

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

### **Discussion paper on the effects of excess Vitamin A on maternal health**

#### **Introduction**

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' (SACN, 2011) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered.
2. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.
3. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments e.g. in the area of food safety advice. This subject was initially discussed during the horizon scanning item at the January 2020 meeting with a scoping paper being presented to the Committee in July 2020. This included background information on a provisional list of chemicals proposed by SACN. It was noted that the provisional list of chemicals was subject to change following discussion by COT who would be guiding the toxicological risk assessment process: candidate chemicals or chemical classes can be added or removed as the COT considered appropriate. The list was brought back to the COT with additional information in September 2020<sup>1</sup>. Following a discussion at the COT meeting in September 2020, it was agreed that papers on a number of components should be prioritised and to this end, papers on iodine, vitamin D and dietary supplements have been or will be presented to the Committee. The remaining list of compounds were to be triaged on the basis of toxicity and exposure. The current paper presents information intended to aid this process.
4. Following discussion of the first prioritisation paper on substances to be considered for risk assessment by the COT, the Committee decided that Vitamin A should be considered in a single paper.

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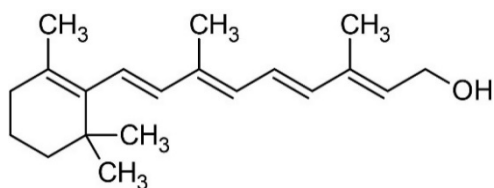
<sup>1</sup> COT Contribution to SACN review of nutrition and maternal health: proposed scope of work and timetable. Available at: [https://cot.food.gov.uk/sites/default/files/2020-09/TOX-2020-%2045%20%20Maternal%20diet%20scoping%20paper\\_0.pdf](https://cot.food.gov.uk/sites/default/files/2020-09/TOX-2020-%2045%20%20Maternal%20diet%20scoping%20paper_0.pdf)

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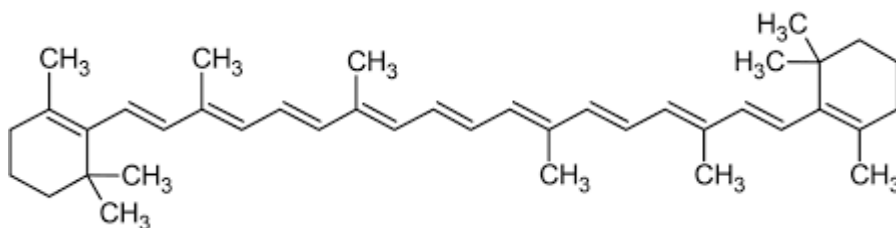
## Background

### Structure and sources

5. In structure, vitamin A is classified as a retinoid, consisting of an alicyclic  $\beta$ -ionone ring and a 9-carbon-long isoprenoid side chain. These compounds are derived from a family of pro-vitamin A carotenoids, the major one being  $\beta$ -carotene. Retinol (vitamin A<sub>1</sub> or vitamin A alcohol) and 3-dehydroretinol (Vitamin A<sub>2</sub>) occur in foods of animal origin and  $\beta$ -carotene is found in red and yellow and leafy green vegetables. (Bowman and Rand, 1982) (Figure 1, Merck Index, 1996).



### Retinol



### $\beta$ -carotene

Figure 1: Structure of retinol and  $\beta$ -carotene

6. Other carotenoids, for example,  $\beta$ -cryptoxanthin,  $\alpha$ -carotene, lycopene, lutein and zeaxanthin are also present in plants. The first two of these carotenoids have a  $\beta$ -ionone ring at only one end of the molecule and hence yield only one molecule of retinol upon hydrolysis but the latter three are not metabolised to retinol and are therefore not classified as pro-vitamin A carotenoids (Collins and Mao, 1999).

7. Therapeutically useful retinol analogues include the naturally occurring 13-cis-retinoic acid (also known as isotretinoin), and the synthetic aromatic retinoids etretin and etretinate.

8. The Expert Committee on Vitamins and Minerals (EVM) published a report in 2003 that included a review of Vitamin A. Vitamin A was defined as "... a group of lipid soluble compounds related metabolically to all-*trans*-retinol. In the diet, vitamin A is found in products of animal origin, as retinyl esters, mainly retinyl palmitate." Vitamin A can be expressed on a weight basis as Retinol Equivalents (1 RE = 1  $\mu$ g

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retinol) = 1.78 µg retinyl palmitate = 6 µg β-carotene = 12 µg other carotenoids with provitamin A activity = 3.33 International Units (IU)<sup>2</sup> vitamin A activity from retinol”  
<https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf>

9. The EVM statement was based on an original detailed review, published in 2002  
<https://webarchive.nationalarchives.gov.uk/20101211080008/http://www.food.gov.uk/multimedia/pdfs/reviewvita.pdf>

10. UK Government advice as given on the [NHS.uk website](https://www.nhs.uk) lists good sources of vitamin A as cheese, eggs, oily fish, fortified low-fat spreads, milk, yoghurt and liver and liver products such as pate (NHS, 2021). Good sources of β-carotene in addition to yellow, red or green (leafy) vegetables are carrots, sweet potatoes, red peppers and spinach are fruit such as mango, papaya and apricots.

#### *Toxicity- summary*

11. Acute clinical features of vitamin A toxicity in age groups other than infants are lethargy, pain in the joints, dry skin, headache and nausea and vomiting, although these vary depending on severity. More severe signs that can diagnose hypervitaminosis A clinically include alopecia, drowsiness, liver and bone damage and visual problems (Loughrill 2016, SCF 2002). In infants, the major symptom of toxicity is bulging fontanelles.

12. Symptoms of chronic toxicity include dry thickening of the skin, cracking of lips, conjunctivitis, erythematous eruption, alopecia, reduced bone mineral density, bone joint pain, chronic headache, intracranial hypertension and hepatotoxicity. Some adverse effects, for example hepatotoxicity, are regarded as reversible with withdrawal of the vitamin but others, such as deficits in the eyes and bone, are not. (Kamm, 1982).

13. Reproductive effects of excess retinoids include toxicity to the central nervous system (hydrocephalus, anencephaly, exencephaly, spina bifida), eyes (anophthalmia, microphthalmia, defects of the retina), face (harelip, cleft palate, brachygnathia, hypoplastic maxilla), dentition, ear (absent or deformed), limb (phocomelia), urinogenital system (hypoplastic kidney, polycystic kidney, absent/hypoplastic genitalia), heart (incomplete ventricular septation, transposition of the great vessels, double aortic arch, hypoplastic aortic valves), thyroid gland (hypoplasia), and the axial skeleton (vertebral and rib fusions, extra vertebrae and ribs, hypoplastic tail). (Maden, 2001). The reproductive effects of vitamin A are considered in more detail later in this paper.

14. UK Government dietary advice, as given on the [NHS website](https://www.nhs.uk) recommends that pregnant women, or women thinking about having a baby, should not consume

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<sup>2</sup> In this paper, in quoting or describing literature where IU are used, the original values have been multiplied by 0.3 to convert them into RE for consistency.

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liver or liver products such as pate, or supplements that contain vitamin A, including fish liver oil, unless advised by a GP, to avoid potential harm to the unborn baby.

15. The World Health Organisation (WHO, 2021) recommend that vitamin A supplementation be given to pregnant women only in areas where vitamin A deficiency is a severe public health problem, to prevent night blindness, ie if  $\geq 5\%$  of women in a population have a history of night blindness in their most recent pregnancy in the previous 3–5 years that ended in a live birth, or if  $\geq 20\%$  of pregnant women have a serum retinol level  $< 0.70 \mu\text{mol/L}$ . Vitamin A supplementation in HIV-positive pregnant women is not recommended as a public health intervention for reducing the risk of mother-to-child transmission of HIV. Vitamin A supplementation in postpartum women for the prevention of maternal and infant morbidity and mortality, is also not recommended.

### *Previous evaluations*

16. In 2002, the EU Scientific Committee on Food (SCF) reviewed the possible adverse effects of long-term intake of retinol and retinyl esters (SCF, 2002). The SCF set a Tolerable Upper Intake Level (UL) for preformed vitamin A of  $3000 \mu\text{g RE/day}$  for women of childbearing age and men, based on the risk of hepatotoxicity and teratogenicity. The UL was proposed to also apply during pregnancy and lactation.

17. EVM (2002, 2003) stated that chronic toxicity in adults was generally attributed to supplemental doses of  $> 7500\text{--}15,000 \mu\text{g RE/day}$ , over weeks, months or years. However, it was noted that there have been cases of toxicity associated with lower doses of  $\sim 1500\text{--}3000 \mu\text{g RE/day}$ . Determination of a threshold dose for chronic toxicity may be confounded by pre-existing disease, alcohol abuse, drug therapy and limited knowledge of dietary intake. EVM (2003) concluded that “Acute vitamin A toxicity in humans is rare but is more likely to occur following ingestion of high dose supplements, rather than following high intakes of vitamin A from food. Vitamin A accumulates in the body and, therefore, individuals who have regular high daily intakes of vitamin A might suffer adverse effects from chronic hypervitaminosis A. Although most manifestations of chronic vitamin A toxicity are reversible on cessation of dose, permanent damage to liver, bone and vision, and chronic muscular and skeletal pain may occur in some cases. Epidemiological studies have indicated that exposure to high levels of vitamin A during pregnancy might increase the risk of birth defects. The available data do not allow identification of a threshold dose, although one study has suggested that effects may occur at modest intakes. Vitamin A has also been shown to be teratogenic in animals. Recent epidemiological data have indicated that post-menopausal women with long-term high intakes of vitamin A have an increased risk of hip-bone fracture. Other supporting epidemiological data have indicated that this effect may occur in men as well as women. These findings are supported by animal data, which have indicated that retinol has a direct effect on bone, possibly via an interaction with vitamin D, and an effect on parathyroid hormone and therefore calcium metabolism.” The EVM did not recommend a maximum level of intake but, in the context of bone health, considered that an intake greater than  $1500 \mu\text{g/day}$  was “inappropriate”.

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18. EFSA (2006) derived a tolerable upper limit for vitamin A of 3000 µg of RE per day for women of childbearing age. This was based upon a study by Rothman *et al* (1995), which indicated a rise in the ratio of prevalence of birth defects associated to the cranial-neural crest at doses greater than 3000 µg RE/day of vitamin A (from food and supplements). See paragraph 45 for further discussion of this study.

19. EFSA (2015) published a Scientific Opinion on dietary reference values (DRV)<sup>3</sup> for vitamin A. Average requirements (ARs) of 570 µg retinol equivalent (RE)/day for men and 490 µg RE/day for women were derived and Population Reference Intakes (PRIs) of 750 µg RE/day for men and 650 µg RE/day for women were set. ARs ranged from 190 µg RE/day for 7– 11 month-old infants to 580 µg RE/day for boys aged 15–17 years. For pregnancy and lactation, additional vitamin A requirements related to the accumulation of retinol in fetal and maternal tissues and transfer of retinol into breast milk were considered and Population Reference Intakes of 700 and 1300 µg RE/day, respectively, were set. The TUL established by the SCF was not revised.

20. The COT last considered vitamin A in relation to the diet of infants and children aged 1 – 5 years, in 2017. The Committee concluded that the Tolerable Upper Level (TUL) of 200 µg RE/kg bw/day derived by themselves, based on a LOAEL of 800 µg RE/kg bw/day for an endpoint of bulging fontanelles, "...was appropriate to evaluate the effect of vitamin A exposures in infants. However no TULs could be established for the ages 12-60 months on the basis of the available data. Comparisons were therefore made with a conservative TUL based on teratogenic effects in adults. High- level consumers are approaching or exceeding levels of vitamin A reported in the literature as causing toxicity and the possibility of adverse effects from these levels cannot be excluded. However, if effects did occur they would only be in a small proportion of consumers. Though the data on liver consumption are limited, frequent consumption could be a cause for concern and the current Government recommendation that infants over six months old should not have more than one portion of liver per week is appropriate."

### *Functions*

21. Retinol performs many important physiological functions in animals. It is involved with the synthesis of collagen and elastin fibres by fibroblasts, as well as the processes of cell division, and differentiation and the functioning of skin and mucous membranes. Vitamin A positively influences the development of the skeleton by regulating the activities of osteoblasts and osteoclasts. It decreases the secretion of thyroxine from the thyroid gland by suppressing production of thyrotropin by the pituitary. Vitamin A also stimulates the immune system and hence improves resistance to infections. (Rutkowski and Grzegorzcyk, 2012)

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<sup>3</sup> EFSA defines dietary reference values (DRVs) as an umbrella term for a set of nutrient reference values that includes the average requirement (AR), the population reference intake (PRI), the adequate intake (AI) and the reference intake range for macronutrients (RI). These values guide professionals on the amount of a nutrient needed to maintain health in an otherwise healthy individual or group of people. DRVs also include the tolerable upper intake level (UL), which is the maximum amount of a nutrient that can be consumed safely over a long period of time.

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22. Retinoids are extensively involved in embryogenesis and fetal development and many papers have been written on this function. Clagett-Dame and Knutson (2011), for example, reviewed this area of physiology. It is now generally believed that all-*trans* retinoic acid supports both male and female reproduction as well as embryonic development. This conclusion is based on the ability of RA to reverse most reproductive and developmental blocks found in vitamin A deficiency induced in experimental animals either by nutritional or genetic means, and the fact that the majority of embryonic defects arising from vitamin A deficiency are also observed in retinoic acid receptor null mutants. The differential activity of CYP26 enzymes in tissues is a key regulatory mechanism. If severely vitamin A-deficient pregnant rats are given small amounts of carotene or limiting quantities of RA early in organogenesis, embryos form but show a collection of defects called the vitamin A deficiency syndrome or late vitamin A deficiency. Vitamin A is essential for the maintenance of the male genital tract and spermatogenesis and participates in a signalling mechanism that initiates meiosis in the female gonad during embryogenesis, and in the male gonad postnatally. Both nutritional and genetic approaches have been used to elucidate the vitamin A-dependent pathways upon which these processes depend.

23. Vitamin A is an antioxidant: the conjugated C = C bonds in the side chain are oxidised by reactive oxygen species (ROS) and free radicals and thus protect those bonds in the polyunsaturated fatty acids in cell membrane lipids. This also protects against neoplastic transformation (promotion) induced by uncontrolled oxidation of the glycosyl residues of proteins in cell membranes. The antioxidative function also stabilises thiol groups (–SH) of membrane proteins and suppresses oxidatively stimulated expression of the c-myc oncogene. Epithelial cells in particular are protected by vitamin A, including tissues of the nasal and throat cavity, oesophagus, stomach, intestines, respiratory tract, bladder, and prostate. (Rutkowski and Grzegorzczuk, 2012)

24. Retinol is oxidised to retinal (vitamin A aldehyde or retinaldehyde) which, as its 11-*cis* isomer, functions as an essential component in the process of visual signal transduction in the retina, in the pigment rhodopsin in the rods as well as the pigments in the cones. (EVM, 2002).

25. Retinal is further oxidised to retinoic acid and thence undergoes further side-chain isomerisation and oxidation into a range of different products. Retinoic acid has pleiotropic effects in development and is well documented in the literature as a teratogen (Collins and Mao, 1999).

#### *Mechanism of action.*

26. The majority of the effects of ingested vitamin A are thought to be mediated by the action of retinoic acid. Since retinoic acid is produced endogenously and combines with specific nuclear receptor proteins that bind to DNA and regulate the expression of various genes, it is classified as a hormone. It is a ligand for specific nuclear receptors, the most studied of which are retinoic acid receptor (RAR) or retinoid X receptor (RXR), that regulate the transcription of numerous target genes,

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as homo- or hetero-dimers. More than 500 genes are known to be regulated by retinoic acid, many of which control embryonic development. Retinoic acid signalling is turned off by ligand degradation by CYP450 enzymes, such as CYP26A1.

27. Das *et al* (2013) and Huang *et al* (2014) detail the molecular biology and functions of the retinoid receptors. In the presence of retinoids, the holo-receptor binds to the chromosomal retinoic acid response element (RARE) and activates histone acetyl transferases (HATs). This results in histone acetylation, which opens the chromatin so that transcription can take place. In the absence of ligands, the apo receptor pair binds with the RARE in a complex with corepressors and activates histone deacetylase (HDAC). As a result, histone deacetylation prevails causing chromatin condensation and gene silencing. A critical role for RA during somite development was uncovered by studies showing that RA regulates the expression of the transcription factor Cdx1, a factor crucial for the somatic expression of multiple Hox genes<sup>4</sup> during skeletal development. RA also has a crucial role in ensuring the suppression of left-right asymmetries during developmental pattern formation in embryos. RA is not produced by all cells of the body at all stages of development, but is produced in a unique spatiotemporal pattern which orchestrates development.

28. Both deficiency and excess of retinoic acid causes the ectopic induction and the down-regulation of many genes as a prelude to changing the anatomy of the embryo. For example, excess retinoic acid causes the chick limb bud to develop six digits instead of the normal three. This effect is elicited by the induction of a nested set of Hox genes, the fibroblast growth factor-4 gene, the bone morphogenetic protein-2 gene, the sonic hedgehog gene, and others forming interacting networks of genes to control outgrowth in the three axes of the limb. Conversely, quail embryos deficient in retinoic acid have down-regulated sonic hedgehog, fibroblast growth factor-4, engrailed and others, but also express ectopically induced genes such as Wnt-7a, probably by the down-regulation of a repressor.

29. The hindbrain of the embryo is also profoundly affected. Retinoic acid administration to mouse embryos induced the hindbrain Hox genes in an altered expression pattern which resulted in an altered anatomy, with the seven structures in this tissue known as rhabdomeres developing in the wrong order, leading to malfunction of the whole brain region.

## ADME

30. Spiegler *et al* (2012) reviewed the absorption, distribution, metabolism and excretion of vitamin A. Nearly all retinyl esters in the diet are hydrolysed to retinol in the intestinal lumen. Retinol is absorbed by intestinal epithelial cells, where it is re-esterified to long-chain fatty acids, primarily by the enzyme lecithin:retinol acyltransferase (LRAT), which is widely expressed in tissues, and is incorporated into chylomicra, which circulate in the intestinal lymph before moving into the general circulation. Once in the general circulation, lipoprotein lipase (LPL), which is bound to the luminal surface of the vascular endothelium, catalyses the lipolysis of triglycerides to generate free fatty acids and chylomicron remnants. Chylomicron remnants are cleared mainly by the liver, but extrahepatic uptake of the remnants

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<sup>4</sup> Transcription factor genes that control the sequence of development.

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may be important in the delivery of vitamin A to mammary tissue, bone marrow, adipose tissue, and spleen. Retinyl esters in serum are normally below 0.2  $\mu\text{mol/L}$  in the fasting state but they increase significantly after a large influx of vitamin A, such as occurs after a vitamin A-rich meal.

31. Once taken up by the hepatocytes, retinyl esters are again hydrolysed to retinol to be transferred to stellate cells and then re-esterified by LRAT for storage. Alternatively, retinol can bind to retinol-binding protein (RBP) and be secreted into the bloodstream as a 1:1 molar complex with the serum protein transthyretin. RBP thus functions to mobilise hepatic retinoid stores and deliver retinol to peripheral tissues and developing embryos. In fasting conditions, retinol-RBP accounts for approximately 95-99% of all serum retinoids. Upon vitamin A intake, the concentration of retinoids in chylomicrons and chylomicron remnants can greatly exceed that of plasma retinol. Blood levels of retinol-RBP in both humans and animals are tightly controlled, except in extreme cases of insufficient intake of vitamin A, protein, calories and zinc; or in response to hormonal factors, stress; and in certain disease states.

32. Spiegler *et al* (2012) also stated that the mechanisms that regulate the secretion of the complex retinol-RBP from the liver have yet to be fully elucidated. Tissue uptake of vitamin A seems to be mediated by Stra6 ("Stimulated by retinoic acid 6"), the receptor for the circulating complex where this is expressed, but this uptake mechanism is unclear. Stra6 may also act as a cytokine receptor to transduce signalling by holo-RBP and regulate insulin response. In addition, Stra6 may also mediate the efflux of retinol from the cell and thus act as a bi-directional transporter of retinol, with intracellular retinol concentration determining influx or efflux dominates. In some tissues with high retinoid content, such as skin and liver, Stra6 is expressed at very low levels and other mechanisms such as spontaneous transfer of free retinol across the phospholipid bilayer, may regulate retinol uptake. Even in the fasting state there are low concentrations of RE that are associated with circulating lipoproteins (in VLDL and LDL) and small amounts of circulating retinoic acid bound to albumin.

33. Within cells, retinol is reversibly oxidized to retinal by members of the alcohol dehydrogenases, medium-chain dehydrogenase/reductases, retinol dehydrogenases and short-chain dehydrogenase/reductases. Retinal is further oxidized to retinoic acid by retinal dehydrogenases. Several intracellular binding proteins for retinol, retinal and retinoic acid have been identified and characterised, including cellular retinol-binding proteins I, II and III, cellular retinaldehyde binding protein and cellular retinoic acid-binding proteins I and II. Each of these retinoid-binding proteins has a distinct expression pattern and plays a specific role in vitamin A transport and metabolism.

34. Penniston and Tamuihardjo (2006) found that few human studies have looked at the acute effects of a large dose of vitamin A on circulating vitamin A concentrations. Evidence suggested that sub-toxicity without clinical signs of toxicity may be a growing concern, because intake from preformed sources of vitamin A often exceeded the recommended dietary allowances (RDA) for adults, especially in developed countries. Osteoporosis and hip fracture have been associated with preformed vitamin A intakes of only twice the current RDA. Assessing vitamin A



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status in cases of sub-toxicity or toxicity is complicated because serum retinol concentrations are non-sensitive indicators in this range of liver vitamin A reserves. The metabolism of pre-formed vitamin A in well-nourished people, provided by either liver in the diet or supplements, had been studied by several research groups. To control vitamin A deficiency, large therapeutic doses are administered in developing countries to women and children, who often are undernourished. Nevertheless, little attention has been given to the short-term kinetics (ie, after absorption but before storage) of a large dose of vitamin A or to the short- and long-term effects of such a dose given to lactating women on serum and breastmilk concentrations of retinol and its metabolites. Moreover, appropriate dosing regimens have not been systematically evaluated to ascertain the quantitative improvement in vitamin A status of the women and children who receive these supplements. The authors concluded that further research was needed to ascertain the areas of the world in which subclinical toxicity exists and to evaluate its effects on overall health and well-being.

#### *Vitamin A levels in pregnant women and newborns*

35. Söderlund *et al* (2005) measured serum concentrations of all-trans retinoic acid and 13-cis retinoic acid in newborns and their mothers and in women in the first trimester of pregnancy. Ten newborns from normal deliveries and their mothers as well as 16 healthy women in their first trimester of pregnancy were studied, with 17 healthy women as controls. All-trans and 13-cis retinoic acid and retinol concentrations were measured by HPLC. The newborns had significantly lower retinol concentrations (1.0  $\mu\text{mol/L}$ ) than did their mothers (1.7  $\mu\text{mol/L}$ ;  $p = 0.013$ ). Serum all-trans retinoic acid was also significantly lower in the newborns (3.4 nmol/L) than in their mothers (5.8 nmol/L;  $p = 0.008$ ). Serum concentrations of 13-cis retinoic acid were significantly lower in the newborns (2.0 nmol/L) than in their mothers (2.6 nmol/L;  $p = 0.005$ ). The serum concentrations of all-trans retinoic acid and retinol did not correlate in any group. The authors concluded that retinol concentrations did not accurately reflect the concentrations of the biologically active derivative all-trans retinoic acid.

36. Pregnant women and parturient mothers had significantly lower serum concentrations of retinol than control subjects. The concentration of all-trans retinoic acid was higher in the parturient mothers than in the control subjects. In contrast, the concentrations of 13-cis retinoic acid were lower in parturient mothers than in the control subjects. No difference was observed in the concentrations of all-trans and 13-cis retinoic acid between pregnant women and control women. Pregnant women had significantly higher concentration of 13-cis retinoic acid than did the parturient mothers.

## **Reproductive effects of vitamin A**

### *Overview*

37. The teratogenic effects of retinoic acid have been documented both in animals and in humans (Zile 1998). Retinoic acid induces differential patterns of malformations in mammalian embryos based on the different stages of embryonic

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development (Collins and Mao, 1999). Children exposed *in utero* to isotretinoin (13-*cis*-retinoic acid, used primarily to treat severe acne) have been found to exhibit congenital malformations, known as “the retinoic acid syndrome”. The malformations include small or absent external ears and auditory canals, cleft palate, micrognathia and low set ears. Defects of the central nervous system (micro- or anophthalmia, cerebellar or cortical defects, microcephaly), the thymus and the cardiovascular system (transposition of the heart vessels, aortic arch hypoplasia, ventricular septal defects) have also been observed.

38. Ozaki *et al* (2017) showed that decidual transformation<sup>5</sup> of human endometrial stromal cells (HESCs) resulted in reprogramming of the retinoic acid signalling and metabolic pathways. Differentiating HESCs downregulate the intracellular carrier proteins CRABP2 and FABP5 that are responsible for transfer and binding of retinoic acid to the nuclear receptors RAR and PPAR $\beta/\delta$ , respectively. The expression of the RAR receptor, which mediates the pro-apoptotic effects of retinoic acid, was also inhibited. The PPAR $\beta/\delta$  receptor, which transduces the differentiation responses of retinoic acid, was upregulated. Decidualisation was also associated with increased expression of retinol-binding protein 4 (RBP4) and various enzymes involved in the metabolism of retinoic acid and retinal, including CYP26A1, DHRS3, and RDH12. Exposure of differentiating HESCs to retinoic acid or retinal reversed the inhibition of the CRABP2-RAR pathway, perturbed the expression of decidual marker genes and triggered cell death. The authors concluded that the data showed that decidualizing HESCs silence retinoic acid signalling by downregulating key cytoplasmic binding proteins and by increasing retinoid metabolism. However, excessive retinoic acid exposure is toxic for decidual cells and triggers a response that may lead to pregnancy failure.

### *Animal studies*

39. Within embryos of experimental animals, too little or too much vitamin A/RA causes malformations. Rat fetuses in mothers reared on vitamin A-deficient diets show a range of anomalies known as “fetal vitamin A deficiency”(VAD) syndrome, which comprises defects of hind-brain, eye, ear, heart, lung, diaphragm, kidney, testis, limbs, and skeleton. Mice with compound null mutations of RA nuclear receptors and RA-synthesizing enzymes also have malformations resembling the VAD syndrome. Excess vitamin A/RA in humans and animal models causes malformations resembling the fetal VAD syndrome. Lee *et al* (2012) investigated the effect of excess retinoic acid on the development of rodent embryonic kidneys. It was stated that both vitamin A excess and deficiency were known to lead to lack of kidney development (bilateral renal agenesis) in the hamster and the mouse before there was any morphologically identifiable precursor of the organ present. The authors presented evidence that, paradoxically, the malformations observed following maternal high dose (100 mg/kg bw) RA may have been due to RA deficiency at a crucial stage in development. The mechanism appeared to be RA-induced inhibition of its own endogenous synthesis and increased expression of RA-metabolising CYP isoforms. Pleiotropic mutations resulted, many of which were

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<sup>5</sup> In preparation for implantation of the fertilised ovum, progesterone released from the corpus luteum causes the cells of the superficial layer of the endometrium to enlarge and compact. These cells are known as decidual cells because they are shed after birth and the process is decidualisation (Bowman and Rand, 1980)

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ameliorated by supplementation with a lower dose of RA given to the mother after fetal clearance of the original high dose.

40. The potential adverse effects of retinoids have been assessed in animal studies using both oral and dermal routes of exposure.

#### Dermal exposure

41. Willhite *et al* (1990, from abstract) found that a single application of 17 micrograms/kg or 8.7 mg/kg of radiolabelled all-*trans*-[10,11-<sup>3</sup>H<sub>2</sub>]-retinoic acid dissolved in acetone to shaved dorsal hamster skin was rapidly absorbed and showed a dose-dependent rate of elimination. An equation describing a two-compartment open model with a very brief lag time and first-order uptake and elimination was used to describe the central plasma compartment kinetics. Unchanged all-*trans*-retinoic acid represented up to 4% of the total circulating radioactivity. Peak circulating concentrations of parent all-*trans*-retinoic acid were less than those observed after an equivalent oral dose, but prolonged absorption from the skin contributed to high total bioavailability of retinoid applied topically. Topical administration to intact skin of up to three consecutive doses of 10.5 mg/kg/d all-*trans*-retinoic acid or a single 5 mg/kg dose of etretinate (Ro 10-9359) during a critical stage of embryogenesis in hamsters caused erythema and/or dose-dependent epidermal hyperplasia at the site of application, but failed to induce a significant teratogenic response. Topical application of 0.01-1.0 mg/kg of artificial carotenoid Ro 13-6298 resulted in dose-dependent mucocutaneous toxicity and an increase in the numbers of dead embryos and malformed offspring. The marked skin toxicity and attenuated concentrations in maternal blood, compared to the oral route, limited the amounts of retinoid that reached the hamster embryo. Therefore, it was considered more important to compare the absorbed dose than the applied dose, when interpreting the bioassays. The data suggested that in human skin, toxicity limits the amounts of retinoid that can be applied during pregnancy and subsequently reaches the embryo whereas in the rodent, overt skin toxicity under continued dosing could increase the penetration.

42. A technical report in 2012 by the US National Toxicology Program ([https://ntp.niehs.nih.gov/ntp/htdocs/lt\\_rpts/tr568\\_508.pdf](https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr568_508.pdf)) quotes a study by Seegmiller *et al* (1990) in which time-mated Sprague-Dawley rats were administered retinoic acid topically to clipped intact dorsal skin on gestational days 11 to 14 at 12, 100, or 250 mg/kg bw. Maternal weight gain, pup weight, number of resorptions, number of fetuses with gross malformations, and skeletal and organ anomalies were determined. Dams treated dermally with retinoic acid exhibited skin lesions at the site of application from gestational day 15, and most dams showed vaginal bleeding by day 16. Approximately 20% did not survive to day 19. Maternal weight gains in the treated groups were decreased by approximately 50% relative to control animals at the lowest dose, with essentially no weight gain at the intermediate- and high-dose levels. Decreases in fetal weights at the two higher dose levels were significant, but there were no differences from controls in the number of resorptions or malformation frequencies.

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#### Oral exposure

43. Schnorr *et al* (2011) dosed rats with vitamin A at 750, 375 7500  $\mu\text{g RE/kg}$  and observed an increase of oxidative damage markers in the reproductive tissues and plasma of dams. The activity of glutathione-S-transferase was modulated by vitamin A supplementation, increasing in the liver of dams and decreasing in the kidneys of mothers and offspring. In pups, supplementation decreased the total antioxidant potential of the liver as well as the superoxide dismutase/catalase activity ratio in the kidney. Lipoperoxidation increased in male offspring but decreased in female pups. Although no clear explanation was given for the sex difference in response, the authors suggested that male offspring were more susceptible to free radical injury than were females. The results suggested that excessive vitamin A intake during gestation and lactation might be toxic for mothers with adverse effects for the developing offspring.

#### Human studies

##### Teratogenicity- Food and food supplements

44. Werler *et al* (1990) used data from a case-control study to assess the maternal use of vitamin A supplements alone and vitamin A-containing multivitamin supplements in relation to the occurrence of certain birth defects involving structures derived, at least in part, from cranial neural crest cells. The cases were 2,658 infants with such defects (primarily craniofacial and cardiac malformations) with the controls being 2,609 infants with other malformations. Vitamin A supplementation was defined as daily use for at least 7 days of retinol alone or with vitamin D, or of fish oils. Information on vitamin A dose and nutrition was not available. The mothers of the six controls used vitamin A supplements in each of the first trimester of pregnancy in comparison to the mothers of 15, 14, and 10 cases in months 1, 2, and 3, respectively. Relative risk estimates and 95% confidence intervals were 2.5(1.0-6.2) for month 1, 2.3(0.9-5.8) for month 2, and 1.6(0.6-4.5) for month 3. However, the findings were considered tentative because no dose information was available, only small numbers of cases and controls were exposed to vitamin A supplements, and relative risk estimates were not statistically significant.

45. Rothman *et al* (1995) obtained vitamin A supplement data on 22,748 pregnant women when they had screening for maternal serum alpha-fetoprotein or underwent amniocentesis. Information on the outcomes of pregnancy was obtained from the obstetricians who delivered the babies or from the women themselves. Of the 22,748 women, 339 had babies with birth defects; 121 of these babies had defects occurring in sites that originated in the cranial neural crest. For defects associated with cranial-neural crest tissue, the ratio of the prevalence among the babies born to women who consumed more than 4500  $\mu\text{g RE}$  of preformed vitamin A per day from food and supplements to the prevalence among the babies whose mothers consumed 1500  $\mu\text{g RE}$  or less per day was 3.5 (95 percent confidence interval, 1.7 to 7.3). For vitamin A from supplements alone, the ratio of the prevalence among the babies born to women who consumed more than 3000  $\mu\text{g RE}$  per day to that among the babies whose mothers consumed 4500  $\mu\text{g RE}$  or less per

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day was 4.8 (95 percent confidence interval, 2.2 to 10.5). Using a smoothed regression curve, an apparent threshold was identified near 3000 µg RE per day of supplemental vitamin A. The increased frequency of defects was concentrated among the babies born to women who had consumed high levels of vitamin A before the seventh week of gestation. The authors concluded that among the babies born to women who took more than 3000 µg RE of preformed vitamin A per day in the form of supplements, about 1 infant in 57 had a malformation attributable to the supplement.

46. Azaïs-Braesco and Pascal (2000) reviewed reported cases of teratogenicity associated with high intakes of vitamin A in pregnancy. Up to 20 case reports of the relationship between high vitamin A intake and an adverse pregnancy outcome in humans had been published over the preceding 30 years; however, the authors found these to be of limited use for establishing a quantitative link between vitamin A intake and teratogenic events. The malformations observed were not always consistent with the retinoic acid syndrome, thus calling their true origin into question. The authors found five case-control studies since 1990 retrospectively estimated the intake of vitamin A in control subjects and mothers of malformed babies (see Table 1 below). The design of these studies varied in the classification of malformations, statistical power, and vitamin A consumption data. In most cases, no association was found between moderate doses of vitamin A (<3000 µg RE) and fetal malformations. Moreover, the number of women consuming high amounts of vitamin A was too limited to be statistically significant. Only one prospective study, that of Rothman (1995) had been conducted and the results were inconsistent with the retrospective studies, showing that an intake exceeding 3000 µg RE significantly increased the risk of malformations (prevalence ratio: 4.8; 95% CI: 2.2,10.5). However, the latter paper had been largely criticized in relation to a suspected misclassification of the malformations, but the authors felt it should not be ignored. Another clinical trial had been carried out in Hungary in which a supplement of 1800 µg RE vitamin A did not increase the incidence of fetal malformations, but since folic acid was administered simultaneously with vitamin A only limited conclusions could be drawn regarding the incidence of neural tube defects.

Table1. Case-controlled studies identified by Azaïs-Braesco and Pascal (2000)

Cases	Controls	Exposure (µg RE/day)	Odds ratio for defects	Reference
11 193	11 293	> 3 000 > 13 000	2.7 (0.8, 11.7) 1.1 (0.5, 2.5)	Biesalski HK, 1989
2658	2609	No information on the vitamin A doses	2.3 (0.9, 5.8) 1.6 (0.6, 4.5) 2.5 (1.0, 6.2) NTDs	Martines-Frias <i>et al.</i> , 1990
158	3026	Multivitamin supplements	0.57 (0.33, 1.00) Conotruncal defects	Werler <i>et al.</i> , (1990)

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548 (NTDs)	573	> 2400	NTDs: 0.91 (0.31, 3.68) Other defects: 1.05 (0.51,	Botto <i>et al.</i> , 1996
		>3 000	NTDs: 0.73 (0.40, 1.53) Other defects: 0.92 (0.40, 2.11)	
426	432	0–3333	1.0	Mills <i>et al.</i> , 1996
16	12	3 000–4500	1.4 (0.6, 2.8)	
6	7	>4500	NTDs only	

NTD, neural tube defect. Conotruncal refers to the outflow region of the developing heart.

47. The pharmacokinetics of vitamin A have been investigated in the context of the reported adverse effects.

48. Buss *et al* (1994) dosed 10 health female volunteers with 5 different doses of vitamin A and studied the effects on plasma vitamin A and its metabolites. The single supplements were provided as either retinyl palmitate (15 000 and 45 000 µg RE) or an equivalent dose in fried calf liver. Blood was collected at intervals within 12 h of dosing and thereafter for 6 days. The results showed substantial increases in plasma retinyl palmitate, 13-cis- and all-trans-retinoic acid, and 13-cis and all-trans-4-oxoretinoic acid. Women who received the supplement had significantly higher concentrations of retinoids than did those who received the liver, possibly because the food matrix may have ameliorated the absorption rate or altered the circulating forms of vitamin A. However, plasma retinol changed only slightly, which supported the view that this method was not an appropriate means by which to evaluate a vitamin A supplementation trial. Based on the formation of all-*trans*-retinoic acid, it was concluded that liver and supplements were not of equivalent teratogenic potential. The authors suggested that advice to pregnant women on the consumption of liver based on the reported teratogenicity of vitamin A supplements should be reconsidered.

49. Hartmann *et al* (2005) evaluated plasma concentration-time curves of retinyl esters, retinol and their metabolites at increasing doses of vitamin A in 3 groups (12 per group) of non-pregnant women aged 18-40 years. received once daily oral doses of vitamin A palmitate up to 30,000 IU (9000 µg RE) /day over 21 days. The area under the plasma concentration-time curve (AUC(24h)) served as indicator for exposure. The AUC(24h) of retinyl esters increased linearly with dose. Retinol concentrations were unaffected. All-trans RA exhibited a diurnal-like concentration-time profile (Maximum blood concentration (C<sub>max</sub>) at 3 h; minimum blood concentration (C<sub>min</sub>) at 8 h), concentrations decreasing below pre-dose levels at 5 h

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and regaining pre-dose levels at 16 h. The maximum temporary increase in exposure was 33% (single dose) and 19% (repeated doses) above baseline, but the AUC(24h) remained unaltered. The AUC(24h) increased linearly with dose for 13-cis RA and 13-cis-4-oxo RA. Repeated doses caused a 25% increase in exposure with the highest vitamin A intake. Accumulation of 13-cis-4-oxo RA at 30,000 IU (9000 µg RE) /day doubled compared to the 4,000 IU (1200 µg RE) /day intake. The authors concluded that repeated oral doses of up to 30,000 IU (9000 µg RE) of vitamin A in addition to dietary vitamin A were without safety concern. Safe doses were probably higher, since plasma concentrations and exposure to RA remained at levels earlier shown to be without increased risk of teratogenicity in pregnant women.

50. Nohynek *et al* (2005) investigated the effect of topical vitamin A on human endogenous plasma levels of Vitamin A and its metabolites. Two groups of 14 female volunteers of child-bearing age were kept on a vitamin A-poor diet and treated topically for 21 days with creams containing 0.30% retinol or 0.55% retinyl palmitate on approximately 3000 cm<sup>2</sup> of their body surface area. This gave a total dose of approximately 30,000 IU (9000 µg RE) vitamin A/subject/day. After a 12-day wash-out period, the study groups received single oral doses of 5600 and 16800 µg RE retinyl palmitate (RP), corresponding to the maximal EU allowance during pregnancy or three-times higher, respectively. Blood samples were collected over 24h on study days -3 (pre-study), 1, 21 (first and last days of topical treatment) and 34 (oral administration) at 0, 1, 2, 4, 6, 8, 12, 14-16 h and 24 h after treatment. Plasma concentrations of retinol (REL), retinyl palmitate (RP), retinol oleate (RO) and retinol stearate (RS), 9-cis-, 13-cis-, all-trans- (AT), 13-cis-4-oxo- or AT-4-oxo-retinoic acids (RAs) were analysed. With the exception of transient mild (RP-group) to moderate (REL-group) local irritation on the treatment sites, no adverse local or systemic effects were noted. On days 1 or 21 of topical treatment, no changes were measured in individual or group mean plasma C<sub>max</sub>, AUC (0-24 h) or other pharmacokinetic parameters of REL, retinyl esters or RAs relative to pre-study data. In contrast, single oral doses of RP at 3000 or 9000 µg RE produced dose-related and sustained increases in C<sub>max</sub> and AUC (0-24 h) values of plasma RP, RO, RS, 13-cis- and 13-cis-4-oxo-RAs, as well as a transient increase in AT-RA. Topical exposure to retinol- or retinyl ester-containing cosmetic creams at 9000 µg RE /day and maximal use concentrations were therefore found to not affect plasma levels of retinol, retinyl esters or RAs, whereas single oral doses at 3000 or 9000 µg RE produced significant increases in plasma retinyl esters and RAs.

#### Teratogenicity- oral and topical medications

51. The potential teratogenicity of topically applied retinoic acid prescribed clinically for treatment of acne has been a subject of debate in the past (Wilkinson 1975, Danby, 1978).

52. Lammer *et al* (1985, from abstract) investigated 154 human pregnancies with fetal exposure to isotretinoin, a synthetic retinoid prescribed for severe recalcitrant cystic acne. The outcomes were 95 elective abortions, 26 infants without major malformations, 12 spontaneous abortions, and 21 malformed infants. A subset of 36 of the 154 pregnancies was observed prospectively. The outcomes in this cohort were 8 spontaneous abortions, 23 normal infants, and 5 malformed infants.

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Exposure to isotretinoin was associated with a relative risk of 25.6; (95% confidence interval, 11.4 to 57.5). Among the 21 malformed infants there was a characteristic pattern of malformation involving craniofacial, cardiac, thymic, and central nervous system structures. These included microtia/anotia (15 infants), micrognathia (6), cleft palate (3), conotruncal heart defects and aortic-arch abnormalities (8), thymic defects (7), retinal or optic-nerve abnormalities (4), and central nervous system malformations (18). The pattern of malformation closely resembled that produced in animal studies of retinoid teratogenesis. The authors deemed it possible for a major mechanism of isotretinoin teratogenesis leading to these effects to be a deleterious effect on cephalic neural-crest cells in the fetus.

53. Kizer et al (1990) reviewed the teratogenic effects of isotretinoin. An evaluation of 154 pregnancies with exposure to the drug showed that 14% (21 cases) resulted in malformed infants, 17% (26 cases) in infants without major defects, 8% (12 cases) in spontaneous abortions, and 62 % (95 cases) in elective abortions. The risk for serious birth defects in infants of pregnant women with exposure to isotretinoin was about 25%. Willhite *et al* (1986) reported that isotretinoin administered orally to 64 women during the first trimester of pregnancy resulted in 34 cases of fetal defects and 30 cases of spontaneous abortion. Defects involved pathological changes in the central nervous system, facial malformations with small or absent external ears, and cardiovascular impairments. The total number of infants with birth defects consistent with those associated with isotretinoin use was unclear, with the estimates ranging from 62 to 1,300

54. Kizer *et al* (1990) stated further that human birth defects and spontaneous abortions had been associated with the use of etretinate, the trimethylmethoxyphenyl ethyl ester of all-trans-retinoic acid. Etretinate is currently approved for use in the treatment of psoriasis. In Europe, seven cases of fetal malformations due to etretinate exposure during pregnancy had been reported: these included meningocele, craniofacial and skeletal abnormalities, severe brain defects with anophthalmia, and low-set ears. A case of congenital malformation was reported in a child born to a woman from Brazil who had discontinued etretinate therapy almost a year before she conceived (Lammer *et al*, 1988). There had been no reports of birth defects associated with its use in the United States, but it was approved only in late 1986. The lowest human teratogenic doses for the two retinoids, isotretinoin and etretinate, are estimated to be 0.4 and 0.2 mg per kg per day, respectively (Ross, 1983). Vitamin A is metabolized to the all-trans-retinoic acid, which differs from isotretinoin (13-cis-retinoic acid) only in the conformation of the isoprenoid side chain.

55. All-trans-retinoic acid also produces 13-cis-retinoic acid as a metabolite. Whether vitamin A itself (as retinol or retinyl esters) is a human teratogen is unclear. There have been several isolated case reports of human birth defects with high levels of maternal vitamin A exposure. Some of the malformations are consistent with the pattern of defects produced by isotretinoin, but a causal relationship has not been established. Although poor exposure surveillance confounded by the simultaneous intake of other nutritional supplements makes the available data inconclusive, the evidence certainly raises concerns about possible human teratogenicity of high doses of vitamin A. Isotretinoin, etretinate, and vitamin A as retinol or retinyl esters have been confirmed as embryotoxic and teratogenic in



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studies of animals. These findings contrast with those related to naturally occurring carotenoids, which are metabolised in mammals to vitamin A and have not been identified as teratogenic or embryotoxic in studies of either animals or humans (Howard *et al.* 1986). The existing guidelines from the manufacturer (Hoffmann-LaRoche Inc) for the use of Accutane by women stress the necessity of obtaining a negative pregnancy test two weeks before initiating therapy with Accutane and the importance of using an effective form of contraception a month before, during, and for a month after taking Accutane. Women who become pregnant while using isotretinoin are advised to discuss with their physicians the advisability of continuing the pregnancy. Despite these restrictions and warnings to physicians and consumers, women taking Accutane continue to become pregnant and produce malformed infants (Kizer, 1990).

56. Zomerdijk *et al* (2014) estimated isotretinoin exposure in 203,962 Dutch pregnant women and analysed the occurrence of adverse fetal or neonatal outcomes in these pregnancies. Proportions of adverse fetal or neonatal outcomes, defined as intrauterine deaths  $\geq 16$  week of gestation and neonates with major congenital anomalies were measured in relation to isotretinoin exposure in the 30 days before or during pregnancy. ORs with 95% CIs adjusted for maternal age were calculated to estimate the risk of adverse fetal or neonatal outcome. Of 51 pregnancies, 2.5 (95% CI 1.9 to 3.3) per 10 000 pregnancies, were exposed to isotretinoin despite a pregnancy prevention programme being in place in the EU since 1988. Forty-five of these pregnancies were exposed to isotretinoin and six women became pregnant within 30 days of discontinuing treatment. In five out of the 51 isotretinoin exposed pregnancies (53 fetuses), 9.4% (95% CI 1.3% to 17.6%), had an adverse fetal or neonatal outcome (OR 2.3 95% CI 0.9 to 5.7 after adjustment for maternal age). The authors concluded that isotretinoin exposed pregnancies and adverse fetal and neonatal events potentially related to the exposure still occur and that in the Netherland at least there was no full compliance to the isotretinoin prevention programme.

57. MacDonald *et al* (2019) used the 2011–2015 Truven Health MarketScan® Database to identify pregnancies, including losses and terminations, in a cohort of non-pregnant women filling a prescription for isotretinoin or tretinoin and a second group of women without either prescription. Women were followed for 365-days or until conception, medication discontinuation, or enrolment discontinuation (“prescription episode”). Rates of pregnancy, risks of pregnancy losses, and prevalence of infant malformations at birth were assessed by exposure. The authors identified 2,179,192 livebirths, 8,434 stillbirths, 2,521 mixed births, 415,110 spontaneous abortions, 124,556 elective terminations, and 8,974 unspecified abortions. There were 86,834 isotretinoin and 973,587 tretinoin episodes, matched to 5,302,105 unexposed women. Pregnancy rates were 3 (isotretinoin), 19 (tretinoin), and 34 (unexposed) per 1,000 person-years. Risk of pregnancy losses were similar, but terminations were more common in the women exposed to isotretinoin (28% [95% CI: 21–36%]), than those exposed to tretinoin (10% [95% CI: 9– 11%]) or unexposed (6%). Malformations occurred in 4.5% (95% CI: 3.5–5.6%) of the tretinoin-exposed pregnancies and 4.2% of the unexposed pregnancies (adjusted OR: 1.16 [95% CI: 0.85–1.58]); isotretinoin-exposed births were too few to assess malformations.

## Other reproductive and developmental endpoints

58. Cox *et al* (2006) performed a double-blind, randomised, placebo-controlled trial of weekly vitamin A supplementation in pregnant and lactating women and found that supplementation was significantly associated with an increased ratio of mitogen-induced proinflammatory cytokine (IFN-  $\gamma$ ) to anti-inflammatory cytokine (IL-10) levels during pregnancy and in the postpartum period. A group of 89 pregnant Ghanaian women were assigned randomly to receive 3000  $\mu$ g RE weekly of vitamin A, as retinyl palmitate, or placebo (groundnut oil plus tocopherol) until 6 weeks postpartum. While this appeared to be beneficial with regard to the maternal response to infections, the authors recognised that potentiation of pro-inflammatory responses during pregnancy could potentially be a double-edged sword. While stronger Th-1 responses might reduce the risk of infection during pregnancy, providing protection against opportunistic viral, bacterial and protozoal infections that target the placenta and/or the developing fetus, inappropriate overproduction of type 1 cytokines may cause placental damage and threaten the viability of the fetus and the mother, potentially leading to spontaneous abortion (Raghupathy *et al* 1999, Raghupathy *et al* 2000, Kwak-Kim *et al*, 2003).

59. Cohen *et al* (2015) performed a systemic review and meta-analysis searching PubMed, Embase, and several other databases from 1970–2013 for observational studies that measured maternal blood levels of non-enzymatic antioxidants (vitamins A, C, E, and carotenoids) during pregnancy or within 72 hours of delivery. The aim was to explore any association between maternal antioxidant levels during pregnancy and preeclampsia or small-for-gestational-age (SGA) offspring. Retinol was measured in the first trimester in one study, second trimester in two studies, and third trimester in thirteen studies in relation to pre-eclampsia. The meta-analysis of twelve third trimester studies showed a significantly negative standardised mean difference (SMD) but substantial heterogeneity. One additional study reported that blood retinol was non-significantly lower for pre-eclampsia cases versus controls. For mild and severe preeclampsia where there were fewer studies, the pooled SMDs were null with substantial heterogeneity. Three studies found that retinol levels measured in the second trimester were similar among pregnancies resulting in SGA versus appropriate for gestational age (AGA) birth. Three other studies measured retinol in the third trimester, all of which provided raw data for meta-analysis. Results were very heterogeneous. Only one study measured levels before delivery and found significantly higher retinol in mothers who delivered SGA babies. The study in question (Ortega-Senovilla *et al*, 2010, from abstract) suggests that intrauterine growth restriction pregnancies may be partially due to reduced placental transfer of vitamin A, leading to higher than expected maternal blood levels. Two of the studies measured retinol levels shortly after delivery and found no significant differences for mothers who delivered SGA compared to AGA babies.

60. Mawson and Croft (2019) considered the hypothesis that the signs and symptoms of rubella may be due to virus-induced alterations in vitamin A metabolism and its accumulation in the liver, leading to mild hepatic inflammation and dysfunction and to the spillage of stored vitamin A compounds into the circulation in correspondingly low concentrations and hence mild toxicity. The authors' hypothesis suggests that autism due to rubella infection in the early weeks of pregnancy may

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similarly result from maternal liver dysfunction and exposure of the fetus to excess endogenous vitamin A, resulting in embryopathy and long-term metabolic and neurodevelopmental disorders.

61. The authors suggest that it follows that increasing rates of regressive autism result primarily from post-natal factors to which almost all children are exposed, causing liver dysfunction and both acute and chronic forms of hypervitaminosis A. These post-natal factors may include: multiple vaccinations and their ingredients administered together or in close succession, especially when combined with the physiological impact of preterm birth; the intake of high vitamin A-containing and vitamin A-fortified foods such as dairy products, infant formula, and vitamin A supplements; and exposure to certain ubiquitous herbicides that may influence retinoid metabolism. Further studies are awaited on the overall safety and health outcomes of the current vaccination schedule, with a view to optimizing the beneficial impact of vaccines on children's health. An early diagnosis of Autism Spectrum Disorder (ASD) and Congenital Rubella Syndrome-like features in infants may be due to maternal exposures of a liver-damaging nature in the early weeks of pregnancy. Young children with liver-related conditions that include preterm birth and metabolic disorders, as well as genetic factors associated with alterations in vitamin A metabolism, may be especially susceptible to autism and related neurodevelopmental disorders. The authors felt that the model could be tested by comparing children with autism and controls in terms of liver function, vitamin A enzyme activity, and retinoid concentration profiles (retinol, retinyl esters, percent retinyl esters, and retinoic acid). Children with autism would be expected to have significantly reduced vitamin A metabolic and catabolic enzyme activity, increased retinoic acid concentrations and receptor expression, low or normal concentrations of retinol and its transporter, RBP, and an increased percentage of serum retinyl esters as a fraction of total vitamin A (retinyl esters plus retinol). Subject to testing, novel dietary and clinical measures could be investigated for the treatment of ASD and associated allergic and metabolic disorders.

62. Parr *et al* (2009) studied 61,676 school-age children (born during 2002–2007) from the Norwegian Mother and Child Cohort considering data on maternal total (food and supplement) nutrient intake in pregnancy (food-frequency questionnaire validated against biomarkers) and infant supplement use at age 6 months (n = 54,142 children). Linkage with the Norwegian Prescription Database enabled near-complete follow-up (end of second quarter in 2015) for dispensed medications to classify asthma. Maternal subjects were controlled for age at delivery, parity, pre-pregnancy BMI, education, history of asthma and atopy and smoking in pregnancy. Log-binomial regression was used to calculate adjusted risk ratios (aRRs) for asthma with 95% CIs. Asthma increased according to maternal intake of total REs. in the highest ( $\geq 2031$  REs/day) compared with the lowest ( $\leq 779$  REs/day) quintile (aRR: 1.21; 95% CI: 1.05, 1.40). The authors concluded that excess vitamin A ( $\geq 2.5$  times the recommended intake) during pregnancy was associated with increased risk of asthma in offspring.

Interactions

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63. Zachmann and Gummer (2006) reviewed the literature on interactions between ethanol and retinoic acid as a possible mechanism for birth defects described as fetal alcohol syndrome. Different models have been proposed:

- the synthesis of retinoic acid from retinol, catalysed by alcohol dehydrogenase, might be competitively inhibited by ethanol leading to retinoic acid deficiency;
- ethanol consumption might affect maternal retinol, retinyl ester, or retinoic acid levels, RAR binding, and the levels of RAR expression in developing fetal organs, as has been seen in rats, although specific defects resulting from specific RAR changes have not yet been identified;
- ethanol treatment (exposure?) might mimic vitamin A deficiency, since retinoic acid appears to prevent the adverse effects of ethanol in a quail model;
- retinoic acid and ethanol might reverse or block each other's effects, as has been seen in neuroblastoma cells *in vitro*.

64. The authors suggested that these experiments showed definite interactions between ethanol and vitamin A, but further studies would be needed to determine if any of these mechanisms significantly contributed to prenatal ethanol consumption embryopathy.

65. Interactions have been found between vitamin A and various dietary components and pharmaceuticals, including vitamin D, which appears to ameliorate vitamin A toxicity to some extent and vice versa (Parr *et al* 2018).

66. Dietary conjugated linoleic acid (CLA) has been found to increase tissue levels of retinol (vitamin A alcohol) and its sole specific circulating carrier protein retinol-binding protein (RBP or RBP4). However, the precise mechanism of this action has not been elucidated. Carta *et al* (2014) suggest that retinol and CLA may compete for catabolic pathways modulated by the activity of peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ) and RXR heterodimer. The authors also presented preliminary data that may position PPAR- $\alpha$  at the crossroads between the metabolism of lipids and vitamin A.

67. Christian and West (1998) reviewed how zinc status has been purported to influence several aspects of vitamin A metabolism, including its absorption, transport, and utilization. Postulated mechanisms relate to either the regulatory role of zinc in vitamin A transport mediated through protein synthesis, and /or the oxidative conversion of retinol to retinal by a zinc-dependent retinol dehydrogenase enzyme. A curvilinear relation has been suggested to describe an effect of plasma zinc on vitamin A transport but clear evidence of synergy between these two micronutrients and its public health significance in humans is lacking.

68. The EVM (2003) stated that vitamin A may antagonise the action of vitamin K in blood clotting function and may potentiate the development of intracranial hypertension when taken in combination with tetracycline and minocycline type

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antibiotics. Drugs such as ketoconazole, which inhibit cytochrome P450, can significantly increase the half-life of retinoic acid. Hypervitaminosis A may decrease vitamin C tissue storage and may have an anti-thyroid effect.

### *Beta-carotene*

69. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered  $\beta$ -carotene in 1974 and concluded that hypercarotenaemia *per se* was harmless and caused no adverse symptoms or hypervitaminosis A; the condition disappears if excess intake of beta-carotene is discontinued. JECFA quoted an older study, (Greenberg *et al*, 1959) where fifteen subjects received 60 mg beta-carotene daily for three months. Serum carotene levels rose from 128  $\mu$ g to a maximum of 308  $\mu$ g/100 ml after one month while Vitamin A levels remained unchanged. No clinical signs of hypervitaminosis A were seen. Other subjects ate several pounds of raw carrots daily, resulting in some skin discoloration. Beta-carotene appeared in breast milk. High doses of beta-carotene were found to reduce liver storage of labelled dl-gamma-tocopherol acetate (vitamin E) to 70%. In their evaluation, JECFA (1974) found a NOAEL in rat of 50 mg/kg bw and derived a human ADI of 0 – 5 mg/kg bw based on a four-generation study at dietary levels of 0 ppm and 1000 ppm of beta-carotene for 110 weeks that showed no adverse effects in any of the generations.

70. In 2017, at the 84<sup>th</sup> meeting of JECFA, the Committee noted that new data showed large differences in absorption of  $\beta$ -carotene between rodents and humans and therefore considered that rodents were an inappropriate animal models for establishing an ADI for  $\beta$ -carotene. At the 87<sup>th</sup> meeting in 2019, the Committee considered that "...no adverse health effects were observed in the general population in large, well-conducted human intervention studies in which healthy participants were administered 20–50 mg  $\beta$ -carotene per day for up to 12 years, in addition to background exposure from the diet. ...For the general population, the Committee concluded that the estimated high exposure to  $\beta$ -carotene of 9 mg/day for a 30 kg child and 6 mg/day for a 60 kg adult from its current uses as a food additive, in addition to background exposure from the diet, would not be expected to be a safety concern," (JECFA 2019).

71. Allen and Heskell (2002) found no reports of high-carotene intakes from foods ever having caused vitamin A toxicity. It had been assumed that about one-third of a dose of dietary carotenoids was absorbed and half that amount was converted to retinol, resulting in a bioconversion factor of 6:1 for  $\beta$ -carotene to retinol. This bioconversion factor had been used in most food composition tables to convert carotenoids to retinol equivalents. However, in the early 1990s it became apparent that absorption of carotene from plant sources, especially from vegetables, was substantially less than one-third that absorbed from a dose given in oil. More recent estimates of  $\beta$ -carotene absorption from a diet consisting mainly of vegetables showed that absorption was about one half what was previously assumed. Based on such studies, the Institute of Medicine estimated that 1 retinoic acid equivalent was equal to 12  $\mu$ g of  $\beta$ -carotene instead of the 6  $\mu$ g of  $\beta$ -carotene estimate used previously.

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72. Omenn *et al* (1996) reported the commencement of the  $\beta$ -carotene and retinol efficacy trial (CARET) for chemoprevention of lung cancer in high risk populations: smokers and asbestos-exposed workers. CARET was a multicentre, two-armed, double-blinded randomized chemoprevention trial in Seattle, Portland, San Francisco, Baltimore, Connecticut, and Irvine, to test whether oral administration of  $\beta$ -carotene (30 mg/day) plus retinyl palmitate (25,000 IU/day) could decrease the incidence of lung cancer in high risk populations,

73. Goodman *et al* (2004) reported that CARET was stopped ahead of schedule because participants who were randomly assigned to receive the active treatment were found to have a 28% increase in incidence of lung cancer, a 17% increase in incidence of death and a higher rate of cardiovascular disease mortality compared with participants in the placebo group. With follow-up through December 31, 2001, the post-intervention relative risks of lung cancer and all-cause mortality for the treatment group compared with the placebo group were 1.12 (95% confidence interval [CI] 0.97 to 1.31) and 1.08 (95% CI 0.99 to 1.17), respectively. Relative risks remained above 1.0 throughout the post-intervention follow-up but conversely, the relative risk of cardiovascular disease mortality decreased rapidly to 1.0 after the intervention was stopped. During the post-intervention phase, females had larger relative risks of lung cancer mortality (1.33 versus 1.14;  $p=.36$ ), cardiovascular disease mortality (1.44 versus 0.93;  $p=0.03$ ), and all-cause mortality (1.37 versus 0.98;  $p=.001$ ) than males. The reported adverse effects of  $\beta$ -carotene and retinyl palmitate on lung cancer incidence and all-cause mortality in cigarette smokers and individuals with occupational exposure to asbestos persisted after drug administration was stopped although they were no longer statistically significant. Subgroup analyses planned at the time suggested that the excess risks of lung cancer were restricted primarily to females, and cardiovascular disease mortality primarily to females and to former smokers.

74. Tayyem *et al* (2019) conducted a case-controlled study on 400 Jordanian women aged 20 - 65. Two hundred women recently diagnosed with breast cancer were matched in age, income, and marital status to 200 breast cancer-free women. A food frequency questionnaire was used to assess nutrient intake patterns. A significant increase in breast cancer risk was associated with high vitamin C and  $\beta$ -carotene intake (the highest for the fourth quartile; odds ratio [OR], 5.42; 95% confidence interval [CI], 2.11 to 13.91;  $p_{trend}=0.001$ ). Conversely, a significant inverse trend was detected for the risk of breast cancer and high calcium, phosphorus, and vitamin D intake. A high-fat nutrient intake also showed a significant direct association with breast cancer risk in the third (OR, 3.88; 95% CI, 1.58 to 9.51) and fourth (OR, 3.87; 95% CI, 1.53 to 9.77) quartiles ( $p_{trend}=0.001$ ).

75. However, the authors pointed out that there was somewhat weaker evidence for a link between vitamin C and  $\beta$ -carotene with hormone-sensitive breast cancer in the study of Bakker *et al* (2016). Moreover, Nagel *et al* (2010) demonstrated no associations and of breast cancer with high dietary intake of vitamin C and  $\beta$ -carotene. For their study, Tayyem *et al* offered the explanation of Salganik *et al* (2001), who reported that reactive oxygen species in moderate concentrations act as mediators of apoptosis and phagocytosis, and that in people with a low level of reactive oxygen species, an excess of antioxidants could block these mechanisms

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and promote cancer. This would also explain how an excess of antioxidants could be cancer-promoting in people who are regularly exposed to the effect of environmental carcinogenic factors (tobacco smoke, industrial pollutants) that result in a high accumulation of pre-cancerous and cancerous cells.

## Exposure

### *Population estimates*

76. In many regions of the world, for example, regions of Africa and south-west Asia (Harika *et al*, 2017) the issue with vitamin A is deficiency and the deleterious effects this has upon the health of unborn children. However, in developed countries, many people regularly have an intake that exceeds EFSA's dietary reference value, with a range of values across European countries being reported, although values did not exceed the tolerable upper limit of 3000 µg RE/day (Jenab *et al*, 2009). Allen and Haskell (2002) found that in the United States, the 95th percentile of RE intake from foods and supplements for non-pregnant, non-lactating women aged 19–30 years exceeded the UL but was below the NOAEL for women of reproductive age. Specifically, for non-pregnant, non-lactating women aged 19–30 years, the median intake of vitamin A (retinol and provitamin A carotenoids) from food was 530 µg of RE/day, and the 95th percentile was 1112 µg of RE/day. Reportedly, 17% of this group took supplements. For these women, the median level of vitamin A in the supplements was about 1422 µg of RE/day with a 95th percentile of 2543 µg/day. A woman who consumed the 95th percentile of vitamin A from both diet and supplements would consume about 3655 µg of RE/day, which exceeds the UL of 3000 µg/day. However, a daily intake of 4500 µg of RE/day (the NOAEL) among women of reproductive age is not associated with any adverse effects.

77. EFSA (2015) estimated the average dietary intake in adults as being between 816 and 1,498 µg RE/day (retinol and provitamin A carotenoids). Average daily intakes were in most cases slightly higher in males than in females, mainly owing to the larger quantities of food consumed per day.

78. UK Government dietary advice, as communicated via the [NHS.uk website](https://www.nhs.uk) recommends a daily vitamin A intake for adults aged 19 to 64 of 700 µg for men and 600 µg a day for women and that the diet should provide this. Pregnant women are warned about eating liver or liver products such as pate, or supplements that contain vitamin A to avoid potential harm to the unborn baby.

### UK retinoid intake

79. The FSA Exposure Assessment Team have sourced information on vitamin A/pro-vitamin A carotenoid intake in women of childbearing age. Full details are given in Appendix A

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Table 2. Chronic exposure of Vitamin A (retinol equivalents) in women from food sources only (Bates et al., 2014, 2016; 2018)\*\*.

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Age group	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
16 – 49 yrs	760	2600	11	39
19 – 64 yrs	830	2800	12	43

\*Rounded to 2 significant figures

\*\*Based on total population

Table 3. Chronic exposure of Vitamin A from Liver (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018)^.

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
25	3500	7500	50	97

\*Rounded to 2 significant figures

\*\*Consumption or exposure estimates made with a small number of consumers may not be accurate. The number of consumers is less than 60, this should be treated with caution and may not be representative for a large number of consumers.

^Based on food consumers on all types of liver

80. Appendix A, table 16 gives a list of food products fortified with vitamin A. On the basis of one of these products being consumed once daily, the highest contribution that any one of them would make would be an extra 432 µg RE/day (Dr Witt Multivitamin drink).

81. Appendix A Table 17 gives a list of food supplements containing β-carotene or vitamin A. The supplements containing 1 – 7 mg of β-carotene do not have warnings against their use by pregnant women because of the accepted low risk of this provitamin, but the supplements containing various esters of preformed vitamin A (300 – 906 mg/serving) are not recommended in pregnancy.



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## **Risk Characterisation**

82. Based upon the EFSA TUL of 3000 µg RE/day and taking women of childbearing age as a whole, the intake of retinol equivalents from food at the 97.5<sup>th</sup> percentile of consumption is close to, but still below, the TUL and therefore would not be a concern for their health or for the development of a fetus borne by these women. However, the small group in the food surveys who consume liver at the mean level have an intake that marginally exceeds the TUL (117%) and those who are in the highest consumer group have an intake of 250% of the TUL. If the latter level of consumption were continued into a pregnancy, then this may lead to an increased risk of the fetus suffering a neural tube defect or other developmental lesion that may lead to deformity. Despite the caveat that the data on liver consumption is only recorded in a small number of women of childbearing age, this underlines the rationale behind the UK Government's advice for pregnant women to abstaining from consuming liver during pregnancy.

83. Likewise, fortified food products if eaten to excess, may contribute to an exceedance of the TUL, although this would only be marginal.

84. Moreover, although the consumption of vitamin A rich food supplements on their own do not provide enough RE to exceed the TUL, the nature of their consumption, in addition to a normal diet, especially in the case of cod liver oil, could push RE intake over the TUL. This is consistent with the current Government advice that supplements containing vitamin A are not recommended for pregnant women.

## **Discussion and conclusions**

85. Vitamin A in the diet, either as pro-vitamin A carotenoids from plants or as preformed retinol from animal sources is essential for health in general and for fetal development and vision in particular.

86. The functions of vitamin A are mediated by various isomeric forms of retinaldehyde and retinoic acid. Retinaldehyde has a central function in vision that is not specific to any section of the population. Retinoic acid is involved in multiple aspects of embryogenesis and is a known teratogen in excess.

87. Teratogenicity and embryotoxicity have been observed in animals exposed to high doses of vitamin A as retinol or retinyl esters and to the medicinal compounds isotretinoin and etretinate. Oral Isotretinoin exposure has been observed in human case control studies to be correlated with an increased risk of spontaneous abortions and birth defects. However, in general, findings in humans, although suggestive of neural crest defects in development, have been mixed and in some cases, their aetiology uncertain. Despite this ambiguity, pregnant women or those considering becoming pregnant are not recommended to consume foods, such as liver, or take supplements that are rich in pre-formed vitamin A.

88. Intake of vitamin A in developed countries often exceeds the reference dose as set by EFSA.

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89. Topical application of retinoids does not appear to contribute markedly to overall plasma levels and hence are of low risk to pregnant women and their fetuses.

90. Oral supplements of vitamin A or synthetic analogues may lead to retinoic acid levels that could exert teratogenic or other effects in humans, although dietary levels generally do not.

91. Excess intake of  $\beta$ -carotene does not lead to increased plasma retinol concentrations because of its low conversion rate but may, for example in heavy smokers, increase the risk of cancer in specific circumstances.

### **Questions for the Committee**

92. The Committee are asked to consider the following questions.

- a) Does the Committee agree that levels of pre-formed vitamin A in the diet in general, excepting the use of supplements or consumption of liver and liver products, are unlikely to pose a risk to the health of women of childbearing age who are pregnant or considering becoming so, or to the development of their unborn fetus?
- b) Do members agree that the current UK Government advice that pregnant women or those who are considering becoming so should avoid or limit the consumption of liver and liver products is still appropriate?
- c) Does the Committee consider that the use of food supplements rich in pre-formed vitamin A should be avoided by the same groups of women?
- d) Does the Committee consider the use of supplements containing beta carotene to be appropriate for pregnant women or those considering becoming pregnant?
- e) Are there any other end points of potential concern?
- f) Does the Committee have any further comments on this paper?

Secretariat

August 2021

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## Abbreviations

AGA	Adequate for Gestational Age
ASD	Autism spectrum disorder
AUC	Area under the dose-response curve
Bw	Body weight
CARET	Beta Carotene and Retinol Efficacy Trial
CI	Confidence Interval
Cmax	Maximum concentration in plasma
COT	Committee on the Toxicity of Chemicals in Food, the Environment and Consumer Products
CYP	Cytochrome P <sub>450</sub>
DNA	Deoxyribonucleic Acid
DRV	Dietary Reference Value
EFSA	European Food Safety Authority
EVM	Expert committee on Vitamins and Minerals
HIV	Human Immunodeficiency Virus
IFN- $\gamma$	Interferon-gamma
IU	International Units
JECFA	Joint FAO/WHO Committee on Food Additives
LPL	Lipoprotein Lipase
LRAT	Lecithin: Retinoic acid Acyltransferase
mg	milligram
NOAEL	No-Observed Adverse Effect Level
NTD	Neural tube defect
OR	Odds Ratio
PPAR	Peroxisomal Proliferator Activated Receptor
PRI	Population Reference Index
RA	Retinoic acid
RAL	Retinaldehyde
RAR	Retinoic Acid Receptor
RBP	Retinol Binding Protein
RDA	Recommended Daily Allowance
RE	Retinol equivalents
RP	Retinyl palmitate
RXR	Retinoid-X-Receptor
SACN	Scientific advisory Committee on Nutrition
SGA	Small for Gestational Age
TUL	Tolerable Upper Limit
VAD	Vitamin A Deficiency
$\mu$ g	microgram

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

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

#### Literature search

The following terms were input into PubMed and the relevant papers found as well as references therein were cited in this paper:

Vitamin A AND maternal health  
prerconception  
conception  
pregnancy  
postnatal  
fetus OR foetus  
teratogen\*  
abortion  
absorption  
distribution  
metabolism  
excretion  
toxicity  
repro\*  
interactions  
beta carotene  
preeclampsia  
cancer

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## Appendix 1: Vitamin A content of foods, fortified food products and supplements

Table 1. Approximate Vitamin A concentrations in foods (FSA, 2021)

Food type	Retinol Equivalent ( $\mu\text{g}$ /100g)	Type of Vitamin A
Liver calf (fried in corn oil)	25217	Pre formed retinol
Liver, chicken, fried in corn oil	10500	Pre formed retinol
Giblets, turkey, boiled	3100	Pre formed retinol
Eel, yellow, raw	1200	Pre formed retinol
Ghee, butter	1233	Pre formed retinol
Fat spread, low fat (26-39%), polyunsaturated	962	Pre formed retinol
Carrots, raw	1961	Carotenoids
Carrots, boiled	1850	Carotenoids
Spinach, boiled	1101	Carotenoids
Sweet potato, flesh only, boiled in unsalted water	927	Carotenoids
Curly Kale, raw	525	Carotenoids
Melon, Canteloupe-type, flesh only, weighed with skin	194	Carotenoids
Mangoes, ripe, flesh only, raw	116	Carotenoids
Apricots, dried	105	Carotenoids
Peaches, raw, flesh and skin	19	Carotenoids

## Consumption and exposure assessments for vitamin A in various food sources

The following tables (Tables 2 to 13a) details consumption of selected foods containing vitamin A and indicate estimated exposure to vitamin A. The exposure estimates are derived from individual consumption of these foods and take into account various forms of the foods as well as recipes. For example, liver from different animal sources contain varying amounts of vitamin A (Table 1). As such, exposure estimates take account of only some of the concentrations shown in Table 1. All variations of foods available within the NDNS database were used to obtain the consumption and exposure estimates.

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

Table 2. Chronic exposure of Vitamin A (retinol equivalents) in women from food sources only (Bates et al., 2014, 2016; 2018)\*\*.

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Age group	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
16 – 49 yrs	760	2600	11	39
19 – 64 yrs	830	2800	12	43

\*Rounded to 2 significant figures

\*\*Based on total population

### Liver

Table 3. Chronic consumption of all types of liver (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018)^.

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
25	22	38	0.33	0.56

\*Rounded to 2 significant figures

\*\*Consumption or exposure estimates made with a small number of consumers may not be accurate. The number of consumers is less than 60, this should be treated with caution and may not be representative for a large number of consumers.

^Based on food consumers of all types of liver

Table 3a. Chronic exposure of Vitamin A from all types of liver (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018)^.

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
25	3500	7500	50	97

\*Rounded to 2 significant figures

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\*\*Consumption or exposure estimates made with a small number of consumers may not be accurate. The number of consumers is less than 60, this should be treated with caution and may not be representative for a large number of consumers.

^Based on food consumers on all types of liver

## Butter

Table 4. Chronic consumption of butter (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
1474	5.9	25	0.09	0.37

\*Rounded to 2 significant figures

Table 4a. Chronic exposure of Vitamin A from butter / ghee (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
1474	40	230	0.60	3.5

\*Rounded to 2 significant figures

## Milk

Table 5. Chronic consumption of cow's milk (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
1814	150	460	2.2	7.1

\*Rounded to 2 significant figures

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

Table 5a. Chronic exposure of Vitamin A from cow's milk (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
1814	36	120	0.54	1.8

\*Rounded to 2 significant figures

### Egg yolk

Table 6. Chronic consumption of egg yolk (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018)\*\*.

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
903	8.5	25	0.15	0.38

\*Rounded to 2 significant figures

\*\*Assumption – average egg contains 29% yolk.

Table 6a. Chronic exposure of Vitamin A from egg yolk (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018)\*\*.

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
903	12	34	0.17	0.52

\*Rounded to 2 significant figures

\*\*Assumption – average egg contains 29% yolk.

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## Carrots

Table 7. Chronic consumption of carrots (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
1327	21	74	0.31	1.1

\*Rounded to 2 significant figures

Table 7a. Chronic exposure of Vitamin A from carrots (with recipes) in women aged 16-49 (Bates et al., 2014, 2016; 2018)\*.

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
1327	330	1300	4.9	20

\*Rounded to 2 significant figures

## Peppers

Table 8. Chronic consumption of peppers (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
1049	14	60	0.21	0.91

\*Rounded to 2 significant figures

Table 8a. Chronic exposure of Vitamin A from peppers (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
1049	12	51	0.18	0.76

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\*Rounded to 2 significant figures

### Spinach

Table 9. Chronic consumption of spinach (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
222	19	61	0.24	0.97

\*Rounded to 2 significant figures

Table 9a. Chronic exposure of Vitamin A from spinach (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
222	103	517	1.6	8.4

\*Rounded to 2 significant figures

### Cantaloupe melon

Table 12. Chronic consumption of Cantaloupe melon (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
42	46	131	0.78	2.5

\*Rounded to 2 significant figures

\*\*Consumption or exposure estimates made with a small number of consumers may not be accurate. The number of consumers is less than 60, this should be treated with caution and may not be representative for a large number of consumers



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Table 12a. Chronic exposure of Vitamin A from Cantaloupe melon (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
42	135	384	2.3	7.5

\*Rounded to 2 significant figures

\*\*Consumption or exposure estimates made with a small number of consumers may not be accurate. The number of consumers is less than 60, this should be treated with caution and may not be representative for a large number of consumers

### Mango

Table 13. Chronic consumption of mango (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
235	18	105	0.26	13

\*Rounded to 2 significant figures

Table 13a. Chronic exposure of Vitamin A from mango (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
234	15	94	0.22	1.3

\*Rounded to 2 significant figures

### Apricot

Table 14. Chronic consumption of apricot (with recipes) (Bates et al., 2014, 2016; 2018).

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	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
88	5.7	27	0.084	0.40

\*Rounded to 2 significant figures

Table 14a. Chronic exposure of Vitamin A from Apricot (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
88	3.8	20	0.057	0.30

\*Rounded to 2 significant figures

## Peach

Table 15. Chronic consumption of peaches (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
77	24	110	0.34	1.3

\*Rounded to 2 significant figures

Table 15a. Chronic exposure of Vitamin A from peaches (with recipes) (Bates et al., 2014, 2016; 2018).

	(µg/person/day)*	(µg/person/day)*	(µg/kg bw/day)*	(µg/kg bw/day)*
Consumers**	Mean	97.5 <sup>th</sup> percentile	Mean	97.5 <sup>th</sup> percentile
77	4.6	21	0.67	0.28

\*Rounded to 2 significant figures

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## Fortified foods

Foods are sometimes fortified with vitamin A such as butter and other fat spreads, milk and nutritional powders and cereal products. Some foods such as spreads and sports drinks are fortified with beta carotenes which are used for colouration of the product.

Table 16. Estimated exposure from fortified food products containing Vitamin A (Tesco, Sainsbury's, Asda, Boots, Holland & Barret, Morrisons, M&S 2021)

Food product	Vitamin A concentration	Vitamin A concentration ( $\mu\text{g}$ per serving)	Exposure <sup>^</sup>
<b>Butters and Spreads</b>	<b><math>\mu\text{g}</math> per 100 g</b>	<b><math>\mu\text{g}</math> per 10 g serving</b>	<b><math>\mu\text{g}/\text{kg}</math> bw/day*</b>
Flora Original Spread 500G	814	81.4	1.2
Flora Buttery Spread 500g	233	23.3	0.33
Flora Light Spread 500G	839	83.9	1.2
Flora ProActiv Buttery Taste Spread 500G	120	12	0.17
Bertolli Original Spread 500G	800	80	1.1
Bertolli With Butter 400G	800	80	1.1
Benecol Buttery Spread 500G	900	90	1.3
Pure Vegan Dairy Free Olive Spread 500g	800	80	1.1
Pure Vegan Dairy Free Sunflower Spread 500g	800	80	1.1
<b>Nutritional Drink powders</b>	<b><math>\mu\text{g}</math> per 100 g</b>	<b><math>\mu\text{g}</math> per serving</b>	
Complan Nutritional Drink Strawberry 4X55g	551	303 per 55 g	4.3
Complan Nutritional Drink Drink Chocolate 4X55g	522	287 per 55 g	4.1

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Complan Nutritional Drink Banana 4X55g	550	303 per 55 g	4.3
Complan Nutritional Drink Original 425G	547	301 per 55 g	4.3
Slimfast Vitality Meal Replacement Shake Chocolate Intensity 400g	81.9 (as prepared)	243 (as prepared) per 40 g	3.5
USN Diet Fuel Ultralean Strawberry Flavoured Meal Replacement Shake	474	256 per 54 g	3.6
<b>Nutritional Drinks</b>	<b>µg per 100 ml</b>	<b>µg per serving</b>	
Tropicana+ Vitamin Victory Juice 750ml	208	312 per 150 ml	4.4
Benefit Drinks Cleanse Prune Juice	320	800 per 250 ml	11
Oshee Vitamin Cocktail 250ml	160	400 per 250 ml	5.7
Slim-Fast Milkshake Strawberry 6 x 325ml	73.8	240 per 325 ml	3.4
Dr Witt Multivitamin Drink 1 Litre	216	432 per 200 ml	6.1
<b>Nutrient Powder (foods)</b>	<b>µg per 100g</b>	<b>µg per serving</b>	
Funktional Foods Spirulina Powder 100G	3685	369 per 10 g	5.2
Funktional Foods Wheatgrass Powder 100G	1289	258 per 10 g	3.7
<b>Dried Milk</b>	<b>µg per 100 ml as prepared</b>	<b>µg per serving as prepared (200 ml)</b>	
Sainsbury's Skimmed Milk Powder 300g	66.7	133	1.9
Tesco Instant Dried Skimmed Milk 340G	71	142	2.0
Marvel Dried Milk Powder 278G	66	132	1.9
<b>Cereal bars</b>	<b>µg per 100 g</b>	<b>µg per serving</b>	

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Oshee Vitamin Muesli Bar Hazlenut & Raisin 40g	300	120 per 40 g	1.7
Oshee Vitamin Muesli Bar Plum & Cranberry 40g	300	120 per 40 g	1.7
Slimfast Meal Replacement Very Berry Bar 4 x 60g	400	240 per 60 g	3.4
<b>Other products</b>	<b>µg per 100 g</b>	<b>µg per serving</b>	
Blockhead Sugar Free Vitamin D, C, B & A Gum		800 per 2 pieces	11
Tetley Super Fruit Multi Vitamins Berry 20 Tea Bags 40G	30	30 per 100 ml	0.43
Potters Malt Extract with Cod Liver Oil Butterscotch 650g	1720	172 per 10 g	2.4
Boots Malt Extract + Cod Liver Oil - 650g	1400	140 per 10 g	2.0

^Exposure is calculated from the recommended serving size and the average body weight of women aged 16- 49 years (70.3kg)

\*Rounded to 2 significant figures

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## Supplements

Table 17. List of a sample of supplements containing vitamin A (Sources: Lloyds Pharmacy, Boots Pharmacy and Superdrug)

Supplement	Maternal supplement? <sup>^</sup>	Vitamin A form	Recommended intake	Daily exposure (mg/kg)*
Vitabiotics pregnacare tablets range	Yes	Beta carotene	2mg/day	0.028
Vitabiotics Pregnacare Liquid	Yes	Beta carotene	1mg/day	0.014
Vitabiotics pregnacare breastfeeding range	Yes	Beta carotene	2mg/day	0.028
Seven Seas all stages during pregnancy	Yes	Beta carotene	1mg/day	0.014
Seven Seas pregnancy follow on	Yes	Beta carotene	1mg/day	0.014
Proceive Advanced Fertility Supplement Max Women	Yes	Beta carotene	7mg/day	0.10
Seven Seas Adult Complete Multivitamins 28	No	Vitamin A Acetate	800ug/day	0.011
Healthspan women's multivitamin super fruit 30 gummies	No	Vitamin A Palmitate	800ug/day	0.011
Pink simply radiant multivitamin for her gummies 60 gummies	No	Vitamin A	750ug/day	0.011
Superdrug Multivitamin With Iron	No	Vitamin A Acetate	800ug/day	0.011
Bassets Adult Multivitamin Pastilles	No	Vitamin A	800ug/day	0.011
Vitabiotics wellwoman original 30 capsules	No	Beta carotene	2mg/day	0.028
Boots multivitamins	No	Vitamin A Acetate	800ug/day	0.011

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<b>Supplement</b>	<b>Maternal supplement? ^</b>	<b>Vitamin A form</b>	<b>Recommended intake</b>	<b>Daily exposure (mg/kg)*</b>
Centrum Advance multivitamins	No	Vitamin A (RE) (25% as beta-carotene)	800 µg/day	0.011
Centrum Fruity Chewable	No	Vitamin A (RE)	660ug/day	0.009
Centrum MultiGummies	No	Vitamin A (RE)	660ug/day	0.009
Centrum Women	No	Vitamin A (RE)	667 ug/day	0.009
SimplySupplements Cod Liver Oil 1000mg	No	Vitamin A	300-900ug/day	0.004-0.013
Holland & Barrett Cod Liver Oil Pure Liquid 500ml	No	Vitamin A (RE)	691µg/day	0.0098
Seven Seas Cod Liver Oil One-A-Day Omega-3 Fish Oil & Vitamin D 120 Capsules	No	Vitamin A (RE)	750µg/day	0.011
Solgar Super Cod Liver Oil Complex - 60 Tablets	No	Retinyl palmitate	906ug/day	0.014

\*Exposure is calculated from the daily recommended intake and the average body weight of women aged 16- 49 years (70.3kg)

^Indicates whether the supplement is marketed specifically to pregnant or breastfeeding women

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