# COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

## Statement on the potential risks from high levels of vitamin A in the infant diet

### Background

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that bears on the Government's dietary recommendations for infants and young children. The review will identify new evidence that has emerged since the Government's current recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years, but will be considered in two stages, focussing first on infants aged 0 – 12 months, and then on advice for children aged 1 to 5 years. SACN is examining the nutritional basis of the advice, and has asked that evidence on possible adverse effects of diet should be considered by other advisory committees with relevant expertise. In particular, SACN asked COT to review the risks of toxicity from chemicals in the infant diet.

2. This statement provides an overview of the potential risks from high levels of vitamin A in the infant diet. Evaluations of vitamin A in food have been conducted previously by the Scientific Committee on Food (SCF) (SCF, 2002), Expert Group on Vitamins and Minerals (EVM) (EVM, 2003), and the Scientific Advisory Committee on Nutrition (SACN) (SACN, 2005). This statement draws on information from those evaluations and from additional relevant studies published more recently. The statement considers the sources of vitamin A in the diet; its biological function, measurement, toxicokinetics and toxicity (with particular focus on those studies which would assist in the derivation of a tolerable upper level (TUL)); and estimated dietary exposures of infants via breast milk, infant formula and complementary foods.

### *Vitamin A*

3. Vitamin A is a generic term referring to substances including retinol, retinyl esters (fatty acid derivatives of all-*trans* retinol) and retinal (all-*trans* retinol in its aldehyde form), that exhibit qualitatively the biological activity of all-*trans* retinol. In addition, metabolites such as all-*trans and cis*-isomeric retinoic acids can perform some, but not all, of the biological functions of vitamin A (EVM, 2003; SACN, 2005).

The term “retinoids” encompasses vitamin A and synthetic analogues with similar properties.

4. There are two sources of dietary vitamin A: preformed vitamin A and provitamin A carotenoids. Retinol consists of a β-ionone ring with a polar terminal group and conjugated isoprenoid side chain (Figure 1) (EVM, 2003). Provitamin A carotenoids are precursors of vitamin A and can be converted to retinol in the body (SACN, 2005).

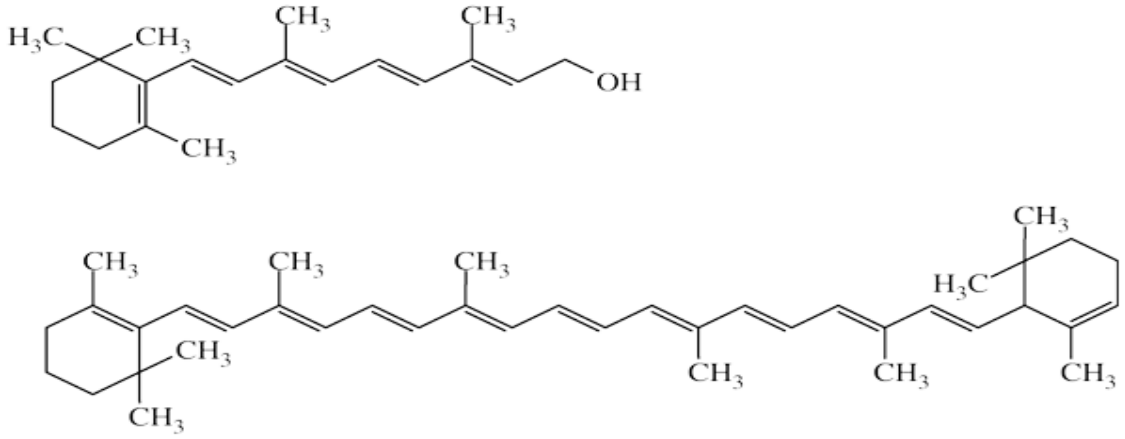


Figure 1: Structural formula of retinol ($C_{20}H_{30}O$) (top) and β-carotene ($C_{40}H_{56}$) (bottom).

*Preformed vitamin A (retinol, retinal, retinyl esters and retinoic acid)*

5. Preformed vitamin A (retinol, retinal, retinyl esters and retinoic acid) is only found in foods of animal origin, predominantly in the form of retinyl palmitate (Allen and Haskell, 2002). Retinyl esters are added to foods such as margarine (Perrotta et al., 2003). Both retinyl palmitate and retinyl acetate are used in dietary supplements (Perrotta et al., 2003). The highest concentration of preformed vitamin A is in carnivore liver (Allen and Haskell, 2002; Schulz et al., 2007).

*Provitamin A carotenoids*

6. Provitamin A carotenoids are present in a variety of fruits and vegetables. Over 600 carotenoids have been identified, of which approximately 50 can be converted to retinol and hence are referred to as provitamin A. The major provitamin A carotenoids in food are β-carotene, α-carotene and β-cryptoxanthin. β-Carotene is the most important provitamin A carotenoid because of its relative provitamin A activity and high content within the diet (SACN, 2005).

*Function of vitamin A*

7. Retinol is pivotal in embryonic development in mammals (Perrotta et al., 2003). It is involved in cell differentiation by acting as a ligand for nuclear retinoic

acid (retinol) receptors), converting them from transcriptional repressors to activators (Rhinn et al., 2012). The distribution and levels of retinol in embryonic tissues are tightly controlled by regulated synthesis through the action of specific retinol and retinaldehyde dehydrogenases and by degradation via specific cytochrome P450s (CYP26s) (EVM, 2003; Griswold et al., 2012; Rhinn et al., 2012). Retinol regulates the differentiation and patterning of various stem/progenitor cell populations (Rhinn et al., 2012).

8. Retinol also has a key function in the maintenance of normal differentiation of the cornea (IOM, 2001). In addition, retinal (11-cis-retinaldehyde) plays a crucial role in visual function, since it is fundamental for the transduction of light into neural signals within the eye (Bok, 1993), and retinol is essential for normal function of the immune system (SACN, 2005).

*Quantification of vitamin A and reference values*

9. Vitamin A is quantified either in international units (IU) or µg retinol equivalents (RE). The total vitamin A content of the diet is usually expressed as RE. RE takes into account the different activities and variable absorption of preformed vitamin A and provitamin A carotenoids, and is a widely accepted unit. For consistency, RE is used throughout this statement. Corresponding IU values can be approximated by multiplying the RE by 3.33; however, this will be completely accurate only if the vitamin A is entirely in the form of retinol (see Table 1). RE can be calculated with certainty only if the relative amounts of the different forms of preformed vitamin A and provitamin A carotenoids are known.

Table 1: The vitamin A activity (in IU and RE) of the three main retinoid compounds and provitamin carotenoids

| **Retinoid compound** | **IU** | | **RE** | |
|---|---|---|---|---|
| | **Conversion factor 1 RE in IU** | **Vitamin A activity in IU per mg compound** | **Conversion factor 1 RE in µg** | **Vitamin A activity in µg RE per mg compound** |
| Retinol | 3.33 | 3330 | 1 | 1000 |
| Retinyl acetate | | 2900 | 1.15 | 870 |
| Retinyl palmitate | | 1830 | 1.78 | 550 |
| β-carotene | 10 | 1667 | 6 | 167 |
| Other provitamin carotenoids | | 833 | 12 | 83 |

Sources: WHO (1965), Perrotta et al. (2003), Health Canada (2010).

10. Table 2 shows dietary reference values for vitamin A.

Table 2: Dietary reference values for vitamin A (µg RE/day)

| **Age** | **Lower Reference Nutrient Intake [a]** | **Estimated Average Requirement [b]** | **Reference Nutrient Intake [c]** |
|---|---|---|---|
| 0 - 12 months | 150 | 250 | 350 |

| | | | |
|---|---|---|---|
| 1 - 6 years | 200 | 300 | 400 |
| 7 - 10 years | 250 | 350 | 500 |
| 11 – 14 years | 250 | 400 | 600 |
| Women including girls from 11 years | 250 | 400 | 600 |
| Pregnant women | 250 | 400 | 700 |
| Women during lactation | 250 | 400 | 950 |
| Men (including boys from 15 years) | 300 | 500 | 700 |

[a] The amount of a nutrient that is considered sufficient to meet the requirements of 2.5% of the population (from SACN, 2005),

[b] The intake level for a nutrient at which the needs of 50 % of the population will be met (from Department of Health, 1991).

[c] The amount of a nutrient that is considered sufficient to meet the requirements of 97.5% of the population (from SACN, 2005),

## Current UK Government advice on maximum intakes in relation to infant diet

11. SACN (2005) reiterated the advice that pregnant women should not consume liver, liver products or supplements containing retinol. Current advice is "*do not take vitamin A supplements, or any supplements containing vitamin A, as too much could harm your baby"* (NHS Choices, 2012).

12. For infants it is advised that liver should be avoided if solid foods are introduced before 6 months (NHS Choices, 2013). For adults and children over the age of 6 months it is recommended not to have more than one portion of liver per week because the vitamin A content in the liver can be harmful in large amounts (SACN, 2005).

13. The Department of Health recommends that all children from six months to five years old be given supplements containing vitamins A, C and D, unless they are receiving 500 ml or more of formula a day (DH, 2009). In the UK, the statutory Healthy Start scheme provides a means-tested nutritional safety net to pregnant women and families with children under four years old in very low income and disadvantaged circumstances. It gives vouchers for fruit and vegetables, cow's milk and formula milk as well as coupons for Healthy Start vitamin supplements. The daily dose of vitamin A in the Healthy Start vitamin drops is 233 µg RE. There is strong advice to keep to the dose recommended on the label and not to give two supplements at the same time. Healthy breastfed infants born at term, and over the age of 1 month, can be supplemented with vitamins if there is any doubt about the mother's vitamin status during pregnancy, as the infant may be born with low vitamin stores (DH, 2012).

## Absorption, distribution, metabolism and excretion

### *Preformed vitamin A uptake and distribution*

14. The absorption of retinol is around 80% if an individual consumes sufficient levels of fat (EVM, 2003; SACN, 2005). Dietary retinyl esters are hydrolysed to retinol in the intestinal lumen by the action of pancreatic triglyceride lipase and intestinal brush border phospholipase B (During and Harrison, 2007; Penniston and Tanumihardjo, 2006). Retinol is the form that is absorbed into the intestinal mucosal cells (During and Harrison, 2007). In the intestinal mucosa, re-esterification takes place to enable incorporation into chylomicra, which are secreted into the lymphatic circulation (EVM, 2003). The retinyl esters in chylomicra are then transported into the blood stream. Once in circulation, the chylomicra are broken down by serum lipases, resulting in release of the retinyl esters. Retinyl esters are subsequently stored in the liver (EVM, 2003). It has been suggested that retinol uptake is facilitated by proteins in the cell membrane (During and Harrison, 2007). The uptake and distribution of preformed vitamin A is illustrated in Figure 2.

15. Serum retinol concentrations are homeostatically controlled to remain constant despite variations in the dietary supply of retinol. Retinol is secreted from the liver bound to plasma retinol-binding protein (RBP) and subsequently distributed to peripheral tissues as a retinol-RBP-transthyretin complex (IOM, 2001). Once it reaches its target cells, retinol is converted to retinoic acid which binds to a specific receptor (SACN, 2005).

### *Provitamin A carotenoid uptake and distribution*

16. For provitamin A carotenoids to be absorbed intestinally, they must be released from the food matrix and incorporated into micelles. Hence, carotenoid absorption requires the presence of fat in a meal. The proportion of β-carotene absorbed is constant for intakes of up to 20-30 mg, but is lower at higher intakes (SCF, 2000; Li and Tso, 2003). Provitamin A carotenoids are dissolved in lipid droplets in the stomach and pass into the duodenum, where they are taken up into micelles which have a finite capacity for carotenoid incorporation (Tanumihardjo, 2002). Like retinol, provitamin A carotenoids are then taken up by enterocytes (Tanumihardjo, 2002). Depending on the type of carotenoid, they can either be transported intact into the lymphatic circulatory system or converted into retinal or retinol through the actions of the enzymes β-carotene 15,15'-monooxygenase (BCMO1) and retinaldehyde reductase (During and Harrison, 2007; Tanumihardjo, 2002). Unhydrolysed carotenoids are transported to the liver in chylomicrons where they are stored (IOM, 2001). The uptake and distribution of provitamin A carotenoid is also illustrated in Figure 2.

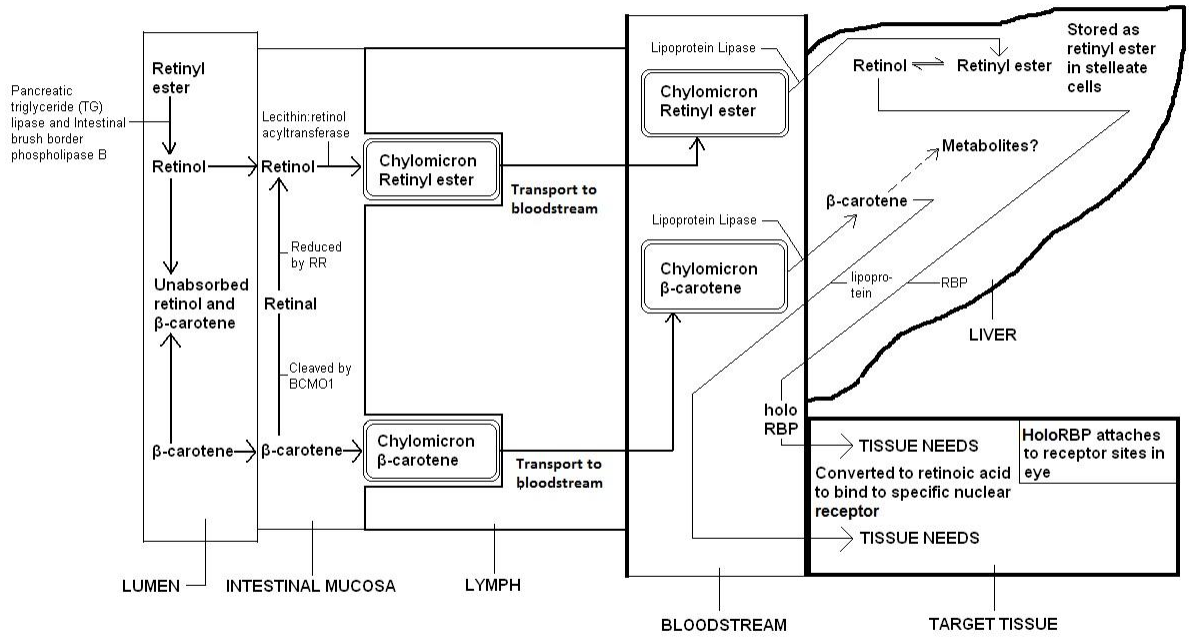


**Figure 2: An overview of retinol and β-carotene absorption and distribution. Adapted from Parker (1996).** Abbreviations: BCMO1 - β-carotene 15,15'-monooxygenase; holo-RBP – retinol bound to retinol binding protein; RBP – retinol binding protein; RR - retinaldehyde reductase**.**

### *Metabolism*

17. Retinol is oxidised to retinaldehyde by the action of cytosolic and microsomal retinol dehydrogenases (Rhee and Plutzky, 2012), which are members of the alcohol dehydrogenase (ADH) families. These include ubiquitously expressed ADH3, as well as ADH1 and ADH4 in some tissues. All three isoforms can oxidize all-trans retinol to all-trans retinaldehyde. This in turn is oxidised irreversibly to retinoic acid through the action of the enzyme, retinaldehyde dehydrogenase. Retinoic acid is then metabolised by CYP26 to oxidative metabolites.

18. Carotenoids can be converted into retinaldehyde through the action of BCMO1, which carries out a central cleavage of the carotene. Retinaldehyde is then metabolised as described in paragraph 17. Alternatively, carotenoids can be converted to apocarotenal by BCMO2 through an asymmetrical cleavage. Subsequently, apocarotenal is converted into apocarotenoic acid and, finally, into retinoic acid. Retinoic acid is transported into cells by cellular retinoic acid binding protein and interacts with the nuclear receptor (D'Ambrosio et al., 2011; Rhee and Plutzky, 2012). As well as in the intestinal mucosa (Figure 2), BCMO1 and 2 are expressed in the liver, lungs and kidneys. They may be important for local synthesis

of vitamin A, but to date no quantitative estimates have been made of extra-intestinal enzymatic bioconversion of provitamin A (Erdman et al., 2012).

19. Vitamin A and derivative compounds can be conjugated in the liver with glucuronic acid or taurine (EVM, 2003; IOM, 2001).

### *Factors that affect provitamin A carotenoid bioavailability and bioconversion*

20. A number of factors have been identified that affect the bioavailability and bioconversion of provitamin A carotenoids to retinol in the gut (Bender, 2003; Lietz et al., 2010; Tang, 2010). These include:

Species of carotenoid
Linkages to alkyl groups
Amount in a meal
Matrix properties of the plant in which the carotenoid is contained
Nutritional status
Genetic factors/predisposition
Food preparation method

21. When vitamin A status is adequate, approximately 50% to 85% of the total body retinol is stored in the liver (Ross, 1999). Retinol returning to the liver is re-esterified before storage in the form of retinyl esters in hepatic stellate cells along with droplets of lipid (Groff et al., 1995). Stellate cells have the property to increase storage capability linearly with increasing retinol levels. However, hypervitaminosis can result once storage capacity is saturated (Ross, 1999). β-carotene is stored in adipose cells in fat depots throughout the body (Bucci, 1998). However, due to its slow release from adipose cells, serum levels of β-carotene are principally indicators of recent intake and not of body stores (Ross, 1999).

### *Excretion*

22. The excretion of vitamin A metabolites has been reported to be about 60% in urine and 40% in faeces (Gropper et al., 2005). The amount of excreted vitamin A compounds in bile increases if the level of vitamin A in liver exceeds a critical concentration, suggesting a protective mechanism (IOM, 2001). The oxidised products of vitamin A metabolism, conjugated to glucuronic acid or taurine, are excreted into the bile for further elimination in the faeces (Gropper et al., 2005). Faecal metabolites include retinoic acid glucuronide and 4-oxoretinoic acid glucuronide, which can be absorbed and returned to the liver through enterohepatic circulation. No information was found on excretion specifically in infants or children.

## Toxicity

23. An excess of vitamin A in the body is termed hypervitaminosis A, and is associated with various adverse effects. The most frequent cause of

hypervitaminosis A in infants is overdosage with vitamin A supplements because parents are unaware of the risks (where supplements are prescribed, this may be because the physician has failed to emphasise the dangers of excessive vitamin A intake) (Perrotta et al., 2003). Hypervitaminosis A from natural food sources is less frequently reported (Perrotta et al., 2003). Toxicity appears to occur when the amount of vitamin A in plasma exceeds the capacity of RBPs, leading to a change in the ratio of free retinol to retinol-RBP complexes (Bendich and Langseth, 1989). In this situation, free retinol binds to lipoproteins (Bendich and Langseth, 1989). While high intakes of preformed vitamin A can be acutely toxic, high intakes of β-carotene and other provitamin A carotenoids from food alone have not been found to cause toxicity, although they can lead to a yellow appearance (Allen and Haskell, 2003). Penniston and Tanumihardjo (2006) have proposed that regulation of the cleavage of vitamin A precursors to retinal makes it almost impossible to develop hypervitaminosis A from high intake of provitamin A carotenoids.

24. Acute vitamin A toxicity is rare and more likely to occur following ingestion of high dose supplements than following high intakes of vitamin A from food (EVM, 2002). Commonly observed clinical features of acute toxicity in children include anorexia, bulging fontanelles, drowsiness, lethargy, irritability and vomiting (Perrotta et al., 2003) which may be associated with raised intracranial pressure. The bulging of fontanelles is a consequence of increased cerebrospinal fluid volume, but in most cases, this has no significant effect on intracranial pressure and resolves spontaneously within 72 hours once the source of high exposure is eliminated (WHO, 2011). Other symptoms of acute toxicity usually resolve within a week (Perrotta et al., 2003), and full recovery normally takes less than a month (Perrotta et al., 2003). Weight, dietary factors (fat content) and general health are all crucial factors in determining the dose of vitamin A that leads to acute toxicity (Bendich and Langseth, 1989). Clinical features of acute vitamin A toxicity in adults include blurred vision, hypercalcaemia and peripheral neuropathy.

25. Chronic vitamin A toxicity is reported more commonly than acute toxicity (Perrotta et al., 2003). Clinical manifestations are variable, but often include bulging fontanelles (in infants), alopecia, anorexia, bone and joint pain, thickening and fissuring of the lips, photophobia, conjunctivitis, hepatoxicity, enlarged spleen, skin desquamation and anaemia (EVM 2003; Perrotta et al., 2003).

### *Reports of vitamin A toxicity in infants*

26. Marie and Sée (1951) described four cases of acute vitamin A toxicity. Three infants aged 3, 3½ and 7 months all rapidly developed a bulging fontanelle and nausea, leading to hospitalisation. In the past 12 to 24 hours, all three had received the same vitamin supplement containing approximately 105,000 µg RE. The intake was equivalent to a single dose of 18,750 µg RE/kg bw for the 3½ month old based on a reported weight of 5.6 kg, and to 15,000 µg RE/kg bw for the 7 month old based on a reported weight of 7 kg. No weight was provided for the infant aged 3 months. In the fourth case, a 2 month old infant rapidly developed a prominent bulge of the fontanelle after receiving approximately 15,000 µg RE per day for six days through prescribed nose drops, and was subsequently hospitalised. The intake was

equivalent to 3,200 µg RE/kg bw/day for the 2 month old based on a reported weight of 4.7 kg.

27. A randomised, double-blind placebo-controlled trial was carried out in Nepal to assess the safety of vitamin A supplementation in early infancy. A total of 10 cases of bulging fontanelle were diagnosed in the group aged one to six months, which had received a single dose of 30,000 µg RE (n=1349; prevalence = 0.7%) (West et al., 1992). Exposure on a body weight basis could not be calculated since infants' weights were not reported in the study.

28. In a randomised, double-blind, placebo-controlled trial assessing the safety of vitamin A supplementation in early infancy, participants (n=167) received doses of either 7,500 µg RE/day of vitamin A or a placebo at about 6.5, 11.8 and 17.0 weeks of age. Twelve infants supplemented with vitamin A were recorded to have bulging fontanelles at some stage. Other side-effects, including drowsiness, anorexia and vomiting, were associated with the occurrence of bulging fontanelles (Bacqui et al., 1995). Exposure on a body weight basis could not be calculated since infants' weights were not reported in the study.

29. A case of bulging fontanelles, dry skin, hepatosplenomegaly, thrombocytopenia and severe anaemia was reported in a 3 month old infant who had been prescribed an aqueous solution of retinyl palmitate from 10 days after birth for approximately 80 days. The infant had been mistakenly given a dose of 20,000 µg RE/day (Perrotta et al., 2002). The intake was equivalent to 3,800 µg RE/kg bw/day based on a reported weight of 5.2 kg at 3 months.

30. Myhre et al. (2003) undertook a meta-analysis of case reports of bulging fontanelles suspected of being induced by excessive intakes of retinol. Cases of hypervitaminosis A (100 in total) in the age range, 0-2 years, were identified through a search of the scientific literature (50 chronic and 50 acute). The COT concluded that most relevant among the cases described were those meeting the following criteria: 1) 0-2 years old, 2) oral exposure and 3) intake of vitamin A at levels ≤ 1,000 µg RE/kg bw/day. Table 3 lists these cases.

Table 3. List of case reports of hypervitaminosis A meeting the specified criteria.

| **Total dose RE (**µg RE/kg bw/day) | **Number of subjects** | **Source of vitamin A** | **Reference** |
|---|---|---|---|
| 300 | 3 | Chicken liver | Carpenter et al., 1987 |
| 600 | 1 | Supplement - Em/w-misc | Lippe et al., 1981 |
| 800 | 2 | Supplement - Em/w-misc | Persson et al., 1965 |
| 800 | 1 | Supplement - Em/w-misc | Scherl et al., 1992 |
| 800 | 1 | Supplement - In oil | Berrey, 1950 |
| 900 | 1 | Supplement - Em/w-misc | Eid et al., 1990 |
| 1,000 | 1 | Unknown | Siegel and Spackman, 1972 |

Em/w-misc. Emulsified/water-miscible.

31. The COT considered that the reports of effects at doses below 800 µg RE/kg bw/day related to unusual circumstances (Pierre Robin syndrome and other possible genetic disorders), and that overall, a dose of 800 µg RE/kg bw per day should be viewed as the LOAEL.

### *Toxicity of vitamin A in population groups other than infants*

32. The SCF (2002) identified four other adverse effects of vitamin A that had been observed in population groups other than infants. These were hepatotoxicity, changes in lipid metabolism, changes in bone density, and teratogenicity.

33. The lowest dose associated with documented hepatotoxicity was a daily intake of 7,500 µg RE/day for six years in a 45 year old woman from an over-the-counter dietary supplement (Kowalski et al., 1994).

34. The SCF also identified 7,500 µg RE/day as the lowest dose associated with changes in lipid metabolism, based on the results of a placebo-controlled trial involving 2,297 subjects with a median age of 63 years old (Cartmel et al., 1999). Administration of 7,500 µg/RE per day for four years resulted in a 2-3% increase in blood cholesterol concentration, which could lead to an increased risk of cardiovascular disease.

35. As regards changes in bone density, the SCF identified a study by Melhus et al. (1998), in which intakes greater than 1,500 µg RE/day were associated with reduced bone density and increased rates of fracture in women aged 40-76 years in comparison with intakes of less than 500 µg RE/day. The SCF commented that it was likely that middle aged and elderly women were the group most sensitive to such effects. It was not known whether the same dose-response relationship would apply in men or in children.

36. Retinoids are teratogenic in animal studies, and isotretinoin, a synthetic retinoid (also known as 13-cis-retinoic acid), was identified as a human teratogen in 1985, at which time it was prescribed for severe forms of acne (EVM, 2002). Major malformations of the heart, thymus, face, jaw, ears, palate and brain were among the congenital anomalies that occurred in 94 confirmed cases in the US (EVM, 2002). An elevated risk of isotretinoin-related malformations was observed if the maternal oral dose exceeded 8,300 µg RE/day (EVM, 2002; Hendrickx et al., 2000).

37. The SCF (2002) identified 3,000 µg/RE/day as the lowest dose that had been associated with teratogenicity. This was in a study by Rothman et al. (1995) involving 22,748 pregnant women whose retinol intakes from food and dietary supplements were assessed by questionnaire. The percentages of babies with cranial-neural-crest defects were 0.52%, 0.62% and 1.06% in women with intakes from food of 0-1,500 µg RE/day, 1,500-3,000 µg RE/day and ≥ 3,000 µg RE/day, respectively. The EVM concluded that a precise threshold for teratogenic effects was uncertain, but that it was prudent to assume it could be 3,000 µg RE/day based on the Rothman et al. (1995) study (EVM, 2002).

### *Allergenicity*

38. Vitamin A plays an integral role in the function of the immune system. Currently available evidence does not indicate a hazard of allergenicity associated with consumption of vitamin A.

### Tolerable Upper Level

39. The SCF (2002) noted that the critical adverse effects of high intakes of vitamin A were different at different stages of life. For example, bulging fontanelles were the critical outcome in infants, decreased bone density and increased bone fracture in middle aged and elderly women, and teratogenicity in women of child-bearing age. Hepatotoxicity and altered lipid metabolism were also relevant for adults. The lowest doses of preformed vitamin A identified by SCF as causing these adverse effects are shown in table 4.

Table 4: Lowest doses identified as associated with adverse effects (SCF, 2002)

| Effect | Lowest dose (per person) |
|---|---|
| Bulging fontanelles | 7,500 µg RE, single dose |
| Hepatotoxicity | 7,500 µg RE/day |
| Altered lipid metabolism | 7,500 µg RE/day |
| Decreased bone density/increased bone fracture | 1,500 µg RE/day |
| Teratogenicity | >3,000 µg RE/day |

40. Table 5 shows the tolerable upper intake levels (ULs[1]) for preformed vitamin A that were established by the SCF for different age groups. The UL of 3,000 µg RE/day for adults was based on the teratogenicity data of Rothman et al. (1995), but was considered to be relevant also to adults other than pregnant women since it was only 2.5-fold less than the lowest chronic daily intake that had been associated with hepatotoxicity. The ULs for infants and children were extrapolated from the 3,000 µg RE/day for adults, on the basis of body weight and differences in basal metabolic rate (SCF, 2002). Using this scaling (body weight$^{0.75}$), the SCF set a UL of 800 µg/RE day for children aged 1-3 years. A UL for the age group below one year was not proposed.

Table 5: Tolerable Upper Intake Levels for various age groups established by SCF (2002)

| **Age (years)** | **Tolerable Upper Intake Level for preformed vitamin A** |
|---|---|

[1] The *Tolerable Upper Intake Level* (UL) refers to the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.

| | (retinol and retinyl esters) (µg RE/day) |
|---|---|
| **1-3** | 800 |
| **4-6** | 1,100 |
| **7-10** | 1,500 |
| **11-14** | 2,000 |
| **15-17** | 2,600 |
| **Adults** | 3,000 |

41. A UL for infants aged 0-12 months has, however, been proposed by the Institute of Medicine (IOM, 2001). This was 600 µg RE/day of preformed vitamin A, derived by applying an uncertainty factor of 10 to a LOAEL of 6000 µg RE (identified by the IOM as the lowest dose associated with bulging fontanelles (Persson et al., 1965)). The factor of 10 was "to account for the uncertainty of extrapolating a LOAEL to a no observed adverse effect level (NOAEL) for a non-severe and reversible effect (i.e., bulging fontanelle) and the interindividual variability in sensitivity" (IOM, 2001). The IOM also noted that there was plenty of evidence to support the reversibility of bulging fontanelles in infants if supplementation ceased.

42. The COT concluded that a tolerable upper intake for infants should not be derived by metabolic scaling from an effect (teratogenicity) that is not relevant to this age group. Also, the relevance of hepatotoxicity, bone effects and lipid changes to this age group was uncertain. Therefore, the tolerable upper level should be based on the most clearly relevant endpoint, bulging fontanelles – for which the LOAEL was 800 µg/RE kg/bw per day (see paragraph 31).

43. An uncertainty factor of 4 was agreed to allow for the small number of case studies that were available, and the limited duration of exposure in those studies. A larger factor was not required because the estimation of the LOAEL on a body weight basis was conservative as it was based on body weight at the time of diagnosis (which would have been higher than when the supplementation commenced), and did not take into account non-supplemental intake. This gave a tolerable upper level (TUL) of 200 µg/RE kg/bw per day (obtained by dividing the LOAEL of 800 µg/RE kg/bw per day by the uncertainty factor of 4).

## Occurrence of vitamin A

### *Breast Milk*

44. Current UK government advice is that infants should be exclusively breastfed for "around the first six months of life" (DH, 2003, NHS Choices, 2012). No data could be found on the occurrence of vitamin A in colostrum in the UK or Europe, but vitamin A levels in the mature breast milk of well-nourished women in Europe are reported to be 40-70 µg RE/100 mL, the higher levels generally being seen in women whose diet included a higher intake of fats, and particularly animal fats (Ross and Harvey, 2003).

45. Only limited information is available about the impact of vitamin A supplementation on levels of vitamin A in breast milk. Bezerra et al. (2009) assessed

the effect of maternal supplementation with a single dose of 200,000 IU as retinyl palmitate immediately postpartum in a cohort of healthy Brazilian women aged 18 to 40 years in the municipality of Natal. The mean vitamin A concentrations in the breast milk of supplemented women 24 h and 30 days after dosage were 165 and 51 µg RE/100 mL, as compared with 93 and 37 µg RE/100 mL in control women who received no supplementation. Data provided to the EVM (2003) indicated that the highest supplemental dose available on the UK market was 2,400 µg RE per day (i.e. 8000 IU) which is substantially lower than that used in the study of Bezerra et al. (2009). It follows that supplementation in the UK would be expected to increase the level of vitamin A in breast milk less than two-fold.

### *Infant formula*

46. Infant formula typically contains a higher concentration of several micronutrients than breast milk, partly to account for lower absorption of nutrients from infant formula than from breast milk, but also to allow for losses during storage (Bender, 2003). Four major brands of infant formula, including whey- and casein-based, were reported to contain 63-82 µg RE/100 mL (Leaf 2007). Information on a pack of follow-on formula for infants aged 6-12 months specified that it contained 75 µg vitamin A (RE)/ 100 mL and that infants should be given 500-600 mL per day. The Infant Formula and Follow-on Formula (England) regulations set out the vitamin A compositional requirements in infant and follow on formula. The minimum content is 60 µg RE/100 mL and the maximum is 180 µg RE/100 mL (European Commission, 2006).

### *Food*

47. In the Western diet, >70% of vitamin A is derived from preformed vitamin A whereas <30% is derived from provitamin A carotenoids (Tang, 2010). Examples of concentrations of preformed vitamin A (retinol and retinyl esters) and provitamin A carotenoids (for example β-carotene) in different foods are shown in table 6.

Table 6: Approximate concentrations of preformed vitamin A and provitamin A carotenoids in foods (FSA, 2002)

| Food type | Concentration (µg RE/100g) | Form of vitamin A |
|---|---|---|
| Liver (calf, fried) | 25200 | Preformed vitamin A |
| Soft margarine (not polyunsaturated) | 745 | Preformed vitamin A |
| Boiled carrots | 13402 | Provitamin A carotenoids |
| Boiled spinach | 6604 | Provitamin A carotenoids |
| Melon, cantaloupe-type | 1765 | Provitamin A carotenoids |
| Boiled broccoli | 475 | Provitamin A carotenoids |

### *Supplements*

48. Numerous multivitamin supplements are marketed in the UK for pre-term infants and infants aged 0-12 months. Most contain vitamin A in the form of retinyl palmitate, but some as retinyl acetate. The amount of vitamin A in daily doses of multivitamin supplements recommended by manufacturers varies between 200 and 757 µg RE/ day (Leaf, 2007). The vitamin supplement provided under the UK government's "Healthy Start" scheme[2] provides 233 µg RE/day.

### *Exposure*

### *Infants exclusively fed on breast milk or infant formula*

49. In calculating exposure to vitamin A, values of 800 mL and 1200 mL have been assumed for average and high-level daily consumption of breast milk or infant formula before introduction of solid foods. Bodyweight data for infants aged >4 to 6 months are from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), with an average of 7.8 kg. Since DNSIYC did not include infants younger than 4 months, a value of 5.9 kg for infants aged 0-3 months, from an older survey (DH, 1994), is applied to infants aged 0-4 months. This approach is consistent with that adopted in other COT statements related to dietary recommendations for infants.

50. Table 7 shows the estimated vitamin A intake of exclusively breastfed infants, based on the upper end of the reported range of vitamin A concentrations in breast milk from developed countries (70 µg RE/100 mL). As discussed in paragraph 45, current levels of supplementation in the UK would be expected to increase the level of vitamin A in breast milk less than two-fold. Thus, the estimated vitamin A intake of an infant breastfed by a mother taking vitamin A dietary supplements would be less than twice the highest value of 142 µg RE/kg bw/day in Table 7 – i.e. less than 284 µg/kg bw/day.

51. Table 7 also shows the estimated vitamin A intake of exclusively formula fed infants, based on a vitamin A concentration at the upper end of the reported range (82 µg RE/100 mL) (Leaf, 2007) and the maximum amount that can be added to infant formula (180 µg RE/100 mL). For the former, all estimates are less than the TUL of 200 µg RE/kg bw/day, whereas there are small exceedances for the latter.

Table 7. Vitamin A exposure (µg RE/kg bw/day) from exclusive feeding on breast milk or formula milk

| | Age in months (consumption volume) | | | |
|---|---|---|---|---|
| | 0-4 (800 mL) | 0-4 (1200 mL) | >4-6 (800 mL) | >4-6 (1200 mL) |
| Breast milk (70 µg RE/100 mL) | 95 | 142 | 72 | 108 |
| Formula milk | 111 | 167 | 84 | 126 |

[2] http://www.healthystart.nhs.uk/

| | | | | |
|---|---|---|---|---|
| (82 µg RE/100 mL) | | | | |
| Formula milk (180 µg RE/100 mL) | 244 | 366 | 185 | 277 |

### *Infants also consuming complementary foods*

52. DNSIYC collected data on 2683 4-18 month old infants whose mothers completed a 4-day food diary on their infant's diet. The total preformed vitamin A intakes from breast milk, infant formula and complementary food sources combined at ages 4-<7, 7-<10, 10-<12 and 12-<19 months, corresponding to average bodyweights of 8.1, 9.1, 9.8 and 10.9 kg, respectively, are shown in Table 8 (DH, 2013).

Table 8: Total daily intakes of preformed vitamin A (µg RE/kg bw/day) from breast milk, infant formula and complementary food sources combined, excluding supplements (DH, 2013)

| | **Age group (months)** | | | |
|---|---|---|---|---|
| | 4-<7 | 7-<10 | 10-<12 | 12-<19 |
| Mean | 116 | 108 | 95 | 62 |
| Median | 106 | 99 | 88 | 55 |
| Standard deviation | 52 | 48 | 46 | 32 |
| 97.5th percentile | 253 | 219 | 203 | 140 |

53. The contribution of infant formula to the total average vitamin A daily intake decreased from 39% at 4-<7 months to 12% at 12-<19 months. Likewise, the contribution of breast milk decreased from 15% at 4-<7 months to 2% at 12-<19 months. Commercially available infant foods provided approximately 24% throughout the first year. Other major contributors to the total intake were foods not specific to infants such as vegetables and potatoes, and milk and milk products – see Table 9 (DH, 2013).

54. DH recommends that infants should be introduced to solid foods at around six months of age. Cooked vegetables (such as parsnip, potato, sweet potato or carrot), mashed banana, avocado, cooked pear or apple, or baby rice or cereal mixed with the baby's usual milk, are recommended as suitable first complementary foods, with progression to other foods such as meat, fish, pasta, noodles, bread, chapatti, lentils, mashed rice, and full fat dairy products like cheese, yoghurt and fromage frais. By 8-9 months, the infant should be eating a wide variety of soft foods, and by 10-12 months, chopped family food can be introduced (NHS Choices, 2013). The data in Table 9 demonstrate that in fact, complementary foods are commonly introduced before 6 months, but are broadly consistent with the types of foods recommended for older infants.

Table 9: Percentage contribution of food sources to daily vitamin A intake, by age group – taken from DNSIYC (DH, 2013)

| Food group[a] | Age group (months) | | | |
|---|---|---|---|---|
| | 4-<7 % | 7-<10 % | 10-<12 % | 12-<19 % |
| **Foods not specific to infants** | | | | |
| Cereals and cereal products | 0 | 2 | 2 | 5 |
| Milk and milk products | 2 | 5 | 9 | 25 |
| Eggs and egg dishes | 0 | 1 | 1 | 2 |
| Fat spreads[a] | 0 | 2 | 3 | 6 |
| Meat and meat products and dishes, total | 3 | 5 | 6 | 8 |
| Fish and fish dishes | 0 | 1 | 1 | 1 |
| Vegetables, potatoes | 16 | 18 | 18 | 21 |
| Savoury snacks | 0 | 0 | 0 | 0 |
| Fruit | 0 | 0 | 0 | 1 |
| Sugar preserves and confectionery | 0 | 0 | 0 | 0 |
| Beverages | 0 | 0 | 0 | 1 |
| Miscellaneous | 1 | 2 | 2 | 3 |
| **Infant specific foods:** | | | | |
| Infant formula | 39 | 33 | 30 | 12 |
| *of which:* | | | | |
| *'First milk'* | *16* | *8* | *6* | *0* |
| *'Hungrier babies milk'* | *11* | *3* | *1* | *0* |
| *Follow-on milk* | *12* | *20* | *20* | *5* |
| *'Growing up milk'* | *0* | *0* | *1* | *6* |
| *Other milk products[b]* | *0* | *2* | *1* | *1* |
| **Breast milk[c]** | 15 | 8 | 3 | 2 |
| **Commercial infant foods:** | 23 | 25 | 23 | 12 |
| *of which:* | | | | |
| *Meat and fish based products and dishes* | *11* | *14* | *12* | *7* |
| *Other savoury based foods and dishes* | *7* | *6* | *7* | *2* |
| *Fruit based foods and dishes* | *1* | *1* | *1* | *0* |
| *Cereal based foods and dishes* | *3* | *3* | *2* | *1* |
| *Snacks (sweet and savoury)* | *1* | *1* | *1* | *1* |
| **Commercial infant beverages** | 0 | 0 | 0 | 0 |
| **Average daily vitamin A intake (food sources) µg RE** | **943** | **982** | **931** | **676** |

[a] Some oils which are used as a condiment on bread or salads are included in this food group; however, this food group does not include cooking oils.

[b] Includes hypoallergenic, goats and 'goodnight' milks.

[c] A typical volume of breast milk for a full feed was estimated from MRC data (Paul et al., 1988) to be approximately 135g for infants aged 4-7 months and 100g for those aged 8 months or older. It was assumed that a feed of 10 minutes or longer was equivalent to a full feed. For a feed of less than 10 minutes duration, weights were calculated proportionately at 13.5g/min for 4-7 months and at 10g/min for 8 months and older.

55. DNSIYC was also used to estimate the intake of vitamin A from liver, based on all types of liver. Liver pate, which tends to be eaten in smaller portions than liver itself, was not included in the data (Table 10). The highest intakes averaged over the four days of the survey were evident in the 7-<10 (143 µg/kg bw/d) and 10-<12 months old (349 µg/kg bw/d) age categories. In most instances the intakes arose

from a single eating occasion during the survey. These data are based on very small numbers of consumers, but indicate that some infants do eat liver and the possible vitamin A intakes from this source.

Table 10: Intake of vitamin A from liver averaged over the four days of DNSIYC records.

| Liver consumption | Age group in months (number of consumers) | | | | Vitamin A Intake | Age group in months (number of consumers) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 4-<7 (3) | 7-<10 (4) | 10-<12 (5) | 12-<19 (3) | | 4-<7 (3) | 7-<10 (4) | 10-<12 (5) | 12-<19 (3) |
| **Mean (g/kg bw/day)** | 0.34 | 0.91 | 0.73 | 0.19 | **Mean (µg/kg bw/d)** | 52 | 143 | 113 | 21 |
| **Max (g/kg bw/d)** | 0.44 | 1.73 | 1.81 | 0.39 | **Max (µg/kg bw/d)** | 77 | 316 | 407 | 43 |

### *Dietary supplements*

56. Potential exposure from vitamin supplements alone at ages 0 to 12 months, based on the brand providing the highest dose of vitamin A (757 µg RE/day), could be 128, 93, 83 and 77 µg RE/kg bw/day for ages 0 – 4, 4 – <7, 7 – <10 and 10 – <12 months respectively. For the 0-4 month age group this could lead to total intakes of 223 and 270 µg RE/kg bw/day respectively, at the mean and high level of consumption of breast milk. For formula fed infants the total intakes could be 239 and 295 µg RE/kg bw/day respectively, at the mean and high level of milk consumption and the upper end of the reported range of vitamin A in formula milk, or 372 and 494 µg RE/kg bw/day respectively, for mean and high level consumption at the maximum permitted level of vitamin A in formula milk. Together with vitamin A intake from milk and food sources (Table 8), this supplement could lead to total intakes of 209, 191 and 172 µg RE/kg bw/day for ages 4 – <7, 7 – <10 and 10 – <12 months, respectively, at the mean and 346, 302, and 280 µg RE/kg bw/day, respectively, at the high level of milk consumption.

57. At the dosage provided under the Healthy Start scheme (233 µg/day), the corresponding exposures could be 39, 29, 26 and 24 µg RE/kg bw/day for ages 0 – 4, 4 – <7, 7 – <10 and 10 – <12 months respectively. For the 0-4 month age group this could lead to total intakes of 134 and 237 µg RE/kg bw/day respectively, at the mean and high level of consumption of breast milk. For formula fed infants, the total intakes could be 150 and 206 µg RE/kg bw/day respectively, at the mean and high level of consumption and the upper end of the reported range of vitamin A in formula milk, and 283 and 405 µg RE/kg bw/day respectively, for mean and high level milk consumption at the maximum permitted level of vitamin A in formula milk. Together with vitamin A intake from milk and food sources (Table 8), this supplement could lead to total intakes of 145, 134 and 119 µg RE/kg bw/day for ages 4 – <7, 7 – <10 and 10 – <12 months, respectively, at the mean and 282, 235, and 227 µg RE/kg bw/day, respectively, at the high level of milk consumption.

## Risk characterisation

58. Based on the upper end of the reported range of vitamin A concentrations in breast milk from developed countries (70 µg RE/100 mL), estimated exposures of exclusively breastfed infants (average and high consumers) range from 72 to 142 µg RE/kg bw/day, depending on the age of infant, and are below the TUL of 200 µg RE kg/bw per day.

59. It is possible that maternal use of dietary supplements containing vitamin A could increase the total exposure in breastfed infants. Based on a study in Brazilian mothers (see paragraph 45), the increase from supplements sold in the UK is likely to be less than two-fold, i.e. it would lead to intakes of less than 284 µg RE/kg bw/day. Whilst high level consumption might cause exceedance of the TUL, it would be only by a small amount and only for a short period.

60. For infant formula containing vitamin A at the upper end of the range reported in the literature (82 µg RE/100 mL), estimated exposures of exclusively formula fed infants (average and high consumers) range from 84 to 167 µg RE/kg bw/day, depending on the age of infant, and are below the TUL. However, if vitamin A were present at the maximal level which is legally permitted in formula (180 µg RE/100 mL), exposures could exceed the TUL in the age group 0 – 4 months for both average (244 µg RE/kg bw/day) and high intake (366 µg RE/kg bw/day) and at >4 to 6 months for high intake (277 µg RE/kg bw/day). Average intake in the >4 to 6 months age group could give an estimated exposure slightly below the TUL at 185 µg/RE kg/bw per day.

61. DNSIYC provided data on the total preformed vitamin A intakes of infants aged 4-18 months from several sources (breast milk, infant formula and complementary foods) with and without dietary supplements. The mean estimated exposure in the absence of supplements was approximately half the TUL (range 62 to 116 µg RE/kg bw/day). However, the 97.5th percentile intakes exceeded the TUL for some age groups (range from 140 to 253 µg RE/kg bw/day). This exceedance of the TUL is small. Moreover, the data are adjusted using average bodyweights for each age group, and it is possible that higher consuming infants have higher than average bodyweights. Thus, while the possibility of adverse effects cannot be excluded, they would not be expected to occur in other than a very small proportion of infants, if at all.

62. The available data specifically on consumption of liver by infants indicate that those consuming large amounts could exceed the TUL by about 75%. In these data the vitamin A intake, primarily from a single eating occasion is averaged over the 4 reporting days of DNSIYC, and it is unclear if the TUL would be exceeded if the intake were averaged over a longer period of time. However, this assessment suggests that the current Government recommendation that infants over the age of 6 months should not have more than one portion of liver per week is appropriate.

63. Some supplements marketed for infants could lead to large increases in vitamin A intake if taken at the highest recommended doses. The brand with the highest recommended dosage could provide an intake that is more than half of the TUL at age 0-4 months (128 µg RE/ kg bw/day). This could result in total intake above the TUL for exclusively breastfed infants, and increase the potential for

exceedance of the TUL for formula-fed infants, and high consumers of complementary foods rich in vitamin A. The recommended dosage provided under the Healthy Start scheme (233 µg/day), would provide a lower exposure (39 µg RE/day at age 0-4 months), and any resultant exceedances of the TUL are likely to be minor.

## Conclusions

64. There are two dietary sources of vitamin A – preformed vitamin A in foods of animal origin, and provitamin A carotenoids in fruit and vegetables. The food with the highest concentration of vitamin A is liver.

65. Preformed vitamin A is more active biologically than provitamin A carotenoids. Vitamin A in the form of retinol has various biological functions in the body, relating among other things, to cell differentiation, particularly during embryonic development, vision and the immune response.

66. Retinyl esters are hydrolysed in the lumen of the intestine to retinol, which crosses the intestinal mucosa. Retinol is then re-esterified to retinyl esters which are transported into the lymph and bloodstream and stored in the liver. Provitamin A carotenoids can either be converted to retinol or remain intact and stored in fat depots. Retinol is released from the liver bound to retinol binding protein (RBP) and delivered to target tissues where it is converted to oxidised metabolites or retinoic acid, which can modulate transcription factors. Excretion in the form of various metabolites (4-oxoretinol, retinyl β-glucuronide and 14-hydroxy-4,14-retro-retinol) is mostly via the kidneys and, to a lesser extent, via the bile.

67. Toxicity of vitamin A is related to high intake of preformed vitamin A, and does not result from high intakes of provitamin A carotenoids. It is most often reported after chronic exposure. Important adverse effects include bulging fontanelles in infants, hepatotoxicity, changes in bone density, changes in lipid metabolism and teratogenicity.

68. The COT concluded that derivation of a TUL for infants should be based on bulging fontanelles as the most relevant adverse effect in that age group. A LOAEL of 800 µg RE/kg bw/day was identified as a point of departure, based on a number of case reports of infants developing bulging fontanelles following vitamin A supplementation at this level. An uncertainty factor of 4 was applied to allow for uncertainties relating to the small number of case studies that were available, and the limited duration of exposure in those studies. A larger factor was not required because the estimation of the NOAEL on a body weight basis was conservative as it was based on body weight at the time of diagnosis, and related to supplemental intake. Thus, a TUL of 200 µg RE/kg bw/day was established.

69. Where mothers are not taking vitamin A supplements, the estimated exposure of exclusively breastfed infants is below the TUL and not a health concern. Maternal use of dietary supplements could increase the exposure. Whilst available data do not allow precise prediction of effects on breast milk in mothers taking supplements on

the UK market, the increase in vitamin A concentrations is likely to be less than twofold. Thus, any resultant exceedance of TUL would only be minor. Moreover, it would be for only a short period of time.

70. Estimated exposures based on reported concentrations of vitamin A in infant formula are below the TUL and not a health concern. However if vitamin A were present in formula at the maximum legally permitted level (180 µg RE/100 mL), resulting exposures could exceed the TUL by up to about 80 %.

71. Data on total exposures to vitamin A from breast milk, infant formula and complementary foods in UK infants aged 4-18 months indicate that the TUL could be exceeded by up to about 25% at high levels of consumption. This exceedance is small. Moreover, adjustments were made using average body weight data for each age group, and it is possible that higher consuming infants have higher than average bodyweights. Thus, while the possibility of adverse effects cannot be excluded, they would not be expected to occur in other than a very small proportion of infants, if at all.

72. Limited data on liver consumption by infants indicate that frequent consumption of liver could lead to exceedance of the TUL, and that the current Government recommendation that infants over the age of 6 months should not have more than one portion of liver per week is appropriate.

73. Dietary multivitamin supplements marketed for infants in the UK were also evaluated. The brand with the highest recommended dosage could produce an estimated exposure of more than half the TUL. This could result in total intake above the TUL for exclusively breastfed infants, and increase the potential for exceedance of the TUL for formula-fed infants, and high consumers of complementary foods rich in vitamin A. The recommended dosage provided under the Healthy Start scheme would provide a lower exposure, and any resultant exceedances of the TUL are likely to be minor.

74. Overall the COT concluded that there is potential for some infants to exceed the TUL under the following circumstances:

- if exclusively breastfed by mothers taking dietary supplements containing high levels of vitamin A,
- if fed with infant formula at the upper limit of the retinol content allowed by regulation,
- if given high dose vitamin A supplements
- if consuming liver more than once per week

The possibility of adverse effects from such exceedances cannot be excluded, but if they do occur, it is likely to be in only a very small proportion of infants.

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## Abbreviations

| | |
|---|---|
| ADH | Alcohol dehydrogenase |
| BCMO1/2 | β-carotene 15, 15' monooxygenases |
| COMA | Committee on Medical Aspects of Food Policy |
| COT | Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment |
| CYP | Cytochrome P450 |
| DH | Department of Health |
| DNSIYC | Diet and Nutrition Survey of Infants and Young Children |
| EVM | The UK Expert Group on Vitamins and Minerals |
| IU | International Unit |
| LOAEL | Lowest Observed Adverse Effect Level |
| NHS | National Health Service |
| NOAEL | No Observed Adverse Effect Level |
| RBP | Retinol Binding Protein |
| RE | Retinol Equivalent |
| RR | Retinaldehyde reductase |
| SACN | Scientific Advisory Committee on Nutrition |
| SCF | The European Union Scientific Committee on Food |
| TUL | Tolerable Upper Level |
| UL | Upper Level |
| WHO | World Health Organization of the United Nations |

Search Strategy

General Vitamin A exposure search
Websites interrogated –

- EFSA
- COT
- FSA

Scientific publications literature search through Pubmed

## Specific search terms:

Vitamin A AND breast milk
**Search Dates (From/To)** - From January 2002 to present*
*Some papers pre-2002 were included if it felt they added value to the paper, particularly with regards to papers which identified previous cases of chronic and acute vitamin A toxicity and where a dose which lead to toxicity was identifiable.
**Exclusion Criteria** –

- Supplementation research in undeveloped countries
- Supplementation programs in undeveloped countries
- Deficiency related research

Vitamin A AND infant formula
**Search Dates (From/To)** - From January 2002 to present*
*Some papers pre-2002 were included if it felt they added value to the paper, particularly with regards to papers which identified previous cases of chronic and acute vitamin A toxicity and where a dose which lead to toxicity was identifiable.
**Exclusion Criteria** –

- Supplementation studies in undeveloped countries
- Supplementation programs in undeveloped countries
- Infant formulas in non-EU countries

Vitamin A AND hypervitaminosis
**Search Dates (From/To)** - From January 2002 to present*
*Some papers pre-2002 were included if it felt they added value to the paper, particularly with regards to papers which identified previous cases of chronic and acute vitamin A toxicity and where a dose which lead to toxicity was identifiable.
**Exclusion Criteria** –

- Supplementation studies in undeveloped countries
- Supplementation programs in undeveloped countries
- Hypervitaminosis in adults

Vitamin A AND infant diet
**Search Dates (From/To)** - From January 2002 to present*
*Some papers pre-2002 were included if it felt they added value to the paper, particularly with regards to papers which identified previous cases of chronic and acute vitamin A toxicity and where a dose which lead to toxicity was identifiable.

**Exclusion Criteria** –

- Supplementation studies in undeveloped countries
- Supplementation programs in undeveloped countries
- Infant diet in undeveloped countries
- Children's diet (above >2 years) in developed countries

Vitamin A AND weaning
**Search Dates (From/To)** - From January 2002 to present*
*Some papers pre-2002 were included if it felt they added value to the paper, particularly with regards to papers which identified previous cases of chronic and acute vitamin A toxicity and where a dose which lead to toxicity was identifiable.
**Exclusion Criteria** –

- Supplementation studies in undeveloped countries
- Supplementation programs in undeveloped countries
- Infant weaning in undeveloped countries
- Children's diet (above >2 years) in developed countries

Retinol AND exposure
**Search Dates (From/To)** - From January 2002 to present*
*Some papers pre-2002 were included if it felt they added value to the paper, particularly with regards to papers which identified previous cases of chronic and acute vitamin A toxicity and where a dose which lead to toxicity was identifiable.

**Exclusion Criteria** –

- Supplementation studies in undeveloped countries
- Supplementation programs in undeveloped countries
- Adult retinol exposure
- Deficiency related research

The above mentioned search terms were also used in google. It identified latest government advice and opinions.

Vitamin A AND Supplementation
**Search Dates (From/To)** - From January 2002 to present*
*Some papers pre-2002 were included if it felt they added value to the paper, particularly with regards to papers which identified previous cases of chronic and acute vitamin A toxicity and where a dose which lead to toxicity was identifiable.
**Exclusion Criteria** –

- Supplementation research in undeveloped countries
- Supplementation programs in undeveloped countries