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

Review of potential risks from vitamin A in the diets of children aged 1 to 5 years and updated exposures for infants

Background

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. SACN is examining the nutritional basis of the advice. The Committee on Toxicity in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants and young children. The reviews will identify new evidence that has emerged since the Government's 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 are being considered in two stages, focusing first on infants aged nought to 12 months, and now on advice for young children aged one to five years.

2. The 2013 COT statement[1] focussed on potential risks from high levels of vitamin A in the diet of infants and is included in Annex A. This discussion paper provides an update for infants and new information for children aged 1 to 5 years. In 2013, the infant age intervals used for expressing exposure were according to the published report of the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH 2013) and were as follows: 4 to <7, 7 to <10 and 10 to<12 and 12 to <19 months. However, following the availability of individual consumption data from DNSIYC exposures in more recent COT papers, including this discussion paper, have been updated and expressed according to the following infant age ranges: 4 to <6, 6 to <9, 9 to <12 months, 12 to <15 and 15 to <18 months.

3. The EC regulations that led to the 2006 Infant Formula and Follow-on Formula (England) regulations, which set out the vitamin A compositional requirements in infant and follow on formula, were amended in 2016 to come into effect in 2020 (European Commission, 2006 and 2016). The amended regulations set out a minimum vitamin A content of 70 µg RE/100 kcal and a maximum vitamin A content of 114 µg RE/100 kcal. The maximum value equates to 77 µg RE/100 mL by applying a conversion ratio of 67 kcal/100mL (FAO/WHO, 2015).

4. Current UK Government guidance regarding vitamin A recommends that, for infants, liver should be avoided if solid foods are introduced before six months. Infants and children over the age of six months should not be given

more than one portion of liver per week. Supplements containing vitamins A, C and D should be given to children aged one to five years (DH 2016).

5. The statutory Healthy Start scheme in the UK provides means-tested nutritional help to pregnant women and families with children under four years old who have a very low income and are in disadvantaged circumstances. It gives vouchers for fruit and vegetables, both cow's and formula milk as well as coupons for Healthy Start vitamin supplements. The amount of vitamin A contained within the daily dose of drops is 233 µg RE. The label includes strong advice to keep to the dose recommended and not to give two supplements at the same time (NHS 2016).

6. The risks associated with exposure to vitamin A are assessed in this discussion paper using the same approach for infants as was taken for the statement[1] in 2013, comparison with the infant-specific tolerable upper intake level (TUL) of 200 µg RE/kg bw/day derived by the COT. This exposure level was based on a LOAEL of 800 µg RE/kg bw/day for an endpoint of bulging fontanelles.

Vitamin A

7. Vitamin A is a group of fat-soluble vitamins which are available from the diet as either preformed vitamin A or provitamin A. High intake of provitamin A is not associated with the same risks as high intake of preformed vitamin A (COT 2013), therefore in line with the previous statement, this discussion paper focuses on preformed vitamin A.

8. Vitamin A is quantified either in international units (IU) or µg retinol equivalents (RE). The total vitamin A content of the diet is usually expressed as RE. For consistency, RE is used throughout this statement. Corresponding IU values can be approximated by multiplying the RE by 3.33; however, this will only be accurate if the vitamin A is entirely in the form of retinol. RE can be calculated with certainty only if the relative amounts of the different forms of preformed vitamin A and provitamin A carotenoids are known.

Toxicity

9. Clinical features of vitamin A toxicity in age groups other than infants include anorexia, alopecia, drowsiness, lethargy, vomiting, liver and bone damage and visual problems (Loughrill 2016). Additional information regarding clinical effects of chronic hypervitaminosis A in children was available in a review by Biesalski (1989) cited by the SCF (2002). Biesalski (1989) stated that a long-term dose of 18000-60000 IU (5405-18018 µg RE/day) vitamin A could be expected to cause toxicity in children. Biesalski also reported that the consequences of chronic hypervitaminosis A in children are dominated by changes in the skeletal system, premature epiphyseal

[1] https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2013/cotstavita

closing, thickening of the cortical regions of long bones and subsequently retarded growth.

10. When considering vitamin A induced hepatotoxicity, the SCF (2002) considered that on a weight basis children were not more sensitive than adults. The lowest continuous daily dose causing hepatotoxicity was 7500 µg RE/day taken by a 45 year old woman over six years. The SCF (2002) established a TUL for adults of 3000 µg RE/day based on teratogenicity data, and considered this to be applicable to all adults as it was only 2.5-fold less than the lowest chronic daily intake associated with hepatotoxicity

11. The SCF (2002) extrapolated TULs for children from the TUL for adults (3000 µg RE/day) with correction for differences in basal metabolic rate using scaling according to body surface area (bodyweight$^{0.75}$), the exact method of scaling was not given in the opinion. The TUL was 800 µg RE/day for children aged 1-3 years and 1100 µg RE/day for children aged 4-6 years.

12. In 2015 the EFSA panel on dietetic products, nutrition and allergies reviewed the dietary reference values for vitamin A. They considered that in adults a liver retinol concentration of 20 µg retinol/g liver maintains plasma retinol concentrations, to provide adequate stores and prevent deficiency. They considered that due to a lack of specific data the same value could be used for infants and children. The value for children is calculated using values specific to children for body weight and liver/body weight ratio and an age specific growth factor. They concluded that average requirements for infants and children up to the age of six years were 190µg RE/day for 7-11 months, 205 µg RE/day for 1-3 years and 245 µg RE/day for 4-6 years. The population reference intakes were 250 µg RE/day for 7-11 months and 1-3 years and 300 µg RE/day for 4-6 year.

13. Due to a lack of data specific to children in the SCF review a literature search was performed. The case reports thought to be most relevant are described below.

Case reports of vitamin A toxicity in children

14. A 4 year old boy presented to the emergency department with a history of lethargy, vomiting, headaches that mainly occurred at night, sores, pain in the legs and feet and a pruritic rash covering the legs and trunk. On examination an enlarged lymph node and a small meatal ulcer was found. Blood tests revealed raised erythrocyte sedimentation rate, C-reactive protein level, aspartate aminotransferase and albumin. An infection was found and the child was treated with oral antibiotics and intravenous fluids, however his condition did not improve. Six days later he was transferred to a different hospital, his condition now included oedema, hepatomegaly and hyperkeratosis and hyperpigmentation. It transpired that the boy had been taking 30000 IU (500 µg/kg bw) of retinol daily for 11 months, then 25000 IU (417 µg/kg bw) daily the month preceding his admission to hospital. These

had been prescribed by a chiropractor to 'build up his strength' as they had identified that he had food allergies. Chronic hypervitaminosis A was diagnosed and the vitamin A was stopped, blood tests showed hypercalcaemia. Three days after admission he was discharged with just some residual tenderness of the soles of his feet. Five weeks later his retinol level was still elevated at 2.17 µmol/L (normal range 0.5-1.5 µmol/L) (Patel et al, 1988).

15. Mendoza *et al* (1988) reported the case of a three year old girl who was failing to thrive. She had a history of two months of pain in her lower extremities, lethargy, erythematous skin that was peeling, a protuberant abdomen and periods of refusing to walk. On examination she was thin, had dry skin and had a head circumference that was at the tenth percentile. All bloods tested were normal. After two weeks she was admitted with ascites and respiratory distress, her abdomen was greatly distended and she had alopecia. Investigations revealed mildly elevated liver enzymes and right pleural effusion. A liver biopsy showed evidence of some sclerosis. On further questioning it was discovered that the child had been given 2730 µg/kg bw/day for one week and then 1365 µg/kg bw/day for six months finishing one month before her presentation. An initial vitamin A level was normal, only when it was repeated after eight weeks was it found to be elevated 838 IU/dL.

16. A boy, 2 years and 9 months old, developed pruritis, xerosis of the skin, sensitivity to light, loss of ambulation and bone pain. X-rays showed thickening of the mid-shaft of one fibula and a bone scan increased uptake of tracer within the femur and fibula. Bloods were normal except for an elevated alkaline phosphatase at 396 IU/L (normal range 70-160 IU/L). On repeated questioning the mother reported that she had been giving the child multivitamins prescribed by a nutritionist. He had been receiving 1903 µg RE/kg bw/day vitamin A for a period of five months for a diarrhoeal disease that did not resolve. The vitamins were stopped and within one week his walking and rash improved, the light sensitivity and lethargy remained for two months. Two weeks after the diagnosis was made the boy's hair started to fall out, it took four months before it started to return (Gamble and Stanley, 1985).

17. A boy, three years old, started to complain of severe pain in his legs. In his first six months his growth was poor and he had persistent otitis media. Radiographs showed that he had new formation of bone on both tibias, femurs and his right radius. He also had hypercalcaemia, a raised intracranial pressure and splayed cranial sutures. The following year otitis returned and his intracranial pressure was still high warranting a ventriculoperitoneal shunt. He then developed alopecia, an exfoliative rash, liver disease and ascites. He died from renal failure associated with pneumonia, coagulopathy and sepsis. Multivitamins containing 2500 IU (750 µg RE) vitamin A had been used intermittently during his first nine months of life and 450 IU (137 µg RE) vitamin A was given in a ten day multivitamin course in his second year. He did however eat chicken liver spread sandwiches (approximately 25g chicken liver fried in fat) two to three times a week. The boy's younger brother who had the same diet reported otitis media, leg pain, nausea and vomiting and

papilledema at the age of two and a half years. His long bones were normal but he had splayed cranial sutures. He was found to be hypercalcaemic. During his third year he developed alopecia, an exfoliative rash, bone pain, hepatomegaly, splenomegaly, pleural effusion and ascites. His serum retinol was found to be 101 µg/dL (normal 30-60 µg/dL) and his retinyl esters 485 µg/dL (normal <7 µg/dL). Samples of three of the brands of chicken liver were tested for vitamin A content and an estimate of the vitamin A content of the chicken liver spread sandwiches was made, the daily intake including other sources was thought to total 15000 IU (4550 µg RE, 283 µg RE/kg bw/day, assuming a bodyweight of 16.1kg [Bates 2014]) (Carpenter *et al*, 1987).

18. Miller and Hayon (1985) reported the case of a three year old with mosaic Down syndrome who was admitted to hospital for pneumonia. He had developed muscle spasm, discomfort on standing and abdominal pain in the preceding week. The child had desquamation of the skin and alopecia, blood tests revealed elevated liver enzymes. A bone scan showed an increased uptake of tracer in the diaphyseal regions of his femurs, tibias, fibulas and ulnas and in his cranial sutures. Radiographs showed new bone along the tibia and fibulas. He had been receiving 20000 IU /day (6006 µg RE, 373 µg RE/kg bw/day, assuming a bodyweight of 16.1kg [Bates 2014]) of vitamin A, subsequent serum vitamin A levels were elevated 867 IU/dL (normal 65-275). The vitamins were stopped and his liver enzymes returned to normal and a repeat bone scan four and a half months later showed no increased uptake of tracer.

19. Lippe *et al* (1981) reported two cases of hypervitaminosis A. The first was a four year old boy who was reported to be in good health until six months prior to admission. He presented with increased intracranial pressure, bone pain and oedema of the face and extremities after having increased frequency of upper respiratory illness. The child had been taking supplements containing 15000 IU/day (4505 µg RE, 246 µg RE/kg bw/day, assuming a bodyweight of 18.3kg Bates 2014) vitamin A for three months, during which he had developed pruritic erythematous papular eruptions on his skin. After three months the vitamin A was increased to 250000 IU/day (75075 µg RE, 4102 µg RE/kg bw/day, assuming a bodyweight of 18.3kg [Bates 2014]) as the respiratory illness had not abated. Within two weeks of starting the new regimen he developed nausea and vomiting, bone pain, peeling and blistering of the mucosa of the lips, restlessness and hyperactivity. All supplementation was stopped and the symptoms improved. However four days before admission he had become unwell again and examination revealed hepatomegaly, bone tenderness and oedema of extremities. Bloods showed hypercalcaemia, a raised alkaline phosphatase and a serum vitamin A of 1626 IU/dL. Radiographs showed metaphyseal bands of increased calcium without formation of new bone. Scans of his brain showed findings consistent with pseudotumor cerebri.

20. The second case from Lippe *et al* (1981) was the presentation of a two and a half year old boy previously diagnosed with Pierre Robin syndrome with

a pruritic rash over his face and trunk, oedema of face and extremities, fever and bone pain. The child was in the tenth percentile for his height and weight and ophthalmologic examination revealed blurred discs. The patient's bone pain meant that he refused to walk. He had hypercalcaemia, an elevated alkaline phosphatase and a serum vitamin A of 1812IU/dL. The child had been taking 25000IU (7508 µg RE, 536 µg RE/kg bw/day, assuming a bodyweight of 14kg [Bates 2014]) vitamin A every day or alternate day plus one or two multivitamins containing 5000 IU of vitamin A and vitamin drops that also contained vitamin A. Once the patient had developed a rash the mother also applied a cream containing vitamin A (unknown strength).

21. A 4 year old boy presented with poor appetite, an intermittent fever, severe abdominal pain, cracking lips and agonising pain in both legs. After a further 2 weeks being treated at the local district hospital and a partial improvement in symptoms, the skin on his hands and feet started to peel and he developed a papular rash on his back. On admission his scalp hair was scarce and weak, the skin on his face and shins was shiny and his tibiae were thickened and painful. Bloods revealed a mild anaemia, and elevated aspartate aminotransferase and alkaline phosphatase. On day three of admission he developed a bony swelling in the mid-thigh and forearm. Radiography revealed thickening of the periosteum along widened diaphyses of all long bones with lifting of the periosteum in the mid-shaft of ulnar bones and right femur, scintigraphy displayed areas suggestive of multifocal osteoblastic skeletal lesions. The effects seemed to be largely consistent with vitamin A toxicity and on further questioning the parents informed them that they had been giving him 600000 IU (180180 µg RE, 9846 µg RE/kg bw/day, assuming a bodyweight of 18.3kg [Bates 2014]) vitamin A every day for over three months. A serum retinol level was raised at 4.19 µmol/L (normal range 1.13-2.63 µmol/L). After stopping the supplements, the AST normalised and the boy was able to walk within 2 weeks. After two months his bone lesions resolved (Baineni 2016).

22. All of the doses of vitamin A reported in the above case studies are higher than the SCF TULs. The lowest dose reported in the studies is around five-fold that of the SCF TUL and the highest dose nearly 200-fold, indicating that the TULs derived by the SCF would be protective against adverse effects.

Occurrence of vitamin A

Breast Milk

23. There were no new data for vitamin A levels in breast milk from the UK. A concentration value of 70 µg RE/100 mL for mature breast milk from developed countries was used for estimating exposure from human milk in the 2013 COT statement (Annex A). It was previously noted (Annex A) that the level of vitamin A in breast milk of lactating mothers taking vitamin A supplements the UK would be expected to increase by less than two-fold.

Infant formula

24. There were no new UK data for vitamin A levels in infant formula. It was previously reported (Annex A) that four major brands of infant formula from the UK, including whey- and casein-based types, contain 63-82 µg RE/100mL. The upper end value of this range (82 µg RE/100 mL) marginally exceeds the maximum value set by the amended EC regulations (77 µg RE/100 mL) (see paragraph 3). The upper end value of the range of levels of vitamin A for different infant formulas as well as the maximum value from the amended EC regulation will be used in the exposure assessment from this source.

Food

25. The concentration of vitamin A in other foods included in the exposure assessments of this paper were derived from food composition databases (McCance and Widdowson, 2015) that support the National Diet and Nutrition Survey (NDNS) (Bates *et al.,* 2014) and the DNSIYC (DH, 2013).

Supplements

26. There were no new UK data for vitamin A levels in supplements that are marketed for infants and young children. The amount of vitamin A in daily doses of multivitamin supplements available for UK infants was provided in the 2013 COT statement (Annex A) and used again for exposure assessments from this source. The brand providing the highest dose of vitamin A would provide 757 µg RE/day at the recommended dose for ages 0 to 12 months and 1500 µg RE/day for a child aged 12 months and above.

Exposure Assessment

Infants exclusively fed on breast milk or infant formula

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

28. It was previously reported (Annex A) that mean and high-level intake of vitamin A in exclusively breastfed infants, based on the upper end of the reported range of vitamin A concentrations in breast milk of 70 µg RE/100 mL are in the region of 72 to 95 µg RE/kg bw/day and 110 to 140 µg RE/kg bw/day, respectively (Table 1). As noted in paragraph 22 vitamin A supplement intake by lactating mothers in the UK would be expected to

potentially increase levels of vitamin A in breast milk by less than two-fold. Thus, the estimated vitamin A intake of an infant breastfed by a mother taking vitamin A dietary supplements would be less than twice the highest value of 140 µg RE/kg bw/day in Table 1 i.e. less than 280 µg RE/kg bw/day.

29. Table 1 also shows the estimated vitamin A exposure of exclusively formula fed infants, based on a vitamin A concentration at the new EU maximum regulatory limit for infant formula 77 µg RE/100 mL (paragraph 3). Using this limit, mean and high level exposure for 0 to 6 month old infants were up 100 and 160 µg/kg bw/day, respectively. These exposures are similar to those that are derived from the upper end of the range (82 µg RE/100 mL) for major brands of infant formula.

Table 1 Vitamin A exposure (µg RE/kg bw/day) from exclusive feeding on breast milk or infant formula.

	Age in months (consumption volume)[a]			
	0-<4 (800 mL)	**0-<4 (1200 mL)**	**4-<6 (800 mL)**	**4-<6 (1200 mL)**
Breast milk (70 µg RE/100 mL)	95	140	72	110
Formula milk[b] (77 µg RE/100 mL)	100	160	79	120
Formula milk (82 µg RE/100 mL)[c]	110	170	84	130

[a] *Exposures were calculated using an average bodyweight of 5.9 kg for 0 to <4 month olds and 7.8 kg for 4 to <6 month olds*.
[b] *Based on the recent EU regulatory limit of* 77 µg RE/100 mL
[c] *Based on the upper-end of the range for major brands of UK infant formula, as reported previously in Annex A.*
Data reported to 2 significant figures.

Infants and young children also consuming other foods

30. Consumption data (on a bodyweight basis) from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), and from the NDNS (Bates *et al*., 2014) have been used for the estimation of dietary exposures for ages 4 to 18 months, and 18 to 60 months, respectively. The combined daily exposure to vitamin A from breast milk, infant formula and other foods in infants and young children is reported in Table 2. The total (excluding supplements) mean and 97.5th percentile dietary exposure to preformed vitamin A at ages 4 to 60 months ranged from 38 to 79 µgRE/kg bw/day and 93 to 210 µg RE/kg bw/day, respectively.

Table 2 Total dietary exposure to preformed vitamin A from breast milk, infant formula and other food sources, excluding supplements

Total daily exposure of preformed vitamin A (µg	**Age group (months)**						
	4-<6	**6-<9**	**9-<12**	**12 - <15**	**15 - <18**	**18 - <24**	**24 - <60**

RE/kg bw/day)							
Mean	62	79	74	59	53	45	38
97.5th percentile	210	200	190	130	120	93	95

Data reported to 2 significant figures

31. The contribution of infant formula to the total average vitamin A daily exposure decreased from 39% at 4 to 6 months to 12% at 12 to 18 months of age (DH, 2013). Likewise, the contribution of breast milk decreased from 15% at 4 to 6 months to 2% at 12 to 18 months of age. Commercially available infant foods provided approximately 24% throughout the first year. Other major contributors to the total exposure were foods not specific to infants such as vegetables and potatoes, and milk and milk products (DH, 2013).

32. For young children aged 18 to 36 months, the major food groups contributing to the total vitamin A daily exposure were: milk and milk products as well as the vegetables and potatoes group (DH, 2013). This was also reported to be the case for children up to the age of 10 years (Bates et al., 2016)

Exposure in consumers of liver

33. DNSIYC and NDNS consumption data were used to estimate exposure to vitamin A from liver, based on all types of liver. Liver pate, which tends to be eaten in smaller portions than liver itself, was not included in the estimation of exposure (Table 3). The highest intakes averaged over the four days of the survey were evident in the 9 to <12 (160 µg/kg bw/day) and 24 to <60 month (110 µg/kg bw/day) age categories. These data are based on very small numbers of consumers, but indicate that some infants and young children do eat liver and the possible vitamin A intakes from this source.

Table 3 Consumption of liver and exposure to vitamin A in consumers of all types of liver.

	Age group in months (number of consumers)						
	4-<6 (0)	**6-<9 (6)**	**9-<12 (6)**	**12 - <15 (1)**	**15 – 18 (2)**	**18 - <24 (1)**	**24 - <60 (5)**
Mean liver consumption (g/kg bw/day)	n/a	0.41	0.96	0.010	0.24	0.41	0.64
Maximum liver consumption (g/kg bw/day)	n/a	0.52	2.4	0.010	0.41	0.41	2.0
Mean vitamin A exposure (µg/kg bw/day)	n/a	57	160	2.6	25	80	110

Maximum vitamin A exposure (µg/kg bw/day)	n/a	87	410	2.6	43	80	350

Data reported to 2 significant figures

Dietary supplements

34. Potential exposure from vitamin supplements alone at ages 0 to 12 months, based on the brand providing the highest dose of vitamin A in this age group (757 µg RE/day), was reported previously (Annex A). Table 4 provides updated estimates for infants, based on the revised age range, as noted in paragraph 2, and also estimates for ages 1-5 years. Use of supplements in the 0 to 6 month age group could lead to total exposures of 220 and 240 µg RE/kg bw/day, if mean exposure from exclusive consumption of breast milk or infant formula is added, respectively; the corresponding exposure arising from use of supplements in infants and young children in addition to high-level exposure from exclusive consumption of breast milk or infant formula is 270 and 300 µg RE/kg bw/day, respectively. For ages 4 to 12 months, supplementation in addition to mean and high-level exposure from the rest of the diet[2], leads to total exposure ranging from 150 to170 µg RE/kg bw/day and 270 to 310 µg RE/kg bw/day, respectively (Table 4).

35. The highest dose of vitamin A in daily doses of multivitamin supplements recommended by manufacturers for children older than 12 months is 1500 µg RE/ day (paragraph 26). For ages 12 to 60 months, use of supplements at this dose in addition to mean and high-level vitamin A exposure from the rest of the diet leads to total exposure ranging from 130 to 200 µg RE/kg bw/day and 190 to 270 µg RE/kg bw/day, respectively (Table 4).

36. Exposure to vitamin A from vitamin drops which are provided under the Healthy Start scheme (paragraph 5) at the dosage of 233 µg/day for infants 6 months and over were reported previously (Annex A). Use of these drops in infants and young children could lead to total exposures of up to 110 and 230 µg RE/kg bw/day, if exposure from these drops are added to the mean and high-level exposure from the rest of the diet, respectively.

[2] Rest of the diet includes breast milk and infant formula as well as other foods, excluding supplements

Table 4 Exposure to vitamin A from supplements (at a dose of 757 and 1500 µg RE/day for infants 0 to 12 months and young children 12 to 60 months, respectively) alone and with contribution from the rest of the diet at ages 0 to 60 months.

Vitamin A Exposure	**Vitamin A exposure (µg/kg bw/day) by age group (months)**							
	0 – <4	**4 - <6**	**6 - <9**	**9 - <12**	**12 - <15**	**15 - <18**	**18 - <24**	**24 - <60**
Vitamin supplements alone [a]	130	97	87	79	140	130	130	93
Vitamin supplements plus **mean** level exposure from **exclusive consumption of breast milk**[a]	220	170	n/a	n/a	n/a	n/a	n/a	n/a
Vitamin supplements plus **high level** exposure from **exclusive consumption of breast milk**[ab]	270	210	n/a	n/a	n/a	n/a	n/a	n/a
Vitamin supplements plus **mean** level exposure from **exclusive consumption of infant formula**[ab]	240	180	n/a	n/a	n/a	n/a	n/a	n/a
Vitamin supplements plus **high-level** exposure from **exclusive consumption of infant formula**[ab]	300	230	n/a	n/a	n/a	n/a	n/a	n/a
Vitamin supplements plus **mean** level exposure from the rest of the diet[c]	n/a	160	170	150	200	180	180	130
Vitamin supplements plus **high-level** exposure from the rest of the diet[c]	n/a	310	290	270	270	250	220	190

[a] *Calculated using average bodyweights of 5.9, 7.8, 8.7, 9.6, 10.6, 11.2, 12.0 and 16.1 kg for 0-<4, 4-<6, 6-<9, 9-<12, 12-<15, 15-<18, 18-<24 and 24-<60 month olds, respectively.*

[b] *The exposure from breast milk (at a vitamin A concentration of 70 µg RE/100mL) and infant formula (at a vitamin A concentration of 82 µg RE/100mL) are as reported in Table1*

[c] *Exposures from the rest of the diet are as reported in Table 2.*

Data reported to 2 significant figures

Table 5 Exposure to vitamin A from vitamin drops provided under the Healthy Start scheme at a dose of 233 µg/day with contribution from the rest of the diet at ages 6 to 60 months

Vitamin A Exposure	**Vitamin A exposure (µg/kg bw/day) by age group (months)**					
	6 - <9	**9 - <12**	**12 - <15**	**15 - <18**	**18 - <24**	**24 - <60**
Vitamin supplements alone (µg/kg bw/day)[a]	27	24	22	21	19	14
Vitamin supplements plus **mean** level exposure from the rest of the diet[b]	110	98	81	74	64	52
Vitamin supplements plus **high-level** exposure from the rest of the diet[b]	230	210	150	140	110	110

[a] *Calculated using average bodyweights of 8.7, 9.6, 10.6, 11.2, 12.0 and 16.1 Kg for 6-<9, 9-<12, 12-<15, 15-<18, 18-<24 and 24-<60 month olds, respectively*
[b] *Exposures from the rest of the diet are as reported in Table 2*
Data reported to 2 significant figures

Risk characterisation

37. Potential risks from the exposure of infants to vitamin A from the diet were characterised by comparison to the TUL of 200 µg RE/kg bw/day established by the COT. This was based on the endpoint of bulging fontanelles, which is specific to infants.

38. The risks to young children are compared in this discussion paper to the TULs derived by the SCF (2002): 75 µg RE/ kg bw/day at age 12-15 months, 71 µg RE/ kg bw/day for 15-18 months, 67 µg RE/ kg bw/day for those aged 18-24 months, for ages 24-48 months 50 µg RE/ kg bw/day and 57 µg RE /day at age 48-60 months. However as exposures are not expressed for the age range 48-60 months, the lower value of 50 µg RE/ kg bw/day was used for comparison to the TUL for the age range 24-60 months.

39. Table 6 shows the exposure to vitamin A for infants fed exclusively on breast or formula milk and the comparisons to the TUL. All exposures are below the TUL.

Table 6 Vitamin A exposure (µg RE/ kg bw/day) from exclusive feeding on breast milk or infant formula and comparison to the TUL

	Age in months (consumption volume)[a]							
	0-<4 (800 mL)		**0-<4 (1200 mL)**		**4-<6 (800 mL)**		**4-<6 (1200 mL)**	
	Exposure	%TUL	Exposure	%TUL	Exposure	%TUL	Exposure	%TUL
Breast milk (70 µg RE/100 mL)	95	48	140	70	72	36	110	55
Formula milk[b] (77 µg RE/100 mL)	100	50	160	80	79	40	120	60
Formula milk (82 µg RE/100 mL)[c]	110	55	170	85	84	42	130	65

[a] *Exposures were calculated using an average bodyweight of 5.9 kg for 0 to <4 month olds and 7.8 kg for 4 to <6 month olds*.
[b] *Based on the recent EU regulatory limit of* 77 µg RE/100 mL
[c] *Based on the upper-end of the range for major brands of UK infant formula, as reported previously in Annex A.*
Data reported to 2 significant figures.

40. Table 7 shows the comparison of vitamin A exposures from breast milk, infant formula and other food sources combined in relation to the TUL for

ages 4-60 months. All high level consumers exceed the TUL except those aged 6-12 months.

41. Table 8 shows the comparison of vitamin A exposures from the supplement providing the highest dose of vitamin A (757µg) plus exclusive breast milk and infant formula, in relation to the TUL. The contribution to exposure from the rest of the diet in relation to the TUL for infants aged 0-12 months is also shown. For the age group 0 <4 months, all exposures except for the vitamin supplement alone exceed the TUL. Infants aged 6-12 months who are high- level consumers, all exceed the TUL.

42. Table 9 summarises the dietary exposures for vitamin A in children aged 12-60 months for the vitamin supplement providing the highest dose of vitamin A (1500 µg), and the supplement plus mean and high-level exposure from the rest of the diet and the comparison to the TULs. All age groups exceed the TULs.

43. Table 10 shows the dietary exposure to vitamin A from the supplement provided by the Healthy Start scheme and the supplement plus mean and high-level exposure from the rest of the diet for children who are aged 6 to 60 months. The age group 0-<6 months has not been included, as the Healthy Start vitamins are not recommended in infants under 6 months of age. All high level consumers exceed the TUL, also mean consumers in the age groups 12-15 and 24-60 months.

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

Table 7 Total daily exposure to preformed vitamin A (µg RE/kg bw/day) from breast milk, infant formula and other food sources compared to the TUL

Total daily exposure of preformed vitamin A (µg RE/kg bw/day)	Age group (months)													
	4-<6		6-<9		9-<12		12 - <15		15 - <18		18 - <24		24-<60	
	Exp	%TUL	Exp	%TUL	Exp	%TUL	Exp	%TUL	Exp	%TUL	Exp	%TUL	Exp	%TUL [a]
Mean	62	31	79	40	74	37	59	78	53	74	45	67	38	76
97.5th percentile	210	110	200	100	190	95	130	170	120	170	93	140	95	190

Data reported to 2 significant figures

[a] *Compared to the smallest TUL*

Table 8 Exposure to vitamin A from supplements alone (dose of 757 µg RE/day) and with contribution from the rest of the diet and comparison to the TUL at ages 0 to 12 months

Source of exposure	0-<4 months		4-<6 months		6-<9 months		9-<12 months	
	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL
Vitamin supplements alone	130	65	97	49	87	44	79	40
Vitamin supplements plus mean level exposure from exclusive consumption of breast milk[ab]	220	110	170	85	N/A	N/A	N/A	N/A
Vitamin supplements plus high level exposure from exclusive consumption of breast milk[ab]	270	140	210	110	N/A	N/A	N/A	N/A
Vitamin supplements plus mean level exposure from exclusive consumption of infant formula[ab]	240	120	180	90	N/A	N/A	N/A	N/A
Vitamin supplements plus high-level exposure from exclusive consumption of infant formula [ab]	300	150	230	120	N/A	N/A	N/A	N/A
Vitamin supplements plus mean level exposure from the rest of the diet[c]	N/A	N/A	160	80	170	85	150	75
Vitamin supplements plus high-level exposure from the rest of the diet[c]	N/A	N/A	310	160	290	150	270	140

[a] *Exposure data from exclusive feeding on breast milk or infant formula (Table 1).*
[b] *Calculated using average bodyweights of 5.9, 7.8, 8.7, 9.6, 10.6, 11.2, 12.0 and 16.1 kg for 0-<4, 4-<6, 6-<9, 9-<12, 12-<15, 15-<18, 18-<24 and 24-<60 month olds, respectively. The exposure from infant formula is based on the upper end of the value from the range 63-82 µg/kg bw/day for major brands of UK infant formula.*
[c] *Rest of the diet includes breast milk and infant formula and other foods, excluding supplements (Table 2).*
Data reported to 2 significant figures

Table 9 Exposure to vitamin A from supplements alone (dose of 1500 µg RE/day) and with contribution from the rest of the diet and comparison to the TUL at ages 12 to 60 months

Source of exposure	12-<15 months		15-<18 months		18-<24months		24-<60 months	
	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL[a]
Vitamin supplements alone	140	190	130	180	130	200	93	190
Vitamin supplements plus **mean** level exposure from the rest of the diet[b]	200	270	180	250	180	270	130	260
Vitamin supplements plus **high-level** exposure from the rest of the diet[b]	270	360	250	350	220	330	190	380

[a] *Calculated using the smallest TUL of 50 µg/kg bw/day*
[b] *Rest of the diet includes breast milk and infant formula and other foods, excluding supplements (Table 2).*
Data reported to 2 significant figures

Table 10 Exposure to vitamin A (µg/kg bw/day), from the dosage provided under the Healthy Start scheme (233 µg/day) alone and with contribution from the rest of the diet and comparison to the TUL for ages 6 to 60 months.

Source of exposure	6-<9 months		9-<12 months		12-<15 months		15-<18 months		18-<24months		24-<60 months	
	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL[a]
Vitamin supplements alone[b]	27	14	24	12	22	30	21	30	19	29	14	28
Vitamin supplements plus **mean** level exposure from the rest of the diet[c]	110	55	98	49	81	110	74	100	64	96	52	100
Vitamin supplements plus **high-level** exposure from the rest of the diet[c]	230	120	210	110	150	200	140	200	110	170	110	220

Data reported to 2 significant figures
[a] *Calculated using the smallest TUL of 50 µg/kg bw/day*
[b] *Calculated using average bodyweights of 8.7, 9.6, 10.6, 11.2, 12.0 and 16.1 Kg for 6-<9, 9-<12, 12-<15, 15-<18, 18-<24 and 24-<60 month olds, respectively*
[c] *Rest of the diet includes breast milk and infant formula as well as other foods, excluding supplements (Table 2)*

Questions on which the views of the Committee are sought

45. Members are invited to comment on the information provided in this paper and to answer the following questions.

i. Do Members agree that the TULs established by the SCF, as described in para 38, should be used in assessing the risks of high dietary intakes of vitamin A in children aged 1-5 years?

ii. Do the estimated exposure levels represent a risk to infants and young children?

iii. Should the information in this paper be summarised in an addendum to the 2013 statement?

Secretariat
November 2016

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

Review of potential risks from Vitamin A in the diets of children aged 1 to 5 years and updated exposures for infants aged 0 to 12 months

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

Available at: https://cot.food.gov.uk/sites/default/files/cot/cotstavita.pdf

Secretariat
November 2016