1 **DRAFT SCIENTIFIC OPINION**

2 # Scientific Opinion on Dietary Reference Values for vitamin A[1]

3 **EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA)**[2, 3]

4 European Food Safety Authority (EFSA), Parma, Italy

5 **ABSTRACT**

6 Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies
7 (NDA) derived Dietary Reference Values for vitamin A. The Panel considered that a concentration of
8 20 µg retinol/g liver can be used as a target value for establishing the Average Requirement (AR) for vitamin A.
9 In the absence of better characterisation of the relationship between intake of vitamin A and liver stores, a
10 factorial approach was applied. This approach considered a total body/liver retinol store ratio of 1.25 (i.e. 80% of
11 retinol body stores in the liver), a liver/body weight ratio of 2.4 %, a fractional catabolic rate of body retinol of
12 0.7 % per day, an efficiency of storage in the whole body for ingested retinol of 50 % and reference weights for
13 adult women and men in the EU of 58.5 and 68.1 kg, respectively. ARs of 570 µg RE/day for men and
14 490 µg RE/day for women were derived. Assuming a coefficient of variation (CV) of 15 %, PRIs of
15 750 µg RE/day for men and 650 µg RE/day for women were set. For infants aged 7–11 months, children and
16 adolescents, the same equation as for adults was applied by using specific values for reference body weight and
17 liver/body weight ratio. For catabolic rate, the adults' value corrected on the basis of a growth factor was used.
18 Estimated ARs range from 190 µg RE/day in infants aged 7–11 months to 580 µg RE/day in adolescent boys.
19 PRIs for infants, children and adolescents were estimated based on a CV of 15 % and range from 250 to
20 750 µg RE/day. For pregnancy and lactation, additional vitamin A requirements related to the accumulation of
21 retinol in fetal and maternal tissues and transfer of retinol into breast milk were considered and PRIs of 700 and
22 1 350 µg RE/day, respectively, were estimated.

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25 **KEY WORDS**

26 vitamin A, retinol, carotenoid, Average Requirement, Population Reference Intake, Dietary Reference Value

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a Scientific Opinion on Dietary Reference Values (DRVs) for the European population, including vitamin A.

Vitamin A is a fat soluble vitamin obtained from the diet either as preformed vitamin A (mainly retinol and retinyl esters) in foods of animal origin, or as provitamin A carotenoids in plant derived foods. The term vitamin A comprises all-*trans*-retinol (also called retinol) and the family of naturally occurring molecules associated with the biological activity of retinol (such as retinal, retinoic acid, retinyl ester), as well as provitamin A carotenoids that are dietary precursors of retinol. The biological value of substances with vitamin A activity is expressed as retinol equivalent (RE). Specific carotenoids/retinol equivalency ratios are defined for provitamin A carotenoids, which account for the less efficient absorption of carotenoids and their bioconversion to retinol. On the basis of available evidence, the Panel decided to maintain the conversion factors proposed by the SCF for the European populations, namely 1 µg RE equals to 1 µg of retinol, 6 µg of β-carotene, and 12 µg of other provitamin A carotenoids. Vitamin A requirement can be met with any mixture of preformed vitamin A and provitamin A carotenoids that provides an amount of vitamin A equivalent to the recommended level in terms of µg RE/day.

Vitamin A is involved in vision as retinal, which plays a central role in the mechanisms of photo-transduction, and in the systemic maintenance of the growth and integrity of cells in body tissues through the action of retinoic acid, which acts as regulator of genomic expression. The most specific clinical consequences of vitamin A deficiency is xerophthalmia, which encompasses a clinical spectrum of ocular manifestations. In low-income countries, vitamin A deficiency in young infants and children has been associated with increased infectious morbidity and mortality, including respiratory infection and diarrhoea.

Preformed vitamin A is efficiently absorbed (70–90 %). The absorption of β-carotene appears to be highly variable (5–65 %), depending on food- and diet-related factors, as well as the nutritional, health, and genetic characteristics of the subject. The intestine is the primary tissue where dietary provitamin A carotenoids are converted to retinol. Retinol, in form of retinyl esters, and provitamin A carotenoids enter the body as a component of nascent chylomicrons secreted into the lymphatic system. Most dietary retinol (chylomicron and chylomicron remnant) is taken up by the liver which is the major site of retinol metabolism and storage. Hepatic retinyl esters are hydrolysed to free retinol, and delivered to the tissues by retinol-binding protein. The efficiency of storage and catabolism of retinol depends on vitamin A status. Low retinol stores are associated with a reduced efficiency of storage and decreased absolute catabolic rate. The majority of retinol metabolites are excreted in the urine, in faeces via the bile and to a lesser extent in breath.

Vitamin A status is best expressed in terms of total body store of retinol (i.e. as free retinol and retinyl esters), or alternatively, of liver concentration of the vitamin. A concentration of 20 µg retinol/g liver (0.07 µmol/g) in adults represents a level assumed to maintain adequate plasma retinol concentrations, prevent clinical signs of deficiency and provide adequate stores. The Panel considered that this can be used as a target value for establishing the Average Requirement (AR) for vitamin A for all age groups. The relationship between dietary intake of vitamin A and retinol liver stores has been explored with the stable isotope dilution methods but data are considered insufficient to date to derive an AR. A factorial approach was applied. This approach considered a total body/liver retinol store ratio of 1.25, a liver/body weight ratio of 2.4 %, a fractional catabolic rate of retinol of 0.7 % per day of total body stores, an efficiency of storage in the whole body for ingested retinol of 50 % and the reference weights for adult women and men in the EU of 58.5 and 68.1 kg, respectively. On the basis of this approach, ARs of 570 µg RE/day for men and 490 µg RE/day for women were derived after rounding. Assuming a coefficient of variation (CV) of 15 % because of the variability in requirement and of the large uncertainties in the dataset and rounding, PRIs of 750 µg RE/day for men and 650 µg RE/day for women were set.

For infants aged 7–11 months, children and adolescents, the same target concentration of retinol in the liver and the same equation as for adults were used to calculate ARs. Specific values for reference body weight and for liver/body weight ratio were used. Although there are some indications that retinol catabolic rate may be higher in children than in adults, data are limited. The Panel decided to apply the value for catabolic rate in adults and correct it on the basis of a growth factor. Estimated ARs range from 190 µg RE/day in infants aged 7–11 months to 580 µg RE/day in adolescent boys. PRIs for infants, children and adolescents were estimated based on a CV of 15 % and range from 250 to 750 µg RE/day.

For pregnant women, the Panel assumed that a total amount of 3 600 µg retinol is accumulated in the fetus over the course of pregnancy. Considering that the accretion mostly occurs in the last months of pregnancy, and assuming an efficiency of storage of 50 % for the fetus, an additional daily requirement of 52 µg RE was calculated for the second half of pregnancy. In order to allow for the extra need related to the growth of maternal tissues, the Panel applied this additional requirement to the whole period of pregnancy. Consequently, an AR of 540 µg RE/day was estimated for pregnant women. Considering a CV of 15 % and rounding, a PRI of 700 µg RE/day was derived for pregnant women.

For lactating women, an increase in AR was based on the vitamin A intake required to compensate for the loss of retinol in breast milk. Based on an average amount of retinol secreted in breast milk of 424 µg/day and an absorption efficiency of retinol of 80 %, an additional vitamin A intake of 530 µg RE/day was considered sufficient to replace these losses. An AR of 1 020 µg RE/day was estimated and, considering a CV of 15 % and rounding, a PRI of 1 350 µg RE/day was proposed for lactating women.

Foods rich in retinol include offal and meat, butter, retinol-enriched margarine, milk products, and eggs, while foods rich in β-carotene include vegetables and fruits, such as sweet potatoes, carrots, pumpkins, dark green leafy vegetables, sweet red peppers, mangoes and melons. On the basis of data from 12 dietary surveys in nine EU countries, vitamin A intake was assessed using food consumption data from the EFSA Comprehensive Food Consumption Database and vitamin A composition data from the EFSA nutrient composition database. Average vitamin A intake ranged between 409–651 µg RE/day in children aged 1 to < 3 years, between 607–889 µg RE/day in children aged 3 to < 10 years, between 597–1 078 µg RE/day in adolescents (10 to < 18 years), and between 816–1 498 µg RE/day in adults.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The scientific advice on nutrient intakes is important as the basis of Community action in the field of nutrition, for example such advice has in the past been used as the basis of nutrition labelling. The Scientific Committee for Food (SCF) report on nutrient and energy intakes for the European Community dates from 1993. There is a need to review and if necessary to update these earlier recommendations to ensure that the Community action in the area of nutrition is underpinned by the latest scientific advice.

In 1993, the SCF adopted an opinion on the nutrient and energy intakes for the European Community.[4] The report provided Reference Intakes for energy, certain macronutrients and micronutrients, but it did not include certain substances of physiological importance, for example dietary fibre.

Since then new scientific data have become available for some of the nutrients, and scientific advisory bodies in many European Union Member States and in the United States have reported on recommended dietary intakes. For a number of nutrients these newly established (national) recommendations differ from the reference intakes in the SCF (1993) report. Although there is considerable consensus between these newly derived (national) recommendations, differing opinions remain on some of the recommendations. Therefore, there is a need to review the existing EU Reference Intakes in the light of new scientific evidence, and taking into account the more recently reported national recommendations. There is also a need to include dietary components that were not covered in the SCF opinion of 1993, such as dietary fibre, and to consider whether it might be appropriate to establish reference intakes for other (essential) substances with a physiological effect.

In this context, EFSA is requested to consider the existing Population Reference Intakes for energy, micro- and macronutrients and certain other dietary components, to review and complete the SCF recommendations, in the light of new evidence, and in addition advise on a Population Reference Intake for dietary fibre.

For communication of nutrition and healthy eating messages to the public it is generally more appropriate to express recommendations for the intake of individual nutrients or substances in food-based terms. In this context, EFSA is asked to provide assistance on the translation of nutrient based recommendations for a healthy diet into food based recommendations intended for the population as a whole.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29(1)(a) and Article 31 of Regulation (EC) No 178/2002,[5] the Commission requests EFSA to review the existing advice of the Scientific Committee for Food on population reference intakes for energy, nutrients and other substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

In the first instance, EFSA is asked to provide advice on energy, macronutrients and dietary fibre. Specifically advice is requested on the following dietary components:

- Carbohydrates, including sugars;
- Fats, including saturated fatty acids, polyunsaturated fatty acids and monounsaturated fatty acids, *trans* fatty acids;

[4] Scientific Committee for Food, Nutrient and energy intakes for the European Community, Reports of the Scientific Committee for Food 31st series, Office for Official Publication of the European Communities, Luxembourg, 1993.

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1-24.

- Protein;
- Dietary fibre.

Following on from the first part of the task, EFSA is asked to advise on population reference intakes of micronutrients in the diet and, if considered appropriate, other essential substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

Finally, EFSA is asked to provide guidance on the translation of nutrient based dietary advice into guidance, intended for the European population as a whole, on the contribution of different foods or categories of foods to an overall diet that would help to maintain good health through optimal nutrition (food-based dietary guidelines).

ASSESSMENT

1. Introduction

In 1993, the Scientific Committee for Food (SCF) adopted an Opinion on nutrient and energy intakes for the European Community and derived Average Requirements (ARs) and Population Reference Intakes (PRIs) for vitamin A for adult men and women. Specific PRIs were set for pregnant and lactating women. PRIs for infants 7–11 months, children and adolescents were also proposed.

Vitamin A is a fat soluble vitamin obtained from the diet either as preformed vitamin A (mainly retinol and retinyl esters) in foods of animal origin, or as provitamin A carotenoids in plant derived foods (Figure 1). The purpose of this Opinion is to review Dietary Reference Values (DRVs) for vitamin A. The Panel notes that possible functions of carotenoids other than as dietary precursors of retinol, and evidence for a requirement for carotenoids as such, have been reviewed by the SCF (1993) and other authoritative bodies (DH, 1991; IOM, 2001; WHO/FAO, 2004; D-A-CH, 2013). This is out of the scope of the present Opinion.

2. Definition/category

2.1. Chemistry

The term vitamin A comprises all-*trans*-retinol (also called retinol) and the family of naturally occurring molecules associated with the biological activity of retinol (such as retinal, retinoic acid and retinyl esters), as well as the group of provitamin A carotenoids (such as β-carotene, α-carotene, and β-cryptoxanthin) that are dietary precursors of retinol (Figure 1).

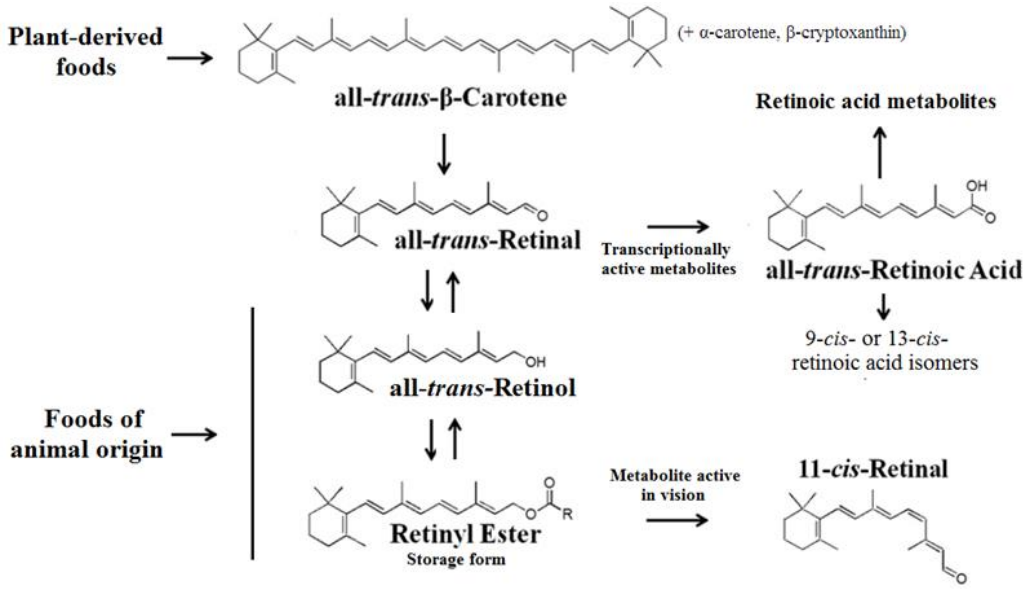


Figure 1: Structure of the naturally occurring forms of vitamin A: all-*trans*-retinol, an all-*trans*-retinyl ester (R=Alkyl chain), all-*trans*-retinal, the active metabolites all-*trans*-retinoic acid (transcriptionally active) and 11-*cis*-retinal (active in vision), and the major provitamin A carotenoid, all-*trans*-β-carotene.

Retinol is composed of a β-ionone ring, a polyunsaturated side chain, and a polar end group (molecular mass 286.5 Da) (Figure 1). This chemical structure makes it poorly soluble in water but easily transferable through membrane lipid bilayers. Preformed vitamin A consists predominantly of retinol and retinyl esters which are supplied in the diet by animal-derived products. The term retinoids refers to retinol and structurally related compounds, including its metabolites (retinyl ester, retinal and retinoic acid), and synthetic analogues (Anonymous, 1983).

Retinol and retinyl esters are the most abundant forms of vitamin A in the body. Retinol is a transport form and a precursor of the transcriptionally active metabolite all-*trans*-retinoic acid, and retinyl esters are retinol storage forms and serve as substrate for the formation of the visual chromophore 11-*cis*-retinal (Al Tanoury et al., 2013). All-*trans*-retinoic acid can be isomerised through a nonenzymatic process to 9-*cis*- or 13-*cis*-retinoic acid isomers. The isomer 13-*cis*-retinoic acid is less transcriptionally active than the all-*trans* and the 9-*cis* isomers. Other forms of retinol and retinoic acid, which include various oxo-, hydroxy- and glucuronide forms, are also present in the body, but at very low concentrations relative to retinol and retinyl esters, and likely appear as catabolic products for elimination from the body (O'Byrne and Blaner, 2013).

Carotenoids are isoprenoids that contain up to 15 conjugated double bonds, synthesised in plants and microorganisms and occuring naturally in fruits and vegetables. Among them, β-carotene, α-carotene, and β-cryptoxanthin are provitamin A carotenoids (Eroglu and Harrison, 2013). To exhibit provitamin A activity, the carotenoid molecule must have at least one unsubstituted β-ionone ring and the correct number and position of methyl groups in the polyene chain (Wirtz et al., 2001).

In this Opinion, the terms retinol, retinoic acid and carotenoids refer to their all-*trans*-isomers, unless specified otherwise.

The biological value of substances with vitamin A activity is expressed as retinol equivalent (RE), with 1 µg RE equal to 1 µg retinol. Specific carotenoids/retinol equivalency ratios are defined for provitamin A carotenoids, which account for the less efficient absorption of carotenoids and their bioconversion to retinol (Section 2.3.9).

2.2. Function of the nutrient

2.2.1. Biochemical functions

Vitamin A is an essential nutrient as humans do not have the capability for *de novo* synthesis of compounds with vitamin A activity. Vitamin A is involved in the visual cycle in the retina and the systemic maintenance of the growth and integrity of cells in body tissues.

In the eye, the active metabolite 11-*cis*-retinal works as a visual chromophore involved in phototransduction. Visual pigments are G-protein-coupled receptors that mediate phototransduction, the process by which light is translated into an electrical (nervous) signal (Palczewski, 2010). In this complex pathway known as the retinoid cycle, 11-*cis*-retinal binds opsin to form rhodopsin and cone pigments (Wald, 1968). Visual perception starts with the absorption of a photon, which induces isomerisation of 11-*cis*-retinal to 11-*trans*-retinal. After bleaching, 11-*trans*-retinal is released from opsin and the 11-*cis*-retinal chromophore is regenerated to sustain vision (von Lintig et al., 2010). In addition, all-*trans*-retinoic acid is also required to maintain normal differentiation of the cornea and conjunctival membranes and of the photoreceptor rod and cone cells of the retina (Blomhoff, 2005).

Retinoic acid is a transcriptionally active metabolite and is thought to account for the regulatory properties of vitamin A upon more than 500 different target genes involved in the differentiation and development of fetal and adult tissues, stem cell differentiation, apoptosis, for support of reproductive and immune functions and regulation of lipid metabolism and energy homeostasis (Al Tanoury et al., 2013; Kedishvili, 2013). Retinoic acid can activate two different types of nuclear receptors, retinoic acid receptors (RARs) and the peroxisome proliferator-activated receptor PPARβ/δ. In the cytosol, retinoic acid binds to cellular retinoic acid-binding protein CRABPII and the resulting complex channels retinoic acid to RARs nuclear receptors. RARs work as heterodimers with retinoic X receptors (RXR) and transduce the retinoic acid signal as ligand-dependent regulators of transcription. Retinoic acid also binds to fatty acid-binding protein FABP5 and activates the nuclear translocation of FABP5, which then delivers the ligand to the PPARβ/δ subtype. In addition, retinoic acid has extranuclear, nontranscriptional effects, such as the activation of the mitogen-activated protein kinase signalling pathway, which influences the expression of retinoic acid target genes via phosphorylation processes (Al Tanoury et al., 2013).

2.2.2. Health consequences of deficiency and excess

2.2.2.1. Deficiency

The main symptoms observed in case of deficiency of vitamin A are intrauterine and post-natal growth retardation and a large array of congenital malformations collectively referred to as the fetal "vitamin A deficiency syndrome" which is well documented in animals (Clagett-Dame and Knutson, 2011). In adults, vitamin A deficiency affects several functions such as vision, immunity, and reproduction, and has been related to the worsening of low iron status, resulting in vitamin A deficiency anemia (Ross, 2014).

The most specific clinical consequences of vitamin A deficiency is xerophthalmia which encompasses the clinical spectrum of ocular manifestations of vitamin A deficiency. It includes night blindness (nyctalopia), due to impaired dark adaptation because of slow regeneration of rhodopsin, Bitot's spots, impaired production of tears, conjunctival xerosis, corneal xerosis, corneal ulceration, and scarring which may result in blindness (WHO, 1982, 1996, 2009). Night blindness, the first ocular symptom of deficiency, responds rapidly to an increase in vitamin A intake (Dowling and Gibbons, 1961; Sommer A, 1982; Katz et al., 1995; Christian et al., 1998b).

Vitamin A deficiency also induces follicular hyperkeratosis that disappears after retinol or β-carotene supplementation (Chase et al., 1971; Sauberlich et al., 1974).

In low-income countries, vitamin A deficiency in young infants and children has been associated with increased infectious morbidity and mortality, including respiratory infection and diarrhoea (Mayo-Wilson et al., 2011). The importance of vitamin A in immune function is well-established (Stephensen, 2001; Field et al., 2002). Mechanisms by which vitamin A may modulate the immune system have been studied *in vitro* and in animal models. Retinoic acid stimulates the proliferation of T-lymphoid cells, inhibits the proliferation of B-cells and B-cell precursors, exerts an effect on the T-helper cell balance by suppressing Th1 development and enhancing Th2 development, enhances macrophage-mediated inflammation by increasing production of IL-12 and IFN-γ, regulates the survival and antigen presentation by immature dentritic cells, as well as the maturation of immature to mature dentritic cells, and impairs the ability of macrophages to ingest and kill bacteria (Ross et al., 2011; Cassani et al., 2012; Ross, 2012). Other effects of vitamin A on the immune system are related to apoptotic effects on immune-competent cells during back regulation of immune reactions and during thymic selection and to the alteration of genes relevant to the immune response (Ruhl, 2007) .

2.2.2.2. Excess

The classical signs and symptoms of acute and chronic hypervitaminosis A comprise skin disorders, nausea, vomiting, disorders of the musculo-skeletal system and liver damage (Biesalski, 1989; Hathcock et al., 1990). Bulging fontanelle in infants and increased intracranial pressure are also classical adverse effects of vitamin A toxicity (Hathcock et al., 1990). The teratogenic effect of excessive intake of vitamin A or specific retinoids is well documented, in both animals and humans (Hathcock et al., 1990).

In 2002, the SCF reviewed possible adverse effects of long-term intake of retinol and retinyl esters (SCF, 2002). The SCF set a Tolerable Upper Intake Level (UL) for preformed vitamin A at 3 000 µg RE per day for women of childbearing age and men, based on the risk of hepatotoxicity and teratogenicity. The UL was proposed to also apply during pregnancy and lactation. ULs for children were extrapolated from the UL for adults, based on allometric scaling (body weight$^{0.75}$). ULs were set at 800 µg RE for children aged 1–3 years, 1 100 µg RE per day for children aged 4–6 years, 1 500 µg RE per day for children aged 7–10 years, 2 000 µg RE per day for children aged 11–14 years and 2 600 µg RE per day for adolescents aged 15–17 years.

The SCF noted that an increased risk of bone fracture was reported for an intake of 1 500 µg RE per day or higher. Presumed mechanisms related to a possible effect of retinoic acid on osteoblasts and

osteoclasts (Scheven and Hamilton, 1990; Kindmark et al., 1995; Cohen-Tanugi and Forest, 1998) and a molecular interaction of vitamin A and vitamin D indicating an antagonism of vitamin A towards the action of vitamin D (Rohde et al., 1999; Johansson and Melhus, 2001) were mentioned. Overall, it was considered that the available data did not provide sufficient evidence of causality, due to the possibility of residual confounding, and were not appropriate for establishing a UL. The SCF noted that "because the tolerable upper level may not adequately address the possible risk of bone fracture in particularly vulnerable groups, it would be advisable for postmenopausal women, who are at greater risk of osteoporosis, to restrict their intake to 1 500 µg RE/day".

In a subsequent assessment which considered studies published until 2004, the Scientific Advisory Committee on Nutrition (SACN, 2005) concluded that the evidence for an association between high intake of retinol and poor bone health was inconsistent. The Committee noted that some epidemiological data suggest that retinol intake of 1 500 µg/day and above is associated with an increased risk of bone fracture ; evidence was considered not robust enough to set a Safe Upper Level and a Guidance Level for retinol intake of 1 500 µg/day was set for adults.

The Panel is aware that additional observational studies on possible associations between retinol and vitamin A intake and bone health have been published since the SCF and SACN assessments. The Panel notes that different definitions of "vitamin A" have been applied among studies (i.e. defined as retinol only, as retinol and provitamin A carotenoids (expressed in IU or µg RE) or undefined). An overview of prospective cohort and nested case–control studies which investigated an association of retinol or "vitamin A" intake with the risk of bone fracture is provided in Appendix A, while intervention and prospective cohort studies which looked at an association with markers of bone health are summarised in Appendix B. These Appendices tabulate studies considered in the SCF and SACN assessments, along with studies published afterwards. Among the latter, no association was observed between a cumulative dose of retinol supplementation and the risk of any fracture or "osteoporotic fracture" (defined as fractures at the spine, hip, femur, arm, ribs or wrist) in 2 322 Australian males and females who received 7.5 mg RE/day as retinyl palmitate for 1 to 16 years (187 subjects experienced 237 fractures) (Ambrosini et al., 2013). No association was also found between retinol or "vitamin A" intake (from food and supplements) and risk of any fracture or hip fracture in the Women's Health Initiative prospective study, which involved 75 747 postmenopausal women in the US (mean follow-up 6.6 years; 10 405 incident total fractures and 588 hip fractures). In contrast in a stratified analysis, modest increases in total fracture risk with high retinol intake (Q5 = 2 488 µg/day vs. Q1 = 348 µg/day) (hazard ratio (HR) = 1.15; 95 % CI = 1.03–1.29; p for trend = 0.056) and high "vitamin A" intake (Q5 = 8 902 µg RE/day vs. Q1 = 4 445 µg RE/day) (HR = 1.19; 95 % CI = 1.04–1.37; p for trend = 0.022) were observed in the women with a vitamin D intake ≤ 11 µg/day (Caire-Juvera et al., 2009). No association between retinol or "vitamin A" intake (from food only or food and supplements) and fracture risk was found in a nested case–control analysis of the Danish Osteoporosis Prevention Study which involved 1 141 perimenopausal women (163 cases, 978 controls) (Rejnmark et al., 2004). Two studies investigated bone mineral density (BMD) as an endpoint: no significant association was observed between BMD change and retinol or "vitamin A" intake (from food and supplements) in 891 women followed for five to seven years in the Aberdeen Prospective Osteoporosis Study (Macdonald et al., 2004); no association between retinol or "vitamin A" intake (from food only or food and supplements) and BMD or change in BMD after a five-year follow-up was found in the Danish Osteoporosis Prevention Study with 1 694 women (Rejnmark et al., 2004).

The Panel is aware of other studies which investigated the association between serum/plasma retinol concentration and fracture risk (Opotowsky and Bilezikian, 2004; Ambrosini et al., 2014). Although serum/plasma retinol concentration has been used as a biomarker of intake, serum/plasma retinol concentration is under homeostatic control and, in the usual range, is not related to observed levels of habitual vitamin A intake. Therefore, it is not considered a reliable marker of vitamin A or retinol intake (Section 2.4.2).

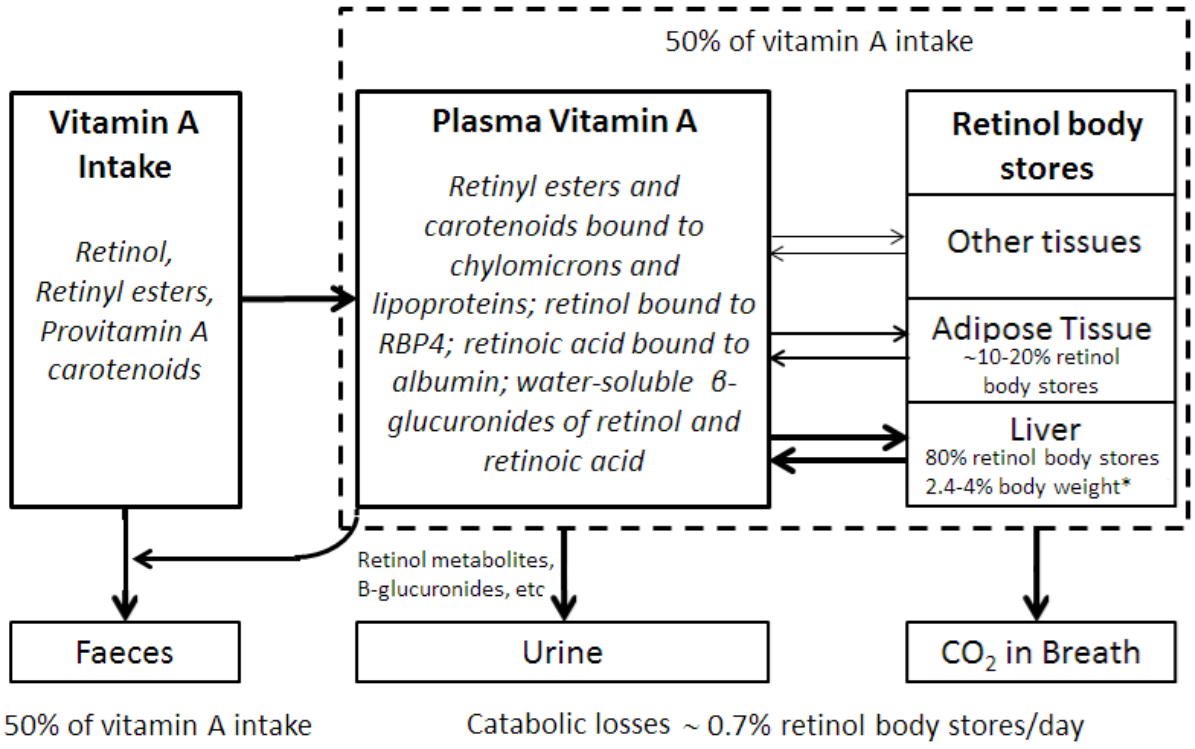
The Panel considers that evaluation of the data published since the SCF assessment does not change the conclusion of the Panel from that of the SCF with respect to the association between retinol or

vitamin A intake and risk of bone fracture in postmenopausal women. One prospective cohort study indicated a possible interaction between vitamin D intake (< 11 µg/day) and retinol intake in relation to the risk of bone fracture in postmenopausal women.

The Panel is aware of other studies which looked at possible associations between preformed vitamin A intake or blood retinol concentration and adverse health outcomes (Grotto et al., 2003; Bjelakovic et al., 2008; Chen et al., 2008; Mayo-Wilson et al., 2011; Beydoun et al., 2012; Bjelakovic et al., 2012; Bjelakovic et al., 2013; Field et al., 2013; Bjelakovic et al., 2014). Available data on individual outcomes are limited or relate to interventions that used large doses of retinol (≥ 6 000 µg) once or several times a year, which are difficult to relate to a potential effect of daily dietary intake of retinol.

2.3. Physiology and metabolism

The different forms of vitamin A undergo a complex metabolic fate with an exchange between the intestine, the plasma, the liver and other peripheral tissues (Figure 2).



(*): according to age.

Figure 2: Vitamin A forms and metabolic fates.

2.3.1. Intestinal absorption

The key digestive processes that occur within the lumen of the intestine include the release of preformed vitamin A and provitamin A carotenoids from the food matrix and their emulsification with dietary fatty acids and bile acids (Parker, 1996). The presence of dietary fat in the intestine usually enhances their intestinal absorption by enhancing the secretion of pancreatic enzymes and of bile salts that provides components (lysophospholipids, monoglycerides, free fatty acids) to form luminal mixed micelles of lipids and for intracellular assembly of chylomicrons involved in their absorption (Roels et al., 1958; Roels et al., 1963; Reddy and Srikantia, 1966; Figueira et al., 1969; Jayarajan et al., 1980; Borel et al., 1997; Jalal et al., 1998; Li and Tso, 2003; Unlu et al., 2005).

2.3.1.1. Absorption of preformed vitamin A

Preformed vitamin A is efficiently absorbed in the intestine, in the range of 70 to 90 % (Reddy and Sivakumar, 1972; Sivakumar and Reddy, 1972; Kusin et al., 1974). Almost complete absorption was observed in five healthy Indian children administered 1 000 µg retinyl acetate in oil (Sivakumar and Reddy, 1972). Absorption remains high even as the amount of ingested preformed vitamin A increases (Olson, 1972). Absorption around 70 % was observed in Indian children when a single high dose of retinol acetate (60 000 µg) was administered (Reddy and Sivakumar, 1972; Kusin et al., 1974). Quantitative data on the absorption of preformed vitamin A from the diet are scarce.

Dietary retinyl esters are unable to enter the intestinal mucosa and must first be hydrolysed by retinyl ester hydrolases to yield free retinol (Harrison, 2012). Retinyl esters can be hydrolysed within the intestinal lumen by nonspecific pancreatic enzymes, such as pancreatic triglyceride lipase and cholesteryl ester hydrolase, or at the mucosal cell surface by a brush border retinyl ester hydrolase (Erlanson and Borgstrom, 1968; Rigtrup and Ong, 1992; Rigtrup et al., 1994; van Bennekum et al., 2000; Reboul et al., 2006).

Free retinol is taken up into the intestinal cells by protein-mediated facilitated diffusion and passive diffusion mechanisms via the action of membrane-bound lipid transporters involved in fatty acid and cholesterol uptake. These include scavenger receptor class B, type 1 (SR-B1), CD36, NPC1L1, and a variety of ABC transporters (Hollander and Muralidhara, 1977; Hollander, 1981; Glatz et al., 1997; Abumrad et al., 1998; van Heek et al., 2001; Turley and Dietschy, 2003; Wang, 2003; Altmann et al., 2004; Davis et al., 2004; Nieland et al., 2004; During et al., 2005; Iqbal and Hussain, 2009). Free retinol then binds to specific cytoplasmic retinol-binding proteins (RBPs), i.e. the cellular retinol-binding proteins CRBPI and CRBPII (Ong, 1994). CRBPII is present at high concentrations in the enterocytes and appears to be uniquely suited for retinol absorption by the intestine (Herr and Ong, 1992; Ong, 1994; Li and Norris, 1996; Newcomer et al., 1998).

CRBP-bound retinol undergoes esterification with long-chain fatty acids, particularly with palmitic acid, catalysed by lecithin:retinol acyltransferase (LRAT) for about 90 %, and to a lesser extent by the intestinal acyl-CoA:retinol acyltransferase (DGAT1) (Huang and Goodman, 1965; MacDonald and Ong, 1988; O'Byrne et al., 2005; Harrison, 2012). The resulting retinyl esters are then packed along with dietary fat and cholesterol into nascent chylomicrons, which are secreted into the lymphatic system for delivery to the blood (Olson, 1989; Blomhoff et al., 1991; Parker, 1996; Harrison, 2012).

2.3.1.2. Absorption of provitamin A carotenoids

Because of physiological differences in provitamin A carotenoid absorption between rodents and humans, rodents are not good animal models for studying human carotenoid absorption (Huang and Goodman, 1965).

Dietary provitamin A carotenoids are absorbed via passive diffusion or taken up by the enterocyte through facilitated transport via SR-B1 (van Bennekum et al., 2005; During and Harrison, 2007; Moussa et al., 2008; Harrison, 2012; von Lintig, 2012).

Once inside the enterocyte, the major part (more than 60 %) of the absorbed provitamin A carotenoids are cleaved at their central double bond (15,15′) by β,β-carotene-15,15′-monooxygenase 1 (BCMO1) into all-*trans*-retinal (Devery and Milborrow, 1994; Nagao et al., 1996; Lindqvist and Andersson, 2002). All-*trans*-retinal either binds CRBPII, is incorporated intact with dietary fat and cholesterol into nascent chylomicrons, or is further oxidised irreversibly to retinoic acid or reduced reversibly to retinol (Harrison, 2012).

Less than 40 % of absorbed provitamin A carotenoids are not cleaved in the intestine (Castenmiller and West, 1998) and are absorbed intact. Along with other lipids, they become incorporated in

chylomicrons for transport to the liver and other tissues and are found associated with circulating lipoproteins (Johnson and Russell, 1992).

Overall, the absorption of β-carotene appears to be highly variable (5–65 %), depending on food- and diet-related factors, as well as the nutritional, health, and genetic characteristics of the subject (Haskell, 2012). This has significant implications as to the bioequivalence of β-carotene to retinol (Section 2.3.9). Data on the absorption of the other provitamin A carotenoids, α-carotene and β-cryptoxanthin, are more limited.

2.3.2. Transport in blood

A number of different forms of vitamin A are found in the circulation, and these differ in the fasting and postprandial states (O'Byrne and Blaner, 2013). They include retinyl esters in chylomicrons, chylomicron remnants, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL); retinol bound to retinol-binding protein (RBP4); retinoic acid bound to albumin; and the water-soluble β-glucuronides of retinol and retinoic acid. Provitamin A carotenoids may be absorbed intact by the intestine (Section 2.3.1) and can be found in the blood bound to chylomicrons and their remnants, VLDL, LDL, and HDL (Redlich et al., 1996; Redlich et al., 1999). LDL is the major carrier of β-carotene in fasting plasma (Romanchik et al., 1995).

Approximately two thirds of absorbed retinol is delivered to the blood via the lymph in esterified form as retinyl palmitate and other retinyl esters present in chylomicrons. Around one third is secreted directly into the portal circulation probably as free retinol (Blomhoff et al., 1990; Blomhoff et al., 1991; Kane and Havel, 1995; Lemieux et al., 1998; Nayak et al., 2001).

Mean fasting concentration of retinyl esters has been reported in the range of 10–40 µg/L in adults (Bankson et al., 1986; Hartmann et al., 2001). In the postprandial circulation, retinyl esters concentrations increase. Following consumption of a retinol-rich meal (~1–1.5 mg/kg body weight), mean retinyl palmitate concentration in plasma was observed to reach 7–9 µmol/L in male volunteers (Arnhold et al., 1996; Relas et al., 2000).

In the fasting circulation, retinol bound to RBP4 is the predominant form of retinoid, with concentrations ranging from 2–4 µmol/L in adults from Western countries (Chuwers et al., 1997; Hartmann et al., 2001). The retinol-RBP4 complex binds another plasma protein, transthyretin (TTR), which stabilises the complex and reduces renal filtration of retinol (van Bennekum et al., 2001).

Retinoic acid is present in both the fasting and postprandial circulations where it is bound to albumin. Immediately following consumption of a retinol-rich meal (~1 mg/kg body weight), mean plasma concentration of retinoic acid was observed to reach 254 nmol/L but was quickly restored to fasting concentrations of 14 nmol/L in 10 male volunteers (Arnhold et al., 1996).

Plasma/serum concentrations of retinyl- and retinoyl-β-glucuronides have been reported to be in the range of 5–15 nmol/L (Barua and Olson, 1986; Barua et al., 1989). Although it has been proposed that retinyl- and retinoyl-β-glucuronides, which are known to be readily hydrolysed by a number of β-glucuronidases, may serve as sources of retinoids for tissues, it is generally believed that these fully water-soluble metabolites are filtered in the kidney and eliminated quickly from the body.

Average fasting blood concentrations of β-carotene in the range 0.2–0.7 µmol/L have been reported in adult European populations (Al-Delaimy et al., 2004; Hercberg et al., 2004). A dose-response relationship between carotenoid intake and appearance in plasma has been shown (Rock et al, 1992). Mean fasting β-carotene concentration of 3.75 µmol/L has been reported in individuals who were administered 30 mg/day β-carotene supplement for five years (Redlich et al., 1999).

2.3.3. Distribution to tissues

The delivery of retinoids to tissues involves many different forms and carriers (Paik et al., 2004; O'Byrne and Blaner, 2013). Quantitatively the two most important pathways are those involving retinol bound to RBP4 and the postprandial delivery pathway.

When needed, hepatic retinyl esters are hydrolysed to free retinol, which is mobilised from the liver bound to its plasma transport protein, RBP4. Retinol-RBP4 is secreted from the liver into the circulation as a means of delivering retinol to peripheral tissues (Goodman et al., 1965; Soprano and Blaner, 1994; Quadro et al., 1999; Packer, 2005). Liver is the major site of synthesis of RBP4 but other tissues, including adipose tissue, kidney, lung, heart, skeletal muscle, spleen, eyes, and testes, also express RBP4, which may be important for recycling retinoids from peripheral tissues back to the liver (Blomhoff et al., 1991). Studies on intestinal cells indicate that retinol enters by diffusion, and this is likely true for other cell types (During et al., 2002; During and Harrison, 2004; During et al., 2005; During and Harrison, 2007), although part of the uptake of RBP-bound retinol into specific target tissues has been shown to be mediated by a cell surface receptor for RBP4 termed STRA6 (stimulated by retinoic acid 6). STRA6 is expressed on the surface of cells of several organs such as Sertoli cells, yolk sac, and chorioallantoic placenta, choroid plexi, and retinal pigmented epithelial cells (Bouillet et al., 1997; Lewis et al., 2002; Blaner, 2007; Kawaguchi et al., 2007; Pasutto et al., 2007; Berry et al., 2013).

In the postprandial delivery pathway, retinyl esters in chylomicrons in the circulation are taken up by tissues as the chylomicron undergoes lipolysis and remodelling. Approximately 66–75 % of chylomicron retinyl esters have been shown to be cleared by the liver in the rat, with the remainder cleared by peripheral tissues (Goodman et al., 1965; Blaner et al., 1994; van Bennekum et al., 1999). Postprandial unesterified retinol taken up by cells is thought to bind immediately to CRBPs that are present in tissues (Noy and Blaner, 1991). Once retinol is formed upon retinyl ester hydrolysis within the hepatocyte, it is quickly bound by apo-CRBPI, which is in molar excess of retinol in these cells (Harrison et al., 1987).

Provitamin A carotenoids in VLDL and LDL are presumably taken up along with the lipoprotein particles by their cell surface receptors. The two major sites of provitamin A carotenoids conversion to retinoids in humans are the intestine (Section 2.3.1) and liver (Harrison, 2012). The maximum capacity for β-carotene cleavage by the two organs combined was estimated to be of 12 mg β-carotene per day in a human adult (During et al., 2001). The liver was shown to have four times the capacity of the small intestine for metabolising β-carotene (During et al., 2001), which is consistent with the prediction, using a multicompartmental model, that β-carotene cleavage takes place in the liver to a greater extent than in the intestine in humans (Novotny et al., 1995). Since many tissues express BCMO1, including the liver, kidney, skin, skeletal muscle, adrenal gland, pancreas, testis, ovary, prostate, endometrium, mammary tissue, eyes and the mammalian embryo (Yan et al., 2001; Lindqvist and Andersson, 2002; Chichili et al., 2005; Lindqvist et al., 2005), intact provitamin A carotenoids delivered to these tissues can also be converted *in situ* to retinoids.

Plasma retinoic acid may also be taken up into tissues through a "flip-flop" mechanism across phospholipid bilayers (Noy, 1992a, 1992b) and contribute to tissue pools (Kurlandsky et al., 1995).

2.3.4. Storage

The main storage form of retinol is retinyl esters. The liver and intestine are the major tissue sites of retinol esterification but other tissues including the eye, lung, adipose tissue, testes, skin, and spleen, are also able to esterify retinol and accumulate retinyl ester stores. The enzyme responsible for most of retinyl ester formation is LRAT. Liver LRAT is thought to be structurally identical to intestinal LRAT (Section 2.3.1.1), although hepatic but not intestinal LRAT expression appears to be regulated by the vitamin A nutritional status (Matsuura and Ross, 1993). The concentration of retinoic acid within tissues is generally very low, usually 100 to 1 000 times less than that of retinol and retinyl esters.

2.3.4.1. Liver stores

It is considered that in healthy individuals with an adequate vitamin A status, 70 % to 90 % of retinol of the body is stored in the liver and that this percentage decreases to 50 % or below in severely deficient individuals (Rietz et al., 1973; Bausch and Rietz, 1977; Olson, 1987). Based on empirical data, Rietz et al. (1973) indicated that 80 % of the retinol content of the body is stored in the liver in rats with an adequate vitamin A intake. There is a lack of direct measurement in human. Using stable isotope and model-based compartmental analysis to study retinol kinetics in one healthy human volunteer in the US, von Reinersdorff et al. (1998) predicted that 80 % of the absorbed dose of labelled retinol was contained in the liver seven days after administration (Section 2.3.6.1).

The major part of retinoids is concentrated in the lipid droplets of hepatic stellate cells (Hendriks et al., 1985; Moriwaki et al., 1988; Blomhoff et al., 1991; Blaner et al., 2009), where nearly all of the retinoids present is stored as retinyl ester (primarily retinyl palmitate, with smaller amounts of retinyl stearate, retinyl oleate, and retinyl linoleate) (Blaner et al., 1985; Blomhoff et al., 1991; Blaner et al., 2009). Unesterified retinol accounts for less than 1 %.

Hepatocytes are responsible for the uptake of chylomicron remnant retinoids into the liver, which are then transferred to hepatic stellate cells (Blaner et al., 1985; Blomhoff et al., 1991). Hepatocytes account for about 10–20 % of all of the retinoids stored within the liver (Blaner et al., 1985; Blaner et al., 2009). Hepatocytes are the sole hepatic cellular site of RBP4 synthesis and possess enzymatic activities needed for the hydrolysis of retinyl esters and the synthesis and catabolism of retinoic acid (Blaner et al., 1985; Blaner et al., 2009).

2.3.4.2. Adipose tissue stores

Adipocytes are able to accumulate significant retinyl ester stores (O'Byrne and Blaner, 2013). Data in rats indicate that the adipose tissue may account for as much as 15–20 % of the total body retinoids (Tsutsumi et al., 1992). Data in humans are lacking. As in the liver, retinyl esters stored in adipose tissue can be mobilised and secreted back into the circulation bound to RBP4 synthesised in adipocytes (Tsutsumi et al., 1992; Zovich et al., 1992; Wei et al., 1997). These retinyl esters are first hydrolysed by hormone-sensitive lipase, which acts as a retinyl esters hydrolase in adipocytes (Wei et al., 1997; Strom et al., 2009).

2.3.5. Efficiency of storage

The efficiency of storage represents the fraction of ingested retinol which is absorbed and retained in the body (and more particularly in the liver).

Upon i.v. administration of [^{3}H]-labelled retinol to rats with different vitamin A stores, the percentage of storage in liver was shown to be relatively constant, between 50 and 63 %, in the range of liver retinol concentrations of 18–54 µg/g (Bausch and Rietz, 1977). The percentage of storage in the liver decreased (6–40 %) when initial hepatic stores of retinol were below 18 µg/g liver (0.06 µmol/g) (Bausch and Rietz, 1977).

Using radio-isotopic method, whole body retinol retention was assessed in groups of Indian children (2–10 years) by measuring radioactivity in urine and faeces over four to six days after administration of a labelled dose (Reddy and Sivakumar, 1972; Sivakumar and Reddy, 1972). When the labelled dose of retinyl acetate was administered with 1 000 µg unlabelled retinyl acetate, the mean retention was 82.2 ± 2.0 % (n = 5) in healthy children and 57.6 ± 6.0 % (n = 8) in a group of children with infection. When the labelled dose of retinyl palmitate was administered with a high dose of 60 000 µg retinyl palmitate in five healthy children, 47 % of the dose was retained, on average. Using similar methodology, retention in the range of 48–54 % was estimated in healthy Indian children (n = 17; 3–6 years), when labelled retinyl acetate dose was administered with a high dose of 60 000 µg unlabelled retinyl acetate (Kusin et al., 1974). The liver retinol content of these children is unknown.

In adult Bangladeshi surgery patients (n = 31) with hepatic concentrations greater than or equal to 20 µg retinol/g of liver (0.07 µmol/g) (mean ± SD estimated hepatic stores 40 ± 18 mg RE (139 ± 64 µmol RE)), stable-isotopic methods have shown an average efficiency of storage in the liver of 42 % (± 13 %) when measured in liver biopsy 9–11 days after the administration of an oral dose of labelled retinol (215 µg/kg body weight (0.753 µmol/kg body weight) as retinyl acetate) (Haskell et al., 1997). The efficiency of storage in the liver was significantly lower (30 % ± 8 %) in subjects with liver content < 20 µg retinol/g of liver (mean ± SD estimated hepatic stores 14 ± 4 mg RE (50 ± 16 µmol RE) (Haskell et al., 1997). The Panel notes the low hepatic retinol stores of the study population and the short timeframe of the study which may not have allowed the retinol dose to fully equilibrate with the hepatic pool (see Section 2.4.1.2).

The Panel notes that available data show that the efficiency of storage depends on vitamin A status. Low retinol stores are associated with a reduced efficiency of storage. Data from adult Bangladeshi subjects with liver concentrations ≥ 20 µg retinol/g indicate an average efficiency of storage of ingested retinol of 42 % in the liver. The Panel notes that this would correspond to an efficiency of storage in the whole body of 52 %, assuming that 80 % of retinol body stores are found in the liver in subjects with adequate liver stores.

2.3.6. Metabolism

Retinoic acid is produced from retinol in two oxidative steps. First, retinol is oxidised to retinal, which is further oxidised to retinoic acid.

Two types of enzymes have been implicated in the oxidation of retinol to retinal: the microsomal dehydrogenases of the short-chain dehydrogenases/reductases family of proteins and the cytosolic alcohol dehydrogenases of the medium-chain alcohol dehydrogenases family (Pares et al., 2008). The latter appear to rather play a role as backup enzymes under extreme dietary conditions (Farjo et al., 2011; Napoli, 2012).

The oxidation of retinal to retinoic acid is irreversible. Excessive retinoic acid is catabolised by several cytochrome P450 (CYP) enzymes, giving rise to better water-soluble oxidised and conjugated retinoid forms, which can be more easily excreted (White et al., 1996; Fujii et al., 1997; Ray et al., 1997; White et al., 1997). CYP26A1, CYP26B1 and CYP26C1 appear to be primarily responsible for the degradation of retinoic acid (Pennimpede et al., 2010; Ross and Zolfaghari, 2011; Kedishvili, 2013). With the exception of liver, where CYP26A1 is the predominant form, and lung, where CYP26A1 is slightly more abundant, all other human adult tissues contain higher levels of CYP26B1 transcript (Xi and Yang, 2008; Topletz et al., 2012). Considering that CYP26A1 expression in the liver is very sensitive to retinoic acid levels, the high catalytic efficiency of this low-affinity enzyme would enable CYP26A1 to rapidly bring down excessive levels of retinoic acid. In addition to the three CYP26 enzymes, several other members of other CYP families have been shown to catabolise retinoic acid (Kedishvili, 2013).

Retinal can be converted back to retinol (Kedishvili, 2013), depending on the availability of the substrates and cofactors. The cytosolic aldo-keto reductases and the microsomal short-chain dehydrogenases/reductases have been proposed to catalyse the reduction of retinal back to retinol. This efficient recycling of retinal back to retinol prevents retinal losses through the irreversible pathway to retinoic acid and constitutes a sparing process of retinol stores.

2.3.7. Elimination

2.3.7.1. Catabolic losses

Retinol absolute catabolic rate (µg/day or µmol/day) and the fractional catabolic rate (% of a defined pool) are defined as the rate at which retinol is irreversibly utilised each day in absolute or relative amount, respectively.

Retinol distribution and catabolism was determined in eight male adult subjects who received intravenous or oral doses of [^{14}C]-labelled retinyl acetate during vitamin A depletion (up to 771 days) and repletion (up to 372 days) (Sauberlich et al., 1974). It took about 26 days for the labelled dose to equilibrate with the total body vitamin pool that was estimated to range from 315–879 mg (1 100–3 070 µmol). A fractional catabolic rate of total body retinol stores of approximately 0.5 % per day (range 0.3–0.9 %) was determined in these subjects consuming a vitamin A free diet, deduced from a mean half-life of retinol in the liver of 154 days (range 75–241 days, CV 35 %) during the depletion phase (Sauberlich et al., 1974; Olson, 1987). The absolute retinol utilisation rate ranged between 1 113 and 2 070 µg (3.9 and 7.2 µmol) per day among subjects at baseline and fell to low levels as depletion progressed (50–180 µg (0.2–0.6 µmol) per day).

The total body retinol store determined by the plasma isotopic ratios of deuterium-labelled retinol was significantly different between groups of four US and Bangladeshi adults (mean ± SD (range): 295 ± 13 mg (106–378 mg) (1 030 ± 45 µmol (370–1 320 µmol)) vs. 286 ± 315 mg (86–745 mg) (100 ± 110 µmol (30–260 µmol)), p = 0.003) (Haskell et al., 1998). Based on the disappearance kinetics of the fraction of labelled dose in plasma at equilibrium derived from the data of Haskell et al. (1998), Furr et al. (2005) estimated the fractional catabolic rate of retinol to be 0.4 % per day (range: 0.1–0.7 % per day) in the US subjects and 0.9 % per day (range: 0.5–1.2 % per day) in the Bangladeshi subjects, respectively. The difference was not statistically significant. It also did not differ from the rate of 0.5 % per day as previously determined (Sauberlich et al., 1974).

Based on the same approach, Haskell et al. (2003) estimated a fractional catabolic rate of 2.2 % per day (95 % CI = 1.4–3.0 % per day) in 107 Peruvian children (12–24 months of age) with total body retinol stores (mean ± SD (range)) estimated as 28 ± 23 mg (4–112 mg) (97 ± 81 µmol (16–392 µmol)). According to the authors, the higher fractional catabolic rate in children aged 12–24 months may reflect greater utilisation of the vitamin to support growth, but other factors may have affected the retinol turnover, given that plasma CRP concentrations were elevated in approximately 50 % of the children. The authors suggested that healthy children (12–24 months of age) may have a fractional catabolic rate lower than 2.2 %.

Applications of model-based compartmental analysis to data from tracer label studies have allowed to estimate parameters of human retinol metabolism, including its catabolic rate (von Reinersdorff et al., 1998; Furr et al., 2005; Cifelli et al., 2008). Such analyses also revealed the important recycling of vitamin A among tissues and plasma before its irreversible utilisation, indicating a sparing process of the vitamin (Reinersdorff et al., 1996; Furr et al., 2005; Cifelli et al., 2008).

Cifelli et al. (2008) investigated retinol kinetics, storage, and catabolic rate through model-based compartmental analysis of data from stable isotope dilution in well-nourished men and women from China (Wang et al., 2004) and the US (Tang et al., 2003). [$^{2}H_{8}$]Retinyl acetate (3 mg (8.9 µmol)) was orally administered to US (n = 12; 59 ± 9 years) and Chinese adults (n = 14; 54 ± 4 years) and serum tracer and retinol concentrations were measured from 3 hours to 56 days. Subjects were instructed not to consume vitamin supplements or foods containing large amounts of retinol or β-carotene during the whole study duration. Serum retinol concentration was significantly higher in the US group (487 ± 92 µg/L (1.70 ± 0.32 µmol/L)) than in the Chinese group (355 ± 106 µg/L (1.24 ± 0.37 µmol/L), p < 0.001) at baseline. Predicted total traced mass (257 ± 182 vs. 68 ± 32 mg (898 ± 637 vs. 237 ± 109 µmol)), absolute catabolic rate ('disposal rate') (4.2 ± 1.7 vs. 1.6 ± 0.6 mg/day (14.7 ± 5.87 vs. 5.58 ± 2.04 µmol/day)), and system residence time (58.8 ± 28.5 vs. 42.9 ± 14.6 days) were significantly greater in US than in Chinese subjects. In both the US and Chinese participants, absolute retinol catabolic rate was significantly correlated with the traced mass in the extravascular compartment (256 ± 182 and 67 ± 32 mg (892 ± 637 and 233 ± 109 µmol), respectively), with the catabolic rate increasing linearly with increasing stores. The Panel notes that estimated mean daily fractional catabolic rates of 1.6 % (14.7/898) in the US population and 2.3 % (5.58/237) in the Chinese population would result from the predicted total traced mass and absolute catabolic rate in these two populations, with large inter-individual variability. The Panel notes that the absorption efficiency of retinol estimated by the model is around 65 %. This is likely to underestimate

the true absorption, as retinol administered in oil is considered to be completely absorbed (Sivakumar and Reddy, 1972). This would lead to an underestimation of the predicted total body pool. Therefore, the fractional catabolic rates derived from these data are likely to overestimate actual fractional catabolic rates.

The Panel notes that the rate of retinol catabolism is related to body stores and that the absolute catabolic rate appears to increase with vitamin A body stores. Overall, retinol catabolism represents a relatively low fraction of the whole body pool, due to the important storage capacity of the body and efficient recycling processes. The Panel notes that available studies were conducted on subjects with a wide range of retinol body stores using different experimental methods and conditions and showing substantial variability. The results of the study from Cifelli et al. (2008) indicate that the fractional catabolic rate may be higher than the value of 0.5 % which has usually been considered (Olson, 1987). The Panel notes that the fractional catabolic rate may be influenced by physiological conditions (such as growth, presence of inflammation or other non-identified factors) and that the fractional catabolic rate may be higher in children than in adults, in relation with a higher retinol utilisation for growth needs and, possibly, to relatively lower body stores compared to adults.

2.3.7.2. Faecal, breath and urinary losses

The majority of retinol metabolites are excreted in the urine but they are also excreted in faeces and breath. The percentage of a radioactive dose of [^{14}C]-labelled retinyl acetate recovered in breath, faeces, and urine ranged from 18 to 30 %, 18 to 37 %, and 38 to 60 %, respectively, after 400 days on a vitamin A-deficient diet (Sauberlich et al., 1974). Retinol is metabolised in the liver to numerous products, some of which are conjugated with glucuronic acid or taurine for excretion in bile (Sporn et al., 1984) and the level of retinol metabolites excreted in bile increases as the liver retinol exceeds a critical concentration. Excretion of labelled retinol metabolites into bile of rats fed increasing levels of retinol traced by [^{3}H]-retinyl acetate was constant when hepatic retinol concentrations were low ($\leq$ 32 µg/g (112 nmol/g) and increased rapidly (by eight-fold) as liver retinol content increased, up to a plateau at hepatic retinol concentration $\geq$ 140 µg/g (490 nmol/g) (Hicks et al., 1984). This increased biliary excretion has been suggested to serve as a protective mechanism for reducing the risk of excess storage of vitamin A.

2.3.7.3. Breast milk

Preformed vitamin A in breast milk primarily occurs as retinyl esters (mainly retinyl palmitate) (Stoltzfus and Underwood, 1995), with a small fraction present as free retinol. Provitamin A carotenoids are also found in breast milk (Canfield et al., 2003). The carotenoid content of breast milk is not described in this Opinion, as carotenoids are not taken into account in estimating the vitamin A supply in infants, owing to a lack of knowledge on the bioconversion of carotenoids in infants (SCF, 2003; EFSA NDA Panel, 2014b), and provitamin A carotenoid loss in the form of breast milk is unlikely to significantly affect the vitamin A status of lactating women.

Preformed vitamin A concentration is higher in colostrum and decreases as lactation progresses (Stoltzfus and Underwood, 1995). It is not related to breast milk fat content during the first weeks of lactation (Macias and Schweigert, 2001). Breast milk content is influenced by the maternal vitamin A status (Underwood, 1994b).

Appendix C reports data on retinol[6] concentration in breast milk from mothers of term infants in Western populations. In a multinational study, Canfield et al. (2003) found mean retinol concentrations between 301 and 352 µg/L in mature milk samples from Western populations (Australia, Canada, UK and US). Studies on samples taken during the first six months of lactation reported average retinol concentrations in mature milk of 831 µg/L in Germany (Schweigert et al., 2004), 815 µg/L in Turkey (Tokusoglu et al., 2008) and 571 µg/L in Poland (Duda et al., 2009). In a

[6] i.e. after saponification to release retinol from retinyl esters.

group of Polish lactating women, Kasparova et al. (2012) found decreasing concentrations of retinol in mature breast milk over the course of lactation, from 458 µg/L at 1–2 months postpartum to 229 µg/L at 5-6 months postpartum and 172 µg/L at 9–12 months postpartum.

During the first six months of lactation, the Panel notes that available data indicate that mean total retinol concentrations in mature breast milk of population from Western countries range between 229 and 831 µg/L. Average values between 450 and 600 µg/L have been previously considered by other committees (DH, 1991; SCF, 1993; Afssa, 2001; IOM, 2001; WHO/FAO, 2004; D-A-CH, 2013; Nordic Council of Ministers, 2014). Based on the average volume of milk intake of 0.8 L/day and a concentration of total retinol in breast milk of 530 µg/L taken as the midpoint of the range (229–831 µg/L), a secretion of 424 µg/day of retinol in breast milk is estimated during the first six months of lactation.

2.3.8. Interaction with other nutrients

Serum retinol concentration was positively associated with serum iron and ferritin concentrations in children (Bloem et al., 1989). Vitamin A deficiency impairs iron mobilisation and vitamin A supplementation improves haemoglobin concentrations (Lynch, 1997). Iron supplementation combined with vitamin A was more effective than iron alone to improve haemoglobin concentrations in anaemic children (Mwanri et al., 2000) and pregnant and lactating women (Suharno et al., 1993; Tanumihardjo et al., 1996; Tanumihardjo, 2002). In a systematic review, vitamin A supplementation during pregnancy was found to reduce anaemia risk (< 11.0 g/dL) among both anaemic and non-anaemic women (Thorne-Lyman and Fawzi, 2012). This is consistent with observational and intervention studies in women and children which showed correlations between anaemia and vitamin A deficiency and the improvement of anaemia observed by improving vitamin A status in deficient populations (Radhika et al., 2002; Semba and Bloem, 2002; Al-Mekhlafi et al., 2013). In non-anaemic subjects, a test meal containing 1 000 µg retinol did not enhance iron absorption (Walczyk et al., 2003). Iron deficiency was shown to alter the distribution of retinol and retinyl ester between plasma and liver and to reduce plasma retinol concentrations in rats, despite adequate vitamin A intake and hepatic stores of retinol (Amine et al., 1970; Staab et al., 1984; Rosales et al., 1999).

Zinc is important in protein synthesis. In animal models, zinc deficiency affects RBPs and transport of retinol from the liver into the circulation (Terhune and Sandstead, 1972; Smith et al., 1974; Duncan and Hurley, 1978; Baly et al., 1984). In addition, zinc deficiency also reduced the synthesis of rhodopsin in the rat (Dorea and Olson, 1986). However, no consistent relationship between zinc and vitamin A status has been established in humans (Christian and West, 1998).

2.3.9. Retinol equivalents

In tissues, blood, milk and food, vitamin A contents are conventionally expressed as RE, with 1 µg RE equal to 1 µg retinol.

The vitamin A activity of provitamin A carotenoids in diets is determined from specific relations between provitamin A carotenoids and retinol to account for the less efficient absorption of carotenoids and their bioconversion to retinol. Conversion factors of 1:6 for β-carotene and 1:12 for other provitamin A carotenoids were initially proposed (FAO/WHO, 1988; SCF, 1993), based on data indicating that 3 µg of dietary β-carotene was equivalent to 1 µg of purified β-carotene in oil and that the β-carotene:retinol equivalency ratio of purified β-carotene in oil was approximately 2:1 (Sauberlich et al., 1974). β-carotene is the most potent retinol precursor of all provitamin A carotenoids (Harrison, 2012). Stoichiometric conversion of one mole of β-carotene (with two β-ionone rings) would give rise to 2 moles of retinol (via retinal), whereas conversion of a mole of either β-cryptoxanthin or α-carotene (each with only a single β-ionone ring) would give rise to a single mole of retinol. α-carotene and β-cryptoxanthin show 30–50 % of the provitamin A activity of β-carotene (Bauernfeind, 1972; van Vliet et al., 1996).

In 2001, IOM revised these factors considering new data (IOM, 2001): 1) absorption of β-carotene from a mixed vegetable diet had been reported to be 14 % compared to β-carotene in oil (van het Hof et al., 1999); 2) absorption from green leafy vegetables appeared to be lower than absorption from fruits (de Pee et al., 1998); 3) a low proportion of β-carotene was consumed from fruits compared to vegetables in the US. Retinol activity equivalency (RAE) ratios of 1:12 for β-carotene and 1:24 for other provitamin A carotenoids were proposed. Considering the data from van het Hof et al. (1999), WHO/FAO (2004) also proposed revised equivalency factors of 1:14 for β-carotene and 1:28 for other provitamin A carotenoids from usual vegetables diets, with possible adjustment depending on the proportion of green leafy vegetables or fruits in the diet. West et al. (2002) discussed that these revised conversion factors might still be too high, especially for populations living in developing countries.

In a recent review of the data on the bioavailability of β-carotene from plant sources in humans, Haskell (2012) reported absorption to range from 5 % to 65 % and retinol equivalency ratios for β-carotene from 3.8:1 to 28:1 by weight. In line with de Pee et al. (1998), there was further indication that β-carotene from fruits is better converted than from green leafy vegetables (Khan et al., 2007). For pure β-carotene diluted in oil, equivalency ratios from 2:1 to 55:1 were reported, with most values being between 2:1 and 4:1. The data collected by Haskell (2012) seem to indicate that the efficiency of conversion of β-carotene from oil might be increased in subjects with "low or marginal" vitamin A status compared to subjects with vitamin A "adequate" status, while it appears to decrease with increasing dose of β-carotene. Overall, there appears to be high variability in retinol equivalency ratios which might originate from either host-related factors (genetics, age, sex, nutritional status, digestive dysfunctions, and illness) or food-related factors (food composition, food matrix) (de Pee and Bloem, 2007; Tanumihardjo et al., 2010; Haskell, 2012). A study in eight healthy free-living adults who received an oral tracer dose of [^{14}C]-β-carotene also confirms that β-carotene catabolism is highly variable (Ho et al., 2009).

Few results are available on the rate of absorption of β-carotene and its bioequivalence to retinol in children. By measuring the plasma ratio of retinol formed from labelled β-carotene compared to a reference dose of labelled retinol, van Lieshout et al. (2001) estimated that the amount of β-carotene in oil required to form 1 µg retinol was 2.4 µg (95 % CI = 2.1–2.7) in 36 Indonesian children aged 8–11 years. In a study in 68 Chinese children (6–8 years) using labelled retinyl acetate as a reference, the mean (± SE) conversion factors of pure β-carotene, β-carotene from Golden Rice and β-carotene from spinach to retinol were 2.0 ± 0.9, 2.3 ± 0.8 and 7.5 ± 0.8 to 1, respectively (Tang et al., 2012). Ribaya-Mercado et al. showed significant improvements in vitamin A status, as assessed by deuterated retinol dilution method, in Filipo schoolchildren receiving controlled diets rich in provitamin A carotenoids from fruit and vegetables sources, but these studies do not allow the estimation of provitamin A carotenoid/retinol equivalency ratios (Ribaya-Mercado et al., 2000; Ribaya-Mercado et al., 2007).

The Panel notes the high variability in the β-carotene/retinol equivalency ratios estimated from these studies, depending on the food matrix, the subjects' vitamin A status and the dose administered. This results in large uncertainties in establishing equivalency ratios from the whole diet of large populations. The Panel considers that current evidence is insufficient to support a change from the conversion factors proposed by the SCF for the European populations, namely 1 µg RE equals to 1 µg of retinol, 6 µg of β-carotene, and 12 µg of other carotenoids with provitamin A activity.

2.4. Biomarkers

2.4.1. Total body and liver stores

Vitamin A status can best be expressed in terms of total body store of retinol (i.e. as free retinol and retinyl esters), or alternatively, of liver concentration of the vitamin (Olson, 1987). Hepatic stores are considered as a marker of vitamin A status because 70 % to 90 % of retinol of the body is stored in the liver in healthy individuals, while this percentage is considered to decrease to 50 % or below in severely deficient individuals (Rietz et al., 1974; Bausch and Rietz, 1977; Olson, 1987) (Section 2.3.4.1).

Olson (1987) has proposed a minimum concentration of 20 µg retinol/g liver (0.07 µmol/g) (i.e. as free retinol and retinyl esters) as a criterion to define adequate vitamin A status, based on the following considerations: 1) no clinical signs of deficiency have been noted in individuals with this or higher liver concentration; 2) at this concentration and above, the liver is capable of maintaining steady-state plasma retinol values, as determined by the relative dose response test in rats (Loerch et al., 1979) and humans (Amedee-Manesme et al., 1987); 3) biliary excretion of retinol has been observed to increase significantly when liver stores rise significantly above this concentration in rats (Hicks et al., 1984), which is suggested to serve as a regulatory mechanism of vitamin A storage; 4) this concentration was calculated to be sufficient to protect an adult ingesting a diet free of vitamin A from a deficiency state for approximately four months as well as to meet vitamin A needs during shorter periods of stress (e.g. infection).

This value has commonly been used as a reference point to define vitamin A adequate status in the scientific literature (Olson, 1987), as well as to derive vitamin A requirements (SCF, 1993; IOM, 2001; WHO/FAO, 2004). The Panel considers that a concentration of ≥ 20 µg retinol/g liver (0.07 µmol/g) can be considered to reflect an adequate vitamin A status.

2.4.1.1. Direct measurement

Vitamin A liver stores have been directly determined by post-mortem liver analysis and liver biopsies analysis. Post-mortem liver analyses reported concentrations of retinol from 10 to 1 807 µg/g liver (0.03 to 6.3 µmol/g) in Western countries (Hoppner et al., 1969; Underwood et al., 1970; Raica et al., 1972; Mitchell et al., 1973; Money, 1978; Huque, 1982; Schindler et al., 1988). Mean and median retinol content were 252 µg/g (0.9 µmol/g) and 198 µg/g (0.7 µmol/g) (range 0–1 201 µg/g (0–4.2 µmol/g) in post-mortem analysis of the liver of 364 British males and females (aged 0 to > 90 years) (Huque, 1982). Mean (± SD) and median retinol content of 597 ± 397 µg/g (2.1 ± 1.4 µmol/g) and 506 µg/g (1.8 µmol/g) (range 36–1 807 µg/g (0.1–6.3 µmol/g)) were found in post-mortem analysis of the liver of 77 adult men and women (mean age 56 years) in Germany (Schindler et al., 1988). Liver biopsy samples performed in low-income countries reported hepatic concentrations from 17 to 141 µg/g (0.1 to 0.5 µmol/g) (Suthutvoravoot and Olson, 1974; Abedin et al., 1976; Olson, 1979; Flores and de Araujo, 1984; Furr et al., 1989; Haskell et al., 1997). However, post-mortem liver analysis and liver biopsies are not feasible in population-based studies as primary status indicators for obvious reasons.

2.4.1.2. Indirect measurement by stable isotope dilution methods

Retinol total body and hepatic stores can be estimated indirectly by stable isotope dilution approaches (Haskell et al., 2005; IAEA, 2008). After administration of an oral dose of deuterium or carbon-^{13}C stable isotope labelled retinol, the dilution of tracer in plasma is measured when the labelled dose has mixed with endogenous stores and equilibrium is reached (14–20 days after administration). Total body exchangeable retinol pool can be derived from a mass balance equation, correcting for the efficiency of absorption and storage of retinol and its fractional catabolic rate (Furr et al., 1989; Furr et al., 2005; IAEA, 2008).

In the deuterated-retinol-dilution (DRD) technique, the retinol pool is calculated from an equation developed by Furr et al. (1989),[7] considering efficiency of absorption and storage of retinol, its catabolic rate and inequality of the plasma to liver ratio of labelled to non-labelled retinol. The absorption and storage efficiency factor is usually assumed to be 50 % based on data from Bausch and Rietz (1977) (see Section 2.3.3). To adjust for the catabolism of the labelled dose during the equilibration period, a fractional catabolic rate of 0.5 % is typically considered, derived from the half-life of retinol turnover in adults (Sauberlich et al., 1974) (see Section 2.3.6.1). To account for the fact that unlabelled retinol is continually consumed in the diet and newly absorbed retinol contributes preferentially to the plasma pool, another factor is applied to correct for the difference in specific activity in liver compared to plasma. A value of 0.65 is usually taken, derived from the ratio observed in rats (Hicks et al., 1984). This factor is not needed if no or as little possible retinol is consumed during the equilibration period.

In the [$^{13}C_2$]-retinol isotope dilution ([$^{13}C_2$]-RID) test, a smaller tracer dose is administered compared to the DRD technique, which reduces the degree to which the dose perturbs the endogenous retinol pool (Furr et al., 2005). For this test, a dose absorption of 90–100 % is assumed and there is no correction for the differences in distribution of the tracer between liver and serum (Valentine, 2013).

For both techniques, hepatic stores can be further determined by considering that the amount of retinol stored in the liver is positively correlated with the size of the total body pool. Between 40 and 90 % of the total retinol body pool are assumed to be stored in the liver, depending on the vitamin A status of the subjects (Rietz et al., 1974; Bausch and Rietz, 1977) (Section 2.3.4.1).

Based on data from 10 adult subjects in the US, the correlation coefficient between liver retinol concentrations calculated from the DRD method (range 19–321 µg/g liver (0.065–1.12 µmol/g)) and directly measured in liver biopsies (range 14–160 µg/g liver (0.049–0.56 µmol/g)) was 0.88, and the Spearman's rank correlation coefficient was 0.95 ($p < 0.002$) (Furr et al, 1989). Based on data from 31 Bangladeshi surgery patients, Haskell et al. (1997) found good agreement between mean total hepatic stores of retinol estimated by the DRD technique (32 ± 21 mg (0.110 ± 0.072 mmol)) and by analysis of the retinol concentration of a liver biopsy (29 ± 19 mg (0.100 ± 0.067 mmol)). A significant linear relation was found between the two techniques ($r = 0.75$, $p < 0.0001$). However, a wide prediction interval was observed for estimates of hepatic retinol stores for individual subjects.

Liver and total body retinol stores assessed by stable isotope dilution method have been shown to be well correlated with measures of habitual vitamin A intake in cross-sectional studies over a wide range of intakes (Pearson correlation coefficients around 0.4) (Ribaya-Mercado et al., 2004; Valentine et al., 2013) and to respond to vitamin A supplementation in intervention studies lasting a couple of weeks (Haskell et al., 1999; Ribaya-Mercado et al., 1999; Haskell et al., 2011).

The Panel notes that there are a number of uncertainties inherent to the stable isotope dilution methods due to the assumptions required in the calculations. Human data on the parameters used are limited, so that inter-individual variability and the influence of factors such as age is not well characterised (IAEA, 2008). The methods also assume that the fractional catabolic rate is independent of the size of the stores of retinol, which is unlikely, as indicated by data in rats (Green and Green, 1994) and humans (Sauberlich et al., 1974; Cifelli et al., 2008) (Section 2.3.7.1). Despite these limitations, they

[7] Total body exchangeable vitamin A pool = *F* dose x [S a ((1/D:H)-1)], where:

- *F* is a factor related to the efficiency of absorption and storage of the orally administered dose;
- dose is the amount of isotope administered (mmol);
- the factor S corrects for the inequality of the plasma to liver ratio of labelled to non-labelled retinol; this correction is not needed if subjects consume as little vitamin A as possible after administering the oral dose, while the isotope is mixing with exchangeable vitamin A pools;
- the factor a corrects for irreversible loss of labelled vitamin A during the equilibration period;
- D:H is the isotopic ratio of labelled to non-labelled retinol in plasma;
- and *-1* corrects for the contribution of the dose to the total body vitamin A reserve (this term is omitted when the mass of the labelled vitamin A is small compared with the mass of total body vitamin A).

have the advantage to enable a quantitative estimation of retinol stores. The Panel notes that these methods provide good estimates at group levels, but lack precision for their determination at individual level, due to the large inter-individual variation in the factors used in the equation.

2.4.1.3. Relative dose response

The relative dose response (RDR) is an indirect measurement of hepatic retinol stores. In conditions of vitamin A deficiency, RBP that is not bound to retinol (apo-RBP) accumulates in the liver, but is rapidly released from the liver into the circulation after a dose of retinol or retinyl esters is administered (Muto et al., 1972; Smith et al., 1973; Loerch et al., 1979).

In this test, after an oral dose of retinol, the relative excess of apo-RBP in the liver binds to retinol and the resulting holo-RBP (RBP bound with retinol), coupled with transthyretin, is released into the circulation. Two blood samples are collected, at baseline and five hours after dosing, and the RDR value is calculated as follows:

RDR (in %) = [(serum retinol concentration at five hours post-dosing – serum retinol concentration at baseline)/ serum retinol concentration at five hours post-dosing] × 100.

Alternative methods have been proposed, e.g. by measuring serum RBP instead of serum retinol concentration (Fujita et al., 2009) or by administrating the 3,4-didehydroretinyl ester analogue instead of retinol as the test dose (modified relative dose response) (Tanumihardjo, 1993).

The RDR test is considered a valid test to determine inadequate vitamin A status. A large positive response to the dose, i.e. RDR value > 20 %, is indicative of vitamin A deficiency, whereas a value < 20 % is considered to reflect hepatic stores equivalent to or above 20 µg retinol/g (0.07 µmol/g) (Tanumihardjo, 1993; WHO, 1996; Tanumihardjo, 2011). However, the synthesis of RBP also depends on the adequacy of energy intake and of other nutrients such as zinc and protein. In addition, plasma retinol concentration and consequently the RDR test are insensitive across a wide range of liver stores above 20 µg retinol/g (0.07 µmol/g) (Solomons et al., 1990).

The Panel considers that the RDR represents a good marker of inadequate vitamin A status, but its sensitivity is limited to liver stores below 20 µg retinol/g (0.07 µmol/g).

2.4.2. Plasma/serum retinol concentration

In the usual range, plasma retinol concentration is neither related to observed habitual vitamin A intake, from either dietary preformed vitamin A or provitamin A carotenoid sources, nor responsive to supplement use (IOM, 2001; Tanumihardjo, 2011).

The concentration of plasma retinol is under tight homeostatic control (Olson, 1984). The relationships between plasma retinol and total body or liver retinol stores are not linear. Serum retinol concentrations reflect liver retinol stores only when they are severely depleted (< 20 µg retinol/g liver (< 0.07 µmol/g)) or very high (> 300 µg/g liver (1.05 µmol/g)) (WHO, 2011). A plasma retinol concentration below 200 µg/L (0.7 µmol/L) is considered to reflect vitamin A inadequacy for population assessment (Sommer, 1982; Olson, 1987; Flores, 1993; Underwood, 1994a; WHO, 2011). The prevalence of values below 200 µg/L (0.7 µmol/L) is a generally accepted population cut-off for preschool-age children to indicate risk of inadequate vitamin A status (WHO, 1996, 2011), whilst values above 300 µg/L (1.05 µmol/L) indicate an adequate status related to the absence of clinical signs of deficiency (Pilch, 1987; Flores et al., 1991).

A low plasma retinol concentration may also originate from an inadequate supply of dietary protein, energy, or zinc, which are required for synthesis of RBP, or may be caused by an infection in relation with the decreases in the concentrations of the negative acute phase proteins, RBP and transthyretin (IOM, 2001; Tanumihardjo, 2011). Infections can lower serum concentrations of retinol on average by as much as 25 %, independently of vitamin A intake (Filteau et al., 1993; Christian et al., 1998a).

The Panel notes that the specificity of plasma/serum retinol concentration is affected by a number of factors unrelated to vitamin A status, including infections and inflammation, which make the interpretation of this biomarker difficult. In addition, plasma/serum retinol concentrations are maintained nearly constant over a wide range of vitamin A intakes.

2.4.3. Markers of visual function

Xerophthalmia is the most specific vitamin A deficiency disorder (Section 2.2.2.1). It encompasses the clinical spectrum of ocular manifestations of vitamin A deficiency, from milder stages of night blindness and Bitot's spots, to potentially blinding stages of corneal xerosis, ulceration and necrosis (WHO, 2009). The prevalence of xerophthalmia is considered a population indicator of vitamin A deficiency (WHO, 2009; Tanumihardjo, 2011).

2.4.3.1. Night blindness

The rhodopsin molecule of the rods in the retina contains 11-*cis* retinal (Section 2.2.1). Without an adequate supply of vitamin A to the retina, the function of the rods in dim light situations is affected, resulting in abnormal dark adaptation, i.e. night blindness (Carney and Russell, 1980).

Numerous tests have been used to assess the presence of night blindness (WHO, 2012). The most common method used at population level involves subjective reports on current or past night blindness status. Objective measures have also been developed based on dark adaptation or the scoptic response to various light stimuli after dark adaptation. They include dark adaptometry, the pupillary response test and the night vision threshold test.

Measures of night blindness and dark adaptometry are sensitive markers of vitamin A status at the lower end of the status continuum (liver concentration < 20 µg retinol/g (0.07 µmol/g)) (Tanumihardjo, 2011). Epidemiological evidence suggests that host resistance to infection is impaired prior to clinical onset of night blindness and laboratory animals fed a vitamin A-deficient diet maintain ocular levels of vitamin A despite a significant reduction in hepatic retinol levels (IOM, 2001).

Besides, zinc deficiency and severe protein deficiency also may affect dark adaptation responses (Morrison et al., 1978; Bankson et al., 1989).

2.4.3.2. Conjunctival impression cytology

Vitamin A deficiency leads to early keratinising metaplasia (Bitot's spot) and losses of mucin-secreting goblet cells on the bulbar surface of the conjunctiva of the eye (IOM, 2001). Cells can be counted and evaluated by microscopic examination of a filter paper impression from the surface of the eye and staining with hematoxylin and eosine (Tanumihardjo, 2011). However, there have been concerns on the performance of this method to assess vitamin A deficiency when compared with biochemical markers (e.g. serum retinol or RDR) (Amedee-Manesme et al., 1988; Gadomski et al., 1989; Rahman et al., 1995; Sommer and West, 1996). This technique was used in the 1990s, but because of its limitations, has not been widely adopted (Tanumihardjo, 2011).

2.4.3.3. Conclusion on markers or visual function

The Panel notes that markers of visual functions have also been used for population evaluation of vitamin A status or to assess intervention efficacy. However, these methods are rather qualitative and their sensitivity is limited to situations of vitamin A deficiency (Tanumihardjo, 2011).

2.4.4. Conclusion on biomarkers

The Panel notes that plasma/serum retinol is under tight homeostatic control and does not reflect vitamin A intakes (or status) until body stores are very low (or very high). In contrast, measures of

total body or liver content by stable isotope dilution methods have shown good correlation with habitual vitamin A intake, over a wide range of intakes.

As reviewed by Tanumihardjo (2011), the sensitivity of markers of visual function is limited to situations of vitamin A deficiency. Relative dose response tests are useful from deficiency to the adequate range of retinol liver stores but do not quantitatively reflect status above the adequate range. In contrast, stable isotope dilution methods give a quantitative estimate of liver stores from deficiency to toxic vitamin A status.

The Panel considers that measures of total body or liver retinol contents are the most specific and sensitive markers of vitamin A status. Liver concentration < 20 µg retinol/g (0.07 µmol/g) (i.e. as free retinol and retinyl esters) can be used as an indicator of vitamin A deficiency, while concentrations above this value are considered to maintain adequate plasma retinol concentrations, prevent clinical signs of deficiency and reflect adequate vitamin A status.

2.5. Effects of genotypes

In recent years, large subsets of molecular components of retinoids metabolism have been identified (D'Ambrosio et al., 2011). Mutations in the corresponding genes can cause various diseases including blinding diseases such as retinitis pigmentosa and Stargardt disease (Palczewski, 2010). Moreover, mutations in these genes can cause Matthew-Wood syndrome, a fatal disease which is associated with anophthalmia, pulmonary and cardiac malfunctions and severe mental retardation (Blaner, 2007).

Many proteins participate in the processes involved in the intestinal metabolism of retinol and carotenoids. Given the important role of these proteins in the absorption of dietary carotenoids, their conversion to retinol, and the incorporation of both carotenoids and retinyl-esters into chylomicrons, it is not surprising that recent work shows that polymorphisms in these genes affect carotenoid transport and metabolism (Erlanson and Borgstrom, 1968; von Lintig, 2010). Single nucleotide polymorphisms in SR-B1 (Borel et al., 2007) and in BCMO1 (Ferrucci et al., 2009; Leung et al., 2009) have been associated with alterations in carotenoids and retinoids metabolism in humans. In humans, a heterozygotic mutation in BCMO1 was described with evidence of both elevated plasma β-carotene concentration and low plasma retinol concentration (Lindqvist et al., 2007).

Mutations in the retinal pigment epithelium specific 65 kDa protein (RPE65) in humans result in chromophore deficiency and blindness (Marlhens et al., 1997).

The Panel considers that genotype probably induces inter-individual differences in vitamin A requirement but present knowledge is limited and cannot be used for setting DRVs.

3. Dietary sources and intake data

3.1. Dietary sources

Foods rich in retinol include offal and meat, butter, retinol-enriched margarine, milk products, and eggs, while foods rich in provitamin A carotenoids, in particular β-carotene, include vegetables and fruits, such as sweet potatoes, carrots, pumpkins, dark green leafy vegetables, sweet red peppers, mangoes and melons (FSA, 2002; Anses/CIQUAL, 2012).

Currently, vitamin A (as retinol, retinyl acetate, retinyl palmitate and β-carotene) may be added to foods[8] and food supplements.[9] The vitamin A content of infant and follow-on formulae[10] and processed cereal-based foods and baby foods for infants and young children[11] is regulated.

[8] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods, OJ L 404, 30.12.2006, p. 26.
[9] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, OJ L 183, 12.7.2002, p. 51.

3.2. Dietary intake

The EFSA Evidence Management Unit (DATA) estimated dietary intake of vitamin A from food consumption data from the EFSA Comprehensive Food Consumption Database (EFSA, 2011a), classified according to the food classification and description system FoodEx2 (EFSA, 2011b). Data from 12 dietary surveys in nine EU countries were used. The countries included were Finland, France, Germany, Ireland, Italy, Latvia, the Netherlands, Sweden and the UK. The data covered all age groups from children to adults (Appendix D).

Nutrient composition data for vitamin A were derived from the EFSA Nutrient Composition Database (Roe et al., 2013). Vitamin A content of foods, expressed as RE, was calculated by considering that 1 µg RE equals 1 µg retinol and 6 µg β-carotene. Other provitamin A carotenoids (i.e. α-carotene and β-cryptoxanthin) were not taken into account because of the limited availability of data concerning these compounds in the database.

Food composition information of Finland, Germany, Italy, the Netherlands and the UK were used to calculate vitamin A intake in these countries, assuming that the best intake estimate would be obtained when both the consumption data and the composition data are from the same country. For vitamin A intake estimates of Ireland and Latvia, food composition data from the UK and Germany, respectively, were used, because no specific composition data from these countries were available.

Average vitamin A intake ranged between 409–651 µg RE/day in children aged 1 to < 3 years, between 607–889 µg RE/day in children aged 3 to < 10 years, between 597–1 078 µg RE/day in adolescents (10 to < 18 years), and between 816–1 498 µg RE/day in adults. Average daily intakes were in most cases slightly higher in males (Appendix E) than in females (Appendix F), mainly owing to the larger quantities of food consumed per day.

Among toddlers, food products for young population, vegetables and vegetable products, milk and milk products contributed significantly to the vitamin A intake. In the older age groups in addition to the vegetable and vegetable products and milk and milk products, also meat and meat products and animal and vegetable fats contributed to the vitamin A intake (Appendices G and H). Differences in the main contributors to vitamin A intake between the sexes were minor.

When available, EFSA vitamin A intake estimates were compared with published intake estimates from the same national surveys. EFSA estimates were found to differ by 1–10 % from the published results of the EsKiMo and VELS surveys in Germany (Kersting and Clause, 2003; Mensink et al., 2007), the UK NDNS survey (Bates et al., 2012) and the IUNA survey in Ireland (IUNA, 2011). Higher differences, up to 24 %, were found with published results from the INCA 2 survey in France (Afssa, 2009) and the third INRAN-SCAI survey in Italy (Sette et al., 2011). Comparisons were not possible for Finland (Helldán et al., 2013), Sweden (Amcoff et al., 2012) and the Netherlands (van Rossum et al., 2011) due to the use of different conversion factors for provitamin A carotenoids for calculating vitamin A content of foods. Uncertainties in the estimates may be caused by differences in disaggregating data for composite dishes before intake estimations; inaccuracies in mapping food consumption data according to the FoodEx2 classification; analytical errors or errors in estimating vitamin A content of foods in the food composition tables; the use of borrowed vitamin A values from other countries; or the replacement of missing vitamin A values by values of similar foods or food groups in the vitamin A intake estimation process. As the intake calculations rely heavily on estimates of both food composition and food consumption, it is not possible to conclude which of these intake estimates would be closer to the actual vitamin A intake.

[10] Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, OJ L 401, 30.12.2006, p.1.

[11] Commission Directive 2006/125/EC of 5 December 2006 on processed cereal-based foods and baby foods for infants and young children, OJ L 339, 06.12.2006, p. 16–35.

4. Overview of dietary reference values and recommendations

4.1. Adults

In their recent revision of the Nordic Nutrition Recommendations (NNR), the Nordic Countries decided to maintain their earlier recommendations of 900 µg retinol equivalent (RE)/day for men and 700 µg RE/day for women (Nordic Council of Ministers, 2014), which was based on the approach adopted by IOM (2001). The experts noted a recent study in men using the deuterated retinol dilution technique to estimate vitamin A requirement (Haskell et al., 2011), but considered that more studies on the variation in the AR were needed before a change in the current recommendations could be proposed.

D-A-CH (2013) derived an AR for men of 600 µg RE/day, which was reported to have been determined experimentally. Using a CV of 30 %, recommended intakes of 1 000 µg RE/day for men and 800 µg RE/day were proposed. The recommended intake for women were set 20 % below those of men, considering that their average plasma concentration is lower (Heseker et al., 1994).

At the FAO/WHO Expert consultation of 1998 (WHO/FAO, 2004), the experts maintained the approach that had been proposed previously (FAO/WHO, 1988). The mean requirement[12] was defined as the minimum daily intake of vitamin A to prevent xerophthalmia in the absence of clinical or subclinical infection. A mean requirement of 4–5 µg/kg body weight was estimated from the depletion-repletion study by Sauberlich et al. (1974). Vitamin A mean requirements of 300 µg RE/day for men and 270 µg RE/day for women were proposed. The "safe level of intake" was defined as the average continuing intake of vitamin A required to permit vitamin A dependent functions and to maintain an acceptable total body store of the vitamin. This store helps offset periods of low intake or increased need resulting from infections and other stresses. Recommended safe intakes of 500 µg RE/day for women and 600 µg RE/day for men were set (9.3 µg/kg body weight per day). It was calculated by estimating the average dietary intake of retinol needed to replace the endogenous stores that are lost[13], following the approach proposed by Olson (1987), and considering a CV of 20 %. The CV was estimated from data on vitamin A half-life reported by Sauberlich et al. (1974). Equivalency factors of 1:14 for β-carotene and 1:28 for other provitamin A carotenoids from usual vegetables diets were recommended (van het Hof et al., 1999), which may be adjusted depending on the proportion of green leafy vegetables or fruits in the diet.

The IOM (2001) estimated the average requirement for vitamin A based on the assurance of adequate stores of vitamin A. A minimum acceptable liver vitamin A concentration of 20 µg/g (0.07 µmol/g) was considered. At this concentration, no clinical signs of deficiency are observed, adequate plasma retinol concentrations are maintained (Loerch et al., 1979), induced biliary excretion of vitamin A is observed (Hicks et al., 1984) and this amount ensures protection against vitamin A deficiency for approximately four months while the person consumes a vitamin A-deficient diet. The Estimated Average Requirement (EAR) was calculated by multiplying the percent of body vitamin A stores lost per day when ingesting a vitamin A-free diet (0.5 %), the minimum acceptable liver vitamin A store (20 µg/g), the liver weight:body weight ratio (1:33), the reference weight for a specific age group and sex (61 and 76 kg for adult women and men, respectively), the ratio of total body:liver vitamin A stores (10:9) and the efficiency of storage of ingested vitamin A (40 %) (Olson, 1987). This resulted in EAR of 627 µg Retinol Activity Equivalent (RAE)/day for men and 503 µg RAE/day for women. A coefficient of variation (CV) of 20 % was used to derive the RDA based on calculated half-life values for liver vitamin A. Recommended daily allowances (RDAs) of 900 µg RAE for men and 700 µg RAE for women were set. The IOM revised conversion factors of carotenoids and retinol to account for data suggesting a lower absorption of provitamin A carotenoids (de Pee et al., 1998; Parker et al., 1999; van het Hof et al., 1999). Retinol activity equivalency factors of 12:1 for dietary β-carotene and 24:1 for other dietary provitamin A carotenoids were proposed.

[12] Previously defined as "basal requirement" by FAO/WHO (1988)
[13] Previously defined as "mean normative storage requirement" by FAO/WHO (1988)

Afssa (2001) considered a minimal vitamin A requirement of 600 µg RE/day, based on data from the depletion-repletion study by Hume and Krebs (1949) and the radioisotope study by Sauberlich et al. (1974). Given the small number of subjects involved in these studies, an individual variation of 30 % was considered and a daily recommended intake of 800 µg RE for men was proposed. For women, the value was extrapolated from the value for men on the basis of energy requirements and set at 600 µg RE. Afssa recommended 350 µg RE/day to be provided by β-carotene (2.1 mg/day). Vitamin A activity of carotenoids in the diet was expressed in retinol equivalent based on conversion factors of 6:1 for dietary vitamin A: β-carotene and 12:1 for vitamin A:other dietary provitamin A carotenoids. Because elderly may be at particular risk for hypervitaminosis A due to protein deficiency or renal failure, Afssa proposed to set the recommended intake at 700 µg RE/day for men and 600 µg RE/day for women over 75 years (Ward, 1996).

As IOM, the SCF (1993) considered the approach proposed by Olson (1987), using a liver concentration of 20 µg retinol/g (0.07 µmol/g) as a criterion for vitamin A sufficiency. The mean dietary intake needed to maintain this concentration was calculated assuming that the liver store represents 90 % of the total body vitamin A pool and the efficiency of storage in the liver is 50 %. Based on studies with radioactive vitamin A, a mean fractional catabolic rate of 0.5 % was considered. This results in a mean daily dietary intake of 6.7 µg RE/kg body weight, corresponding to an average daily requirement of 500 µg RE for men and 400 µg RE for women. A CV of 20 % was considered from the rates of depletion observed experimentally. The PRI was set at 700 µg RE/day for men and 600 µg RE/day for women. Conversion factors of 6:1 for dietary vitamin A: β-carotene and 12:1 for vitamin A:other dietary provitamin A carotenoids were recommended.

The Netherlands Food and Nutrition Council (1992) identified a minimum requirement of vitamin A for adults of 600 µg RE/day, which was observed to be sufficient to prevent deficiency symptoms such as anomalies in electroretinogram and changes in the eyes and the skin, and to maintain plasma retinol concentration at a minimum of 0.7 µmol (Sauberlich et al., 1974). An Adequate intake (AI) of 1 000 µg RE/day for men and 800 µg RE/day for women were proposed. Conversion factors of 6:1 for dietary vitamin A:β-carotene and 12:1 for vitamin A:other dietary provitamin A carotenoids were recommended.

The UK COMA (DH, 1991) referred to the approach proposed by FAO/WHO (1988), which based recommendations on the maintenance of an adequate body pool size, considering the amount of vitamin A in the liver. The PRIs was set at 700 µg RE/day for men and 600 µg RE/day for women.

Table 1: Overview of Dietary Reference Values for vitamin A for adults

	NNR (2014)	D-A-CH (2013)	WHO/FAO (2004)	Afssa (2001)	IOM (2001)	SCF (1993)	NL (1992)	DH (1991)
Age (years)	≥ 19	≥ 19	≥ 19	≥ 19	≥ 19	All	≥ 19	Adults
PRI Men (µg RE/day)	900	1 000	600 [(a)]	800	900 [(b)]	700	1 000 [(c)]	700
PRI Women (µg RE/day)	700	800	500 [(a)]	600	700 [(b)]	600	800 [(c)]	600
Age (years)				≥ 75				
PRI Men (µg RE/day)				700				
PRI Women (µg RE/day)				600				

PRI, Population Reference Intake; RE, Retinol Equivalent; RAE, Retinol Activity Equivalent.
(a): Recommended Safe Intake.
(b): Expressed in µg RAE/day.
(c): Adequate Intake.

4.2. Infants and children

The Nordic Countries maintained their earlier approach and extrapolated the recommendations for children and adolescents from those for adults by using metabolic body weight and growth factors ($kg^{0.75}$) (Nordic Council of Ministers, 2014).

From observed intakes of breast-fed infants in developing countries with no signs of deficiency and normal growth, WHO/FAO (2004) estimated a requirement of 180 µg RE/day for infants from 0 to 6 months and increased it to 190 µg RE/day for infants from 7 to 12 months. Considering vitamin A intakes from breast milk in well-nourished communities, a recommended safe intake of 375 µg RE/day was proposed in early infancy (1.75 µmol/L x 0.75 L/day) and increased to 400 µg RE/day for infants from 7 to 12 months, taking into consideration that vitamin A-deficient populations are at increased risk of death from six months onwards. The requirement and recommended "safe intake" for pre-school children were derived from the values set in late infancy (i.e. 20 and 39 µg RE/kg body weight per day) and estimated to be in the range of 200-400 µg RE/day. Such values were supported by intakes observed to relieve signs of deficiency and reduce risk of mortality in Indian children (Rahmathullah et al., 1990) and maintain serum retinol concentrations of 0.70 µmol/L in American pre-school children (Ballew et al., 2001). Recommendations for older children were derived from adult values.

IOM (2001) proposed an AI of 500 µg RAE/day for infants from 7 to 12 months, considering that the extrapolation from the AI set for infants aged 0–6 months fed breast milk resulted in an estimate of 483 µg RAE/day, and that the estimation of total intakes based on the calculated intake from human milk (485 µg/L x 0.6 L/day = 291 µg/day) and observed intake from complementary foods (244 µg/day, n = 44, Third National Health and Nutrition Examination Survey) resulted in an estimate of 535 µg RAE/day. For children and adolescents, no data were available to estimate an average requirement. The EARs were extrapolated from adults using metabolic weight ($kg^{0.75}$), which provided higher values than using isometric scaling (linear with body weight). This was to ensure a sufficient RDA, based on indications from studies conducted in developing countries that xerophtalmia and serum retinol concentrations of less than 20 µg/dL exist among preschool children with daily intakes of up to 200 µg of vitamin A, whereas 300 µg/day of vitamin A is associated with serum retinol concentrations greater than 30 µg/dL (Reddy, 1985). The RDA was set by using a CV of 20 %, as for adults.

For infants, Afssa considered a daily recommended intake of 350 µg RE, based on a breast milk concentration of 0.5 µg RE/mL and an ingested volume of 750 mL/day. For children, Afssa (2001) extrapolated the data from adults based on energy requirements.

The SCF (1993) proposed a PRI of 350 µg RE/day for infants aged 6–11 months based on vitamin A amounts in breast milk (FAO/WHO, 1988). PRIs for older children were set to make a smooth transition from the infant to adult values. Although there is little evidence to support these values, they appeared unlikely to be underestimates. A daily intake of about 300 µg has been reported to meet requirements of pre-school children (Reddy, 1985).

For infants aged 6–11 months, the Netherlands Food and Nutrition Council (1992) set an AI on the basis of the content of vitamin A in breast milk. For children and adolescents, AIs were calculated by interpolation from the values of infants and adults, allowance being made for body weight and growth.

For infants, the UK COMA (DH, 1991) adopted the approach proposed by FAO/WHO (1988), which is described above. Values for children were interpolated from the values for infants up to adult values.

1230 **Table 2:** Overview of Dietary Reference Values for vitamin A for infants and children

	NNR (2014)	D-A-CH (2013)	FAO/WHO (2004)	Afssa (2001)	IOM (2001)	SCF (1993)	NL (1992)	DH (1991)
Age (months)	6–11	4–12	7–12	0–12	7–12	6–11	6–11	7–12
PRI (µg RE/day)	300	600	400 [(a)]	350	500 [(b)]	350	400 [(c)]	350
Age (years)	1–2	1–4	1–3	1–3	1–3	1–3	1–4	1–3
PRI (µg RE/day)	300	600	400 [(a)]	400	300 [(b)]	400	400 [(c)]	400
Age (years)	2–5	4–7	4–6	4–6	4–8	4–6	4–7	4–6
PRI (µg RE/day)	350	700	450 [(a)]	450	400 [(b)]	400	500 [(c)]	400
Age (years)	6–9	7–10	7–9	7–9	9–13	7–10	7–10	7–10
PRI (µg RE/day)	400	800	500 [(a)]	500	600 [(b)]	500	700 [(c)]	500
Age (years)	10–13	10–13	10–18	10–12	14–18	11–14	10–13	11–14
PRI Boys (µg RE/day)	600	900	600 [(a)]	550	900 [(b)]	600	1 000 [(c)]	600
PRI Girls (µg RE/day)	600	900	600 [(a)]	550	700 [(b)]	600	800 [(c)]	600
Age (years)	14–17	13–15		13–15		15–17	13–16	15–18
PRI Boys (µg RE/day)	700	1 100		700		700	1 000 [(c)]	700
PRI Girls (µg RE/day)	700	1 000		600		600	800 [(c)]	600
Age (years)		15–19		16–19			16–19	
PRI Boys (µg RE/day)		1 100		800			1 000 [(c)]	
PRI Girls (µg RE/day)		900		600			800 [(c)]	

1231 PRI, Population Reference Intake; RE, Retinol Equivalent; RAE, Retinol Activity Equivalent.
1232 (a): Recommended Safe Intake.
1233 (b): Expressed in µg RAE/day.
1234 (c): Adequate Intake.

1235 ### 4.3. Pregnancy

1236 The Nordic Countries considered a retinol accumulation of 50 µg/day in the fetus and set a
1237 recommended intake of 800 µg RE/day for pregnant women to cover individual variation (Nordic
1238 Council of Ministers, 2014).

1239 D-A-CH (2013) estimated that pregnant women should ingest on average one third more than non-
1240 pregnant women and a recommended intake of 1 100 µg RE/day was proposed throughout pregnancy.

1241 WHO/FAO (2004) considered that the newborn infant appears to require around 100 µg RE/day to
1242 meet their needs for normal growth and presumed that the fetus has similar needs during the third
1243 trimester of pregnancy. Recognising that a large portion of the world's population of pregnant women
1244 live under conditions of deprivation, an increment of 200 µg RE/day to the "safe intake level" of
1245 women was proposed during the whole period of pregnancy, in order to enhance maternal storage
1246 during early pregnancy and to cover the needs of the rapidly growing fetus in late pregnancy.

1247 The IOM used a model based on the accumulation of vitamin A in the liver of the fetus during
1248 gestation and assumption that livers contains approximately half of the body's vitamin A when liver
1249 stores are low, as is the case for newborns (IOM, 2001). A concentration of 3 600 µg per fetus was
1250 calculated. Assuming the efficiency of maternal vitamin A absorption to average 70 % and vitamin A
1251 to be accumulated mostly in the last 90 days of pregnancy, the maternal requirement would be
1252 increased by around 50 µg/day during the last trimester. As vitamin A in the maternal diet may be
1253 stored and mobilised later as needed and some vitamin A may be retained in the placenta, the IOM
1254 proposed an additional requirement of 50 µg RAE/day for the entire pregnancy. The RDA was set by
1255 using a CV of 20 % as for non-pregnant adults.

Afssa (2001) noted that fetal requirements are low and low amounts of vitamin A are accumulated in fetal liver. An increase of the recommended intake to 700 µg RE/day during the last trimester of pregnancy was proposed.

The SCF (1993) proposed a PRI of 700 µg RE/day during pregnancy, in order to enhance maternal storage to provide adequate vitamin A for the growing fetus in late pregnancy.

The Netherlands Food and Nutrition Council (1992) proposed an additional intake of 200 µg RE/day during pregnancy, based on fetal needs during the last three months of pregnancy (Olson and Hodges, 1987).

The UK COMA considered that an increment of 100 µg RE/day during pregnancy should enhance maternal storage and allow adequate vitamin A for the growing fetus in late pregnancy (DH, 1991).

Table 3: Overview of Dietary Reference Values for vitamin A for pregnant women

	NNR (2014)	D-A-CH (2013)	FAO/WHO (2004)	Afssa (2001)	IOM (2001)	SCF (1993)	NL (1992)	DH (1991)
Age (years)					14–18			
PRI (µg RE/day)	800	1 100	800 [(a)]	700 [(b)]	750 [(c)]	700	1 000 [(d)]	700
Age (years)					≥ 19			
PRI (µg RE/day)					770 [(c)]			

PRI, Population Reference Intake; RE, Retinol Equivalent; RAE, Retinol Activity Equivalent.
(a): Recommended Safe Intake.
(b): Third trimester of pregnancy.
(c): Expressed in µg RAE/day.
(d): Adequate Intake.

4.4. Lactation

The Nordic Countries proposed an additional intake of 400 µg RE/day for lactating women, to compensate the loss of vitamin A in breast milk considering reported values for vitamin A content of breastmilk of 450–600 µg RE/day in Western countries and an average milk production of 750 mL/day (Nordic Council of Ministers, 2014).

D-A-CH (2013) noted that the intake of breast-fed infants is about 500 µg RE/day (Souci et al., 2000). With prolonged breastfeeding, the vitamin A content of breast milk decreases while the breast-fed infant requires additional vitamin A for growth. Mainly for women breastfeeding longer than four months an allowance of 700 µg RE/day was recommended to satisfy the infant's requirement and to avoid deficits in the mother.

WHO/FAO proposed an increment of 350 µg RE/day to replace the amounts lost through breastfeeding (WHO/FAO, 2004).

The IOM considered that breast-fed infants consume an average of 400 µg RAE/day in the first six months of life and this was proposed as the additional EAR during lactation to maintain adequate body stores of vitamin A of mothers (IOM, 2001). The RDA was set by using a CV of 20 % as for adults.

Afssa considered that breastfeeding women secrete around 350 µg RE/day (based on a concentration of 0.5 µg RE/mL and a secreted amount of 750 mL/day) and this was proposed as the additional average estimated requirement during lactation (Afssa, 2001).

The SCF assumed that 350 µg RE/day is supplied in breast milk and proposed an increment of this amount throughout lactation (SCF, 1993).

The Netherlands Food and Nutrition Council (1992) recommended an additional intake of 450 µg RE/day during lactation, to offset the loss of vitamin A through breast milk, assuming an average concentration of 550 µg/L.

The UK COMA proposed an increment of 350 µg RE/day during lactation to cover vitamin A secreted with breast milk (DH, 1991).

Table 4: Overview of Dietary Reference Values for vitamin A for lactating women

	NNR (2014)	D-A-CH (2013)	FAO/WHO (2004)	Afssa (2001)	IOM (2001)	SCF (1993)	NL (1992)	DH (1991)
Age (years)					14–18			
PRI (µg RE/day)	1 100	1 500	850 [(a)]	950	1 200 [(b)]	950	1 250 [(c)]	950
Age (years)					≥ 19			
PRI (µg RE/day)					1 300			

PRI, Population Reference Intake; RE, Retinol Equivalent; RAE, Retinol Activity Equivalent.
(a): Recommended Safe Intake
(b): Expressed in µg RAE/day.
(c): Adequate Intake

5. Criteria (endpoints) on which to base dietary reference values

Vitamin A average requirement is defined as the average intake required to permit adequate growth and other vitamin A-dependent functions and to maintain an acceptable total body store of the vitamin.

5.1. Indicators of vitamin A requirements

The requirement of vitamin A has been estimated by other expert bodies on the basis of the amount needed to correct deficiency symptoms such as impaired dark adaptation among vitamin A-depleted subjects (Netherlands Food and Nutrition Council, 1992; Afssa, 2001); to raise the concentrations of retinol into normal range in the plasma of depleted subjects (Netherlands Food and Nutrition Council, 1992; Afssa, 2001); and to maintain a given body-pool size of retinol in well-nourished subjects (SCF, 1993; IOM, 2001; WHO/FAO, 2004; Nordic Council of Ministers, 2014).

5.1.1. Symptoms of vitamin A deficiency

Xerophthalmia is the most specific clinical consequence of vitamin A deficiency (Section 2.1.1.1). Markers of visual function have been developed to assess vitamin A status (Section 2.4.3). However, data relating such measurements to dietary vitamin A intake are scarce. In a depletion-repletion study in eight men in whom vitamin A deficiency was induced, daily supplementation with around 300 µg of retinol (4–5 µg/kg body weight) corrected abnormalities in adaptation to dark and electroretinogram patterns (Sauberlich et al., 1974). This may be considered as the minimal dietary requirements of adults to maintain normal visual function. However, the prevalence of ocular manifestations (i.e. xerophthalmia) is often recognised to underestimate the magnitude of functional vitamin A deficiency. Therefore, such amount may not cover other vitamin A-dependent functions (Section 2.4.3) and allow to maintain an adequate total body store of the vitamin.

The Panel considers that these indicators cannot be used for deriving DRVs for vitamin A.

5.1.2. Serum retinol concentration

Serum retinol concentration lacks sensitivity and specificity as a marker of vitamin A status in the general healthy population, because of the tight homeostatic control of retinol concentration over the range of adequate liver retinol concentrations and the influence of a number of confounding factors (Section 2.4.2).

The Panel considers that this marker cannot be used for deriving DRVs for vitamin A.

5.1.3. Maintenance of body and liver stores

Hepatic retinol concentration is a biomarker of vitamin A status. A concentration of 20 µg retinol/g liver (0.07 µmol/g) in adults represents a level assumed to maintain adequate plasma retinol concentrations, prevent clinical signs of deficiency and provide adequate stores (Section 2.4.1). Accordingly, the Panel considers that a concentration of 20 µg retinol/g liver (0.07 µmol/g) can be used as a target value for establishing the requirement for vitamin A in adults. In the absence of specific data for infants, children and adolescents, the Panel considers that the same target value as for adults can be used in those age groups.

Dietary intake of vitamin A required to maintain this liver concentration can be determined from a factorial approach (Olson, 1987). Data on the relationship between dietary intake of vitamin A and retinol liver (or total body) stores measured by stable isotope dilution methods may also be used (Haskell et al., 2005) (Section 2.4.1.2).

5.1.3.1. Factorial approach

The vitamin A intake required to maintain a concentration of 20 µg retinol/g liver (0.07 µmol/g) can be calculated on the basis of the factorial approach proposed by Olson (1987), which takes into account the ratio of total body/liver retinol stores, the fractional catabolic rate of retinol and the efficiency of storage of ingested retinol.

To apply the factorial approach, a number of assumptions have to be made:

- Retinol body store appears to be an important determinant of retinol catabolic rate (Section 2.3.7.1). Limited data are available on the fractional catabolic rate in subjects with adequate retinol body stores. Recent data indicate that the fractional catabolic rate may be higher than the value of 0.5 % which has usually been considered. Taking a conservative approach, the Panel assumes a fractional catabolic rate of 0.7 % for adults using the highest value of the range measured in four US adults at steady state (Section 2.3.7.1).

- It is considered that in healthy individuals with an adequate vitamin A status, 70 % to 90 % of retinol of the body is stored in the liver (Section 2.3.4.1). The Panel notes the paucity of data in humans. The Panel assumes a ratio of 80 % for all age groups.

- Available data in adults indicate an average efficiency of storage of retinol of 42 % in the liver of adult subjects with adequate hepatic stores (≥ 20 µg retinol/g liver). Assuming that liver stores represent 80 % of the whole body stores in this population group, this would correspond to a storage efficiency in whole body of 52 % (Section 2.3.4.3). The Panel assumes an efficiency of storage of retinol in the whole body of 50 % for all age groups.

- Based on available data which show that the liver/body weight ratio decreases with age (Haddad et al., 2001; Young et al., 2009), the Panel assumes average liver/weight ratios of 4.0 % up to 3 years, 3.5 % from 4 to 6 years, 2.8 % from 7 to 14 years and 2.4 % above 15 years and in adults.

- The Panel considers that maintenance needs for vitamin A expressed with respect to body weight are the same for adults and children. A growth component has to be added for children to take into account higher vitamin A utilisation for growth needs (Section 2.3.7.1). Growth factors were calculated as the proportional increase in protein requirement for growth relative to the maintenance requirement at the different ages, as follows: 0.57 for infants aged 7 to 11 months, 0.25 for boys and girls aged 1–3 years, 0.06 for boys and girls aged 4–6 years, 0.13 for boys and girls aged 7–10 years, 0.11 for boys and 0.08 for girls aged 11–14 years, and 0.08 for boys and 0.03 for girls aged 15–17 years (EFSA NDA Panel, 2014a).

The Panel notes that data on total body/liver retinol stores in humans are scarce and available information on retinol daily fractional catabolic rate and retinol efficiency of storage comes from studies involving a small number of subjects and that the influence of factors such as age is not well characterised.

5.1.3.2. Data from stable isotope dilution methods

Haskell et al. (2011) investigated the amount of daily vitamin A required to maintain liver stores in a selected population of Bangladeshi men expected to have concentration in the liver close to 20 µg retinol/g (0.07 µmol/g). During a 60-day intervention period, 16 subjects (18–32 years, body weight of ~50 kg) consumed a basal controlled diet containing 100 µg RAE/day and were randomly assigned to receive one of eight different amounts of retinol (range 100–1 000 µg/day; n = 2 per group) in the form of retinyl palmitate dissolved in corn oil. The retinol pool sizes and liver stores were quantitatively estimated by using the DRD method before and after the intervention. A "semi-quantitative" estimate of the change in retinol pool size was also obtained by estimating the change in plasma isotopic ratios at 3 day after dosing, before and after the intervention. Mean (± SD) estimated retinol body pool sizes were 17 ± 9 mg (59 ± 32 µmol) at baseline and 18 ± 10 mg (64 ± 34 µmol) after the intervention, and retinol concentrations in liver were 13 ± 7 µg/g liver (0.047 ± 0.025 µmol/g) and 14 ± 8 µg/g liver (0.049 ± 0.027 µmol/g), respectively. There were significant linear relationships between daily supplemental retinol intake and the changes in retinol pool size as assessed quantitatively (r = 0.62, p = 0.010) or "semi-quantitatively" (r = 0.68, p = 0.004). From the respective regression lines, the authors estimated that a daily supplement of 400 µg retinol (95 % CI = undefined–640) with the quantitative approach, and 254 µg/day (95 % CI = 156–336) with the "semi-quantitative" approach, would be required to maintain the retinol pool size of 17 mg (60 µmol) (13 ± 7 µg/g liver (0.047 ± 0.025 µmol/g liver)). Considering the background dietary intake, vitamin A intakes of 500 or 354 µg RAE/day were derived from the two methods. The Panel notes that the estimated liver retinol concentration in the study population was lower than the target of 20 µg/g liver (0.07 µmol/g liver). The authors indicate that no signs or symptoms of vitamin A deficiency were identified in the subjects, but the publication does not provide details on the physical examination which were undertaken, including eye/vision assessment.

Ribaya-Mercado et al. (2004) investigated the relationship between vitamin A dietary intake and total body and liver retinol stores in a cross-sectional study in men (n = 31, body weight 53.3 ± 9.7 kg) and women (n = 31, body weight 45.9 ± 10.1 kg) aged 60–88 years in rural Philippines. Total body pool was assessed using the DRD method and vitamin A intake was estimated by three non-consecutive 24-hour dietary recalls. Mean (± SD) (range) estimated retinol pool size was 75 ± 41 mg (11–190 mg) (263 ± 144 µmol (38–664 µmol)) in men and 62 ± 39 mg (6–169 mg) (215 ± 137 µmol (20–590 µmol)) in women. Assuming that liver weight was 2.4 % of body weight in adults and that, in these marginally nourished individuals, 70 % of total body retinol was found in the liver, the authors estimated a mean (± SD) liver retinol concentration of 40 ± 17 (range 7–74) µg/g (0.139 ± 0.058 (range 0.026–0.260) µmol/g) in men and 40 ± 27 (range 5–125) µg/g (0.140 ± 0.095 (range 0.019–0.438) µmol/g) in women. The mean vitamin intake of the men and women with liver concentration ≥ 20 µg retinol/g (0.07 µmol/g) (n = 53) was 135 ± 86 µg RAE/day (n = 27) and 134 ± 104 µg RAE/day (n = 26), respectively.

Valentine et al. (2013) assessed the relationship between vitamin A intake and retinol body pool size in another cross-sectional study in 40 non-pregnant, non-lactating women (22.4 ± 2.3 years, body weight 61.2 ± 7.2 kg). Body pool size and liver stores were estimated by using a [$^{13}C_2$]-RID test. Mean (± SD) estimated body retinol pool size was of 234 ± 154 mg (range 41–893) (816.5 ± 537.4 µmol (range 141.5–3 116)). A total of 80 % of total body retinol was assumed to be found in the liver and the liver weight was assumed to represent 2.4 % of body weight. Estimated mean liver concentration of retinol was 129 ± 89 µg/g liver (0.45 ± 0.31 µmol/g) and ranged from 26 µg/g liver (0.09 µmol/g) to 513 µg/g liver (1.79 µmol/g). Vitamin A intake estimate as assessed by FFQ (including supplements) was 1 213 ± 778 µg RAE/day (range: 378–3 890 µg RAE/day) and was positively

correlated with liver store and body retinol pool size (Pearson correlation coefficient 0.41 and 0.40, p = 0.009 and p = 0.011, respectively). Vitamin A intake was also estimated by a 3-day dietary record; mean estimate was 1 180 ± 705 µg RAE/day (range: 78–3 020 µg RAE/day) and no significant correlation was found with liver store and body retinol pool size. In a subset of women with a mean daily vitamin A intake (521 ± 119 µg RAE/day) similar to the EAR set by IOM (2001) on the basis of the Olson equation and a target liver concentration of 20 µg retinol/g (0.07 µmol/g), the authors found an average liver store of 86 ± 29 µg/g (0.30 ± 0.10 µmol/g).

In a group of 32 young women (19–30 years) in the US with a mean vitamin A intake of 1 148 ± 782 µg RAE (assessed by FFQ, including supplements), Valentine (2013) estimated a mean total body pool size of 234 ± 158 mg (817 ± 550 µmol) by using a [$^{13}C_2$]-RID test. A mean liver concentration of 132 ± 92 µg (0.46 ± 0.32 µmol) retinol/g was derived. Participants consumed a study diet containing 175 µg (0.6 µmol) RAE daily for 12 weeks. For the middle 6 weeks (day 14 to day 56), women were randomised to take a daily supplement of 0, 175 µg, or 525 µg (1.8 µmol) retinol as retinyl palmitate. No changes in liver stores and body vitamin A pool size were found in any group after the intervention. The changes in total body and liver stores were plotted against the mean daily intake of the respective groups. From the regression equations, the daily intake required to maintain the total body vitamin A pool and liver concentration was estimated to be around 300 µg RAE/day.

The Panel notes that current data on the dose-response relationship between vitamin A intake and liver stores are limited and difficult to compare due to differences in the vitamin A status of the study populations and study design. The Panel also notes uncertainties related to the quantitative body pool and liver store estimates derived from the stable isotope dilution methods, due to the different assumptions made, and on vitamin A intake estimates inherent to the dietary assessment methods used and the conversion of provitamin A carotenoids into vitamin A equivalents. Despite these uncertainties, the Panel notes that some studies (Ribaya-Mercado et al., 2004; Valentine et al., 2013) suggest that the amount of dietary vitamin A required to achieve a minimum liver content of 20 µg retinol/g (0.07 µmol/g) may be lower than previously calculated on the basis of the equation proposed by Olson (1987).

The Panel considers that the available data from stable isotope methods are to date insufficient to derive the requirement for vitamin A for adults.

5.2. Indicators of vitamin A requirement in pregnancy and lactation

During pregnancy there is an additional need of vitamin A for the fetus and possibly for the growth of maternal tissues. However, data are scarce.

Based on data from Thai fetuses (n = 46) from healthy mothers with an average liver content of retinol of 1 800 µg (6 µmol) at 37–40 week of gestational age (Montreewasuwat and Olson, 1979) and assuming that the liver contains approximately half of the body's retinol when liver stores are low, as is the case for newborns, a total amount of 3 600 µg (12 µmol) in the fetus was estimated by IOM (2001).

There is no information on the amount of retinol accumulated in maternal tissue formed during pregnancy.

With respect to lactating women, the Panel estimated a secretion of 424 µg/day of retinol in breast milk during the first six months of lactation (Section 2.3.7.3.)

The Panel considers that data on whole body retinol stores in fetus and on retinol secretion in breast milk can be used to derive the additional requirement for, respectively, pregnant or lactating women.

5.3. Vitamin A intake and health consequences

A comprehensive search of the literature published between 1 January 1990 and 1 July 2011 was performed as preparatory work to identify relevant health outcomes upon which DRVs may potentially be based for vitamin A (Heinonen et al., 2012). Additional searches were performed until October 2014.

A number of intervention studies in children have assessed the effect of vitamin A supplementation on the risk of (premature) death, and the incidence and severity of diarrhoea, measles and lower respiratory tract infections (Fawzi et al., 1992; Anonymous, 1993; Beaton et al., 1993; Glasziou and Mackerras, 1993; Grotto et al., 2003; Brown and Roberts, 2004; Wu et al., 2005; Chen et al., 2008; Imdad et al., 2011; Mayo-Wilson et al., 2011; McLaren and Kraemer, 2012). In adults, intervention studies have investigated the effect of supplementation with retinol, often in combination with other nutrients, for the primary prevention of a variety of diseases, including cancer of various sites (Bjelakovic et al., 2006; Bjelakovic et al., 2008; Misotti and Gnagnarella, 2013) and reproduction-related outcomes (Thorne-Lyman and Fawzi, 2012), and in relation to all-causes mortality (Fortmann et al., 2013; Bjelakovic et al., 2014). The Panel notes that these studies typically used high doses of vitamin A (1 000–60 000 µg RE in daily or bolus doses) and background vitamin A intake was not assessed in these studies. The Panel considers that these intervention studies cannot be used for the setting of DRVs for vitamin A.

The relationship between vitamin A intake and health outcomes has been investigated in observational (case–control, cross-sectional, prospective cohort) studies, where an association between vitamin A intake and health outcome might be confounded by uncertainties inherent to the methodology used for the assessment of vitamin A intake, and by the effect of other dietary, lifestyle, or undefined factors on the disease outcomes investigated. The Panel notes that different definitions of "vitamin A" have been applied among studies (i.e. defined as retinol only or as retinol and provitamin A carotenoids expressed in IU, µg RE, µg RAE, or undefined).

No association was observed between retinol intake and all-cause or cardiovascular disease mortality in a cohort study in the UK (Fletcher et al., 2003), or between intake of "vitamin A" or retinol and risk of death from coronary heart disease in the prospective Iowa Women's Health study (Kushi et al., 1996).

Several studies reported on the association between intake of "vitamin A" or retinol and risk of cancer at various sites, including risk of oral premalignant lesions (one prospective cohort (Maserejian et al., 2007)), nasopharyngeal carcinoma (one case–control study (Hsu et al., 2012)), lung cancer (two prospective cohorts (Yong et al., 1997; Takata et al., 2013)), benign proliferative epithelial disorders of the breast (one case–control (Rohan et al., 1990); one nested case–control study (Rohan et al., 1998)), breast cancer (Fulan et al., 2011) gastric cancer (two prospective cohorts (Larsson et al., 2007; Miyazaki et al., 2012)), pancreatic cancer (two case–control studies (Zablotska et al., 2011; Jansen et al., 2013)), colorectal cancer (three case–control studies (Key et al., 2012; Wang et al., 2012; Leenders et al., 2014); one prospective cohort (Ruder et al., 2011); one systematic review (Xu et al., 2013)), prostate cancer (one case–control study (Ghadirian et al., 1996); one prospective cohort (Giovannucci et al., 1995)), cervical cancer (two systematic reviews (Garcia-Closas et al., 2005; Zhang et al., 2012); one prospective cohort (Gonzalez et al., 2011)), ovarian cancer (one case–control study (Zhang et al., 2004); one prospective cohort (Fairfield et al., 2001)), bladder cancer (one case–control study (Garcia-Closas et al., 2007)), melanoma or basal cell carcinoma (one case–control study (Naldi et al., 2004); three prospective cohort studies (Fung et al., 2002; Feskanich et al., 2003; Asgari et al., 2012)) and non-Hodgkin's lymphoma (one case–control study (Mikhak et al., 2012); one prospective cohort (Kabat et al., 2012)). Results were limited and/or inconsistent.

Some observational studies have assessed the association between "vitamin A" or retinol intake and asthma, wheeze or other measures of lung function with inconclusive results (Allen et al. (2009) (systematic review including two prospective cohorts, one nested case–control, ten case–control and

six cross-sectional studies); Nurmatov et al. (2011) (systematic review including two case–control and three cross-sectional studies); Maslova et al. (2014) (prospective cohort)).

Some observational studies investigated the association between "vitamin A" or retinol intake and eye health-related outcomes, including cataract (one cross-sectional study (Cumming et al., 2000); one prospective study (Chasan-Taber et al., 1999)), age-related maculopathy (one cross-sectional study (Smith et al., 1999)) and age-related macular degeneration (one case–control study (Seddon et al., 1994)) and glaucoma (one cross-sectional study (Giaconi et al., 2012); two cohorts (Kang et al., 2003; Ramdas et al., 2012)). Results were limited and/or inconsistent.

In view of the limited and/or inconsistent evidence on an association between vitamin A or retinol intake and these health outcomes, the Panel considers that the data available cannot be used for deriving the requirement for vitamin A.

6. Data on which to base dietary reference values

The Panel expresses DRVs for vitamin A in µg RE/day (Section 2.3.9). Vitamin A requirement can be met with any mixture of preformed vitamin A and provitamin A carotenoids that provides an amount of vitamin A equivalent to the reference level in terms of µg RE/day.

6.1. Adults

The Panel determines the AR for vitamin A in healthy adults as the vitamin A intake required to maintain a liver concentration of 20 µg retinol/g (0.07 µmol/g). The latter is considered by the Panel as indicative of an adequate vitamin A status (or vitamin A body pool) at which the different functions of vitamin A in the body can be fulfilled (Sections 2.4.1, 2.4.4 and 5.1.3).

In the absence of better characterisation of the relationship between dietary intake of vitamin A and liver stores, the requirement to maintain a concentration of 20 µg retinol/g liver (0.07 µmol/g) can be calculated on the basis of the factorial approach as proposed by Olson (1987), as follows:

AR (µg RE/day) = target liver store (µg retinol/g) × body/liver retinol stores ratio × liver/body weight ratio (%) × fractional catabolic rate of retinol (%) × (1/efficiency of body storage (%)) × reference body weight (kg) × 10^3

The Panel uses the following values for adults (Section 5.1.3.1): 1) a total body/liver retinol store ratio of 1.25 (i.e. 80 % of vitamin A in the body is stored in the liver); 2) a liver/body weight ratio of 2.4 %; 3) a fractional catabolic rate of retinol of 0.7 % per day; 4) an efficiency of storage in the whole body for ingested retinol of 50 %. The reference weights for adult women and men in the EU are 58.5 and 68.1 kg, respectively (EFSA NDA Panel, 2013).

On the basis of this calculation, ARs of 570 µg RE/day for men and 490 µg RE/day for women are derived after rounding.

Assuming a CV of 15 % because of the variability in requirement and of the large uncertainties in the dataset (see Section 5.1.3.1), PRIs of 750 µg RE/day for men and 650 µg RE/day for women are set. PRIs were rounded to the closest 50 or 100.

Table 5: Dietary Reference Values for vitamin A for men and women

Reference body weight[(a)] (kg)		AR (µg RE/day) [(b)]		PRI (µg RE/day) [(c)]	
Men	**Women**	**Men**	**Women**	**Men**	**Women**
68.1	58.5	570	490	750	650

(a): Median body weight of 18 to 79-year-old men and women, respectively, based on measured body heights of 16 500 men and 19 969 women in 13 EU Member States and assuming a BMI of 22 kg/m2 see Appendix 11 in (EFSA NDA Panel, 2013)).

(b): Values for ARs were rounded to the closest 5 or 10.

(c): Values for PRIs were rounded to the closest 50 or 100, but PRIs were calculated based on the unrounded ARs.

6.2. Infants and children

Breast milk content is influenced by the maternal vitamin A status and large variations in retinol content of breast milk are observed (Section 2.3.7.3). The adequate intake resulting from observed intakes of retinol of breastfed infants may overestimate the requirement. The Panel considers more appropriate to derive DRVs for infants aged 7–11 months on the same basis as for adults.

For infants aged 7–11 months, children and adolescents, the ARs of vitamin A required to maintain a concentration of 20 µg retinol/g liver is evaluated with the same equation as from adults but with specific values for reference body weight and for liver/body weight ratio (Section 5.1.3.1). Although there is some indications that retinol catabolic rate may be higher in children than in adults, data are limited (Section 2.3.7.1). In the absence of more robust data, the Panel decides to apply the value for catabolic rate in adults and correct it on the basis of a growth factor (Section 5.1.3.1).

This approach is preferred to scaling down from adults based on body weight (either isometric or allometric), as retinol is mainly stored in the liver, the size of which does not linearly change with body weight during growth, and as vitamin A requirement is not directly related to energy needs and expenditure.

The requirement to maintain a concentration of 20 µg retinol/g liver can be calculated in infants and children on the basis of the factorial approach as follows:

AR (µg RE/day) = target liver store (µg retinol/g) × body/liver retinol stores ratio × liver/body weight ratio (%) × fractional catabolic rate of retinol (%) × (1/efficiency of body storage (%)) × reference body weight (kg) × (1 + growth factor) × 10^3

Table 6: Dietary Reference Values for vitamin A for infants, children and adolescents

Age	Reference body weight (kg)	Liver weight (% body weight)	Growth factor	AR [(h)] (µg RE/day)	PRI [(i)] (µg RE/day)
7–11 months	8.6 [(a)]	4.0	0.57	190	250
1–3 years	11.9 [(b)]	4.0	0.25	205	250
4–6 years	19.0 [(c)]	3.5	0.06	245	300
7–10 years	28.7 [(d)]	2.8	0.13	320	400
11–14 years	44.6 [(e)]	2.8	0.11 (M) / 0.08 (F)	480	600
15–17 years (M)	64.1 [(f)]	2.4	0.08	580	750
15–17 years (F)	56.4 [(g)]	2.4	0.03	490	650

F, females; M, males.
(a): Mean of the body weight-for-age at 50th percentile of male or female infants aged 9 months according to the WHO Growth Standards (WHO Multicentre Growth Reference Study Group, 2006).
(b): Mean of body weight-for-age at 50th percentile of boys and girls aged 24 months (WHO Multicentre Growth Reference Study Group, 2006).
(c): Mean of body weight at 50th percentile of boys and girls aged 5 years (van Buuren et al., 2012).
(d): Mean of body weight at 50th percentile of boys and girls aged 8.5 years (van Buuren et al., 2012).
(e): Mean of body weight at 50th percentile of boys and girls aged 12.5 years (van Buuren et al., 2012).
(f): Body weight at 50th percentile of boys aged 16 years (van Buuren et al., 2012).
(g): Body weight at 50th percentile of girls aged 16 years (van Buuren et al., 2012).
(h): Values for ARs were rounded to the closest 5 or 10.
(i): Values for PRIs were rounded to the closest 50 or 100, but PRIs were calculated based on the unrounded ARs.

The Panel uses the following values for infants aged 7–11 months, children and adolescents (Section 5.1.3.1): 1) a total body/liver retinol stores ratio of 1.25 (i.e. 80 % of retinol in the body is stored in the liver); 2) an age-specific liver/body weight ratio; 3) a fractional catabolic rate of retinol of 0.7 % per day; 4) an efficiency of storage in the whole body of ingested retinol of 50 %; 5) a growth factor of 0.57 for infants aged 7 to 11 months, 0.25 for boys and girls aged 1–3 years, 0.06 for boys and girls

aged 4–6 years, 0.13 for boys and girls aged 7–10 years, 0.11 for boys and 0.08 for girls aged 11–14 years, and 0.08 for boys and 0.03 for girls aged 15–17 years (EFSA NDA Panel, 2014a).

As for adults, a CV of 15 % is used for setting PRIs for the respective age categories (Table 6). PRIs were rounded to the closest 50 or 100.

6.3. Pregnancy

The Panel assumes that a total amount of 3 600 µg retinol is accumulated in the fetus over the course of pregnancy (Section 5.2). Considering that the accretion mostly occurs in the last months of pregnancy, and assuming an efficiency of storage of 50 % for the fetus, an additional daily requirement of 52 µg RE vitamin A is calculated for the second half of pregnancy (i.e. 3 600 µg/140 days × 2). In order to allow for the extra need related to the growth of maternal tissues (e.g. placenta), the Panel applies this additional requirement to the whole period of pregnancy.

Consequently, an AR of 545 µg RE/day is estimated for pregnant women by adding the additional requirement of pregnancy to the AR for non-pregnant non-lactating women and rounding. Considering a CV of 15 % and rounding, a PRI of 700 µg RE/day is derived for pregnant women.

6.4. Lactation

Based on an average amount of retinol secreted in breast milk of 424 µg/day (Section 2.3.6.3) and an absorption efficiency of retinol of 80 % (Section 2.3.1.1), an additional vitamin A intake of 530 µg RE/day is considered sufficient to replace these losses. An AR of 1 020 µg RE/day is estimated by adding the additional requirement of lactation to the AR for non-pregnant non-lactating women and rounding. Considering a CV of 15 % and rounding, a PRI of 1 350 µg RE/day is proposed for lactating women.

CONCLUSIONS

The Panel concluded that ARs and PRIs for vitamin A in healthy adults can be derived from the vitamin A intake required to maintain a concentration of 20 µg retinol/g liver (0.07 µmol/g). In the absence of better characterisation of the relationship between dietary intake of vitamin A and liver stores, ARs for adult men and women were calculated on the basis of a factorial approach which takes into account the ratio of total body/liver retinol stores, the fractional catabolic rate of retinol and the efficiency of storage of ingested retinol. For infants aged 7–11 months, children and adolescents, ARs were derived on the basis of the same equation as for adults, by using specific values for reference body weight and liver/body weight ratio. For catabolic rate, the value for adults corrected on the basis of a growth factor was used. It was considered unnecessary to give sex-specific values for infants and children up to 14 years. The estimated amount of retinol accumulated in the fetus over the course of pregnancy was used as a basis to increase the AR for pregnant women. For lactating women, an increase in AR was based on the vitamin A intake required to compensate for the loss of retinol in breast milk. Because of the variability in requirement and of the large uncertainties in the dataset, a CV of 15 % was used to calculate PRIs for all population groups (Table 7).

1634 **Table 7:** Summary of Population Reference Intakes for vitamin A

Age	Population Reference Intake (µg/day)
Age	
7–11 months	250
1–3 years	250
4–6 years	300
7–10 years	400
11–14 years	600
15–17 years (M)	750
15–17 years (F)	650
≥ 18 years (M)	750
≥ 18 years (F)	650
Pregnancy	700
Lactation	1 350

1635 F, females; M, males.

1636 ## RECOMMENDATIONS FOR RESEARCH

1637 The Panel recommends:

1638 • To pursue the characterisation of provitamin A carotenoid bioconversion into retinol.

1639 • To pursue development of indirect measurement of liver stores by stable isotope dilution methods
1640 and application of the method to inform the dose–response relationship between vitamin A intake
1641 and retinol liver stores.

1642 • To further investigate and characterise retinol catabolic rate and its determinants, including the
1643 influence of retinol hepatic stores, age (e.g. children) and physiological state (e.g. pregnancy).

1644 • To characterise efficiency of storage of a physiological dose of retinol in population with adequate
1645 status.

1646 • To further characterise the relationship between vitamin A intake and health effects across the
1647 dietary range.

1648 • To further investigate the genetic basis of the differences in efficiency in provitamin A carotenoid
1649 and retinol metabolism in humans.

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APPENDICES

Appendix A. Prospective cohort and nested case–control studies on the association between intake of vitamin A and retinol and risk of bone fracture

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [(a)]) and retinol (µg/day)	Other factors considered in the analysis	Results
Melhus et al. (1998) [(b)(c)]	Nested case–control within the Swedish Mammography Cohort	1 120 women aged 40–76 years in Sweden 247 cases/873 controls	One FFQ covering previous 6 months performed at baseline. No information on inclusion of supplements.	Incidence of hip fracture. Hospital discharge records.	Mean ± SD (range) of retinol intake Cases: 960 ± 480 (260–3 210) µg Controls: 880 ± 430 (260–5 510) µg	Energy intake, BMI, age at menopause, lifetime physical activity, smoking status, hormone replacement therapy, diabetes mellitus, oral contraceptive or cortisone use, previous osteoporotic fracture, intake of iron, magnesium, vitamin C, and calcium.	Retinol Multivariate OR = 2.05 (95 % CI = 1.05–3.98) with retinol intake >1 500 µg/day (highest category) compared to ≤ 500 µg/day (lowest category) P for trend = 0.006 β-carotene No association found (data not shown).
Feskanich et al. (2002) [(b)(c)]	Prospective study 18 years follow up (Nurses' Health Study, 1980–1998)	72 337 postmenopausal women aged 34–77 years in the US	Semi-quantitative FFQ performed five times over study duration. Mean intake value determined from the mean of the five FFQs. Retinol and carotenoid content of foods from US Department of	Incidence of hip fracture. Self-reported by questionnaire every two years.	Quintiles of vitamin A: *From food only (n = 34 386, excluding supplement users)* Q1: < 1 000, Q2: 1 000–1 299, Q3: 1 300–1 599, Q4: 1 600–1 999, Q5: ≥ 2 000 µg RE *From food and supplements (n*	Age, follow-up cycle, intake of calcium, vitamin D, vitamin K, protein, alcohol and caffeine, smoking status, number of cigarettes smoked per day, use of	Vitamin A *Food only (excluding supplement users)* No association (multivariate RR). *Food and supplements* Multivariate RR = 1.48 (95 % CI = 1.05–2.07) with vitamin A intake ≥ 3 000 µg RE/day (Q5) compared to < 1 250 µg RE/day (Q1)

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [a]) and retinol (µg/day)	Other factors considered in the analysis	Results
			Agriculture and National Cancer Institute sources. Use of brand-specific supplements included.		*= 72 337)* Q1: < 1 250, Q2: 1250–1 699, Q3: 1 700–2 249, Q4: 2 250–2 999, Q5: ≥ 3 000 µg RE <u>Quintiles of retinol intake</u>: *From food only (n = 34 386, excluding supplement users)* Q1: < 400, Q2: 400–549, Q3: 550–699, Q4: 700–999, Q5: ≥ 1 000 µg *From food and supplements (n = 72 337)* Q1: < 500, Q2: 500–849 Q3: 850–1 299, Q4: 1 300–1 999, Q5: ≥ 2 000 µg	postmenopausal hormones, body weight, hours of physical activity a day, use of thiazide diuretics.	P for trend = 0.003 <u>Retinol</u> *Food only (excluding supplement users)* Multivariate RR = 1.69 (95 % CI = 1.05–2.74) with retinol intake ≥ 1 000 µg/day (Q5) compared to < 400 µg/day (Q1) P for trend = 0.05 *Food and supplements* Multivariate RR = 1.89 (95 % CI = 1.33–2.68) with retinol intake ≥ 2 000 µg/day (Q5) compared to < 500 µg/day (Q1) Multivariate RR = 1.43 (95 % CI = 1.04–1.96) with retinol intake 1 300–1 999 µg/day (Q4) compared to < 500 µg/day (Q1) P for trend = < 0.001 <u>β-carotene</u> No association (multivariate RR).
Michaelsson et al. (2003) [c]	Prospective study 30 years follow-up	1 221 men aged 49–51 years in Sweden	Seven-day dietary assessment, 20 years after entry into study. Food composition from Swedish National Food	Incidence of any fracture. Hospital discharge register.	Not provided.	Energy intake.	<u>Retinol</u> *Food only* Rate ratio (energy-adjusted) = 2.00 (95 % CI = 1.00–3.99) for any fracture with retinol intake >1 500 µg/day (Q5) compared to < 530 µg/day (Q1).

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [(a)]) and retinol (µg/day)	Other factors considered in the analysis	Results
			Administration database. Use of brand-specific supplements included.				*Food and supplements* Rate ratio (energy-adjusted) = 1.99 (95 % CI = 0.98–4.01) for any fracture for Q5 (no value reported) vs. Q1 (no value reported).
Lim et al. (2004) [(c)]	Prospective study 9.5 years follow-up (Iowa Women's Health Study 1986–1997)	34 703 postmenopausal women aged 55–69 years in the US	One semi-quantitative FFQ performed at baseline. Use of brand-specific supplements included.	Incidence of hip and non-hip fracture. Self-reported by questionnaire at the end of follow up period.	Mean (range) for each quintile of vitamin A intake (in IU): *From food only (n = 22 410, excluding supplement users)* Q1: 4 440 (221–5 975), Q2: 7 223 (5 976–8 5445), Q3: 10 043 (8 545–11 699); Q4: 13 793 (11 700–16 431); Q5: 24 163 (16 432–215 392) IU *From food and supplements (n = 34 703)* Q1: 5 113 (221–7 055), Q2: 8 771 (7 056–10 484), Q3: 12 256 (10 485–14 209); Q4: 16 764 (14 210–19 892); Q5: 29 239 (19 893–236 991) IU Mean (range) for each quintile of retinol intake: *From food only (n =*	For hip fracture: Age, BMI, waist-to-hip ratio, diabetes mellitus, physical activity, occurrence of past irregular menstrual duration, steroid medication, oestrogen replacement, energy intake. For all fractures: Age, BMI, waist-to-hip ratio, diabetes mellitus, cirrhosis, past irregular menstrual duration, thyrotropic, sedative, antiepileptic, or diuretic medications,	Vitamin A and retinol No association (multivariate RR) between vitamin A or retinol intake, from supplements only, food and supplements, or food only (excluding supplement users), and risk of hip fracture or risk of all fractures.

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [(a)]) and retinol (µg/day)	Other factors considered in the analysis	Results
					22 410, excluding supplement users) Q1: 223 (8–326), Q2: 427 (327–537), Q3: 707 (538–978); Q4: 1 190 (979–1 398); Q5: 2 063 (1 398–62 872) µg *From food and supplements (n = 34 703)* Q1: 274 (8–422), Q2: 609 (423–886), Q3: 1 157 (887–1 397); Q4: 1 730 (1 398–2 100); Q5: 3 783 (2 101–63 315) µg	education, alcohol use and energy intake.	
Rejnmark et al. (2004)	Nested case–control	1 141 perimenopausal women aged 45–58 years in Denmark 163 cases/978 controls	Four- or seven-day food record at baseline and after five years. Composition data from official Danish food tables. Use of supplements included.	Incidence of fractures. Self reported, confirmed by hospital discharge records.	<u>Median (interquartile range 25–75 %) of vitamin A intake</u> *From food only* Cases: 1 150 (730–1 720) µg RE Controls: 1 140 (800–1 660) µg RE *From food and supplements* Cases: 1 730 (1 280–2 380) µg RE Controls: 1 710 (1 290–2 260) µg RE <u>Median (interquartile range 25–75 %) of retinol intake</u>		<u>Vitamin A, retinol and β-carotene</u> No association (multivariate OR) between vitamin A, retinol or β-carotene intake, from food only or food and supplements, and risk of fracture.

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [(a)]) and retinol (µg/day)	Other factors considered in the analysis	Results
					From food only Cases: 510 (350–700) µg Controls: 520 (380–740) µg *From food and supplements* Cases: 1 190 (700–1 420) µg Controls: 1 210 (740–1 430) µg		
Caire-Juvera et al. (2009)	Prospective study 6.6 years follow-up (Women's Health Initiative Observational Study 1993-2005)	75 747 postmenopausal women, mean age at baseline 63.6 years, in the US	FFQ at baseline and at 3 year follow up. Mean intake value determined from the mean of the two FFQs. Retinol and carotenoid contents of foods from the University of Minnesota Nutrition Coding Center nutrient database. Use of brand-specific supplements included.	Incidence of hip and non-hip fracture. Questionnaire every year from participants or proxy respondents. Hip fractures were confirmed by medical records.	<u>Quintiles of vitamin A:</u> *From food and supplements* Q1: < 5 055, Q2: 5 055–5 824, Q3: 5 825–6 550, Q4: 6 551–7 507, Q5: ≥ 7 508 µg RE <u>Mean ± SD intake of retinol, for each quintile of vitamin A intake:</u> *From food and supplements* Q1: 412 ± 187; Q2: 727 ± 284; Q3: 983 ± 341; Q4: 1 227 ± 407; Q5: 1 968 ± 1266 µg	Age, intake of protein, vitamin D, vitamin K, calcium, caffeine, and alcohol, BMI, hormone therapy, smoking, metabolic equivalents hours per week, ethnicity, and region of clinical center.	<u>Vitamin A and retinol</u> No association (multivariate HR, including vit D and calcium) between vitamin A intake or retinol, from food and supplements, and risk of hip fracture or risk of total fracture. Among the women with lower vitamin D intake (≤ 11 µg/day), there was a higher risk of total fractures in Q5 of vitamin A intake (8 902 µg RE/day) compared with Q1 (4 445 µg RE/day) (HR: 1.19; 95% CI: 1.04, 1.37; p for trend = 0.022) and in Q5 of retinol intake (2 488 µg/day) compared with Q1 (348 µg/day) (HR: 1.15; 95% CI: 1.03, 1.29; p for trend = 0.056) . Given the

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [(a)]) and retinol (µg/day)	Other factors considered in the analysis	Results
							smaller number of hip fractures, stratified analysis by vitamin D and calcium intake was not conducted.
Ambrosini et al. (2013)	Retrospective analysis of the Vitamin A Program	664 women and 1 658 men in Australia (99 % participants of the Vitamin A Program), mean age at enrolment 55 years	Background dietary intake not assessed. Supplementation with 7 500 µg/day retinol as retinyl palmitate for 1 to 16 years (median 7 years).	Database on hospital admissions for fracture and self-reported by questionnaire sent to all surviving Program participants after the end of the intervention. Self-reported fractures occurring at the spine, hip, femur, arm, ribs or wrist were classified as osteoporotic fractures.	Background dietary intake not reported. Cumulative dose of retinol supplements was estimated by summing the number of days the supplement was taken between each annual follow-up, multiplying by the dose administered and adding to the previous year's total. Cumulative doses of retinol were analysed in units of 10 g. The maximum cumulative dose of retinol was 42 g, equivalent to taking 7 500 µg/day for 15.3 years.	Age, sex, smoking, BMI, medication use and previous fractures.	<u>Retinol</u> No associations (multivariate OR) between cumulative dose of retinol and risk for any fracture or osteoporotic fracture.

BMI: body mass index; CI: confidence interval; FFQ: food frequency questionnaire; HR: hazard ratio; OR: odds ratio; Q: quintile; RR: relative risk ; IU: International Unit
(a): unless stated otherwise.
(b): Study considered in SCF (2002).
(c): Study considered in SACN (2005).

Appendix B. Intervention and prospective cohort studies on the association between intake of vitamin A and retinol and measures of BMC, BMD or serum markers of bone turnover

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [a]) and retinol (µg/day)	Other factors considered in the analysis	Results
Measures of BMC, BMD							
Freudenheim et al. (1986) [b][c]	Prospective study 4 years follow-up within a calcium-supplementation trial	99 women pre- & postmenopausal aged 35–65 years, in the US.	Seventy-two 24h-dietary records collected for each participant over 3 years, including supplements. Subjects were assigned to a 500 mg calcium-supplemented or placebo group.	BMC of left arm bones (radius, humerus and ulna). By SPA. Eleven measurements, every three months for the first year and then every six months.	Mean ± SD (range) "vitamin A"[d] intake from food and supplements (in IU) *Postmenopausal Non-Ca supplemented* (n = 33): 8 624 ± 3 553 (3 615–17 763) IU *Ca supplemented* (n = 34): 7 619 ± 2 729 (3 256–14 624) IU	None.	"Vitamin A" [d] In postmenopausal calcium supplemented group, negative correlation between "vitamin A" and rate of change in ulna BMC – correlation not significant when one subject with very high supplemental "vitamin A" intake omitted. No correlation observed in the postmenopausal calcium unsupplemented group. No correlation in groups of calcium supplemented (n = 8) and non supplemented (n = 9) premenopausal women
Houtkooper et al. (1995) [b][c]	1 year follow-up within a physical exercise trial	66 premenopausal women aged 28–39 years, in the US.	Dietary records over 4 to 12 randomly assigned days. Vitamin supplements not included.	BMD of total body, lumbar vertebrae 2-4, femoral neck, Ward's triangle, trochanter. By DXA.	Mean ± SD "vitamin A" [d] *From food only* 1 220 ± 472 µg RE	Fat mass at baseline and change in fat mass over one year, exercise status.	"Vitamin A" [d] Significant variables in models predicting total body BMD slope included the initial fat mass and fat mass slope plus either "vitamin A" [d] intake (R^2 = 0.31) or β-carotene

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [a]) and retinol (µg/day)	Other factors considered in the analysis	Results
			All subjects were administered a 500 mg calcium-supplement.	Four measurements, at baseline and months 5, 12 and 18.			intake (R^2 = 0.28).
Promislow et al. (2002) [c]	Prospective study 4 years follow-up within the Ranchi Bernardo Heart and Chronic Disease Study	570 women and 388 men aged 55–92 years at baseline, in the US.	FFQ at baseline. Supplement use included.	BMD of total hip, femoral neck, lumbar spine. By DXA. Two measurements, taken at baseline and follow-up.	<u>Mean ± SD of retinol intake:</u> *From food only* Women: 497 ± 460 µg Men: 624 ± 585 µg *From food and supplements* Women: 1 247 ± 1 573 µg Men: 1 242 ± 1 442 µg	Age, weight change, BMI, calcium intake, diabetes status, menopausal status, exercise, smoking status, alcohol use, thiazide drug use, thyroid hormone use, steroid use, oestrogen use, supplemental retinol.	<u>Retinol</u> No association between retinol intake and BMD at baseline or BMD change when supplement users and non-users were pooled. *For supplement users only:* Women: a significant negative association was found between retinol intake and BMD at the femoral neck (p=0.02) and total spine (p=0.03) measured at follow-up and for BMD change at femoral neck (p=0.05) and total hip (p=0.02). Men: no significant association.
Macdonald et al. (2004)	Prospective study, within the Aberdeen Prospective	891 women aged 45–55 years at baseline, in the UK.	FFQ at baseline and 5 years later. Composition	BMD of lumbar spine, femoral neck. By DXA.	<u>Vitamin A intake:</u> Not reported. <u>Mean ± SD (range,</u>	Energy intake, age, weight, annual percentage	<u>Vitamin A</u> In multiple regression analysis, vitamin A intake from food only was a weak

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [(a)]) and retinol (µg/day)	Other factors considered in the analysis	Results
	Osteoporosis Screening Study 5–7 years follow-up		data from McCance and Widdowson's food composition tables Royal Society of Chemistry database. Use of brand-specific supplements included.	Two measurements, at baseline and follow-up.	median) of retinol intake: *From food only* Baseline: 820 ± 602 (39–4 354, 588) µg Follow up: 665 ± 513 (70–5 237, 480) µg *From food and supplements* Baseline: 924 ± 666 (85–4 354, 702) µg Follow up: 882 ± 654 (70–5 237, 627) µg	change in weight, height, smoking status, socioeconomic status, physical activity level, baseline BMD measurement, menopausal status and hormone replacement therapy use	but significant negative predictor of femoral neck BMD change (variation explained: 0.3 %, coefficient (95 % CI): –1.24 (–2.47–0.17), p = 0.047). No significant relation when intake from supplements was included. Retinol In multiple regression analysis, retinol intake from food only was a weak but significant negative predictor of femoral neck BMD change (variation explained: 0.4 %, coefficient (95 % CI): –1.73 (–3.20– –0.30), p = 0.018). No significant relation when intake from supplements was included.
Rejnmark et al. (2004)	Prospective study 5 years follow-up within the DOPS cohort study	1 694 perimenopausal women aged 45–58 years, in Denmark.	Four- or seven-day food record at baseline and after five years. Intake at baseline was considered in the analysis. Composition data from	BMD of lumbar spine, femoral neck. By DXA. Two measurements, at baseline and 5-years follow up.	Median (interquartile range 25–75 %) vitamin A intake (baseline) *From food only* 1 150 (800–1 730) µg RE *From food and supplements* 1 740 (1 290–2 360) µg RE	Age, years postmenopausal, hormone therapy, previous fracture, body weight, baseline BMD, physical activity, energy intake, intake of calcium,	Vitamin A and retinol Multiple regression analysis showed no association between baseline vitamin A or retinol intake, from food only or food and supplements, and change in BMD at any site. β-carotene

Reference	Design	Study sample	Dietary assessement	Outcomes	Daily intake of vitamin A (µg RE/day [(a)]) and retinol (µg/day)	Other factors considered in the analysis	Results
			official Danish food tables. Use of supplements included.		Median (interquartile range 25–75 %) retinol intake (baseline) *From food only* 530 (390–750) µg *From food and supplements* 1 210 (680–1 450) µg	vitamin D, alcohol, smoking status, use of thiazide or loop diuretics, thyroide hormones, antipsychotic / anxiolytic / antidepressant, diagnosis of thyrotoxicosis, diabetes mellitus.	No association between β-carotene intake, from food only, and change in BMD at any site.
Measures of serum markers of bone turnover							
Kawahara et al. (2002) [(b)(c)]	Randomised single-blind trial 6 weeks	80 men aged 18–58 years, in the US.	Subjects were assigned to 7 576 µg retinol palmitate/day or a placebo. Background retinol intake not assessed.	Serum osteocalcin, bone specific alkaline phosphatase, N-telopeptide of type-1 collagen. Blood sampled at baseline and weeks 2, 4 and 6.	Not reported.		Retinol Supplementation did not affect serum osteocalcin, bone specific alkaline phosphatase, N-telopeptide of type-1 collagen.

BMC: bone mineral content; BMD: bone mineral density; DXA: dual energy X-ray absorptiometry; FFQ: food frequency questionnaire; IU: International Unit; SPA: single-photon absorptiometry

(a): unless stated otherwise.

(b): Study considered in SCF (2002).

(c): Study considered in SACN (2005).
(d): It is unclear from the article whether it refers to vitamin A or retinol only.

Appendix C. Retinol concentration in breast milk from mothers of term[14] infants

Reference	Number of women	Country	Maternal vitamin A intake	Stage of lactation (time *post partum*)	Concentration (µg/L)			Methods [(a)]
					Mean ± SD	Median	Range	
Canfield et al. (2003)	53	Australia	Not reported. Mothers who were taking supplements containing carotenoids or vitamin A (> 8000 IU/day) were excluded.	Mature milk (months 2–12)	311 ± 16 (SE)			Single complete breast expression by electric breast pump collected mid-afternoon from each mother. Samples were collected from the breast from which the infant had most recently fed. Samples were saponified before analysis of retinol by HPLC.
	55	Canada		Mature milk (months 2–12)	340 ± 19 (SE)			
	50	UK		Mature milk (months 2–12)	301 ± 14 (SE)			
	49	US		Mature milk (months 2–12)	352± 25 (SE)			
Schweigert et al. (2004)	21	Germany	Not reported. Mothers taking supplements containing carotenoids or vitamin A were excluded.	Colostrum (days 4 ± 2)	1 532 ± 725			Total milk volume of one breast was collected. Samples were saponified before analysis of retinol by HPLC.
	21			Mature milk (days 19 ± 2)	831 ± 321			
Schulz et al. (2007)	26	Germany	Mean ± SD: Retinol intake: 0.95 ± 0.64 mg/day. Carotenoid intake: 6.9 ± 3.6 mg/day. Total vitamin A intake: 2.11 ± 0.89 mg RE/day. By FFQ. Mothers taking supplementation > 2 000 IU vitamin A or > 2 mg/day beta-carotene were excluded.	Colostrum (days 1–2)	1 106 ± 851			Samples collected by hand expression or electric pump up to a volume of 4 mL, collected at one or more times. Samples were saponified before analysis of retinol by HPLC.

[14] Infants from studies which did not report whether the infants were born at term or not are presumed to be born at term.

Reference	Number of women	Country	Maternal vitamin A intake	Stage of lactation (time *post partum*)	Concentration (µg/L)			Methods [a]
					Mean ± SD	Median	Range	
Tokusoglu et al. (2008)	92	Turkey	Not reported.	Mature milk (days 60–90)	815 ± 120.6			Milk samples (10 mL) collected from both breasts by hand expression, at least two hours after previous breastfeeding. Samples were saponified before analysis of retinol by HPLC.
Duda et al. (2009) [b]	30	Poland	Mean ± SD: 'vitamin A-equivalent' intake: 1 012 ± 735 µg/day. β-carotene intake: 2 096 ± 2 465 µg/day. By 24-hour recall (repeated 3 consecutive days).	Mature milk (months 2–4)	571 ± 500	294	157–1 424	Milk samples expressed by hand or using a sterile pump 1 or 2 hours prior to actual feeding of the baby. Samples were saponified before analysis of retinol by HPLC.
Orhon et al. (2009)	20	Turkey	Mean ± SEM: 4 965.2 ± 538.5 IU/day. By 5-day dietary record. Significant correlation between dietary vitamin A intake and retinol content of breast milk (r = 0.621, p = 0.006). No correlation between dietary vitamin A intake and beta-carotene content of breast milk.	Transitional milk (day 7)	2 463 ± 200 (SE)			Milk samples (5 mL) were collected from each breast using an electric pump. Treatment of the samples not described. Retinol analysed by HPLC.
Kasparova et al. (2012) [b]	12	Czech Republic	Not reported.	Mature milk: months 1–2	458 ± 286			Milk samples obtained from a University Hospital; method of expression not described. Samples were saponified before analysis of retinol by HPLC.
				Mature milk: months 3–4	315 ± 258			
				Mature milk: months 5–6	229 ± 115			
				Mature milk: months 9–12	172 ± 115			

Studies were identified by a comprehensive literature search for publications from January 2000 to January 2014 (LASER Analytica, 2014).

(a): determination of total breast milk retinol requires saponification (typically with alcoholic potassium hydroxide (KOH)) and retinol is then extracted with an organic solvent, usually hexanes, before HPLC analysis (Tanumihardjo and Penniston, 2002).
(b): it was not reported whether the infants were born at term or not.

Appendix D. Dietary surveys in the Comprehensive database update dataset included in the nutrient intake calculation and number of subjects in the different age classes

Country	Dietary survey (Year)	Year	Method	Days	Number of subjects [a]					
					Children 1–< 3 years	Children 3–< 10 years	Adolescents 10–< 18 years	Adults 18–< 65 years	Adults 65–< 75 years	Adults ≥ 75 years
Finland/1	DIPP	2000–2010	Dietary record	3	500	750				
Finland/2	NWSSP	2007–2008	48-hour dietary recall [b]	2x2 [b]			306			
Finland/3	FINDIET2012	2012	48-hour dietary recall [b]	2 [b]				1 295	413	
France	INCA2	2006–2007	Dietary record	7		482	973	2 276	264	84
Germany/1	EsKiMo	2006	Dietary record	3		835	393			
Germany/2	VELS	2001–2002	Dietary record	6	347	299				
Ireland	NANS	2008–2010	Dietary record	4				1 274	149	77
Italy	INRAN-SCAI 2005-06	2005–2006	Dietary record	3	36 [a]	193	247	2 313	290	228
Latvia	FC_PREGNANTWOMEN 2011	2011	24-hour dietary recall	2			12 [a]	991 [c]		
Netherlands	DNFCS 2007–2010	2007–2010	24-hour dietary recall	2		447	1 142	2 057	173	
Sweden	RISKMATEN	2010–2011	Dietary record (Web)	4				1 430	295	72
United Kingdom	NDNS - Rolling Programme (1-3 years)	2008–2011	Dietary record	4	185	651	666	1 266	166	139

DIPP, type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; EsKiMo, Ernährungstudie als KIGGS-Modul; FINDIET, the national dietary survey of Finland; INCA, étude Individuelle Nationale de Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - Studio sui Consumi Alimentari in Italia; FC_PREGNANTWOMEN, food consumption of pregnant women in Latvia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELS, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): 5^{th} or 95^{th} percentile intakes calculated over a number of subjects lower than 60 cautious interpretation as the results may not be statistically robust (EFSA, 2011a) and therefore for these dietary surveys/age classes the 5^{th}, 95^{th} percentile estimates will not be presented in the intake results.
(b): A 48-hour dietary recall comprises of two consecutive days.
(c): One subject was excluded from the dataset due to only one 24-hour dietary recall day was available, i.e. the final n = 990.

Appendix E. Vitamin A intake among males in different surveys according to age classes and country (µg RE/day)

Age class	Country	Survey	n	Average	P5	P50	P95
1 to < 3 years	Finland	DIPP_2001_2009	245	491	116	419	1 134
	Germany	VELS	174	651	264	582	1 294
	Italy	INRAN_SCAI_2005_06	20	554	(a)	499	(a)
	United Kingdom	NDNS-RollingProgrammeYears1-3	107	576	260	496	1 032
3 to < 10 years	Finland	DIPP_2001_2009	381	751	243	550	2 022
	France	INCA2	239	702	240	579	1 353
	Germany	EsKiMo	426	889	329	754	1 951
	Germany	VELS	146	685	331	656	1 271
	Italy	INRAN_SCAI_2005_06	94	873	293	618	1 475
	Netherlands	DNFCS 2007–2010	231	741	204	589	1 876
	United Kingdom	NDNS-RollingProgrammeYears1-3	326	607	245	531	1 104
10 to < 18 years	Finland	NWSSP07_08	136	776	285	644	1 391
	France	INCA2	449	758	259	635	1 475
	Germany	EsKiMo	197	949	361	803	2 213
	Italy	INRAN_SCAI_2005_06	108	891	360	688	1 766
	Netherlands	DNFCS 2007–2010	566	866	249	664	2 076
	United Kingdom	NDNS-RollingProgrammeYears1-3	340	686	236	600	1 351
18 to < 65 years	Finland	FINDIET2012	585	1 078	325	867	2 154
	France	INCA2	936	978	279	747	2 068
	Ireland	NANS_2012	634	1 023	356	891	1 864
	Italy	INRAN_SCAI_2005_06	1 068	984	345	750	1 924
	Netherlands	DNFCS 2007–2010	1 023	1 097	340	858	2 662
	Sweden	Riksmaten 2010	623	995	311	880	2 005
	United Kingdom	NDNS-RollingProgrammeYears1-3	560	930	268	768	1 847
65 to < 75 years	Finland	FINDIET2012	210	1 086	307	823	2 345
	France	INCA2	111	1 279	367	892	5 080
	Ireland	NANS_2012	72	1 243	360	1173	2 558
	Italy	INRAN_SCAI_2005_06	133	1 036	353	772	2 058

Age class	Country	Survey	n	Average	P5	P50	P95
	Netherlands	DNFCS 2007–2010	91	1 029	316	871	2 604
	Sweden	Riksmaten 2010	127	1 042	437	911	1 879
	United Kingdom	NDNS-RollingProgrammeYears1-3	75	1 423	345	1077	5 360
≥ 75 years	France	INCA2	40	1 057	(a)	794	(a)
	Ireland	NANS_2012	34	992	(a)	881	(a)
	Italy	INRAN_SCAI_2005_06	69	949	291	722	1 635
	Sweden	Riksmaten 2010	42	1 270	(a)	1059	(a)
	United Kingdom	NDNS-RollingProgrammeYears1-3	56	1 353	(a)	798	(a)

n, number of individuals; P5, 5th percentile; P50, 50th percentile; P95, 95th percentile.
DIPP, type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; EsKiMo, Ernährungstudie als KIGGS-Modul; FINDIET, the national dietary survey of Finland; INCA, étude Individuelle Nationale de Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - Studio sui Consumi Alimentari in Italia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELS, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): 5th or 95th percentile intakes calculated from less than 60 subjects requires cautious interpretation, as the results may not be statistically robust (EFSA, 2011a) and, therefore, for these dietary surveys/age classes, the 5th and 95th percentile estimates will not be presented in the intake results.

Appendix F. Vitamin A intake among females in different surveys according to age classes and country (µg RE/day)

Age class	Country	Survey	n	Average	P5	P50	P95
1 to < 3 years	Finland	DIPP_2001_2009	255	409	125	358	255
	Germany	VELS	174	598	240	525	174
	Italy	INRAN_SCAI_2005_06	16	446	(a)	428	16
	United Kingdom	NDNS-RollingProgrammeYears1-3	78	437	182	422	78
3 to < 10 years	Finland	DIPP_2001_2009	369	647	234	501	369
	France	INCA2	243	609	230	537	243
	Germany	EsKiMo	409	793	279	715	409
	Germany	VELS	147	654	301	590	147
	Italy	INRAN_SCAI_2005_06	99	696	262	592	99
	Netherlands	DNFCS 2007–2010	216	716	203	545	216
	United Kingdom	NDNS-RollingProgrammeYears1-3	325	610	225	576	325
10 to < 18 years	Finland	NWSSP07_08	170	724	345	631	170
	France	INCA2	524	662	217	557	524
	Germany	EsKiMo	196	892	320	752	196
	Italy	INRAN_SCAI_2005_06	139	799	280	680	139
	Latvia[b]	FC_PREGNANTWOMEN_2011	12	1 078	(a)	970	12
	Netherlands	DNFCS 2007–2010	576	713	236	573	576
	United Kingdom	NDNS-RollingProgrammeYears1-3	326	597	225	518	326
18 to < 65 years	Finland	FINDIET2012	710	960	312	799	710
	France	INCA2	1 340	979	301	713	1 340
	Ireland	NANS_2012	640	897	319	765	640
	Italy	INRAN_SCAI_2005_06	1 245	885	322	708	1 245
	Latvia[b]	FC_PREGNANTWOMEN_2011	990 (b)	1 319	375	886	990
	Netherlands	DNFCS 2007–2010	1 034	906	268	690	1 034
	Sweden	Riksmaten 2010	807	958	379	854	807
	United Kingdom	NDNS-RollingProgrammeYears1-3	706	891	266	697	706
65 to < 75 years	Finland	FINDIET2012	203	913	314	730	203
	France	INCA2	153	1 281	408	874	153

Age class	Country	Survey	n	Average	P5	P50	P95
	Ireland	NANS_2012	77	1 041	345	927	77
	Italy	INRAN_SCAI_2005_06	157	873	329	736	157
	Netherlands	DNFCS 2007–2010	82	905	317	712	82
	Sweden	Riksmaten 2010	168	1 159	373	875	168
	United Kingdom	NDNS-RollingProgrammeYears1-3	91	1 139	354	839	91
≥ 75 years	France	INCA2	44	1 498	(a)	740	44
	Ireland	NANS_2012	43	1 050	(a)	922	43
	Italy	INRAN_SCAI_2005_06	159	816	308	706	159
	Sweden	Riksmaten 2010	30	1 331	(a)	987	30
	United Kingdom	NDNS-RollingProgrammeYears1-3	83	991	374	771	83

n, number of individuals; P5, 5th percentile; P50, 50th percentile; P95, 95th percentile.
DIPP, type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; EsKiMo, Ernährungstudie als KIGGS-Modul; FINDIET, the national dietary survey of Finland; INCA, étude Individuelle Nationale de Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - Studio sui Consumi Alimentari in Italia; FC_PREGNANTWOMEN, food consumption of pregnant women in Latvia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELS, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): 5th or 95th percentile intakes calculated from less than 60 subjects requires cautious interpretation, as the results may not be statistically robust (EFSA, 2011a) and, therefore, for these dietary surveys/age classes, the 5th and 95th percentile estimates will not be presented in the intake results.
(b): Pregnant women only.

Appendix G. Minimum and maximum % contribution of different food groups to vitamin A intake among males

Food groups	Age					
	1 to < 3 years	3 to < 10 years	10 to < 18 years	18 to < 65 years	65 to < 75 years	≥ 75 years
Additives, flavours, baking and processing aids	0	0	0	0	0	0
Alcoholic beverages	0	0	< 0.1	< 0.1	< 0.1	< 0.1
Animal and vegetable fats and oils	2.2–9.9	3.2–18.2	4.4–27.3	3.8–21.9	3.1–22.7	3.2–20.3
Coffee, cocoa, tea and infusions	0–0.1	< 0.1–0.3	< 0.1–0.4	< 0.1–1.6	< 0.1–1.6	0–1.2
Composite dishes	0.5–11.4	0.6–11.8	0.8–14	0.4–24.3	0.5–19.3	0.3–19.4
Eggs and egg products	1.2–2.8	1–6.6	0.9–6.3	0.9–4.6	0.6–4.3	1–4.2
Fish, seafood, amphibians, reptiles and invertebrates	0.1–0.4	0.1–1	0.1–1.1	0.2–1.5	0.6–1.7	0.5–1.4
Food products for young population	4.9–10.2	< 0.1–1.4	< 0.1	< 0.1	-	-
Fruit and fruit products	0.9–8.9	0.5–3.2	0.4–2.2	0.3–3.4	0.5–4.2	0.4–4
Fruit and vegetable juices and nectars	0.2– 9.4	1–10.4	1.1–9.1	0.6–5.4	0.3–2.9	0.1–3.2
Grains and grain-based products	0.3–7.2	0.1–9	0.2–10	3–6.5	2.7–6.1	2.9–6.2
Human milk	< 0.1–3.8	-	-	-	-	-
Legumes, nuts, oilseeds and spices	0.3–1	0.1–0.7	0.1–0.8	0.2–1.3	0.3–0.6	0.4–0.8
Meat and meat products	0.7–10	5.1–24.5	8.4–16.6	7.4–25.1	14.6–32.5	3.4–38.4
Milk and dairy products	11.6–31.8	14.7–24.1	16.9–23.8	14–18.3	10.7–16.5	11.7–17.8
Products for non-standard diets, food imitates and food supplements or fortifying agents	0–0.1	0–0.1	< 0.1–0.2	< 0.1–0.4	< 0.1–0.5	0
Seasoning, sauces and condiments	< 0.1–2.1	< 0.1–6.2	< 0.1–5.7	< 0.1–5.4	< 0.1–3.6	< 0.1–2.6
Starchy roots or tubers and products thereof, sugar plants	< 0.1–0.3	< 0.1–0.9	< 0.1–0.8	< 0.1–0.9	< 0.1–1.4	< 0.1–0.3
Sugar, confectionery and water-based sweet desserts	< 0.1–0.5	0.1–1.1	0.1–1.1	< 0.1–0.5	< 0.1–0.2	< 0.1–0.1
Vegetables and vegetable products	23.6–58.2	25.3–38.2	19–44.5	15.3–48.5	16.8–52.2	20–49.5
Water and water-based beverages	0	< 0.1–0.1	< 0.1–0.1	< 0.1–0.1	0	< 0.1–0.1

"-" means that there was no consumption event of the food group for the age and sex group considered, whereas "0" means that there were some consumption events, but that the food group does not contribute to the intake of the nutrient considered, for the age and sex group considered.

Appendix H. Minimum and maximum % contribution of different food groups to vitamin A intake among females

Food groups	Age					
	1 to < 3 years	3 to < 10 years	10 to < 18 years	18 to < 65 years	65 to < 75 years	≥ 75 years
Additives, flavours, baking and processing aids	0	0	0	0	0	0
Alcoholic beverages	0	0	0	< 0.1–0.2	< 0.1–0.1	0–0.3
Animal and vegetable fats and oils	2–11.6	3.9–18.4	3.7–25	3.6–18.6	3.3–17.7	3.1–15.9
Coffee, cocoa, tea and infusions	0–0.1	< 0.1–0.2	< 0.1–0.4	< 0.1–1.4	< 0.1–1.5	< 0.1–0.9
Composite dishes	0.1–12.8	0.7–11.4	0.4–15.6	0.4–24.7	0.4–16.7	0.3–19.4
Eggs and egg products	0.8–3.4	1–6.5	0.8–6.4	1–4	0.8–3.8	0.6–4.4
Fish, seafood, amphibians, reptiles and invertebrates	0.1–0.6	< 0.1–0.7	0.2–1.4	0.2–1.2	0.2–1.2	0.4–0.7
Food products for young population	4–16.2	< 0.1–0.6	< 0.1–0.1	< 0.1–0.1	-	0.1
Fruit and fruit products	1–9.2	0.6–2.9	0.5–4.8	0.4–4.5	0.7–5.4	0.6–5.8
Fruit and vegetable juices and nectars	0.2–8.4	0.9–8.6	1.3–10.9	0.7–4.2	0.7–3.8	0.2–4.9
Grains and grain-based products	0.4–6.5	0.1–9.1	0.1–9.8	2.7–6	2.9–4.5	2.9–4.4
Human milk	< 0.1	-	-	-	-	-
Legumes, nuts, oilseeds and spices	0.3–0.8	0.1–1	0.2–0.7	0.2–1	0.1–1	0.3–0.6
Meat and meat products	0.5–5.7	0.9–23.1	4.6–16.1	7.8–29.6	5.7–35.1	4.2–45.8
Milk and dairy products	13.4–31.3	15.7–25.9	15.9–25.4	11.7–18	8.2–16.8	9.1–18.3
Products for non-standard diets, food imitates and food supplements or fortifying agents	0–0.3	0–0.1	0–0.3	< 0.1–0.5	0–0.3	0–0.6
Seasoning, sauces and condiments	< 0.1–2.9	< 0.1–6.4	< 0.1–6.1	< 0.1–4.3	< 0.1–2.8	< 0.1–2.5
Starchy roots or tubers and products thereof, sugar plants	< 0.1–1.1	< 0.1–0.8	< 0.1–0.9	0.1–0.8	< 0.1–0.7	< 0.1–0.2
Sugar, confectionery and water-based sweet desserts	< 0.1–0.5	0.2–1.1	< 0.1–1.1	< 0.1–0.5	< 0.1–0.2	< 0.1–0.2
Vegetables and vegetable products	27.2–59.2	19.6–41.1	21–40.9	22.1–51.7	21.7–55.1	23.8–56.9
Water and water-based beverages	0	< 0.1–0.1	0–0.1	< 0.1–0.1	0	< 0.1

"-" means that there was no consumption event of the food group for the age and sex group considered, whereas "0" means that there were some consumption events, but that the food group does not contribute to the intake of the nutrient considered, for the age and sex group considered.

ABBREVIATIONS

Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
AR	Average Requirement
BCMO1	β,β-carotene-15,15′-monooxygenase 1
BMD	bone mineral density
CI	confidence interval
COMA	Committee on Medical Aspects of Food Policy
CRABP	cellular retinoic acid-binding protein
CRBP	cellular retinol-binding protein
CRP	c-reactive protein
CV	coefficient of variation
CYP	cytochrome P450
D-A-CH	Deutschland- Austria- Confoederatio Helvetica
DGAT	acyl-CoA:retinol acyltransferase
DH	UK Department of Health
DIPP	type 1 Diabetes Prediction and Prevention survey
DNFCS	Dutch National Food Consumption Survey
DRD	deuterated-retinol-dilution
DRV	Dietary Reference Value
EAR	Estimated Average Requirement
EC	European Commission
EFSA	European Food Safety Authority
EsKiMo	Ernährungstudie als KIGGS-Modul
EU	European Union
EVA	Epidemiology of Vascular Ageing study
FABP	fatty acid-binding protein
FAO	Food and Agriculture Organization of the United Nations

FINDIET	the national dietary survey of Finland
FFQ	Food Frequency Questionnaire
HDL	high-density lipoprotein
HR	hazard ratio
IFN	interferon
IL	interleukin
INCA	étude Individuelle Nationale de Consommations Alimentaires
INRAN-SCAI	Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - Studio sui Consumi Alimentari in Italia
IOM	US Institute of Medicine of the National Academy of Sciences
LDL	low-density lipoprotein
LRAT	lecithin:retinol acyltransferase
NANS	National Adult Nutrition Survey
NDNS	UK National Diet and Nutrition Survey
NHANES III	US Third National Health and Nutrition Examination Survey
NNR	Nordic Nutrition Recommendations
NPC	Nutritional Prevention of Cancer
NWSSP	Nutrition and Wellbeing of Secondary School Pupils
PPAR	peroxisome proliferator-activated receptor
PRI	Population Reference Intake
RAE	retinol activity equivalency
RAR	retinoic acid receptor
RBP	retinol-binding protein
RDA	Recommended Dietary Allowance
RDR	relative dose response
RE	retinol equivalent
RID	retinol isotope dilution
RNI	Reference Nutrient Intake

RXR	retinoic X receptor
SACN	UK Scientific Advisory Committee on Nutrition
SCF	Scientific Committee for Food
SD	standard deviation
SE	standard error
SR-B	scavenger receptor class B
UK	United Kingdom
UL	Tolerable Upper Intake Level
UNU	United Nations University
US	United States
VELS	Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln
VLDL	very low-density lipoprotein
WHAS	Women's Health and Ageing Study
WHO	World Health Organization