinal), which is isomerized to 11-*cis*-retinal. In rod cells, 11-*cis*-retinal is linked to a protein (opsin) to form the pigment rhodopsin. This molecule, through a cascade of photochemical reactions, maintains visual capacity in a very low luminosity context. The ability to regenerate rhodopsin depends on retinol availability, and nocturnal blindness (hemeralopia) is an early sign of vitamin A deficiency. In cone cells, the linkage of retinal to a similar protein allows the synthesis of pigments (photopsins) that are involved in the vision of forms and colors [6–8,10,13].

3.5.1.2. In other tissues

Retinoic acid, the other active metabolite of vitamin A, acts on transcriptional regulation of hundreds of genes involved in many processes, e.g., embryogenesis, growth, cell multiplication and differentiation, apoptosis, immunity, hematopoiesis, spermatogenesis and tissue homeostasis (particularly epithelial barriers such as conjunctiva, skin and lung) [6–8,10,13].

4. Assessment of vitamin A status

The concentration of vitamin A in liver, its main storage site, is considered the most reliable marker of vitamin A status. Normal values are above 20 μg/g (20–250 μg/g). This measurement requires a liver biopsy and cannot be obtained in standard clinical practice. An indirect evaluation of vitamin A body stores can be performed by using stable isotopes but the high cost and the technical complexity restricts this method to research settings. In routine practice, vitamin A status is assessed by the plasma retinol level, although the latter does not directly reflect the body's vitamin A pool. The plasma retinol level may decrease when RBP4 is low as a result of infection or zinc deficiency for example, even when the liver vitamin A content remains normal [6,15,16]. On the other hand, plasma retinol can remain normal despite low hepatic levels as a result of homeostatic mechanisms.

The plasma retinol level is considered normal between 1.05 and 4 μmol/L (30–114 μg/dL) *(table I)*. A value below 0.7 μmol/L (20 μg/dL) indicates a deficiency. Values above 1.05 μmol/L indicate a normal vitamin A status [6–8,19,20]. Clinical signs appear below 0.35 μmol/L when hemeralopia can be interpreted as related to vitamin A deficiency. The relative dose–response test based on hepatocyte accumulation of apoRBP4 when liver retinol stores are exhausted and the conjunctiva impression test are no longer used in clinical settings. The very reliable darkness adaptation test cannot be used in children less than 3 years old [6,7,19,20].

5. Food sources

5.1. Retinol

Retinol-containing foods are all of animal origin. Retinol is present as retinyl-ester, mainly retinyl-palmitate. Liver is the richest vitamin A-containing food (10–15 mg/100 g) because it is the storage tissue for vitamin A in animals and humans: 10–15 g of cooked liver is sufficient to provide 1 to 1.5 mg of retinol. A 100-g portion of veal or poultry liver every 2 weeks maintains vitamin A stores in adults. Other foods that contain high levels of vitamin A are butter, cheese and whole milk; 150 g of butter, 200 g of camembert, 300 g of Emmentaler or 3 L of milk provide the same amount of vitamin A as 10 g of cooked liver. Eggs, fish and meats have a lower vitamin A content *(table II)* [6,7]. Retinol concentrations in human milk (in industrialized countries) range between 229 and 831 μg/L during the first 6 months of lactation depending on dietary intake [7,21].

5.2. Carotenoids

The other sources of vitamin A are plant foods that have high carotenoid content (mainly β-carotene) [6,7,11,22]. These are yellow or orange fruit and vegetables such as yam, pumpkin, carrot, apricot, mango, some melons and dark-green leafy vegetables, such as spinach, lettuce, broccoli and Brussels sprouts *(table III)*. In these vegetables, the carotenoid concentration varies in parallel with the chlorophyll content. However, the β-carotene provided by green leafy vegetables is less well absorbed and converted into retinol than the β-carotene from yellow or orange fruit [23]. Genetically modified "golden rice" can contain up to 3500 μg/100 g of β-carotene. The mean β-carotene content of this rice ranges from 2000 to 3000 μg/100 g. With a mean conversion factor of β-carotene to retinol of 3.8, the RE of this rice is about 500–800 μg/100 g. This rice could increase the vitamin A intake in countries in which rice is the main staple food [24]. Finally, vitamin A is sensitive to heat, light and oxidation, which has implications for storage [8].

Table II
Main sources of retinol according to the 2016 CIQUAL table [53].

Foods	Retinol average content (μg/100 g)
Cod liver oil	30,000
Cooked veal liver	10,500
Cooked chicken liver	3980
Duck terrine	2000
Butter	716
Camembert Cheese	470
Soft boiled egg	132
UHT whole milk	31.4
Natural yogurt	11
Cooked trout	19
Cooked salmon	5

CIQUAL: Information Center on Food Quality (Centre d'information sur la qualité des aliments); UHT: ultra-high temperature.

Table III
Main sources of beta-carotene according to the 2016 CIQUAL table [53].

Foods	Beta-carotene average content (μg/100 g)
Sweet potato	10,500
Cooked pumpkin	6020
Cooked chards	3650
Lettuce	3640
Cooked carrots	3340
Melon	2020
Vegetable soup	1710
Cooked spinach	1610
Apricot	1090
Bell pepper	834
Tomato concentrate	784
Cooked broccolis	597
Raw tomatoes	449
Cooked peas	414
Orange	71

CIQUAL: Information Center on Food Quality (Centre d'information sur la qualité des aliments).

6. Dietary reference values for vitamin A

In 2015, the European Food Safety Authority (EFSA) published dietary reference values (DRVs) in RE for adults and children aged 7 months to 17 years. These DRVs are equivalent to the recommended daily intake used in France (*Les apports nutritionnels conseillés*) [7,25]. For adults, the total vitamin A DRV (preformed vitamin A plus vitamin A obtained from carotenoids) is set at 750 μg RE/day for men, 650 μg RE/day for women and 1300 μg RE/day for breastfeeding women *(table IV)*. For children, these values are set at 250 μg ER/day from 7 months to 3 years and to 750 μg and 650 μg RE/day for boys and girls from 15 to 17 years, respectively *(table IV)*. For adults and children, DRV values are overall below the French recommendations and those published by the Institute of Medicine (IOM) [6] except for breastfeeding women *(table IV)*. The new DRVs are lower in young children, mainly from 7 months to 3 years (250 μg/day), compared with the previous recommendations of the European Scientific Committee on Food (SCF) [26], of many European and North American countries, and those of the World Health Organization (WHO). This decrease in DRVs stems from the application of Olson's factorial method [7] in all age groups, while it was only applied to adults in earlier recommendations because of the lack of data in children. In children born at full term, there is no DRV based on real needs below 6 months but adequate intakes are based on observed intakes of exclusively breastfed children. The content of vitamin A in human milk is variable. Assuming a mean concentration of 450 μg/L in human milk and a daily intake of 0.8 L, in 2013, the EFSA estimated that 350 μg/day is an adequate vitamin A intake for infants from birth to 6 months of age in Europe [26].

Table IV
Recommended intakes of total vitamin A.

Age	ANC[a] (2001)	DRV[b] (2015)
Months (M), Years (Y)	**μg RE/day**	**μg RE/day**
Birth to 12 M	350	
7–12 M		250
1–3 Y	400	250
4–6 Y	450	300
7–9 Y	500	
7–10 Y		400
10–12 Y	550	
11–14 Y		600
13–15 Y		
Boys	700	
Girls	600	
15–17 Y		
Boys		750
Girls		650
16–19 Y		
Boys	800	
Girls	600	
Adults		
Men	800	750
Women	600	650
Pregnant women	700	700
Breastfeeding women	950	1300

RE: retinol equivalent.
[a] *ANC: apports nutritionnels conseillés (recommended dietary intakes) [25]*
[b] *DRV: Dietary Reference Values of the EFSA (European Food Safety Authority) [7]*

Table V
Upper safe limits for preformed vitamin A (Scientific Committee on Food, 2002) [27].

Age (years)	Retinol and retinyl-esters μg RE/day
Birth to 1 year[a]	600
1–3 years	800
4–6 years	1100
7–10 years	1500
11–14 years	2000
15–17 years	2600
Men	3000
Women of childbearing age	
Pregnant women	

RE: retinol equivalent.
[a] *Value suggested by the Institute of Medicine [6]. No value given by the Scientific Committee on Food for that age group.*

The safe upper limit for vitamin A intake only takes into account preformed retinol. In 2002, the SCF estimated these limits to be 3000 μg/day for men and women of childbearing age. In children, these limits (in μg RE/day) are at 800 from 1 to 3 years, 1100 from 4 to 6 years, 1500 from 7 to 10 years, 2000 from 11 to 14 years, and 2600 from 15 to 17 years *(table V)* [27]. The safe upper limit for children from birth to 1 year has been estimated at up to 600 μg/day by IOM in 2001. This value was obtained by dividing by 10 (as a safety factor) the lowest dose (6000 μg/day) that produced side effects [6].

7. Vitamin A deficiency

Based on a low plasma retinol concentration (<0.70 μmol/L), over a 10-year period (2005–2015), the WHO estimated that 190 million preschool-aged children (95% confidence interval [CI]: 178–202 million) and 19.1 million pregnant women (95% CI: 9.9–23 million) had vitamin A deficiency. Therefore, vitamin A deficiency affected 33% of preschool-aged children and 15% of pregnant women in the population at risk of vitamin A deficiency worldwide [2]. In industrialized countries, vitamin A deficiency is very rare apart from the above-described pathological conditions.

7.1. Ocular manifestations: hemeralopia and xerophthalmia

Vitamin A deficiency is one of the leading causes of blindness worldwide [6–8].

7.1.1. Hemeralopia

Hemeralopia is often the first clinical sign of vitamin A deficiency (WHO integrates it into the first stage of xerophthalmia). Retinol deficiency increases the regeneration time of rhodopsin with consequently a delay in adaptation to darkness. Young children and pregnant and breastfeeding women stumble when moving from a well-lit to a dark place. At this stage, vitamin A supplementation ensures a complete recovery without sequelae.

7.1.2. Xerophthalmia

Xerophthalmia refers to the epithelial ocular disease involving the conjunctiva and the cornea. It causes conjunctival dryness and atrophy and sometimes Bitot's spots, which are produced by cellular debris on the temporal conjunctiva [28]. Bitot's spots are white or yellow with a bullous aspect because of bacterial gas production (*Corynebacterium xerosis*). At a later stage, corneal lesions appear. Corneal xerosis occurs first, followed by keratomalacia with a softening, deformation and corneal ulcerations leading to eye destruction. Corneal opacification can also lead to blindness [6–8].

7.2. Skin manifestations

Skin manifestations usually take the form of a follicular keratosis by atrophy of the sebaceous and sweat glands, with dry skin, papular rash and hyperkeratosis [6–8].

7.3. The effect on the immune system and mortality

In 1928, Green et al. reported an increased frequency of infections in vitamin A-deficient rats [9]. In 1983, an association between clinical signs of vitamin A deficiency and prevalence of diarrhea, respiratory diseases and mortality was reported in Indonesian children [29]. These observations led to numerous randomized trials to assess the effect of vitamin A supplementation on mortality. A meta-analysis published in 1993 showed that vitamin A supplementation decreased mortality by about 23% [30]. As a result, high-dose vitamin A (200,000 IU or 60 mg every 6 months) supplementation programs were implemented in more than 100 developing countries over the last 20 years. The relevance of these programs is now questioned because only one of the seven trials conducted since 1993 demonstrated a benefit on mortality [31]. The largest of these trials, conducted in 2 million Indian children, did not show a decrease in mortality [32]. Methodological problems may explain the negative results of some of these trials but the oldest trials were conducted in regions where vitamin A deficiency was more prevalent and more severe. Differences in the disease pattern in the studied populations could also account for this lesser impact of vitamin A supplementation on mortality. Vitamin A supplementation seems to have mainly had an impact on mortality related to measles and to a lesser extent to diarrhea [33]. Clinical trials examining the effect of vitamin A supplementation in hospitalized children showed an effect on mortality only in measles [34,35]. No effect was demonstrated for diarrhea [36] and some studies even showed a deleterious effect for respiratory diseases [37]. The oldest studies were conducted in populations with low immunization coverage and in which the diarrhea-related mortality was higher than observed with current treatments (oral rehydration and zinc supplementation). The most recent estimates suggest that mortality related to vitamin A deficiency in children less than 5 years of age with measles or diarrhea was no more than 1.7% of the total number of deaths [38]. This could explain the negative results of the most recent studies. These negative results question the relevance of high-dose vitamin A capsule distribution programs for reducing mortality. The need to consume foods naturally rich in vitamin A or fortified to provide a daily dose of vitamin A corresponding to requirements is not questioned. The trial results mentioned above have also led to a new interest in the relationship between vitamin A deficiency, high-dose supplementation and immunity. Several experimental studies suggest the importance of the active metabolite, retinoic acid, on the modulation of the immune system, dendritic cell maturation, the "homing" (domiciliation) of T and B cells in the intestinal mucosa, and the development and differentiation of T cells [39]. A recent interpretation of the discordant results on mortality ascribes the effect of high doses of vitamin A on nonspecific immunity to the amplification of nonspecific effects of vaccines on immunity [40]. The effects of vitamin A vary depending on whether or not the population is vaccinated and depend on whether the vaccines given before vitamin A are live vaccines (very strong positive effect of measles vaccine) or killed vaccines (negative effect in girls of anti-tetanus–polio–diphtheria vaccine). The current discussion on whether to distribute high doses of vitamin A as a supplement highlights the need for a better understanding of the mechanisms involved and for distinguishing between physiological doses and high doses of vitamin A given to children who are deficient or not deficient.

7.4. Embryonic and fetal damage

In animals, vitamin A deficiency can result in fetal resorption or eye, lung, cardiovascular or urogenital malformations. The same malformations are observed in fetal knockout rat for the nuclear retinoid receptor. In humans, the teratogenesis related to vitamin A deficiency is poorly documented. In late pregnancy and the perinatal period, when retinol storage takes place in the liver, various studies show that vitamin A deficiency can slow fetal and postnatal growth [7] and pre- and postnatal lung maturation [41], and it plays a role in bronchopulmonary dysplasia in premature infants [22].

8. Hypervitaminosis A

Only an excess of retinol can cause acute or chronic disorders [5–7]. Excessive intakes of carotenoids, which cause hypercarotenemia, never cause hypervitaminosis A and are only expressed by yellow skin pigmentation ("carrot" color) without pathological effects, and without any rise in plasma or hepatic retinol concentrations. Rarely, hyper-β-carotenemia can also be due to a lack of the enzyme β-carotene 15,15-prime-mono-oxygenase 1 (OMIM 115300), preventing the conversion of β-carotene to retinol and resulting in a yellow-orange skin color with very high levels of β-carotene and a risk of vitamin A deficiency.
A good indicator of hypervitaminosis A is a persistently high fasting retinyl-ester level in the plasma.

8.1. Acute intoxication

Acute intoxication can occur when the intake of retinol has exceeded (more than 100 times in adults and more than 20 times in children) the recommended daily intake [5]. Most children aged from 1–6 years old tolerate doses of 200,000 IU (60 mg) administered every 4–6 months. Signs of acute intoxication include headache, dizziness, vomiting and irritability, reflecting intracranial hypertension and diarrhea. Intracranial hypertension, which induces a bulging of the fontanels in infants, has been explained by a lack of cerebrospinal fluid resorption through a yet unknown mechanism [42].

8.2. Chronic intoxication

Chronic intoxication results from excessive intake of retinol for months or years. In adults, daily doses greater than 25,000 IU (7.5 mg) for 6 years or 100,000 IU (30 mg) for 6 months is considered toxic. In young children, doses of 1500 IU/kg/day (450 μg/kg/day) can lead to hypervitaminosis [5]. In adults, chronic hypervitaminosis is associated with asthenia, anorexia, vomiting and alopecia as well as liver disease of varying severity, ranging from an isolated and reversible increase in transaminases to liver fibrosis or cirrhosis. Hypervitaminosis A also induces osteopenia with increased fracture risk [5–7]. The clinical picture in children may include headache, vomiting, irritability, lethargy, bone pain, peeling skin, brittle nails, cheilitis, fever, liver enlargement and infants present with bulging fontanels. Hypercalcemia is common because of increased bone resorption with long bones remodeling by default. These alterations are the consequences of the direct action of activated derivatives of vitamin A on the bone. Hypercalcemia can cause nephrocalcinosis and periosteal calcifications. Transaminases and alkaline phosphatases are elevated. There is an increase in plasma retinol, RBP4 and retinyl-esters. The liver vitamin A content is very high (higher than 572 mg/g) and there are too many, and enlarged, Ito cells [5–7].

8.3. Pregnancy

A worrying complication of excessive vitamin A intake is the occurrence of birth defects; their severity and nature depend on the time of exposure to high levels of vitamin A. Malformations may affect the nervous system, skeleton, heart and urinary tract. Hypervitaminosis in pregnant women may result from excessive consumption of supplements but also, to a lesser extent, from excessive intake of foods extremely rich in vitamin A, such as animal liver, mainly from veal and poultry. The teratogenic effect of vitamin A has been shown in many studies and is due to the teratogenicity of 13-*cis*-retinoic acid. Although this risk is well acknowledged, the threshold beyond which it occurs remains a matter of debate (between 3000 and 10,000 μg/day [10,000–33,000 IU/day]). Considering this risk, the SCF set the upper limit of intake in pregnant women, or in women of childbearing age to 3000 μg RE/day, which is the same as proposed for men or women [27]. In a recent study, E. Elefant, in A. Jardel [43] concluded that an intake of retinol up to 10,000 IU/day (3 mg/day) in the first trimester (this intake cannot be reached with a normal diet) does not expose the fetus to any risk of malformation. Between 10,000 and 30,000 IU/day (3–9 mg/day) the risk seems nonexistent or minimal. Pharmacokinetic studies in humans and monkeys suggest that a dose causing malformations would probably be higher than 30,000 IU/day (9 mg/day).

9. Intakes of vitamin A in France

9.1. Adults and children over 3 years of age

A nationwide survey on individual food consumption (INCA 2) was conducted in 2006–2007 among 1918 adults and 1444 children aged 3–17 years. The results of the initial report [44] were reviewed by the National Agency for Safety of Foods, Environment and Labor (ANSES) in 2015 [45]. Mean intakes (±standard deviation) in total vitamin A (retinol + β-carotene) estimated from nonfortified diets were 833 ± 261 μg RE/day for adults and 571 ± 204 μg RE/day for children. The prevalence of inadequate intakes was estimated by comparing these intakes with the average nutritional requirements established by the Agence française de Sécurité sanitaire des aliments (AFSSA) [45]. The prevalence is low in adults and children from 3 to 12 years but higher in adolescents, especially boys 16–17 years of age, with a possible risk of insufficient intake. In the INCA 2 survey, the prevalence of intakes exceeding the safe upper limits for retinol is zero in adults and 0.1% in children over 3 years [45]. In children, the foods that contribute the most to high retinol intakes are: processed meat (19%), offal, including liver (15%), butter (11%), cheese (9%), milk (8%), and pastries and cakes (8%) [44]. As the livers of animals are very rich in vitamin A, the "Nutrition during and after pregnancy" guide of the French National Programme for

Nutrition and Health (PNNS: Programme National Nutrition Santé) recommends that pregnant women should avoid eating liver or liver products [46].

9.2. Children less than 3 years of age

9.2.1. Children exclusively breastfed until 6 months

Assuming a mean milk retinol concentration of 530 μg/L and an average daily consumption of 800 mL of breast milk, the average daily intake of retinol can be estimated at 424 μg in breastfed infants [7,21].

9.2.2. Non-breastfed children

The Babies' food consumption survey (Nutri-Bébé Study, 2013; unpublished results) conducted in France among 1035 children aged 15 days to 35 months determined the daily intake of total vitamin A in this population, including preformed vitamin A. The means and 90th percentile values are shown in *table VI*. For all age groups, the mean intakes of total vitamin A are higher than those recommended by the AFSSA, EFSA, and IOM [6,7,25,26]. The average intake of preformed retinol, 531 μg ER/day in the age range from 15 days to 3 months, declines from 5 months to reach 247 μg ER/day in the 30- to 35-month-old age group. The proportion of preformed retinol is high in the first months and then decreases in favor of β-carotene at the time of complementary feeding with the introduction of vegetables and fruits. In some infants, retinol intakes are increased by vitamin A supplements: 8% in the age group from 15 days to 3 months and 3–4% in the 7- to 9-month-old age group receiving a mixture of vitamins A, D, E and C. The intake of retinol in some infants from birth to 12 months can even exceed 600 μg RE/day, which is the safe upper limit still specified by IOM *(table V)*. For children aged 1–3 years, the upper safe limit of 800 μg RE/day set in 2002 by the SCF was not reached [27]. In children less than 3 years old, foods contributing most to retinol intake are among "specific baby foods" infant formulas, follow-on formulas, the so-called growing-up milks, meat and vegetable dishes and, for other foods, dairy products.

The Commission Directive 2006/141/EC of 22 December 2006 on infant formulas and follow-on formulas sets the total vitamin A content (total RE) for these preparations to a minimum of 60 μg RE and a maximum of 180 μg RE/100 kcal, which theoretically allows values from 360 to 1260 μg/L [47]. In infant formulas sold in France, according to data from the French Association of Ambulatory Pediatrics (AFPA), the concentrations of vitamin A are between 500 and 810 μg/L for infant formula, 580 and 810 μg/L for follow-on formula, and 450 and 878 μg/L for the so-called growing-up milks [48]. Dietary intakes of vitamin A greater than the DRV in infants are also reported in other countries. Thus, the EFSA noted in 2014 mean or median values ranging from 510 μg RE/day to 980 μg RE/day before 6 months and from 530 to 1090 μg RE/day from 6 to 12 months [49]. In a survey based on the supply and consumption of vitamin A supplements conducted in 2008 in the US, safe upper limits are exceeded in 26% of infants aged from 6 to 11 months, 31% of children from 12 to 23 months, and 59% of children from 24 to 47 months [50]. The new European regulation for infant and follow-on formulas (2015) that will be enforced in 2020 set the minimum content of preformed vitamin A to 70 μg and the maximum at 114 μg/100 kcal [51]. This means an increase of 10 μg for the minimum content and a decrease of 66 μg for the maximum content level. These values do not take into account the ER contributions by carotenoid intake as was done previously.

Many infants and young children receive vitamin A intakes exceeding the safe upper limits adopted by the IOM and SCF, 600 and 800 μg ER/day, respectively *(table V)*, without an apparent clinical symptom, presumably because of the very large difference between the intakes that have led to clinical effects and the safety limits. In 1990, Hathcock et al. [52] considered clinical observations and estimated the amount of vitamin A that can lead to hypervitaminosis in infants at 450 μg RE/kg/day.

Table VI
Dietary intake of total vitamin A and retinol.

Age (months)	Total vitamin A (μg RE/day)		Retinol (μg RE/day)	
	Mean	90th percentile	Mean	90th percentile
15 days to 3 months	540	700	531	681
4	625	841	563	733
5	685	888	518	698
6	771	1060	462	649
7	825	1114	446	608
8–9	823	1120	405	553
10–11	952	1342	428	645
12–17	833	1439	362	541
18–23	627	1055	328	537
24–29	482	883	248	472
30–35	492	899	247	411

Nutri-Bébé Study, Secteur français des aliments de l'enfance (SFAE) 2013, unpublished results.
RE: retinol equivalent.

10. Recommendations

10.1. In developing countries

In countries where vitamin A deficiency in children is a public health problem, the use of regular supplementation or fortified foods is essential. The latter approach seems preferable to the periodic use of high-dose supplements.

10.2. In developed countries

For children aged from 7 months to 3 years, intakes of total vitamin A should be closer to the recent EFSA recommendation published in 2015, i.e., 250 μg RE/day.

The new regulation on infant formula and follow-on formulas of 2015, applicable in 2020, reduced the maximum levels from 180 to 114 μg RE/100 kcal. This should eliminate the risk of excessive intakes. The maximum levels of vitamin A preparations from cereals and baby food for infants and young children should also be reduced.

For infants born at full term receiving adequate food, regardless of whether the child is breastfed, vitamin A supplements are not recommended except in specific pathological situations.

In humans, the teratogenic risk from vitamin A has only been demonstrated with very high intakes at pharmacological doses (more than ten times the DRV). However, because of the high vitamin A content of animal livers, in France the nutrition guidelines during and after pregnancy recommends, as a precautionary measure, that pregnant women should avoid eating liver (whatever the species) and liver-based products [46].

11. Conclusion

Vitamin A plays an essential role in vision and regulation of many genes involved in growth, cell differentiation, embryonic and fetal development, maintenance of epithelial barriers and immunity. Animal foods (particularly liver) contain a high concentration of retinol and retinyl-esters. Some fruits and vegetables are rich in provitamin carotenoids, of which the most important is β-carotene. The dietary allowances for vitamin A and safety limits for children and adults have been defined. Hypervitaminosis A in pregnant women may cause fetal malformations but this risk appears only for very high intakes of preformed retinol.

Vitamin A deficiency in children remains a public health problem in many developing countries. In France and in other industrialized countries, food consumption surveys conducted in recent years have shown average daily vitamin A intake corresponding to intakes recommended for adults and children more than 3 years of age. In children less than 3 years of age, mean intakes are above the recommended dietary allowances and some even exceed safety limits without apparent clinical consequences.

Disclosure of interest

The authors ABo, ABr, JPC, DD, FF, MLF, JPG, RH, DR, JCR, US, MV and DT declare that they have no competing interest.
CD: Sanofi.

Appendix A. Supplementary data

The French version of this update is available at: www.sfpediatrie.com, http://www.sciencedirect.com or at: http://dx.doi.org/10.1016/j.arcped.2016.11.021.

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