First 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 allergenicity of food and 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. A review paper (TOX/2012/16) was presented to COT in May, 2012. Members made initial comments (see minutes in Annex A). A draft COT statement on the potential risks from high levels of vitamin A in infant diet is included in Annex B.

Questions for the Committee

2. Members are invited to comment on the first draft statement on the potential risks from high levels of vitamin A in infant diet and any other issues that arise.

   i. Do Members agree with the structure of the draft statement?

   ii. Are there some aspects that need further elaboration, or could be shortened?

   iii. Do Members agree with the tolerable upper level of 600 µg RE/day proposed for infants?

   iv. Can Members advise on the conclusions they would like to see in the next draft?

Secretariat
October 2012
COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

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

Section of the minutes of the COT meeting of 8 May 2012

These minutes are available at http://cot.food.gov.uk/cotmtgs/cotmeets/cotmeet2012/cotmeet8may2012/cotfinalmins8may2012
Item 6: Review of potential risks from high levels of vitamin A in infant nutrition - TOX/2012/16

29. Dr John Thompson declared a personal specific interest in that he had carried out research on vitamin A uptake in the past. This was considered a lapsed interest and not a conflict and therefore Dr Thompson could participate in the discussions.

30. At the February 2012 meeting, Members had agreed that more detailed review of vitamin A was needed because data on the exposures of weaning infants to vitamin A from liver and dietary supplements and toxicological information relevant to infants were sparse. Members were provided with paper TOX/2012/16 and asked to comment on whether the intakes of vitamin A by infants indicated a concern, and whether revision of current advice on liver consumption by infants might be needed.

31. The paper focused primarily on toxicity in relation to preformed vitamin A (retinol, retinyl palmitate) and Members requested further clarification of the relevance of provitamin A carotenoids (which included β-carotene), including information on uptake, metabolism, toxicity and contribution to the exposure assessments. Retinol metabolism and toxicity needed to be described in more detail.

32. The lowest doses of preformed vitamin A leading to specific adverse effects as listed by the Scientific Committee on Food (SCF, 2002)\(^1\) were discussed. Members commented that it would be helpful to identify which of the effects, in addition to bulging fontanelle, were potentially relevant to infants. Clarification was requested on the SCF’s approach to scaling of the tolerable upper level (UL) from 3000 µg RE/day in adults to 800 µg RE/day in young children aged 1-3 years, and on the basis for the UL of 600 µg RE/day for infants aged 0-12 months proposed by the U.S. Institute of Medicine. It was considered that animal data, specifically from carnivores, might be helpful in identifying a suitable approach for extrapolating the UL from adults to children.

33. It was commented that there was apparent inconsistency in the doses cited as leading to acute toxicity in children, which needed clarification. Members also asked for further details on the report of chronic toxicity of vitamin A in twins fed homogenised chicken liver over a four month period (Mahoney, et al., 1980)\(^2\).

34. Consideration was needed of the impact of a mother taking vitamin A supplements during breast feeding on vitamin A levels in breast milk. A WHO systematic review on vitamin A and the neonate, which had been published in 2008, might provide useful information. Members asked if hypervitaminosis A had been reported in UK infants, and if this condition would be expected to be diagnosed when it occurred. The Royal College of Paediatrics and Child Health could be contacted for advice.

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\(^1\) Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Preformed Vitamin A (retinol and retinyl esters) available at [http://ec.europa.eu/food/fs/sc/scf/out145_en.pdf](http://ec.europa.eu/food/fs/sc/scf/out145_en.pdf)

35. Members concluded that more information was required before they could address the answers posed in paper TOX/2012/16. This would be provided at a future meeting.
This is a draft statement for discussion.
It does not reflect the views of the Committee and should not be cited.

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

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

**Vitamin A**

1. Vitamin A is a lipid soluble, light yellow substance, which is an essential micronutrient responsible for promoting normal growth, vision and immunity. Vitamin A (retinol) plays a critical biological role in embryogenesis (Perrotta, et al., 2003). Typically the structure consists of a β-ionone ring with a polar terminal group and conjugated isoprenoid side chain (EVM, 2003). There are 3 distinct forms of vitamin A: retinoids, β-carotene and other provitamin A carotenoids. The highest proportion of vitamin A in the diet exists as either retinyl esters or provitamin A carotenoids (the form with the highest vitamin A value of all provitamin A carotenoids is β-carotene) and both can be converted to retinol in the human body (During and Harrison, 2007).

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

**Preformed Vitamin A**

2. Retinyl esters are found in animals and animal-based products, predominantly in the form of retinyl palmitate (Allen and Haskell, 2002). They can also be found in enriched fortified foods (Perrotta, et al., 2003). Both retinyl palmitate and retinyl acetate are used in the preparation of supplements (Perrotta, et al., 2003). Collectively, retinyl esters and retinol are preformed vitamin A and are often referred to as retinoids (Perrotta, et al., 2003). The highest concentration of retinol can be found in carnivore liver at concentrations ranging from 30,000 to 50,000 µg of retinol
per kg, making it the highest source of preformed vitamin A (Allen and Haskell, 2002; Schulz, et al., 2007). Retinyl esters can be converted to retinol in intestinal cells. Retinyl esters are hydrolysed by retinyl ester hydrolase (REH) enzymes within the gastrointestinal tract lumen to enable absorption to take place (Perrotta, et al., 2003). Retinyl ester is the predominant form of vitamin A in human lymph, regardless of whether it originated from dietary preformed vitamin A or provitamin A carotenoids (IOM, 2001).

**Provitamin A Carotenoids**

3. Provitamin A carotenoids, which include the vitamin A precursor β-carotene, can be found in a variety of fruits and vegetables. Over 600 carotenoids have been identified however only a small proportion of these (approximately 50) exhibit provitamin A nutritional activity (Tanumihardjo, 2002). The three major provitamin A carotenoids are α-carotene, β-carotene and β-cryptoxanthin and all have at least one unsubstituted β-ionone ring (Tanumihardjo, 2002). Data on levels in foods are only available for these three carotenoids (IOM, 2001). Some provitamin A carotenoids can be cleaved in the small intestine to become retinol or they may be absorbed intact (Perrotta, et al., 2003). It has been estimated that 6-12 times more dietary β-carotene is required to meet the nutritional equivalent of vitamin A (IOM, 2001). For other provitamin A carotenoids, at least 12 times the amount of retinol is required to ensure the equivalent value of vitamin A is met (see figure 2) (Perrotta, et al., 2003).

![Figure 2. Bioconversion of the different provitamin A carotenoids and their vitamin A equivalency value (IOM, 2001).](image)

**Function of Vitamin A (Retinol)**

4. The 11-cis-retinaldehyde (retinal) form of vitamin A is fundamental for the transduction of light into neural signals within the eye, resulting in vision. The retinoic acid form is also active within the eye, however it serves to maintain normal differentiation of the cornea (IOM, 2001). Vitamin A also plays key roles in embryonic development and the immune response (IOM, 2001). In addition, vitamin A
metabolites, such as retinoic acid, play a role in the controlling of gene expression (EVM 2003).

**Vitamin A Measurements**

5. Vitamin A is expressed either as international units (IU) or 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 vitamin A and provitamin A carotenoids and is now the widely accepted unit based on a recommendation of the Food Agricultural Organisation (FAO) and World Health Organisation (WHO) (EVM, 2002). For consistency, RE is used in this paper. 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 tables 1 and 2). RE can only be calculated with certainty if it is known what proportions of preformed vitamin A, provitamin A carotenoids and other vitamin A precursors are in a specified diet.

Table 1: The widely accepted conversion factors for vitamin A (Perrotta, et al., 2003)

<table>
<thead>
<tr>
<th>1 RE</th>
<th>1.00 µg retinol</th>
<th>1.78 µg retinyl palmitate</th>
<th>6.00 µg β-carotene</th>
<th>12.00 µg other provitamin A carotenoids</th>
<th>3.33 IU vitamin A activity as retinol</th>
<th>10.00 IU vitamin A activity as β-carotene</th>
</tr>
</thead>
</table>

Table 2: The vitamin A activity (in IU and RE) of the three main retinoid compounds (EVM, 2003)

<table>
<thead>
<tr>
<th>Retinoid compound</th>
<th>Vitamin A activity in IU</th>
<th>Vitamin A activity in RE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol (1 mg or 1000 µg)</td>
<td>3330</td>
<td>1000</td>
</tr>
<tr>
<td>Retinyl acetate (1 mg or 1000 µg)</td>
<td>2900</td>
<td>870</td>
</tr>
<tr>
<td>Retinyl palmitate (1 mg or 1000 µg)</td>
<td>1830</td>
<td>550</td>
</tr>
</tbody>
</table>
This is a draft statement for discussion. It does not reflect the views of the Committee and should not be cited.

The reference nutrient intakes\(^3\) (RNIs) established for vitamin A are shown in Table 3.

**Table 3: The RNIs for vitamin A (µg RE/day)**

<table>
<thead>
<tr>
<th>Age category</th>
<th>RNI (in µg RE/day)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 12 months old</td>
<td>350</td>
<td>SACN (2005)</td>
</tr>
<tr>
<td>1 – 6 years old</td>
<td>400</td>
<td>Department of Health (1991)</td>
</tr>
<tr>
<td>7 – 10 years old</td>
<td>500</td>
<td>Department of Health (1991)</td>
</tr>
<tr>
<td>11 – 14 years old</td>
<td>600</td>
<td>Department of Health (1991)</td>
</tr>
<tr>
<td>Women (including girls from 11 years old)</td>
<td>600</td>
<td>SACN (2005)</td>
</tr>
<tr>
<td>Men (including boys from 15 years old)</td>
<td>700</td>
<td>SACN (2005)</td>
</tr>
</tbody>
</table>

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

6. In 1990, the Chief Medical Officer issued a letter to all doctors in the UK advising pregnant women, or those who may become pregnant, to refrain from self-medication with vitamin A supplementation. It was also advised to remove liver or liver-based products from the diet (Hansard, 1990). 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).

7. For infants it is advised that liver should be avoided if solid foods are introduced before 6 months (DH, 2012; Caroline Walker Trust, 2011a). After 6 months of age, it is recommended that children do not have more than one portion of liver per week because it can be harmful in large amounts (Caroline Walker Trust, 2011a).

8. The Department of Health recommends that all children from six months to five years old are given supplements, in the form of vitamin drops (NHS Choices, 2011). These drops include vitamin A. There is strong advice to keep to the recommended dose stated on the label and to not give two supplements at the same time.

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\(^3\) The Reference Nutrient Intake (RNI) is the amount of a nutrient that is considered sufficient to meet the requirements of 97.5% of the population.
Hazard identification and Characterisation

Biochemistry and Toxicokinetics

9. Vitamin A ingested by humans as retinyl esters or as provitamin A carotenoids can undergo a series of enzymatic reactions before being transported into the bloodstream (Biesalski and Nohr, 2004). In the western diet, >70% of vitamin A is derived from preformed vitamin A whereas <30% of vitamin A is derived from provitamin A carotenoids (Tang, 2010). Fat-soluble vitamins, including vitamin A, are actively transported across the placenta towards the end of pregnancy (Leaf, 2007). If vitamin A levels are adequate, 90% of the total amount is located in the liver (IOM, 2001).

Figure 3: Schematic diagram of the pathways of preformed vitamin A and provitamin A carotenoid absorption as it moves from food into the intestinal wall (adapted from Tanumihardjo, 2002).

Preformed Vitamin A Uptake

10. Approximately 80% of preformed vitamin A is absorbed if an individual consumes sufficient levels of fat (EVM, 2003). There are contradicting reports on whether dietary fat increases absorption of vitamin A (Borel, et al., 1997; Reddy and
Srikantia, 1966). Jayarajan and co-workers (1980) found that adding 5g of fat into the diet significantly improved serum vitamin A concentrations among malnourished children.

11. Dietary retinyl ester is converted to retinol by the actions of pancreatic triglyceride (TG) lipase and intestinal brush border phospholipase B (During and Harrison, 2007). Retinol is subsequently taken up by enterocytes, where some is re-esterified (EVM, 2003). The reformed retinyl esters are then transferred into chylomicra before they are released into the lymph circulation. Once in circulation, the chylomicra are broken down by serum lipases, resulting in release of the retinyl esters (EVM, 2003). Free retinyl esters are then re-hydrolysed in hepatocytes and stored as retinol in the body’s fat storing stellate cells (EVM, 2003). Retinol not re-esterified in enterocytes is released into the portal circulation (During and Harrison, 2007).

Provitamin A Carotenoid Uptake

12. Provitamin A carotenoids not converted to retinol can be taken up unchanged. The absorption of β-carotene has been reported to be in the region of 9 to 22%, based on 3 studies in which single doses ranging from 45 µg to 39 mg were administered (Blomstrand and Werner, 1967; Goodman, et al., 1966; Novotny, et al., 1995). IOM (2001) reported that absorption decreases as the amount of provitamin A carotenoids increases.

13. Provitamin A carotenoids are dissolved in lipid droplets, if available, in the stomach and pass into the duodenum, where they are taken up into micelles (Tanumihardjo, 2002). Tanumihardjo (2002) commented that micelles have a finite capacity for provitamin A carotenoid incorporation which may indicate poor uptake regardless of the availability of high concentrations of provitamin A carotenoids. Li and Tso (2003) also commented that a saturable process may occur in mucosal cells when there is an increased concentration of provitamin A carotenoids. Like retinyl esters, provitamin A carotenoids are then taken up by enterocytes and can follow a number of different pathways (Tanumihardjo, 2002). The provitamin A carotenoids can either be transported intact into the lymphatic system or be transformed into retinal or retinol and follow the outcomes as previously discussed (Tanumihardjo, 2002). Goodman et al., (1966) observed that 60-70% of labelled β-carotene fed to humans was converted to retinyl esters whereas approximately 30% remained as β-carotene. Nonhydrolysed carotenoids are transported to the liver in chylomicrons where they will be stored (IOM, 2001).

14. The majority of β-carotene conversion to retinal and subsequent reduction to retinol takes place in the intestinal mucosa, with a much smaller percentage occurring in other tissues (Tang, 2010). The enzymes β-carotene 15,15'-monooxygenase (BCMO1) and retinaldehyde reductase are responsible for converting β-carotene to retinol (During and Harrison, 2007).
Factors that Affect Provitamin A Carotenoid Bioavailability and Bioconversion

15. A number of factors affect the bioavailability and bioconversion of provitamin A carotenoids. In 1996, de Pee and West penned the term SLAMENGHI to represent the main factors to affect provitamin A carotenoid bioavailability (Bender, 2003). They are:
   - Species of carotenoid
   - Linkages to alkyl groups
   - Amount in a meal
   - Matrix properties of the plant in which the carotenoid is incorporated
   - Effectors of absorption and bioconversion
   - Nutrition status
   - Genetic factors/predisposition
   - Host-related factors
   - Interaction between factors

16. Bioconversion of dietary provitamin A carotenoids to retinol was recently reviewed by Tang et al. (2010) who noted that methods to assess both the bioavailability and bioconversion had improved over the previous 10 years. The conversion rate is influenced by three main factors; (1) food matrices, (2) food preparation and (3) the fat content of the food (Tang, 2010).

17. A study by Ribaya-Mercado et al., (2007) assessed the impact of dietary fat on the bioavailability and bioconversion of provitamin A carotenoids in Filipino schoolchildren in order to identify how vitamin A status could be improved. They concluded that a minimum fat content of 2.4g in a meal rich in provitamin A carotenoids enhances the absorption of provitamin A carotenoids (Ribaya-Mercado, et al., 2007). Tanumihardjo (2002) reported that dietary fibre decreases β-carotene absorption. Alcohol consumption can also decrease β-carotene absorption but the mechanism is unclear (Tanumihardjo 2002).

18. The ability to convert provitamin A carotenoids to vitamin A is also influenced by single nucleotide polymorphisms (SNPs) in the gene for the BCMO1 enzyme, which converts β-carotene to retinal. Three polymorphisms reduced the activity of BCMO1 in female volunteers by 59, 51, and 48%, respectively (Lietz, et al., 2010).

Excretion

19. Vitamin A excretion is mainly via the kidneys. Oxidised vitamin A compounds are excreted in the urine (EVM 2003). If vitamin A compounds are conjugated with glucuronic acid they can also be excreted in bile (EVM 2003).

Toxicity

20. Newborn infants generally show liver vitamin A concentrations of ≤ 20 µg RE/g (Olson, et al., 1984). The majority of children are born with low levels of vitamin A however these levels are increased during the first six months of life (Olson, et al., 1984).
21. Toxicity appears to arise when the amount of vitamin A present exceeds the amount of retinol binding protein (RBPs), and as a result free retinol binds to lipoproteins (Bendich and Langseth, 1989). Preformed vitamin A can lead to acute toxicity whereas 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, 2002). The European Union Scientific Committee on Food (SCF) noted that the toxicity of provitamin A carotenoids is different to that of retinoids. Consequently, dietary β-carotene and other provitamin A carotenoid intake would not contribute significantly to the toxicity of high intakes of vitamin A (SCF, 2002).

**Acute Toxicity**

22. Vitamin A excess, known as hypervitaminosis A, can occur when large amounts of liver and/or retinol supplements are consumed, although acute adverse effects from dietary sources of vitamin A are rare (EVM, 2002). Commonly observed signs and symptoms of acute toxicity include nausea, vomiting, lethargy, abdominal pain, anorexia, blurred vision, irritability and headaches (Penniston and Tanumihardjo, 2006). Bulging of the fontanelles occurs in neonates and in infants (Penniston and Tanumihardjo, 2006). Body size, weight, dietary factors and general health are all crucial factors in determining the onset of acute toxicity (Bendich and Langseth, 1989). Hypervitaminosis is considered a very minor problem with only an estimated 200 cases worldwide, annually (Perrotta, et al., 2003).

23. Acute toxicity occurs at doses in excess of 100,000 µg RE/day in adults and 10,000 µg RE/day in children (Perrotta, et al., 2003). EVM reported that infants below the age of 6 months have shown symptoms associated with acute toxicity following a single dose of 7,500-15,000 µg RE/day, whereas infants aged 6-9 months generally appeared to tolerate single doses of 30,000 µg RE/day (EVM 2003). Whilst it cannot be assumed that results from studies in which experimental animals are given high doses of a vitamin can be extrapolated to humans, Macapinalac and Olson (1981) reported a median lethal dose (LD50) in young monkeys of approximately 560,000 IU/kg bodyweight (bw), equivalent to 168,000 RE/kg bw.

24. A fatal case of vitamin A overdose has been reported, in which a newborn baby accidentally received an aqueous solution containing approximately 27,000 µg RE/day for 11 days (Bendich and Langseth, 1989).

**Chronic Toxicity**

25. Chronic vitamin A toxicity is more common than acute toxicity (Perrotta, et al., 2003). Common signs and symptoms of chronic vitamin A toxicity include chronic headache, intracranial hypertension and alopecia as well as adverse effects on the skin (thickening and cracking of the lips), eyes (conjunctivitis), bone (reduced mineral density and joint pain) and liver (hepatotoxicity) (EVM, 2003; (Penniston and Tanumihardjo, 2006).
26. Toxicity has been reported to occur in infants given 6,600 – 20,000 µg RE/day of vitamin A within approximately 3 weeks, mainly as a result of vitamin A supplement abuse rather than from ingestion of food sources (Perrotta, et al., 2003). Vitamin A levels quickly return to normal range if high intake is ceased (Bendich and Langseth, 1989). Lasting effects such as bone malformations and cirrhosis may rarely be associated with chronic hypervitaminosis A (Perrotta, et al., 2003).

27. A case of bulging fontanelles, dry skin and hepatosplenomegaly was reported in a 3 month old infant who had been prescribed an aqueous solution of vitamin A palmitate 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). Twin 7 month old infants were identified as having chronic vitamin A toxicity symptoms as a result of consuming 120 g of homogenised chicken liver every day for four months (Mahoney, et al., 1980). From 3 months old, they were fed chicken liver twice daily, which was initially about 60 grams per day but soon increased to 120 grams per day. It was estimated that the twins received approximately 36,000 IU (12,100 µg RE) per day from the liver alone. Both twins developed irritability, vomiting and bulging anterior fontanelles. Computed tomograms (CT) of the brain showed enlarged ventricles in both infants and dilated subarachnoid spaces in one.

28. The SCF (2002) identified 7,500 µg RE/day (as a single dose in infants) as the lowest dose possible to result in adverse effects (bulging fontanelle) in infants. This was observed in the Baqui et al (1995) study which assessed the safety of vitamin A supplementation in early infancy. It was a randomised, double-blind placebo controlled trial which included one hundred and sixty-seven infants. The infants 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. Nine infants supplemented with vitamin A had episodes of bulging of the fontanelle (Baqui et al, 1995).

29. The SCF (2002) also identified the lowest possible doses of vitamin A that resulted in four other adverse effects. The effect of hepatotoxicity has been identified if 7,500 µg RE/day is received for six years. The same would also apply for changes to lipid metabolism as this has been observed at 7,500 µg RE/day over a four year period.

30. The SCF (2002) also identified 1,500 µg RE/day for decreased bone density/increased bone fracture in women aged 40-76 and 3,000 µg RE/day for teratogenicity.

**Teratogenicity**

31. Retinol was identified as a teratogen in 1985 when isotretinoin, a retinoid, was prescribed for certain skin disorders (EVM, 2002). Severe malformations of the heart, thymus, face, jaw, ears, palate and brain were some of the characteristics 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).
32. Rothman et al., (1995) reported a study in which approximately 23,000 pregnant women answered a questionnaire aiming to identify vitamin A intake via the diet and supplements. Of the children born, 339 were classified as having a birth defect, with 121 malformations classified to be of cranial-neural-crest origin (Rothman et al., 1995). 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 Rothman et al., (1995) study has been criticised because only 76.5% of pregnancy outcomes were assessed by physicians, with the remaining information being provided by the mother (SCF, 2002).

33. Mastroiacovo et al, (1999) collected data from 423 newborn babies whose mothers were previously exposed to high doses of vitamin A (3000, 7500, 9000 and 15,000 µg RE/day) during pregnancy. Malformations were reported in only 3 of the babies. No abnormalities were observed in women whose intake exceeded 15,000 µg RE/day (Mastroiacovo, et al., 1999). The UK Expert Group on Vitamins and Minerals (EVM) concluded that a precise threshold for any teratogenic effects is uncertain, but that it was prudent to assume it could be 3000 µg RE/day (EVM, 2002).

**Allergenicity**

34. Vitamin A plays an integral role in the function of the immune system, and available evidence does not indicate a risk of allergenicity.

**Tolerable Upper Intake Level**

35. 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 identifiable in middle aged and elderly women, and teratogenicity being relevant for women of child bearing age. The lowest doses for hepatotoxicity and 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 4.

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

<table>
<thead>
<tr>
<th>Effect</th>
<th>Lowest dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulging fontanelles</td>
<td>7,500 µg RE, single dose (based on Baqui et al., 1995)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>7,500 µg RE/day for 6 years (based on Kowalski et al., 1994)</td>
</tr>
<tr>
<td>Lipid metabolism (minor change)</td>
<td>7,500 µg RE/day for 4 years (based on Cartmel et al., 1999)</td>
</tr>
<tr>
<td>Decreased bone density/increased bone fracture</td>
<td>1,500 µg RE (analyses do not show a threshold) (based on Melhus et al., 1998)</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>&gt;3,000 µg RE/day (based on Rothman et al., 1995)</td>
</tr>
</tbody>
</table>
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36. Table 5 shows the tolerable upper intake levels (ULs\textsuperscript{4}) for preformed vitamin A established by the SCF for different age groups. The UL of 3000 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 3000 µg RE/day for adults, on the basis of body weight and difference in basal metabolic rate (SCF, 2002). Using this scaling (body weight\textsuperscript{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 1 year was not proposed.

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Tolerable Upper Intake Level for preformed vitamin A (retinol and retinyl esters) (µg RE/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>800</td>
</tr>
<tr>
<td>4-6</td>
<td>1100</td>
</tr>
<tr>
<td>7-10</td>
<td>1500</td>
</tr>
<tr>
<td>11-14</td>
<td>2000</td>
</tr>
<tr>
<td>15-17</td>
<td>2600</td>
</tr>
<tr>
<td>Adults</td>
<td>3000</td>
</tr>
</tbody>
</table>

37. A UL of 600 µg RE/day 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 (which IOM identified as the lowest dose associated with bulging fontanelle) with an uncertainty factor (UF) of 10. The UF of 10 was “selected to account for the uncertainty of extrapolating a LOAEL to a NOAEL for a nonsevere and reversible effect (i.e., bulging fontanelle) and the interindividual variability in sensitivity”.

38. The metabolic scaling approach has been applied using the bodyweights of UK children as shown in Table 6. The calculated values are very similar to those established by the SCF. An additional age category for infants aged 6 months to 1 year of age was also calculated. Upon extrapolating the 3000 µg RE/day for adults, the calculated UL for 6 months – 1 year old infants equals 589 µg/RE per day, which is very similar to the 600 µg/RE per day established by the IOM. The COT therefore concluded that a UL of 600 µg/RE per day should be applied in considering the vitamin A intakes of infants.

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\textsuperscript{4} 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.
This is a draft statement for discussion. It does not reflect the views of the Committee and should not be cited.

Table 6: Calculated upper intake levels for different UK age groups.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Body weight (Kg) (NDNS reported body weights)</th>
<th>Source</th>
<th>(Bodyweight (Kg))^{0.75}</th>
<th>UL (µg RE/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 – 1</td>
<td>8.7</td>
<td>Mills and Tyler (1992)</td>
<td>5.06</td>
<td>589</td>
</tr>
<tr>
<td>1-3</td>
<td>14</td>
<td>Gregory et al., (1995)</td>
<td>7.24</td>
<td>843</td>
</tr>
<tr>
<td>4-6</td>
<td>21</td>
<td>Gregory et al., (2000)</td>
<td>9.81</td>
<td>1143</td>
</tr>
<tr>
<td>11-14</td>
<td>53</td>
<td>Gregory et al., (2000)</td>
<td>19.64</td>
<td>2289</td>
</tr>
<tr>
<td>Adults (19+)</td>
<td>76</td>
<td>Henderson et al., (2002)</td>
<td>25.74</td>
<td>3000</td>
</tr>
</tbody>
</table>

* The ULs are calculated for the specific age groups by using 3000 and dividing by the bodyweight\^{0.75} of an adult (25.74) and multiplying by the relevant bodyweight\^{0.75} for that age group.

Occurrence of Vitamin A

Breast Milk

39. The highest concentrations of vitamin A in breast milk are found up to 10 days after birth. Average vitamin A levels in colostrum (0-3 days) in developed countries are approximately 100 µg RE/100 ml (Underwood, 1994). The range of vitamin A levels in the mature breast milk of well-nourished women in Europe is 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).

40. There is limited information on the impact vitamin A supplementation has upon levels of vitamin A in breast milk in a Western population. Although there is no data, it is likely that the vitamin A content in breast milk will increase slightly if a mother takes a daily vitamin A supplement, despite recommendations that breastfeeding mothers can acquire all their vitamin A needs from the diet alone.

Infant Formula

41. Infant formula typically contains a higher concentration of several micronutrients than does breast milk, partly to account for the fact that absorption of breast milk is greater than infant formula, but also to allow for losses during storage (Bender, 2003). Major brands of infant formula 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) per 100 ml and infants should be given 500-600 ml per day (Caroline Walker Trust 2011b). The vitamin A compositional requirements in both infant formula and follow on formula are the same as stated by the Infant formula and follow-on formula (England) regulations. The minimum content is 60 µg RE/100ml and the maximum is 180 µg RE/100ml (Caroline Walker Trust, 2011b).

**Food**

42. Preformed vitamin A (retinol and retinyl esters) are found in the following foods at the stated concentrations; liver (approximately 3500 µg RE/kg), fortified margarine (approximately 330 µg RE/kg) and dairy products (90-300 µg RE/kg) (EVM 2003). Provitamin A carotenoids are found in the following stated concentrations: carrots (approximately 1500 µg RE/kg), spinach (approximately 795 µg RE/kg), melon (approximately 784 µg RE/kg) and broccoli (approximately 146 µg RE/kg). As noted in paragraphs 12 and 13, the absorption of provitamin A carotenoids is lower than preformed vitamin A therefore uptake is likely to be lower than the levels shown for provitamin A carotenoids.

**Supplements**

43. There are numerous multivitamin supplements on the UK market that are marketed for pre-term infants and infants aged 0-12 months. The vitamin A content provided from a recommended daily dose of listed multivitamin supplements are as follows (in order of recommended daily dose) (Leaf, 2007):

- 66.5 µg RE/day (3-6 months)
- 100 µg RE/day (1-4 months)
- 133 µg RE/day (7 months to 5 years)
- 200 µg RE/day (4 months to 4 years)
- 233 µg RE/day (1 month to 5 years)
- 300 µg RE/day (4 months to 12 months)
- 757 µg RE/day (6 weeks to 12 months)

The majority of supplements are in the form of retinyl palmitate and some are in acetate form. Retinyl acetate exert a much higher vitamin A activity in RE than the palmitate therefore the dose in acetate preparations are usually lower to account for that (see table 2). Leaf (2007) noted that it is recommended to double a 200 µg RE dose if this particular product is prescribed to pre-term infants.

**Exposure**

**Exclusively Breastfed**

44. Estimates of average and high level consumption of breastmilk or infant formula before weaning are 800 ml and 1,200 ml, respectively (see e.g. EFSA, 2012). Based on these consumption figures and the upper end of the reported range
of vitamin A in breastmilk from developed countries (70 µg RE/100 ml), vitamin A intake of exclusively breast-fed infants aged 0-6 months would be 560 and 840 µg RE/day for average and high level consumption, respectively.

**Infant Formula**

45. For UK infant formula with a vitamin A concentration at the upper end of the reported range (82 µg RE/100 ml (Leaf, 2007)), average and high level consumption of 800 or 1200 ml/day would result in intakes of 656 or 981 µg RE/day. The maximum amount that can be added to infant formula is 180 µg vitamin A (RE) per 100 ml, which would result in an intake of 1440 or 2160 µg RE/day for average and high level consumption, respectively.

46. Given that a typical pack of follow-on formula for infants aged 6-12 months contains 75 µg vitamin A (RE) per 100 ml, 600 ml would provide the 6-12 month old infant with 450 µg RE/day, before taking into account consumption of solid foods. The maximum amount that can be added to follow-on formula is 180 µg vitamin A (RE) per 100 ml. If 600 ml per day is consumed, the intake would be 1080 from the follow-on formula alone, before taking into consideration any additional intake from supplements and complementary foods.

**Weaning Diet**

47. From a 1986 survey by the Ministry of Agriculture, Fisheries and Food (MAFF) on 488 6-12 month old infants, in which mothers completed a food diary on their baby’s diet, a mean total vitamin A intake of 765 µg RE/day was estimated, of which 200 µg RE/day (approximately 34%) was from infant formula. Significant contributions also came from milk and milk products (23%) and meat (largely liver and foods containing liver) (17%) (MAFF, 1992). It should be noted that the UK Government advice on liver consumption by infants was introduced after this survey was conducted. The estimated daily intakes and average are shown in Table 7 (MAFF, 1992).

**Table 7: Estimated vitamin A intakes (µg RE/day) by age and sex (MAFF, 1992)**

<table>
<thead>
<tr>
<th></th>
<th>6-9 months</th>
<th>Males 9-12 months</th>
<th>6-12 months</th>
<th>6-9 months</th>
<th>Females 9-12 months</th>
<th>6-12 months</th>
<th>Infants 6-12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>816</td>
<td>711</td>
<td>771</td>
<td>784</td>
<td>769</td>
<td>759</td>
<td>765</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>733</td>
<td>593</td>
<td>685</td>
<td>678</td>
<td>617</td>
<td>655</td>
<td>670</td>
</tr>
<tr>
<td><strong>Lower 2.5%</strong></td>
<td>298</td>
<td>209</td>
<td>254</td>
<td>295</td>
<td>284</td>
<td>291</td>
<td>282</td>
</tr>
<tr>
<td><strong>Upper 2.5%</strong></td>
<td>1757</td>
<td>1840</td>
<td>1800</td>
<td>1871</td>
<td>2653</td>
<td>1976</td>
<td>1873</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>404</td>
<td>396</td>
<td>403</td>
<td>389</td>
<td>605</td>
<td>510</td>
<td>463</td>
</tr>
<tr>
<td><strong>Number of Infants</strong></td>
<td>130</td>
<td>96</td>
<td>226</td>
<td>128</td>
<td>134</td>
<td>262</td>
<td>488</td>
</tr>
</tbody>
</table>
This is a draft statement for discussion. It does not reflect the views of the Committee and should not be cited.

Estimates of retinol and β-carotene intake values are shown in Annex C. The RE was calculated in the above table by adding the individual β-carotene and retinol values together as follows:

- Retinol (µg) sum of trans retinol + (0.75 x cis-retinol) + (0.9 x retinaldehyde) + (0.4 x dehydroretinol)
- Carotene (µg) largely as β-carotene

Calculation of RE (µg) = \( \text{retinol} + \frac{\beta\text{-carotene}}{6} \)

48. One quarter of the estimated average vitamin A intake from food (excluding supplements) of infants aged 6-12 months was from carotene, with the remainder from retinol as seen below:

\[
\text{Retinol (581 µg) + β-carotene (1104 µg) } = \frac{765}{6} \text{ µg RE/day}
\]

\[
100 / 765 \text{ µg RE (mean vitamin A) x 581 µg (retinol) } = 75.9 \% \text{ of retinol (\( \approx \) 24.1 } % \text{ of β-carotene).}
\]

49. The estimated average daily intakes of vitamin A from different food types in infants aged 6-12 months are shown in table 8 (MAFF, 1992).

**Table 8: Average daily intakes of vitamin A from food types for infants (aged 6-12 months) who received supplements and those who did not (MAFF, 1992)**

<table>
<thead>
<tr>
<th>Food Type</th>
<th>Vitamin A (µg RE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infants taking</td>
</tr>
<tr>
<td></td>
<td>supplements</td>
</tr>
<tr>
<td>Commercial baby food</td>
<td>104</td>
</tr>
<tr>
<td>Breast milk</td>
<td>32</td>
</tr>
<tr>
<td>Infant formulas</td>
<td>174</td>
</tr>
<tr>
<td>Cows' milk</td>
<td>150</td>
</tr>
<tr>
<td>Family foods</td>
<td>309</td>
</tr>
</tbody>
</table>

50. For 6-9 month olds, those taking a multivitamin supplement (47% of the group) received on average an additional 165 µg RE, with total average intake estimated at 933 µg RE. For 9-12 month olds, those taking a multivitamin supplement (40% of group) received on average an additional 168 µg RE, with an estimated average total intake of 936 µg RE (MAFF, 1992).

**The U.S. Feeding Infants and Toddlers Study (FITS) surveys (2002 and 2008)**

51. The Feeding Infants and Toddlers Study (FITS) 2002 survey recorded the food intake of 3,022 U.S. infant and toddlers (aged 4-24 months) over a 24 hour period in order to determine the intake of nutrients and energy, including vitamin A (Fox, et al., 2006). Briefel et al., (2006) assessed the results of the FITS 2002 study for the use of dietary supplements in infants. Some type of dietary supplement was received by 8% of infants aged 4-5 months and by 19% of infants aged 6-11 months. The median and 90th percentile of vitamin A intake in 6-11 month old supplement users were 1,053 and 1,451 µg RE/day, respectively, which was an additional 367
and 480 µg RE/day in comparison to the median and 90th percentile vitamin A intake in non-users (see table 9).

52. The FITS 2008 surveyed usual nutrient intake in 3,273 US infants and toddlers aged 0-47 months. Table 9 shows vitamin A intake distributions between infants aged 0-5 months and 6-11 months. In the survey, 8.8% and 12.6% of infants aged 0-5 months and 6-11 months, respectively, received vitamin A supplementation (Butte, et al., 2010). Similarly, in the US 1999-2002 National Health and Nutrition Examination Survey (NHANES) 8.8% of infants aged 0-11 months (n=1040) received vitamin A supplementation (Picciano, et al., 2007). The actual intakes of vitamin A amongst infants aged 6-11 months may have been lower than those calculated because infants may spill the solids/liquids that are being given to them to consume. Younger infants are also prone to being sick after feeding which could lower actual intake at this age group.

Table 9: Estimates of vitamin A intake of food and beverages (with or without supplementation) from the FITS (2002) and (2008) surveys in the US.

<table>
<thead>
<tr>
<th>Age (Months)</th>
<th>Numbers</th>
<th>Supplement user</th>
<th>Median intake percentile (µg RE/day)</th>
<th>Mean ± Standard Deviation (µg RE/day)</th>
<th>90th intake percentile (µg RE/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 5 (Butte et al, 2010)</td>
<td>382</td>
<td>Y</td>
<td>491</td>
<td>582 ± 18.2</td>
<td>815</td>
</tr>
<tr>
<td>6 -11 (Butte et al, 2010)</td>
<td>505</td>
<td>Y</td>
<td>720</td>
<td>744 ± 8.2</td>
<td>987</td>
</tr>
<tr>
<td>6 – 11 (Briefel et al, 2006)</td>
<td>187</td>
<td>Y</td>
<td>1,053</td>
<td>1,083 ± 21.4</td>
<td>1,451</td>
</tr>
<tr>
<td>6 – 11 (Briefel et al, 2006)</td>
<td>1,208</td>
<td>N</td>
<td>686</td>
<td>707 ± 5.6</td>
<td>971</td>
</tr>
</tbody>
</table>

53. The COT has previously noted that the food consumption data for UK infants were likely to be outdated and that assumptions about feeding patterns may represent an overestimate of food consumption (COT 2003). The Diet and Nutrition Survey of Infants and Young Children (DNSIYC) is a survey that aims to provide detailed, quantitative information on food consumption, nutrient intakes, nutritional status and related characteristics in UK infants and young children living in private households aged between 4 and 18 months. This one-off survey complements the NDNS and the Infant Feeding Survey, sampling the age group falling between the two surveys. The sample collected data for individuals, allowing breakdown by age and analysis of the distribution of intakes within the population. The publication of the final DNSIYC report is anticipated by February 2013.
Predictions for High Level Intakes from Liver and other Food Sources

54. It is currently advised by the Department of Health (DH) that mashed and soft food should be introduced at 6 months of age. Cooked vegetables (such as parsnip, potato, sweet potato or carrot), mashed banana, avocado, pear or cooked apple are recommended as suitable weaning foods. Some of these foods are a good source of β-carotene. Once the infant is comfortable, the infant can be offered different foods such as meat, fish, pasta, noodles, bread, chapatti, lentils, mashed rice, low sugar 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 food can be introduced (DH, 2012).

55. Mashed carrot is a popular choice for 6-12 month olds, which made up 10% of total RE intake in the 2002 FITS survey of US infants (Fox, et al., 2006). Based on this, 10% of a total intake of 987 (90th intake percentile for 6-12 month old infants, Butte et al, 2010) would give an intake of vitamin A intake from carrot consumption at approximately 98 µg RE/day.

56. Liver consumption is not completely discouraged above the age of 6 months. Consumption data are not available for UK infants. An iron rich meal containing 125 g of chicken liver is listed on a homemade baby food recipe website (Homemade baby food recipes 2012). 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. This recipe could provide about 5000 µg RE/day from the chicken liver alone. If this is consumed over the course of a week, averaged intake from this source would be in the region of 720 µg RE/day, before taking into account other dietary sources. 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.

57. Tables 10 to 13 summarise the potential exposure scenarios described above at age 0-6 and 6-12 months.

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http://www.homemade-baby-food-recipes.com/baby-dinner-recipes.html
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Table 10: The estimated exposure of infants aged ~0-6 months to vitamin A (before the introduction of weaning foods)

<table>
<thead>
<tr>
<th></th>
<th>Breastfed infant</th>
<th>Formula fed infant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average consumer (800 ml)</td>
<td>High level consumer (1200 ml)</td>
</tr>
<tr>
<td>µg RE per day from milk</td>
<td>600</td>
<td>900</td>
</tr>
<tr>
<td>µg RE per day from a recommended supplement</td>
<td>233</td>
<td>233</td>
</tr>
<tr>
<td>Estimated total µg RE per day</td>
<td>833</td>
<td>1133</td>
</tr>
</tbody>
</table>

Table 11: The estimated exposure of infants aged ~6-12 months continuing to be fed on breast milk

<table>
<thead>
<tr>
<th></th>
<th>Average consumer (800 ml)</th>
<th>High level consumer (1200 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg RE per day from milk</td>
<td>600</td>
<td>900</td>
</tr>
<tr>
<td>µg RE per day from a recommended supplement</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>µg RE per day from other weaning food</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>µg RE per week from one portion of liver</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td>Estimated total µg RE per week</td>
<td>9900</td>
<td>12000</td>
</tr>
<tr>
<td>Estimated total µg RE per day</td>
<td>1414</td>
<td>1714</td>
</tr>
</tbody>
</table>

Table 12: The estimated exposure of infants aged ~6-12 months fed infant formula

<table>
<thead>
<tr>
<th></th>
<th>Average consumer (800 ml)</th>
<th>High level consumer (1200 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg RE per day from milk</td>
<td>656</td>
<td>981</td>
</tr>
<tr>
<td>µg RE per day from a recommended supplement</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>µg RE per day from other weaning food</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>µg/RE per week from one portion of liver</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td>Estimated total µg RE per week</td>
<td>10292</td>
<td>12567</td>
</tr>
<tr>
<td>Estimated total µg RE per day</td>
<td>1470</td>
<td>1795</td>
</tr>
</tbody>
</table>
Table 13: The estimated exposure of infants aged ~6-12 months fed follow-on formula

<table>
<thead>
<tr>
<th>Recommend level of intake (600 ml)</th>
<th>µg RE per day from milk</th>
<th>450</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg RE per day from a recommended supplement</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>µg RE per day from other weaning food</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>µg RE per week from one portion of liver</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td>Estimated total µg RE per week</td>
<td>8850</td>
<td></td>
</tr>
<tr>
<td>Estimated total µg RE per day</td>
<td>1264</td>
<td></td>
</tr>
</tbody>
</table>

58. The highest estimated daily intake of vitamin A for a high level consumer fed infant formula when weaning foods are introduced is 1795 µg RE/day. This includes a daily supplement and one portion of liver per week. This amount is similar to the 1900 µg RE/day of high level intakes as identified in the MAFF (1992) survey.

**Risk Characterisation**

59. Estimates of vitamin A intake by exclusively breast-fed infants are in the region of 600 and 900 µg RE/day for average and high level consumption. Exclusively formula-fed infants could have slightly higher levels, in the region of 1000 µg RE/day.

60. Estimates of vitamin A intake for UK infants following introduction of solid foods are based on data from the 1980s and it is unclear whether they would be representative of current intake. It should also be noted that the survey required mothers to complete a food diary of the foods and supplements their child had therefore it may be an overestimate of actual uptake of nutrients, including vitamin A. Nevertheless they indicate mean and high level intakes in the region of 800 and 1900 µg RE/day, respectively. These data are supported by more recent data from the USA.

61. Thus exposure of some infants exceeds the UL of 600 µg RE/day. Use of dietary supplements and/or the consumption of foods containing liver have the potential to further increase the intakes.

**Conclusions**

62. [To be drafted after COT discussion].
This is a draft statement for discussion.  
It does not reflect the views of the Committee and should not be cited.

References


Caroline Walker Trust (2011a) Eating well. First Year of Life. URL: [http://www.firststepsnutrition.org/pdfs/First%20Year%20of%20Life%20Practical%20Guide.pdf](http://www.firststepsnutrition.org/pdfs/First%20Year%20of%20Life%20Practical%20Guide.pdf)


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URL: http://www.food.gov.uk/multimedia/pdfs/reviewvita.pdf


URL: http://www.nap.edu/catalog.php?record_id=10026


URL: http://www.nap.edu/openbook.php?record_id=1577&page=R3
This is a draft statement for discussion.
It does not reflect the views of the Committee and should not be cited.

Hansard (1990) Vitamin A. The CMO statement.
URL: http://hansard.millbanksystems.com/written_answers/1990/oct/18/vitamin-a


Mills A and Tyler, H (1992) Food and Nutrient Intakes of British Infants Aged 6-12 months. HMSO. London


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This is a draft statement for discussion.
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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCMO1</td>
<td>β-carotene 15, 15’ monooxygenases</td>
</tr>
<tr>
<td>COMA</td>
<td>Committee on Medical Aspects of Food Policy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomograms</td>
</tr>
<tr>
<td>DH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>DRV</td>
<td>Dietary Reference Values</td>
</tr>
<tr>
<td>EVM</td>
<td>The UK Expert Group on Vitamins and Minerals</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agriculture Organization of the United Nations</td>
</tr>
<tr>
<td>FITS</td>
<td>Feeding Infants and Toddlers Study</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>LD₅₀</td>
<td>Median Lethal Dose</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Lowest Observed Adverse Effect Level</td>
</tr>
<tr>
<td>MAFF</td>
<td>Ministry of Agriculture, Fisheries and Food</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No Observed Adverse Effect Level</td>
</tr>
<tr>
<td>RBP</td>
<td>Retinol Binding Protein</td>
</tr>
<tr>
<td>RDA</td>
<td>Recommended Daily Allowance</td>
</tr>
<tr>
<td>RE</td>
<td>Retinol Equivalent</td>
</tr>
<tr>
<td>RNI</td>
<td>Reference Nutrient Intake</td>
</tr>
<tr>
<td>SACN</td>
<td>Scientific Advisory Committee on Nutrition</td>
</tr>
<tr>
<td>SCF</td>
<td>The European Union Scientific Committee on Food</td>
</tr>
<tr>
<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
</tr>
<tr>
<td>TG</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>UL</td>
<td>Upper Level</td>
</tr>
<tr>
<td>VAD</td>
<td>Vitamin A Deficiency</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization of the United Nations</td>
</tr>
</tbody>
</table>
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 –
This is a draft statement for discussion.
It does not reflect the views of the Committee and should not be cited.

- 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
This is a draft statement for discussion.
It does not reflect the views of the Committee and should not be cited.

TOX/2012/34 Annex C

Table A1: Average retinol intakes (µg/day) by age and sex (MAFF, 1992)

<table>
<thead>
<tr>
<th>Retinol (µg)</th>
<th>6-9 months</th>
<th>Males 9-12 months</th>
<th>6-12 months</th>
<th>6-9 months</th>
<th>Females 9-12 months</th>
<th>6-12 months</th>
<th>Infants 6-12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>621</td>
<td>505</td>
<td>571</td>
<td>602</td>
<td>576</td>
<td>589</td>
<td>581</td>
</tr>
<tr>
<td>Median</td>
<td>519</td>
<td>391</td>
<td>475</td>
<td>509</td>
<td>387</td>
<td>441</td>
<td>449</td>
</tr>
<tr>
<td>Lower 2.5%</td>
<td>172</td>
<td>110</td>
<td>140</td>
<td>166</td>
<td>146</td>
<td>158</td>
<td>157</td>
</tr>
<tr>
<td>Upper 2.5%</td>
<td>1507</td>
<td>1681</td>
<td>1581</td>
<td>1708</td>
<td>2533</td>
<td>1813</td>
<td>1707</td>
</tr>
<tr>
<td>SD</td>
<td>388</td>
<td>351</td>
<td>376</td>
<td>380</td>
<td>586</td>
<td>495</td>
<td>444</td>
</tr>
<tr>
<td>Number of Infants</td>
<td>130</td>
<td>96</td>
<td>226</td>
<td>128</td>
<td>134</td>
<td>262</td>
<td>488</td>
</tr>
</tbody>
</table>

Table A2: Average β-carotene intakes (µg/day) by age and sex (MAFF, 1992)

<table>
<thead>
<tr>
<th>β-carotene (µg)</th>
<th>6-9 months</th>
<th>Males 9-12 months</th>
<th>6-12 months</th>
<th>6-9 months</th>
<th>Females 9-12 months</th>
<th>6-12 months</th>
<th>Infants 6-12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1173</td>
<td>1238</td>
<td>1201</td>
<td>880</td>
<td>1157</td>
<td>1021</td>
<td>1104</td>
</tr>
<tr>
<td>Median</td>
<td>875</td>
<td>968</td>
<td>903</td>
<td>692</td>
<td>908</td>
<td>812</td>
<td>829</td>
</tr>
<tr>
<td>Lower 2.5%</td>
<td>258</td>
<td>184</td>
<td>240</td>
<td>191</td>
<td>156</td>
<td>195</td>
<td>225</td>
</tr>
<tr>
<td>Upper 2.5%</td>
<td>3185</td>
<td>4837</td>
<td>3887</td>
<td>2214</td>
<td>3058</td>
<td>2805</td>
<td>3140</td>
</tr>
<tr>
<td>SD</td>
<td>891</td>
<td>1004</td>
<td>939</td>
<td>639</td>
<td>772</td>
<td>722</td>
<td>834</td>
</tr>
<tr>
<td>Number of Infants</td>
<td>130</td>
<td>96</td>
<td>226</td>
<td>128</td>
<td>134</td>
<td>262</td>
<td>488</td>
</tr>
</tbody>
</table>

The nutrients, which included retinol equivalents, were calculated from the records of food consumption using a specially developed nutrient databank. The values of each nutrient in the databank referred to were originally included in the fourth edition of McCance and Widdowson’s *The Composition of Foods (CoF)* (Paul et al., 1978) and *Immigrant Foods* (Tan et al., 1985). The values were examined again to confirm validity. If more up to date reliable data was available on some of the entries, they would be used in place of the original data in the databank. Where nutrient data failed to exist in some food types, a similar food product was used as an alternative to avoid marking “zero” vitamin A levels.