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

Fourth draft statement on the potential risks from high levels of vitamin A in infant diet

1. The COT has been asked to provide advice on toxicity of chemicals in food, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. An initial paper (TOX/2012/03), highlighting some of the areas requiring consideration was discussed by the COT in February, 2012. Members noted that data on exposure of weaning infants to vitamin A from liver and dietary supplements were limited. Toxicological information relevant to infants was also sparse therefore it was agreed that a more in-depth review was needed to consider risks to infants.

2. A review paper (TOX/2012/16) was presented to COT in May, 2012 followed by a first draft statement in October 2012 (TOX/2012/34). Members agreed that the priority was to address the toxicology of vitamin A in the first instance, and then, when data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) became available, to complete the exposure assessment. A second draft statement (TOX/2012/41) in December therefore focussed on the relevant toxicology and effects reported in infants. In setting a tolerable upper level for infants (0 -12 months old), Members requested a paper focussing on reported cases of hypervitaminosis A in infants that had been associated with a bulging fontanelle, and this was provided in the meeting held in February 2013 (TOX/2013/05). Based on the evidence presented, Members concluded that only studies meeting specific criteria would be adequate to form the basis of the lowest observed adverse effect level (LOAEL) leading to establish a tolerable upper level. Hence, a subset of studies was presented in the meeting held in March (TOX/2013/14) which allowed Members to propose a tolerable upper level. A draft statement, incorporating the the tolerable upper level, estimated vitamin A exposures using DNSIYC and provisional conclusions was presented to COT in May (TOX/2013/20).

3. The fourth draft statement in Annex A has been revised taking into account minor editorial amendments suggested by COT Members, clarification on the terminology of vitamin A and specific biological aspects of vitamin A.

Questions for the Committee

4. Members are invited to agree on the fourth draft statement on the potential risks from high levels of vitamin A in infant diet.

Secretariat
June, 2013

TOX/2013/30 Annex A

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

Fourth draft statement on the potential risks from high levels of vitamin A in 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 in food have been conducted by the Scientific Committee on Food (SCF) (SCF, 2002), Expert Group on Vitamins and Minerals (EVM) (EVM, 2003), the Scientific Advisory Committee on Nutrition (SACN) (SACN, 2005). This statement draws on information from those evaluations and adds additional relevant studies published more recently. The statement considers the sources of vitamin A, function, measurements, toxicokinetics, toxicity with particular focus on those studies which would assist in the derivation of a tolerable upper level (TUL) and estimated dietary exposure 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 that 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, see figure 1 (EVM, 2003). Provitamin A carotenoids are precursors of vitamin A and can be converted to retinol in the body (SACN, 2005). The total vitamin A content of food is the sum of preformed vitamin A and provitamin A carotenoids, however it is measured relative to the activity of retinol. This is expressed as micrograms (µg) of retinol equivalents (RE) (see paragraph 7).

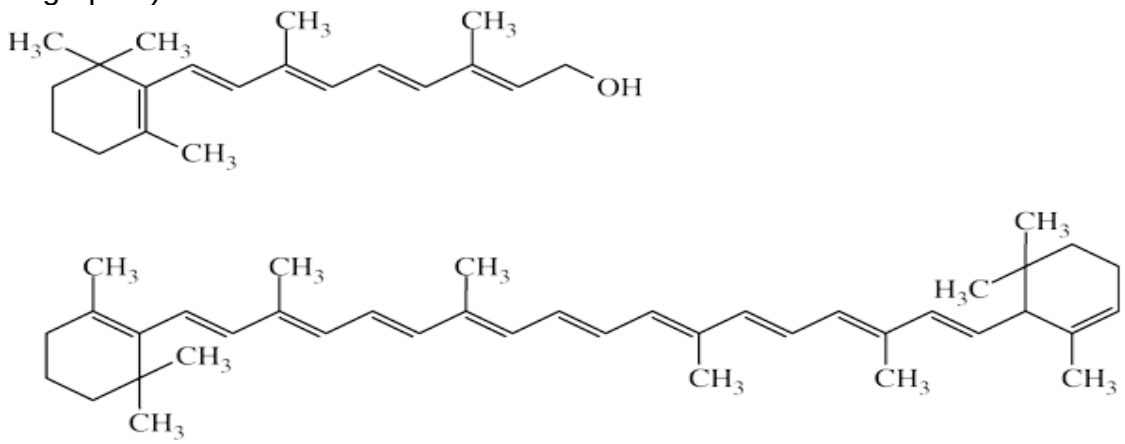

Figure 1: Structural formula of retinol ($C_{20}H_{30}O$) (top) and β-carotene ($C_{40}H_{56}$) (bottom).

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 retinol equivalents is in carnivore liver at concentrations ranging from 30,000 to 50,000 µg per kg (Allen and Haskell, 2002; Schulz et al. 2007). Retinol is more biologically active than the carotenoids.

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

Vitamin A Measurements

9. Vitamin A is expressed either as international units (IU) or 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 (EVM, 2002)[1]. For consistency, RE is used in this statement. Generally, the IU value can be calculated by multiplying the RE by 3.33; however, this will only be accurate if the total vitamin A content is entirely retinol (see table 1 and footnote 1 below). RE can only be calculated with certainty if the relative amounts of preformed vitamin A and provitamin A carotenoids are known. Table 2 shows the dietary reference values for vitamin A.

Table 1: The vitamin A activity (in IU and RE) of the three main retinoid compounds (EVM, 2003)

Retinoid compound	Vitamin A activity in IU	Vitamin A activity in RE
Retinol (1 mg or 1000 µg)	3330	1000
Retinyl acetate (1 mg or 1000 µg)	2900	870
Retinyl palmitate (1 mg or 1000 µg)	1830	550

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

[1] As set by WHO (1949). http://whqlibdoc.who.int/trs/WHO_TRS_3.pdf. The widely accepted conversion factors for 1 RE = 1.00 µg retinol, 1.78 µg retinyl palmitate, 6.00 µg β-carotene, 12.00 µg other provitamin A carotenoids, 3.33 IU vitamin A activity as retinol and 10.00 IU vitamin A activity as β-carotene

7 - 10 years	250	350	500
11 – 14 years	-	-	600
Women (including girls from 11 y. o.)	-	-	600
Men (including boys from 15 y.o.)	-	-	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 percent 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

10. 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, 2011).

11. 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 not recommended to have more than one portion of liver per week because it can be harmful in large amounts (SACN, 2005).

12. The Department of Health recommends that all children from six months to five years old are given supplements for vitamins A, C and D (DH, 2012). The Healthy Start scheme is available for eligible families (i.e. low income or claiming specific benefits). The daily dose of vitamin A in the Healthy Start vitamin drops is 233 µg RE. There is strong advice to keep to the recommended dose stated on the label and to not give two supplements at the same time. DH also states that children who are receiving 500 ml or more of formula a day do not need to be given supplementary vitamins (DH, 2012). Breastfed infants 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).

Toxicokinetics

Preformed Vitamin A Uptake and distribution

13. 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 (TG) 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 in the lymph circulation (EVM, 2003). The chylomicra retinyl ester is 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 a facilitated process by integral proteins in the cell membrane (During and Harrison, 2007). The uptake and distribution of preformed vitamin A is illustrated in figure 2.

14. Serum retinol concentrations are homeostatically controlled to remain constant, despite variations in the dietary supply of retinol. When retinol is required, it is secreted from the liver bound to plasma retinol-binding protein (RBP) and is 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 to allow for binding to the specific receptor (SACN, 2005).

Provitamin A Carotenoid Uptake and distribution

15. 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. Absorption decreases as the amount of provitamin A carotenoids increases up to a point of saturation (IOM, 2001; 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). Goodman et al. (1966) reported 60-70% of β-carotene was converted to retinyl esters in the intestinal mucosa of humans whereas approximately 30% remained as β-carotene. 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.

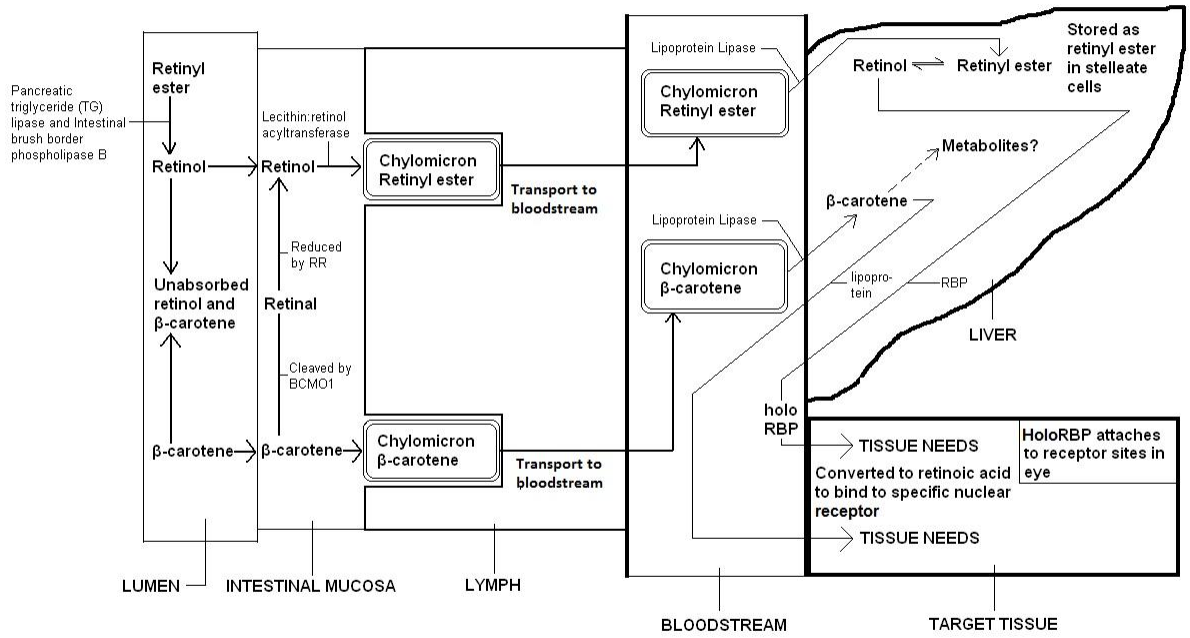

Figure 2: An overview of retinol and β-carotene absorption and distribution. Adapted from Parker (1996). Abbreviations: BCMO1 - β-carotene 15,15'-monooxygenase; holo-RBP – retinol bound to retinol binding protein; RBP – retinol binding protein; RR - retinaldehyde reductase**.**

Metabolism

16. Retinol is oxidised to retinaldehyde by the action of cytosolic and microsomal enzymes retinol dehydrogenases (Rhee and Plutzky, 2012), which are members of the alcohol dehydrogenase (ADH) families. Retinol metabolism is catalyzed by ubiquitously expressed ADH3 as well as by the tissue-dependent forms ADH1 and ADH4. All three isoforms could oxidize all-trans retinol to all-trans retinaldehyde. This is followed by the oxidative step from retinaldehyde to retinoic acid which is irreversible and catalysed by the enzyme retinaldehyde dehydrogenase. In turn, retinoic acid is metabolised by CYP26 into oxidative metabolites.

17. Carotenoids can be converted into retinaldehyde through the action of BCMO1, which carries out a central cleavage of the carotene. Retinaldehyde would then in turn follow the same metabolism described for retinol. Alternatively, carotenoids can be converted to apocarotenal by BCMO2 through an asymmetrical cleavage. Subsequently, apocarotenal is converted into apocarotenoic acid which is transported to the cell by the cellular retinoic acid binding protein and interacts with the nuclear receptor (D'Ambrosio et al., 2011; Rhee and Plutzky, 2012)

18. Vitamin A and derivative compounds are conjugated in the liver with glucuronic acid or taurine and excreted in the urine and bile (EVM, 2003; IOM, 2001).

Factors that Affect Provitamin A Carotenoid Bioavailability and Bioconversion

19. A number of factors affecting the bioavailability and bioconversion of provitamin A carotenoids in the gut have been identified (Bender, 2003; Lietz et al., 2010; Tang, 2010) as:

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

20. Approximately 50 to 85% of the total body retinol is stored in the liver when vitamin A status is adequate (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 saturated (Ross, 1999). β-carotene has been widely established to be stored in adipose cells of fat depots throughout the body (Bucci, 1998). However, serum levels of β-carotene are principally indicators of recent intake and not body stores due to their slow release (Ross, 1999).

Excretion

21. 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). Some examples of faecal metabolites are retinoic acid glucuronide and 4-oxoretinoic acid glucuronide, which can be absorbed and returned to the liver through enterohepatic circulation. No relevant information has been found on excretion specific to infants or children.

Toxicity

22. Having too much vitamin A in the body is referred to as hypervitaminosis A, and is associated with a range of adverse effects. The two most frequent causes of hypervitaminosis A in infants are parents overdosing infants with vitamin A

supplements and physicians failing to stress to parents the dangers of excessive vitamin A levels in prescription-related cases (Perrotta et al. 2003). Hypervitaminosis A through natural food sources is less frequently reported (Perrotta et al. 2003). Toxicity appears to arise when the amount of vitamin A present 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). As a result, free retinol binds to lipoproteins (Bendich and Langseth, 1989). Preformed vitamin A can lead to acute toxicity whereas a high intake of β-carotene and other provitamin A carotenoids from food alone have not shown evidence of toxicity although it can lead to a yellow appearance (Allen and Haskell, 2003). Penniston and Tanumihardjo (2006) commented that it is almost impossible to suffer from hypervitaminosis A from provitamin A carotenoid sources as the cleavage of vitamin A precursors to retinal is a highly regulated step.

23. Acute vitamin A toxicity is rare and usually related to consumption of high quantities of liver and/or retinol supplements (EVM, 2002). Commonly observed clinical features of acute toxicity in children include anorexia, bulging fontanelles, drowsiness, increased intercranial pressure, lethargy, irritability and vomiting (Perrotta et al. 2003). Clinical features in adults include blurred vision, hypercalcemia and peripheral neuritis. An anterior bulging fontanelle is often observed in both infants and young children following both chronic and acute doses of vitamin A intake. The WHO commented that a bulging fontanelle is the most frequently observed side effect and occurs as a result of a transient increase in cerebrospinal fluid volume (WHO, 2011). Weight, dietary factors (fat content) and general health are all crucial factors in determining the dose leading to acute vitamin A toxicity (Bendich and Langseth, 1989). In the majority of cases, many symptoms associated with acute toxicity, including bulging of the fontanelles, are resolved within a week (Perrotta et al. 2003). Full recovery of the patient will usually take less than a month (Perrotta et al. 2003).

24. More cases of chronic vitamin A toxicity have been reported than acute toxicity (Perrotta et al. 2003). Common clinical features associated with chronic toxicity, although highly variable, include bulging fontanelles (in infants), alopecia, anorexia, bone joint pain, thickening and fissuring of the lips, photophobia, conjunctivitis, hepatoxicity, enlarged spleen, skin desquamation and anaemia (EVM. 2003; Perrotta et al. 2003).

Case studies with reported bulging fontanelles associated to hypervitaminosis

25. Marie and Sée (1951) identified four incidents of acute vitamin A toxicity. Three infants aged 3, 3 ½ months and 7 months all rapidly developed a bulging fontanelle and nausea and were subsequently hospitalised. All three had received the same vitamin supplement containing approximately 105,000 µg RE in the past 12 to 24 hours. The intake is equivalent to a single dose of 18,750 µg RE/kg bw for the 3 ½ month old based on a reported weight of 5.6 kg and 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 3 months old infant. In the other case, a 2 month old infant rapidly developed a prominent bulge of the fontanelle and was subsequently hospitalised after receiving

approximately 15,000 µg RE per day for six days through prescribed nose drops. The intake is equivalent to 3,200 µg RE/kg bw/day for the 3 ½ month old based on a reported weight of 4.7 kg.

26. A randomised, double-blind placebo controlled trial was performed 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 one to six month age category which had received a single dose of 30,000 µg RE (n=1349; incidence= 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.

27. Infants (n=167) received three 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 in a randomised, double-blind placebo controlled trial assessing the safety of vitamin A supplementation in early infancy. Twelve infants supplemented with vitamin A were recorded to have bulging fontanelles at some stage. Other side-effects included drowsiness, anorexia and vomiting were positively associated with the bulging fontanelle incidences (Bacqui et al. 1995). Exposure on a body weight basis could not be calculated since infants' weights were not reported in the study.

28. 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 vitamin A palmitate from 10 days after birth lasting for approximately 80 days. The infant had been mistakenly given a dose of 20,000 µg RE/day (Perrotta et al. 2002). The intake is equivalent to 3,800 µg RE/kg bw/day based on a reported weight of 5.2 kg at 3 months.

29. Myhre et al. (2003) undertook a meta-analysis of case reports of bulging fontanelles suspected of being induced by excessive levels of dietary retinol. Cases of hypervitaminosis A (100 in total) were identified in the age range of 0-2 years old in the scientific literature (50 chronic and 50 acute). The COT concluded that data on parenteral administration were of limited relevance, and that the focus should be on reports meeting the following criteria: 1) 0-2 years old, 2) oral exposure and 3) vitamin A at levels ≤ 1,000 µg RE/kg bw/day. Table 3 lists the reports meeting the criteria which were evaluated by COT.

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.

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

Effects of vitamin A in population groups other than infants

31. 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.

32. The lowest dose associated with hepatotoxicity was from a severe case of hepatotoxicity associated with the daily ingestion of 7,500 µg RE/day for six years, bought as an over-the-counter dietary supplement (Kowalski et al. 1994).

33. 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 2297 subjects, with a moderate risk of contracting skin cancer (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.

34. For 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 decreased bone density/increased bone fracture compared to intakes less than 500 µg RE/day in women aged 40-76 years. 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 if the same dose response would apply to men or children.

35. Retinoids are teratogenic in animal studies. Isotretinoin, a synthetic retinoid (also known as 13-cis-retinoic acid), was identified as a human teratogen in 1985 when it was prescribed for certain skin disorders, specifically severe forms of acne (EVM, 2002). Severe malformations of the heart, thymus, face, jaw, ears, palate and brain were some of the congenital fetal anomalies identified in the 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).

36. The SCF (2002) identified 3,000 µg/RE/day as the lowest reported dose for teratogenicity, based on a study by Rothman et al. (1995) involving 22,748 pregnant women answering a questionnaire to identify retinol intake via the diet and supplements. The percentages of babies with cranial-neural-crest defects were 0.52%, 0.62% and 1.06% in women with intakes from food of 0-1500 µg RE/day, 1500-3000 µg RE/day and more or equal to 3000 µg RE/day, respectively. The UK

Expert Group on Vitamins and Minerals (EVM) concluded that a precise threshold for teratogenic effects was uncertain, but that it was prudent to assume it could be 3000 µg RE/day based on the Rothman et al. (1995) study (EVM, 2002).

Allergenicity

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

Tolerable Upper Level

38. The SCF (2002) noted that different groups in the population would be affected differently, bulging fontanelles in infants, decreased bone density and increased bone fracture being more reported in middle aged and elderly women, and teratogenicity being relevant for women of child bearing age. The lowest doses for hepatotoxicity and altered lipid metabolism were relevant for adults. The lowest doses of preformed vitamin A identified by SCF as leading to specific adverse effects are shown in table 3.

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

Effect	Lowest dose
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

39. Table 5 shows the tolerable upper intake levels (ULs[2]) for preformed vitamin A established by the SCF for different age groups. The UL of 3,000 µg RE/day was based on the teratogenicity data of Rothman et al. (1995), but also considered to be relevant to adult subgroups other than pregnant women since it was 2.5-fold lower than the lowest daily intake that had been associated with hepatotoxicity during chronic intake. The ULs for infants and children were extrapolated from the 3,000 µg RE/day for adults, on the basis of body weight and difference 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 however a UL for the age group below one year was not proposed.

[2] 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.

Table 5: Tolerable upper intake levels for various age groups established by SCF (2002)

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

40. A UL of 600 µg RE/day of preformed vitamin A has been established by the Institute of Medicine for infants aged 0-12 months (IOM, 2001). This was based on the LOAEL of 6000 µg RE (identified by the IOM as the lowest dose associated with bulging fontanelles (Perrson et al. 1965)) with an uncertainty factor of 10. The IOM selected an uncertainty factor of 10 "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 reported that there is plenty of evidence to support the reversibility of the adverse effect bulging fontanelles in infants if supplementation is ceased.

41. 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. The relevance of hepatotoxicity, bone effects and lipid changes to this age group were also unclear. The COT therefore concluded that consideration of potential adverse effects of high levels of vitamin A intake by infants should be based on the relevant endpoint, i.e. bulging fontanelles, for which the LOAEL was 800 µg/RE kg/bw per day (see paragraphs 29 and 30)

42. An uncertainty factor of 4 was agreed to allow for uncertainties in relation to the dose on a body weight basis (because body weight increases during infancy, dose at diagnosis could be an underestimate of the LOAEL), the small number of case studies that were available, and the limited duration of exposure in those studies. The COT therefore established a tolerable upper level (TUL) of 200 µg/RE kg/bw per day by dividing the LOAEL of 800 µg/RE kg/bw per day by the uncertainty factor of 4.

Occurrence of Vitamin A

Breast Milk

43. Current UK government advice is that infants should be exclusively breastfed around the first six months of life (DH, 2003). No occurrence data on vitamin A in colostrum in UK or European cohorts have been found in literature searches. The range of vitamin A levels in the mature breast milk of well-nourished women in

Europe is reported to be 40-70 µg RE/100 mL, with the higher levels generally seen in women whose diet includes a higher intake of fats, particularly animal fats (Ross and Harvey, 2003).

44. There is limited information on the impact vitamin A supplementation has upon levels of vitamin A in breast milk in a Western population. Bezerra et al. (2009) assessed the effect of maternal supplementation with either a single dose or two doses 24-hours apart of 200,000 IU (60,060 µg RE, a dose recommended by WHO for use in vitamin A deficiency) retinyl palmitate immediately postpartum, compared to controls with no supplementation in a cohort of healthy Brazilian women in the municipality of Natal, age 18 to 40 years old with no infants born with malformations. The mean vitamin A concentration in breast milk of supplemented women was 165 and 51 µg RE/100 mL at 24 h and 30 days after dosage compared to 93 and 37 µg RE/100 mL, respectively, in control women. The retinol content did not differ significantly between the single and double dose of supplementation. Data provided to the EVM indicated that the highest dose was 2,400 µg RE per day (EVM, 2003) and therefore the dose of vitamin A in this study was considerably higher than that in dietary supplements on the UK market. However it indicates that supplementation would increase the level of vitamin A in breast milk by less than 2-fold.

Infant Formula

45. Infant formula typically contains a higher concentration of several micronutrients than does breast milk, partly to account for the fact that absorption of nutrients from breast milk is greater than infant formula, 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 specifies that it contains 75 µg vitamin A (RE)/ 100 mL and infants should be given 500-600 mL per day. The Infant formula and follow-on formula (England) regulations sets 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 (EC, 2006).

Food

46. 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 vitamin A in foods (µg/RE) (DSM, 2007)

Food type	Concentration (µg RE/kg)	Form of vitamin A
Liver	3,500	Preformed vitamin A
Fortified margarine	330	Preformed vitamin A

Typical dairy products	90-300	Preformed vitamin A
Carrots	1,500	Provitamin A carotenoids
Spinach	795	Provitamin A carotenoids
Melon	784	Provitamin A carotenoids
Broccoli	146	Provitamin A carotenoids

Supplements

47. There are numerous multivitamin supplements that 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 with some in acetate form. The recommended daily doses of multivitamin supplements according to several manufacturers vary between 200 and 757 µg RE/ day (Leaf, 2007). The vitamin supplement provided under the UK government "Healthy Start" scheme[3] provides 233 µg RE/day.

Exposure

48. In calculating dietary exposures, it is reasonable to assume values of 800 mL and 1200 mL for average and high-level daily consumption of breast milk or infant formula before weaning (e.g., EFSA, 2012). In its dietary exposure estimations, the COT has previously used bodyweight data from a relatively old survey (DH, 1994). Bodyweight data are now available from the recently published DNSIYC (DH, 2013), with an average bodyweight of 7.8 kg for infants aged 4.0-6.0 months old. Since DNSIYC did not include infants younger than 4 months, in this statement the value of 5.9 kg for infants aged 0-3 months (DH, 1994) is applied to infants aged 0-4 months.

Infants exclusively fed on breast milk or infant formula

49. Table 7 shows the estimated vitamin A intake of exclusively breastfed infants based on the upper end of the reported range of vitamin A in breast milk from developed countries (70 µg RE/100 mL). Data indicates that the vitamin A intake of an infant from maternal use of vitamin A dietary supplements in the UK would be less than 284 µg/kg bw/day.

50. 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).

Table 7. Vitamin A exposure (µg RE/kg bw/day) from exclusive feeding on breast milk or formula milk estimated for average and high level consumption

	Age in months (consumption volume)

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

	0-4.0 (800 mL)	0-4.0 (1200 mL)	>4.0-6.0 (800 mL)	>4.0-6.0 (1200 mL)
Breast milk (70 µg RE/100 mL)	95	142	72	108
Formula milk (82 µg RE/100 mL)	111	167	84	126
Formula milk (180 µg RE/100 mL)	244	366	185	277

Infants also consuming complementary foods

51. DNSIYC collected data on 2683 4-18 month old infants whose mothers completed a 4-day food diary on their infant's diet. The mean vitamin A intakes from breast milk, infant formula and complementary food sources were 116, 108, 95 and 62 µg RE/day at age 4-6, 7-9, 10-11 and 12-18 months old, respectively, see Table 8 (DH, 2013).

Table 8: Daily intakes of vitamin A from breast milk, infant formula and complementary food sources (DH, 2013)

Vitamin A (RE) µg/kg bw/day	**Age group (months)**			
	4-6	7-9	10-11	12-18
Mean	116	108	95	62
Median	106	99	88	55
Standard deviation	52	48	46	32
97.5th percentile	253	219	203	140

52. The contribution of infant formula to the total average vitamin A daily intake decreased from 39 % at 4-6 months to 30 % at 10-11 months. Likewise, the contribution of breast milk decreased from 15% at 4-6 months to 2% at 12-18% months. Commercial products provide approximately 24% throughout the first year. Major contributors to the total intake were non-infant specific foods such as vegetables and potatoes, and milk and milk products, see Table 9 (DH, 2013).

Table 9: Percentage contribution of food sources to daily vitamin A intake, by age group

Food group[a]	Age group (months)			
	4-6 %	7-9 %	10-11 %	12-18 %
Non-infant specific foods:				
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[b]	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[c]	*0*	*2*	*1*	*1*
Breast milk[d]	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 food groups are not included due to small numbers of consumers; e.g. nuts and seeds and savoury snacks.

[b] 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.

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

[d] 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.

53. DNSIYC also included estimates of vitamin A intake from all sources including dietary supplements as shown in Table 10). Daily intake including supplements was about 1-3% higher than without supplements at the mean and 0-9 % higher than without supplements at the 97.5th percentile (DH, 2013). Data on consumption of specific foods with high vitamin A content, such as carrot and liver, are not yet available from DNSIYC.

Table 10: Daily intake of vitamin A from all sources including dietary supplements (DH, 2013)

Vitamin A (RE) µg/kg bw/day	Age group (months)			
	4-6	7-9	10-11	12-18
Mean	118	109	97	64
Median	106	101	89	56
Standard deviation	52	49	48	34
97.5 percentile	253	229	219	153

Predictions for High Level Intakes from Liver and other Food Sources

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, pear, cooked apple or mashed baby rice are recommended as suitable weaning foods. Some of these foods are a good source of β-carotene. At a later stage, the infant can be offered different foods such as meat, fish, pasta, noodles, bread, chapatti, lentils, mashed rice, 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 meals 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.

55. Liver consumption is not completely discouraged above the age of 6 months, therefore a scenario has been developed to predict high level intake from this source. An iron rich meal containing 125 g of chicken liver is listed on a homemade baby food recipe website (Homemade baby food recipes 2012[4]). It is mixed with 125 g of mince, 250 g of butternut squash and 250 mL of chicken stock and blended into a puree for the infant. In addition to the chicken liver, the other ingredients also contain a proportion of vitamin A, albeit as provitamin A carotenoids (predominantly β-carotene). A typical jar of infant food is approximately 125 g. The average vitamin A content of chicken liver is about 40 µg RE/g. If a typical portion size for an infant meal is 125 g, a serving of this recipe would contain about 20 g of chicken liver (proportion of chicken liver is 1/6 of the entire contents), which would contain about 800 µg RE. Based on average bodyweights, this exposure would equate to 99 µg RE/kg bw/day for the age group 4 to 6 months (8.1 kg), 88 µg RE/kg bw/day for the age group 7 to 9 months (9.1 kg) and 82 µg RE/kg bw/day for the age group 10 to 11

[4] http://www.homemade-baby-food-recipes.com/baby-dinner-recipes.html

months (9.8 kg). As liver is the highest source of vitamin A, this scenario will represent the highest dietary source for vitamin A (retinol) intake in weaning infants.

56. Potential exposure from vitamin supplements alone from 0 to 12 months based on the brand providing the highest dose of vitamin A (757 µg RE/ day) would be 128, 93, 83 and 77 µg RE/day for 0 – 4, > 4 – 6, 7 – 9 and 10 – 11 months respectively. At the more common dose of 233 µg/ day, the estimated exposures would be 39, 29, 26 and 24 for 0 – 4, > 4 – 6, 7 – 9 and 10 – 11 months respectively.

Risk Characterisation

57. Based on the upper end of the reported range of vitamin A 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, which are below the TUL of 200 µg/RE kg/bw per day.

58. It is possible that maternal use of dietary supplements containing vitamin A would increase the exposure in breastfed infants. Based on a study in Brazilian mothers (see paragraph 44), the increase is likely to be less than two-fold, and any exceedance of the TUL would be minor.

59. 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, which are also below the TUL. However, if the maximum legal amount of vitamin A that can be added into formula (180 µg RE/100 mL) was used, the exposure would 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 – 6 months for high intake (277 µg RE/kg bw/day). Average intake infants in the > 4 – 6 months provided an estimate exposure slightly below the TUL at 185 µg/RE kg/bw per day.

60. DNSIYC compiled consumption data on the vitamin A intakes of infants 4 to 18 months old combined from different sources (breast milk, infant formula and complementary food) including and excluding dietary supplements. The mean estimated exposure in the absence of supplements was approximately half the TUL value (range 116 to 62 µg RE/kg bw/day). Little impact was observed in the exposure estimations when dietary supplements were included with a 1- 3 % increase over the mean without supplements (range 118 to 64 µg RE/kg bw/day). However, the 97.5 percentile with and without supplements exceeded the TUL (range from 253 to 219 µg RE/kg bw/day supplemented) for all infant age groups. Taking into account that these data are adjusted using average body weight data for each age group, and that higher consuming infants could have higher than average bodyweight, it is unlikely that this small exceedance of the TUL represents a health concern.

61. Whilst these data show a low impact of supplements on the total diet, some supplements have a potential to result in a more marked increase in exposure. The brand recommending the highest intake provides an exposure that is more than half of the TUL at age 0-3 months (128 µg RE/day) which, together with breast milk or infant formula could result in exposure above the TUL.

62. A prediction for high level intake of the highest source of retinol (liver) was undertaken based on an internet recipe indicating the consumption of 20 g of chicken liver per serving, the exposures estimated in the age range from 4 to 12 months were less than half the TUL (range 99 µg RE/kg bw/day in age group 4 – 6 to 82 µg RE/kg bw/day in age group 10 to 11 months old). Addition of this scenario to the rest of the diet, is unlikely to result in total exposure greatly in excess of the TUL.

Conclusions

61. There are two sources of vitamin A intake, preformed vitamin A in foods of animal origin, and provitamin A carotenoid in fruits and vegetables. The food with the highest concentration of vitamin A is liver.

62. Preformed vitamin A is more biologically active than provitamin A. Vitamin A in the form of retinol is involved in a variety of biological functions in the body such as vision, immune response and mostly cell differentiation processes particularly during the embryonic development.

63. Retinyl esters are metabolised into retinol in the lumen of the intestine, which crosses the intestinal mucosa, into the lymph and bloodstream, and is stored in the liver. Provitamin A 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 several 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.

64. Toxicity of vitamin A is related to retinol intake, not to provitamin A, and it is more frequently reported after chronic exposure. Key adverse effects include bulging fontanelles in infants, hepatotoxicity, changes in bone density, changes in lipid metabolism and teratogenicity.

65. The COT concluded that derivation of a TUL for infants should be based on bulging fontanelles as the relevant adverse effect. A LOAEL of 800 µg RE/kg bw/day was identified based on a number of case reports of infants developing bulging fontanelles as a result of vitamin A supplementation. An uncertainty factor of 4 was applied to allow for uncertainties relating to the dose per body weight, the small number of case studies that were available, and the limited duration of exposure in those studies. Hence, the TUL was established at 200 µg RE/kg bw/day.

66. 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 good data are not available to predict the possible increase in mothers taking supplements on the UK market, the increase is likely to be less than two-fold. Any increase in total exposure above TUL would be minor and for a short period of time.

67. Estimated exposures based on reported concentrations of vitamin A in infant formula were also below TUL and not a health concern. However if the maximum legal amount of vitamin A that can be added into formula (180 µg RE/100 mL) is used, then the resulting exposure could exceed the TUL by up to about 80 %.

68. Newly obtained data on exposure of UK infants aged 4 to 18 months to vitamin A from breast milk, infant formula and complementary foods showed that the TUL could exceeded by up to about 25 % at a high level of consumption. Taking into account that these data are adjusted using average body weight data for each age group, and that higher consuming infants could have higher than average bodyweight, it is unlikely that this small exceedance of the TUL represents a health concern.

69. Dietary multivitamin supplement marketed for infants in the UK with recommended intakes available in the literature where evaluated. The brand with the maximum recommended intake produced an estimated exposure below the TUL which would be decreased further throughout the first year. However, the TUL would be exceed if exposures from breast milk or infant formula were to be added.

70. Based on a prediction of exposure to vitamin A from a liver-containing recipe, inclusion of liver in the infant diet is unlikely to result in adverse effects.

71. Overall the COT concluded that, based on the available evidence, intake of vitamin A from the infant diet is unlikely to be high enough to result in adverse effects.

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Abbreviations

ADH	Alcohol Dehydrogenase
BCMO1/2	β-carotene 15, 15' monooxygenases
COMA	Committee on Medical Aspects of Food Policy
CT	Computed Tomograms
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
DH	Department of Health
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
DRV	Dietary Reference Values
EFSA	European Food Safety Authority
EVM	The UK Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organization of the United Nations
IU	International Unit
LOAEL	Lowest Observed Adverse Effect Level
MAFF	Ministry of Agriculture, Fisheries and Food
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NOAEL	No Observed Adverse Effect Level
RBP	Retinol Binding Protein
RDA	Recommended Daily Allowance
RE	Retinol Equivalent
RNI	Reference Nutrient Intake
RR	Retinaldehyde reductase
SACN	Scientific Advisory Committee on Nutrition
SCF	The European Union Scientific Committee on Food
SD	Standard deviation
SNP	Single Nucleotide Polymorphism
TG	Triglyceride
TUL	Tolerable Upper Level
UL	Upper Level
WHO	World Health Organization of the United Nations

Search Strategy

General Vitamin A exposure search
Databases interrogated –

- EFSA
- COT
- FSA

Scientific publications literature search

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