TOX/2020/32

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

COT Contribution to SACN review of the effects of diet on maternal health: proposed scope of work and timetable.

Background

1. In 2009 SACN's subgroup on Maternal and Child Nutrition (SMCN) agreed to review the scientific evidence underpinning UK Government infant and young feeding policy. The last review of this evidence was completed in 1994 by the Committee on Medical Aspects of food policy (COMA).[1i] It was considered that since this time new recommendations have been published and new evidence has emerged and it would therefore be appropriate to conduct a thorough assessment of this evidence. This would allow a holistic review of the current UK Government advice on infant and young child feeding to be completed. The reviews of infant and young child feeding by the COT are now complete and the review of diet and maternal health is beginning.

2. The SACN meetings aimed at finalising the working terms of reference and scope for this review have been postponed until later in the year because of the ongoing coronavirus pandemic, although a preliminary list has been agreed upon and can be found in Annex 1.

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.

4. For the chemicals on the preliminary list, background information including EFSA, JECFA and COT statements have been reviewed along with recent references found in PubMed literature searches covering the periods of preconception and pregnancy, birth outcomes and any effects of physiological changes in lactating women, with the following general format:

> (Condition) AND (maternal health) AND (human) AND (xenobiotic) AND (date of publication [last Statement year to present])

It is hoped that his information will allow the Committee to identify which components will need limited or full reviews and which are the priorities.

The Dietary Components

Vitamin A

5. The term vitamin A describes fat-soluble substances in the diet that are derived either from plant carotenoids (accessory pigments involved in photosynthesis) or carotenoid metabolites in animal products such as cod liver oil. Vitamin A therefore comprises all-trans-retinol (also called retinol) and the family of naturally occurring molecules associated with the biological activity of retinol (such as retinal, retinoic acid, retinyl esters). Vitamin A is essential because it constitutes the light-sensitive element of the visual pigment rhodopsin (as retinal) and is an effector of cellular differentiation in development (as retinoic acid) The biological value of substances with vitamin A activity is expressed as retinol equivalents (RE).

6. As well as its essentiality to the vision process, vitamin A is also essential to the processes of reproduction, embryonic development, morphogenesis, growth and cellular differentiation.

7. EFSA (2015) derived a Population Reference Intakes (PRIs[1]) of 650 µg RE/day for women in general, raising this to 700 µg RE/day during pregnancy; and 1300 µg RE/day during lactation.

8. Current UK Government guidance regarding vitamin A states that high amounts of vitamin A can harm an unborn baby. It is recommended that pregnant women should not eat liver/liver products or take high-dose multivitamin supplements, or any supplements with vitamin A in them (NHS, 2017a). in the case of pregnant women, the WHO advised that vitamin A supplementation for pregnant women should only be used when vitamin A deficiency leads to a severe public health problem. If ≥5% of women in a population have a history of night blindness in their most recent pregnancy; or in the previous 3-5 years that ended in a live birth; or if ≥20% of pregnant women have a serum retinol level <0.70 µmol/L, then deficiency is considered to be a public health concern (WHO, 2019a).

9. The Expert Group on Vitamins and Minerals (EVM, 2003) conducted a risk assessment for Vitamin A. A Safe Upper Level was not established for vitamin A; since an increased risk of bone fractures was considered to be continuous, an intake above 1500 RE µg/day was considered inappropriate. However, teratogenicity was highlighted as a potential adverse maternal effect as a result of vitamin A in excess of 3000 RE µg/day.

10. In 2002, the SCF reviewed the possible adverse effects of long-term vitamin A intake. A Tolerable Upper Intake Level of 3000 µg RE/day was set for women of childbearing age and for pregnant women based on a risk of hepatotoxicity and teratogenicity.

[1] Population Reference Intakes: the level of (nutrient) intake that is adequate for virtually all people in a population group

11. In 2012 and 2016, the COT reviewed the potential risks from high levels of vitamin A in the diets of children aged 1 to 5 years.[2]

12. A clinical feature of vitamin A toxicity observed in neonates and infants is the bulging of fontanelles. Doses well in excess of 100,00 µg RE/day and 10,000 µg RE/day, in adults and children, respectively were associated with acute toxicity (EVCM, 2003; SCF, 2006). Other signs and symptoms of vitamin A toxicity include skin disorders, nausea, vomiting, disorders of the musculoskeletal system and liver damage (EFSA, 2015a).

13. Some studies have shown that high doses of vitamin A causes teratogenic effects during pregnancy (Matthew-Roth et al, 1988). At the beginning of the first quarter of pregnancy, congenital malformations involving the central nervous and cardiovascular systems and spontaneous abortion are adverse effects associated with excessive vitamin A intake (Miller et al, 1998).

Vitamin C

14. Vitamin C is described as a six-carbon compound that is structurally related to glucose, consisting of two inter-convertible compounds: L-ascorbic acid, which is a strong reducing agent, and its oxidised derivative, L-dehydroascorbic acid.

15. Vitamin C deficiency in humans can cause scurvy. Early symptoms of this in adults include fatigue, weakness, aching joints and muscles. In the later stages, scurvy is characterised by bleeding gums, anaemia, petechial and sheet haemorrhages, and delayed wound healing (EVM, 2003).

16. A Tolerable Upper Intake Level (UL) for vitamin C was not set by EFSA based on the limited available data. The EVM stated that there was insufficient data to set a Safe Upper Level for vitamin C. However, consuming quantities of vitamin C greater than 1000 mg/day was found to cause gastrointestinal effects such as diarrhoea (EVM, 2003).

17. During pregnancy, plasma ascorbate concentration decreases due to haemodilution and active transfer to the fetus. EFSA (2013) proposed recommended intakes of 10 mg/day and 60 mg/day for pregnant and lactating women in addition to the PRI for women of 95 mg/day.

18. The WHO (2015) reported that vitamin C supplementation during pregnancy reduced the risk of placental abruption but increased the risk of term prelabour rupture of membranes. There was no evidence to support the routine use of vitamin C in pregnancy for the prevention of fetal or neonatal death, preterm birth, preeclampsia, or intrauterine growth restriction for women without high risk of adverse pregnancy outcomes.

19. Current UK Government guidance regarding vitamin C states that adults aged 19 to 64 need 40 mg of vitamin C a day (NHS, 2017b). Vitamin C supplementation

[2] https://cot.food.gov.uk/sites/default/files/tox2016-40.pdf

is not recommended for pregnant women to improve maternal and perinatal outcomes (WHO, 2019b).

Vitamin D

20. Vitamin D is described as a fat-soluble-seco-steriod compound. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are two nutritionally significant compounds. Vitamin D3 is metabolised to the active steroid hormone 1.25-hydroxyvitamin D3 by successive hydroxylations that occur in the liver and kidney. Vitamin D2 is metabolised to the active steroid 1.25-dihydoxyvitamin D2 by enzymatic systems in the kidney and liver (EVM, 2003).

21. Vitamin D is essential for maintaining normal blood levels of calcium and phosphate which are required for the normal mineralisation of bone, muscle contraction, nerve conduction, and general cellular function in all cells in the body. Once vitamin D is converted to its active form 1.25-dihyroxyvitamin D [1,25-$(OH)_2D$], or calcitriol it regulates the transcription of a number of vitamin D-dependant genes coding for calcium-transporting proteins and bone matrix proteins (EVM, 2003).

22. Vitamin D is produced in the skin in response to light and occurs naturally in oily fish such as mackerel and herring, cod liver oil, salmon and egg yolk. The NHS advises that pregnant women should not eat more than 2 portions of oily fish a week, such as salmon, mackerel or herring (NHS, 2018) due to the effects of contaminants on the unborn fetus.

23. The NHS (2017c) recommends a supplement of 10 µg/day of vitamin D a day for pregnant and breastfeeding mothers.

24. EFSA (2016) set an adequate intake (AI) of 15 µg/day for pregnant and lactating women which is the same for non-pregnant women. The Panel recommended that studies are needed that are specifically designed to identify cut-off values for serum 25(OH) D concentration or other suitable markers to derive DRVs for vitamin D in pregnant and lactating women.

25. The WHO (2019c) advises that sunlight is the most important source of vitamin D for pregnant women. Pregnant and lactating women with documented vitamin D deficiency are recommended to take 5 µg/Vitamin D/day. Experts did not recommend vitamin D supplementation for pregnant women to improve maternal and perinatal outcomes.

26. Vitamin D deficiency in pregnancy has found to be associated with adverse effects such as pre-eclampsia, gestational diabetes mellitus, preterm birth, infant rickets and reduced bone mass.

27. Excess vitamin D2 during gestation in rabbits lead to adverse effects such as decreased foetal viability, an increased number of abortions due to a putative placental synthesis of the hormone. High doses of vitamin D appear to affect maternal calcium, phosphate and cholesterol homeostasis and neonatal calcium homeostasis. In rodents, administration of high levels of vitamin D2 during gestation

resulted in retarded foetal and placental growth, loss of ossification of foetal bones and foetal skeletal degeneration, resulting particularly in facial malformations (WHO, 2012).

28. In 2018, EFSA set a UL of 100 µg/Vitamin D/day for adults including pregnant and lactating women (EFSA, 2018b) which was endorsed by the Scientific Advisory Committee on Nutrition (SACN, 2016).

Vitamin E

29. Vitamin E is a generic designation for a group of eight lipid soluble compounds synthesised by plants. These compounds fall into two classes, tocopherols and tocotrienols, which exhibit the biological antioxidant activity of vitamin E. Vitamins in both classes are designated by the Greek letters α, ß, and δ. The most biologically active antioxidant is d-α- tocopherol. Vitamin E activity is expressed as d-α-tocopherol equivalents (EVM, 2003).

30. Vitamin E is only synthesised by plants and is found primarily in plant products such as plant oils. Higher plants (plants other than algae) contain α-tocopherol in leaves, γ-tocopherol is generally present in lower concentrations. Animal tissues tend to have low concentrations of vitamin E, with the highest levels occurring in fatty tissues though this varies according to the intake of vitamin E (EVM, 2003).

31. EFSA (2015) set an AI of 11 mg/day for pregnant and lactating women which is the same for non-pregnant/non-lactating women.

32. There are currently no Government dietary recommendations for pregnant women which relate to vitamin E. However, a dose of 3 mg a day is recommended for women (NHS, 2017d).

33. The WHO (2015) reported that vitamin E supplementation during pregnancy reduced the risk of placental abruption but increased the risk of term prelabour rupture of membranes. There was no evidence to support the routine use of vitamin E in pregnancy for the prevention of fetal or neonatal death, preterm birth, preeclampsia, or intrauterine growth restriction for women without high risk of adverse pregnancy outcomes.

34. Vitamin E supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes (WHO, 2019b).

35. The EVM established a Safe Upper Level for vitamin E of 800 IU (540 mg d-α-tocopherol equivalents/day) supplemental for daily consumption (equivalent to 9.0 mg/kg bw/day in a 60 kg adult) (EVM, 2003) based on several studies where adverse effects were not found in a range of biochemical parameters. EFSA established a UL of 300 mg/vitamin E/day (EFSA, 2018b).

Selenium

36. Selenium is a group VI metal with both metallic and non-metallic properties (EVM, 2003). It exists in four oxidation states (-2, 1, +2, +6) and forms compounds analogous to those formed by sulphur.

37. In food, selenium is mainly present in organic compounds, as L-selenomethionine and L-selenocysteine, with lower amounts in inorganic compounds, as selenate and selenite, and is an essential micronutrient to human health. It is present in a number of foodstuffs, notably nuts, offal, eggs and poultry, and mushrooms and in lower quantities in fruits and vegetables with the exception of members of Brassica genus (cabbage, cauliflower etc) which contain relatively high amounts of selenium (SCF, 2000; Kieniszek and Stanislaw, 2016).

38. Selenium compounds are readily absorbed in the small intestine. Selenium is widely distributed throughout the body and is found in breastmilk. It has also been reported to cross the placenta in animals. Selenium compounds are incorporated in selenoproteins, which play a role in a variety of biological functions including antioxidant defence, T-cell immunity, thyroid hormone metabolism, selenium homeostasis and transport, and skeletal and cardiac muscle metabolism.

39. In 2014, the EFSA Panel on Dietetic Products, Nutrition and Allergies (EFSA, 2014) derived DRVs for selenium the criterium for establishing the DVR in adults was the levelling off of plasma selenoprotein P which would indicate adequate supply of selenium to all tissues. Considering the adaptive changes in the metabolism of selenium that occurs during pregnancy the AI of 70 µg/day selenium that was set for adult women also applies to pregnant women. For lactating women, an AI of 85 µg/day selenium was set to account for the amount of selenium secreted in breast milk.

40. There are currently no Government dietary recommendations for pregnant women which relate to selenium. However, a dose of 60 µg/day a day is recommended for women between the ages of 19 to 64 years (NHS, 2017e).

41. High exposure to selenium can lead to acute toxicity effects such as hypersalivation, emesis, severe vomiting and diarrhoea, hair loss, neurological disturbance and fatigue. Chronic toxicity can lead to changes in the hair and nails, and skin lesions (EVM, 2003). Studies have shown that selenium supplementation can decrease thyroid peroxidase antibody levels which can then reduce the risk of thyroid function abnormalities after pregnancy (Mao et al, 2014).

42. The Scientific Committee on Food (SCF) established in 2000 an UL for selenium of 300 µg/day for adults, including pregnant and lactating women. This was based on a NOAEL of 850 µg/day for clinical selenosis (Yang et al., 1989) and application of an uncertainty factor of 3. The NOAEL was based on the absence of clinical signs in individuals with selenium levels below 1000 µg/L.

Mycotoxins

43. Mycotoxins are produced as secondary metabolites by filamentous fungi and are toxic to vertebrates and other animal classes at low concentrations (Bennett and Klich, 2003). The mycotoxins that are deemed as a major threat to human health include aflatoxins (AF), fumonisins (FB), ochratoxin A (OTA), deoxynivalenol (DON) and zearalenone (ZEN) (Bennett and Klich, 2003; Richard et al, 2007; Smith el al, 2012).

44. Mycotoxins can cause a variety of adverse health effects in humans such as cancer (some being genotoxic), kidney and liver damage, gastrointestinal disturbances, reproductive disorders or suppression of the immune system. Aflatoxins are the most harmful type of mycotoxin, they can potentially cause cancer or problems with digestion, reproduction or the immune system (FSA, 2018).

45. Some studies have reported that exposure to aflatoxins during pregnancy may cause intrauterine growth restriction (Smith et al, 2017). It was also found that maternal FB exposure may be associated with hypertensive emergencies in pregnancy and neural tube defects (Gelineau-van Waes et al, 2012; Wolf and Horugel et al, 1994). Due to a lack of valid biomarkers to accurately measure maternal exposure, no human studies on maternal or fetal exposure to DON or ZEN mycotoxins were identified (Kyei et al, 2020). In humans, the transfer of aflatoxins into the placenta has been confirmed (De Vries et al., 1989; Partanen et al., 2010).

46. Teratogenic effects such as craniofacial abnormalities and reduced birth weight were documented in animals after maternal exposure to OTA (Malir et al, 2013).

47. EFSA calculated a $BMDL_{10}$ (for a 10% increase in incidence of hepatocellular carcinomas in male rats) of 0.4 mg/kg body weight (bw)/day following aflatoxin B1 exposure (EFSA, 2020a). For OTA, EFSA calculated a $BMDL_{10}$ of 4.73 µg/kg bodyweight (bw) per day from kidney lesions observed in pigs. For characterisation of neoplastic effects, a $BMDL_{10}$ of 14.5 µg/kg bw per day was calculated from kidney tumours seen in rats. (EFSA, 2020b). The EFSA Panel established a tolerable daily intake for fumonisin B1 of 1.0 µg/kg body weight (bw) per day based on increased incidence of megalocytic hepatocytes found in a chronic study with mice (EFSA, 2018a).

48. As mycotoxins are naturally occurring, their presence in foods cannot be completely avoided. It is however essential for food business operators to ensure that controls are in place to ensure that exposure from food is as low as reasonably achievable.

49. There are currently no Government dietary recommendations for pregnant women which relate to mycotoxins.

Process contaminants

Acrylamide

50. Acrylamide is chemical substance formed when starchy foods, such as potatoes and bread, are cooked at high temperatures (above 120°C). It can be formed when foods are baked, fried, grilled, toasted and roasted. It is natural by-product of the cooking process and has always been present in food. It can be found in roasted potatoes/root vegetables, chips, crisps, toast, cakes, biscuits, cereals and coffee.

51. The toxicological properties of acrylamide include neurotoxicity, genotoxicity, carcinogenicity and reproductive toxicity. In 1994 the International Agency for Research on Cancer (IARC) classified acrylamide as a Group 2A carcinogen (probably carcinogenic to humans).

52. In 2015 the EFSA CONTAM panel agreed that acrylamide in food could potentially increase the risk of developing cancer for all consumers in all age groups based on animal studies. The potential adverse effects of acrylamide on the nervous system, pre- and post-natal development and reproduction were not considered to be a concern, based on current levels of dietary exposure.

53. Since acrylamide is genotoxic and carcinogenic it is not possible to establish a safe level of exposure to quantify the risk. Therefore, benchmark dose lower confidence limits (BMDLs) were calculated from the results of studies in rodents.

54. For the carcinogenicity of acrylamide, the EFSA CONTAM panel calculated a $BMDL_{10}$ (for a 10% increase in incidence of tumours) of 0.17 mg/kg body weight (bw)/day. For effects on the nervous system, EFSA calculated a $BMDL_{10}$ of 0.43 mg/kg bw/day, and concluded that other effects, such as on the reproductive system would only occur at higher doses. Evidence from human studies that dietary exposure to acrylamide causes cancer is currently limited and inconclusive. EFSA's Scientific Committee stated that, for substances that are genotoxic and carcinogenic, a MOE of 10,000 or higher is of low concern for public health. The calculated MOEs across surveys and age groups for acrylamide indicated concern with regard to neoplastic effects.

55. Consumption of specific foods during pregnancy was associated with higher acrylamide exposure in utero. Dietary exposure to acrylamide was associated with reduced birth weight and head circumference. However, further studies are required to establish whether the association between dietary acrylamide exposure and these outcomes is casual (EFSA, 2015; Pederson et al, 2012).

56. The FSA currently recommends consumers aim for a golden yellow colour or lighter when frying, baking, toasting or roasting starchy foods. The food industry has undertaken a lot of work to identify and implement measures to reduce acrylamide levels in food.

57. Commission Recommendation 2013/647/EU on investigations into levels of acrylamide in food, specifies Indicative Values and groups of foodstuffs to which they apply. Indicative values are not statutory maximum limits and are intended only as a guide to prompt investigation of higher levels to understand how to reduce levels of acrylamide in food. The Indicative Values are to be kept under regular review.

58. There are currently no Government dietary recommendations for pregnant women which relate to acrylamide.

Heterocyclic amines

59. Heterocyclic amines (HCAs) are a group of mutagenic compounds which are detected in well-done cooked meats. HCAs are formed as a result of reactions between amino acids and creatine when meat is exposed to cooking temperatures above 150°C. HCAs were found to be genotoxic in vivo and in vitro tests and carcinogenic to rats and mice rats (Aeschbacher, 1991; Carthew et al., 2010). The formation of HCA can be reduced if meat is exposed to temperatures below 150 °C (Ali et al, 2019).

60. Four types of HCAs are formed during cooking. This includes 2-amino, 3-methylimidazo[4,5-f]quinolone (IQ), 2-Amino-3,4-dimethylimidazo[4,5-f]quinolone (MeIQ), 2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-Amino-1-methyl-6-phenylimiazo[4,5-b]pyridine (PhiP). PhiP has been shown to cause cancer of the colon and mammary glands in a dose dependant manner in rat studies. PhIP can also be transferred from mothers to their offspring via the mother's milk (Li et al, 2012; Bellamri et al, 2018).

61. No health-based guidance has been set for HCAs and there are currently no Government dietary recommendations for pregnant women which relate to HCAs.

Organic contaminants

Dioxins and dioxin-like Polychlorinated Biphenyls (PCBs)

62. Dioxins and dioxin-like substances, including some PCBs, are persistent organic pollutants (POPs) covered by the Stockholm Convention. They can travel long distances from the source of emission, and bioaccumulate in food chains. Human exposure to dioxins and dioxin-like substances has been associated with a range of toxic effects, including chloracne; reproductive, developmental and neurodevelopmental effects; immunotoxicity; and effects on thyroid hormones, liver and tooth development; they are also carcinogenic. Developmental effects in males are the most sensitive toxic end-point, making children – particularly breastfed infants – the population most at risk.(WHO https://www.who.int/ipcs/assessment/public_health/dioxins/en/)

63. The toxicity of members of the diverse chemical family of dioxins is related the toxicity of the most toxic member of the group, TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), to produce a toxic equivalent value for each compound. The COT last evaluated dioxins and dioxin-like PCBs in 2001. The COT agreed with the evaluation of the EU Scientific Committee on Food (SCF) that in 2000 recommended a temporary tolerable weekly intake (t-TWI of 7 pg WHO-TEQ/kg bw. SCF re-evaluated this t-TWI based on rat studies which investigated only reproductive effects only on male offspring. Applying an overall uncertainty factor of 10 to the Lowest Observed Adverse Effect Dose (LOAEL) derived from estimated human daily

intakes (EHDI) the SCF concluded that 14 pg/kg bw per week should be considered as a tolerable intake for 2,3,7,8-TCDD.

64. In 2010, the COT published a report on halogenated dioxins and biphenyls in food and concluded that these derivatives only contributed a very minor amount to the total level of dioxin TEQs in the diet and hence their presence was not a major concern for health.

65. JECFA (2002) stated “The Committee considered adverse effects on the reproductive tracts of prenatally-exposed male rats to be the critical endpoint for risk assessment. The maternal LOEL and NOEL values of 25 ng/kg bw and 13 ng/kg bw, respectively, from the pivotal studies were converted to equivalent human monthly intake (EHMI) values of 630 pg/kg & 330 pg/kg by addition of 3 ng/kg bw to account for background body burden levels and calculation of the equivalent human body burdens at steady-state, based on assumed 1st-order kinetics at low-doses, 50% oral absorption & systemic half-life in humans of 7.6 years. To the EHMI values, the Committee applied total safety factors of 9.6 and 3.2, respectively, to account for intraspecies variation (3.2) & use of a LOEL instead of a NOEL (3). From the resultant range of PTMIs of 40–100 pg/kg bw per month, the Committee chose the mid-point, 70 pg/kg bw per month, as the PTMI to be applied to intake of PCDDs, PCDFs and coplanar PCBs expressed as TEFs.”

66. The best-known study of the effects of dioxins on humans is the Seveso Women’s Health Study (Eskenazi et al, 2000). After the industrial accident in Seveso, Italy in 1979, when an explosion caused the release of dioxins into the surrounding area, blood samples were taken from the exposed population and the reproductive health of exposed females who were, or who became of child-bearing age over the following 20 years, was followed. Wesselink et al (2014) followed up the initial findings and found no association between TCDD estimated at pregnancy and spontaneous abortion, fetal growth, or gestational length. However, there was a non-significant inverse association between maternal serum concentrations from 1979 and birthweight and this association was stronger among first post-explosion births, but was still non-significant

67. EFSA (2018) considered recent studies on female reproductive health, mainly among dioxin-exposed women from Seveso, and decided that there was insufficient evidence of effects on the incidence of endometriosis, pubertal development., menstrual cycle characteristics, ovarian function, time to pregnancy, uterine leiomyoma, or age at menopause.

68. EFSA (2018) used toxicokinetic modelling to estimate that the exposure of adolescents and adults should be less than 0.25 pg WHO-TEQ/kg bw/ day. The CONTAM panel established a TWI of 2 pg TEQ/kg bw /week. This was based on the critical effect of sperm concentrations that were inversely associated with serum concentration of TCDD, PCDD-TEQ and PCDD/F-TEQ in a study of Russian children whose parents had been exposed to dioxins (mainly TCDD) during manufacture of trichlorophenol and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) (Ryan et al, 2002). Consumption data from European countries by EFSA (2018) showed that the mean and 95th percentile intakes of total TEQ by adolescents, adults, elderly and very elderly sections of the population varied between 2.1 and

10.5 and 5.3 and 30.4 pg TEQ/ kg bw/week and thus could represented a considerable exceedance of the TWI. The COT reviewed the draft EFSA opinion and agreed with the selection of the critical endpoint for the establishment of an HBGV and accepted that if possible, human data should be used for this purpose but was unable to conclude this was robust (COT, 2018). The Committee also agreed that the model then used for establishing the HBGV would be appropriate. Discussing the TWI established, the Committee questioned its applicability to the whole population.

Dioxins- recent findings

69. Ames et al (2019) found that the children (82 male, 79 female) from the Second Generation Seveso Health Study (average13.1 (± 2.9) years of age) showed that a 10-fold increase in maternal serum TCDD was not adversely associated with reverse learning/set-shifting, memory, attention/impulsivity, or non-verbal intelligence. In sex-stratified models, prenatal TCDD was associated with more non-perseverative errors in boys but not in girls (pint=0.04). TCDD was also associated with attention deficits but only among children with the shortest breastfeeding histories.

70. A review by Viluksela and Pohjanvirta (2019) noted that A study by Ryan (2002), as well as a later one by ‘t Mannetje et al (2017) implicated the exposure of fathers in an altered sex ratio of offspring, rather than mothers.

Non-dioxin-like (NDL) PCBs

71. Some PCBs do not share the same toxic endpoints as the dioxins and have different effects, for example oestrogenic and anti-oestrogenic effects, and are therefore regarded as a separate group of persistent organic chemicals that are present in the environment and food.

72. The COT considered the health risks of exposure to PCBs in 1997. They concluded that PCBs do not have significant mutagenic activity and that any carcinogenesis in animal studies was likely to be due to a "non-genotoxic" mechanism and accepted the advice of the COM and COC that it would be prudent to assume that all PCB congeners are potential human carcinogens. The Committee noted that preliminary work indicated that current human body burdens of PCBs may be affecting thyroid hormone levels. Further work was thought to be needed to develop an approach to assessing the health risks of the non-coplanar PCB congeners, but it was felt unlikely that there was a health risk from current intakes of PCBs from food. PCBs were likely to persist as contaminants of the environment for many years and the Committee recommended that levels in food and in human milk should continue to be monitored at regular intervals to confirm that the downward trend continued. Otherwise a further review would be recommended to determine how human exposure could be reduced.

73. EFSA published a scientific opinion on non-dioxin-like PCBs in feed and food in 2005 concluding that “no health-based guidance value for humans can be established for NDL-PCB because simultaneous exposure to NDL-PCB and dioxin-like compounds hampers the interpretation of the results of the toxicological and epidemiological studies, and the database on effects of individual NDL-PCB

congeners is rather limited. There are however indications that subtle developmental effects, being caused by NDL-PCB, DL-PCB, or polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans alone, or in combination, may occur at maternal body burdens that are only slightly higher than those expected from the average daily intake in European countries. Because some individuals and some European (sub)-populations may be exposed to considerably higher average intakes, a continued effort to lower the levels of NDL-PCB in food is warranted."

74. Taylor *et al* (2007, from abstract) found changes in the sex ratio of children for mothers who had measurable levels of PCBs in their blood before they became pregnant. Higher levels of estrogenic PCBs correlated with a preponderance of male, offspring and higher levels of anti-estrogenic PCBs correlated with higher numbers of female offspring. However, Rocheleau *et al* (2011) did not find such a relationship

75. Cohn *et al* (2012) tested the hypothesis that polychlorinated biphenyls (PCBs) measured during the early postpartum period could predict increased risk of maternal breast cancer diagnosed before age 50. They found strong breast cancer associations with three PCB congeners: PCB 167 and PCB 187 were associated with a lower risk whereas PCB 203 was associated with a sixfold increased risk of breast cancer. The net association of PCB exposure was nearly a threefold increase in risk among women with a higher proportion of PCB 203 in relation to the sum of PCBs 167 and 187. Postpartum PCB exposure was deemed likely to represent pregnancy exposure, and could predict increased risk for early breast cancer depending on the mixture that represents internal dose

76. JECFA last evaluated the non-dioxin-like PCBs in 2015. Six of these (PCB 28, PCB 52, PCB 101, PCB 138, PCB 153 and PCB 180) are often called "indicator PCBs". The Committee focused on the six indicator PCBs, as there were sufficient data (toxicological, biomonitoring, occurrence and dietary exposure) available for review. National and international estimates of dietary exposure to the sum of the six indicator PCBs ranged, for mean exposure, from <1 to 82 ng/kg bw per day and, for high percentile exposure, from <1 to 163 ng/kg bw per day. None of the available studies on the six indicator PCBs was suitable for derivation of health-based guidance values or for assessment so a comparative approach using the minimal effect doses was used to estimate MOEs to provide guidance on human health risk. Because the MOEs are based on minimal effect doses, they were considered to give some assurance that dietary exposures to were unlikely to be of health concern for adults and children, based on the available data.

77. Zhang *et al* (2018, from abstract) found that plasma levels of PCBs, particularly PCB52, in a cohort of Chinese women in the first trimester of pregnancy were associated with a greater risk of developing gestational type 2 diabetes mellitus later in pregnancy (measured by oral glucose tolerance test at 24 – 28 weeks). A similar conclusion was reached by Vefiadi *et al* (2017) and Rahman *et al* (2019).

Oily Fish

78. In 2004 a SACN/COT inter-committee subgroup produced a report on the benefits and risks of oily fish consumption for different members of the population, including women of childbearing age, pregnant and lactating women. Oily fish makes

a major contribution to the intake of ω-3 polyunsaturated fatty acids that are essential for fetal neurodevelopment but also harbour, environmental toxins whose intake should be controlled. From the toxicological standpoint, the main hazards highlighted in the report were intake of methyl mercury from consuming top-predator fish like swordfish and marlin, and lipophilic compounds like dioxins, dioxin-like PCBs and brominated flame retardants in oily fish and tuna. The group agreed that a provisional tolerable weekly intake (PTWI) of 1.6 μg/kg bw/week for methyl mercury, as set by JECFA in 2003, based on neurodevelopment of the fetus, was protective for women who were pregnant or of childbearing age. A weekly portion of 140 g of shark, swordfish or marlin would result in a dietary methylmercury exposure close to or above 3.3μg/kg bodyweight per week in all age groups and this was considered harmful to the fetus of women who are pregnant or become pregnant within a year, but not to other adults.

79. Women of reproductive age and girls were advised to consume only one to two portions of oily fish a week, based on maintaining consumption of dioxins and dioxin-like PCBs below the Tolerable Daily Intake (TDI) of 2 pg WHO-TEQ/kg bodyweight per day. The TDI was derived from effects on the developing male reproductive system resulting from the maternal body burden of dioxins.

80. However, as noted above, EFSA (2018) reduced the TWI for dioxins to 2 pg WHO-TEQ per week, so the consumption advice would require updating.

Bisphenol A

81. Bisphenol A (BPA, 2,2-bis(4-hydroxyphenyl)propane) is mainly used in the manufacture of plastics and resins, for example, polycarbonates, high performance transparent, rigid plastics used to make food containers, such as reusable beverage bottles, tableware (plates and mugs) and storage containers. BPA is also used to produce epoxy resins used to make protective coatings and linings for food and beverage cans and vats. BPA can migrate in small amounts into food and beverages stored in materials containing the substance. (EFSA https://www.efsa.europa.eu/en/topics/topic/bisphenol)

82. EFSA published a Scientific Opinion on BPA in the diet in 2015. Adverse effects on kidney and mammary gland in animals underwent benchmark dose modelling. A $BMDL_{10}$ of 8 960 μg/kg bw per day was calculated for changes in the mean relative kidney weight in a two-generation toxicity study in mice but no $BMDL_{10}$ could be calculated for mammary gland effects. Using toxicokinetic data this $BMDL_{10}$ was converted to a human equivalent dose (HED) of 609 μg/kg bw per day. The CEF Panel applied a total uncertainty factor of 150 (for inter- and intra-species differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) and a temporary Tolerable Daily Intake (t-TDI) of 4 μg/kg bw per day was derived.

83. Women of childbearing age had dietary exposures comparable to men of the same age (up to 0.388 μg/kg bw per day). Comparing this t-TDI with the exposure estimates, there was no health concern for this or any other group from dietary exposure.

BPA- recent findings

84. Kasper et al (2016) investigated the relationship between BPA exposure and breastfeeding in a cohort of Mexican women. They found that approximately 97% of mothers with the lowest tertile of blood BPA concentrations were still breastfeeding their infants at 1 month postpartum compared with approximately 90% of those with the highest blood levels of BPA. Overall their results supported the hypothesis that BPA, acting as an oestrogenic chemical could be having an inhibitory effect on lactation.

85. Mustieles et al (2018) estimated preconception and prenatal exposures to BPA and BPS (an analogue of BPA where the bridging propyl group is replaced by a sulphone (OSO) group) by averaging urinary concentrations in multiple maternal and paternal urine samples collected before pregnancy, and maternal pregnancy samples collected in each trimester. They reported that maternal preconception urinary BPA concentrations were inversely associated with birth weight and head circumference in adjusted models: each ln-unit increase was associated with a decrease in birth weight of 119 g (95% CI: -212, -27), and a head circumference decrease of 0.72 cm.

86. Bellavia et al (2018) found an association between urinary BPA concentration and the occurrence of gestational diabetes that was significant in obese/overweight pregnant women but not in women of average weight.

Heavy metals

Lead

87. For adults, the critical effects of the intake of lead in the diet are cardiovascular and renal. For the cardiovascular effects, EFSA (2010) derived a $BMDL_{01}$ intake value of 1.50 µg/kg b.w. per day from the lead levels in blood, based on human dose-response data. For effects on the kidney, a $BMDL_{10}$ intake value of 0.63 µg/kg b.w. per day was derived from blood lead levels.

88. Women of 20 to 40 years of age were used as a surrogate for pregnant women to calculate the risk of lead exposure in utero on neurodevelopment in the offspring. Estimates of exposure were at or above the BMDL for neurodevelopmental effects, and the CONTAM Panel concluded that it was not possible to exclude a risk to the developing fetus through exposure of some pregnant female consumers.

89. The CONTAM Panel concluded that the risk of clinically important effects on either the cardiovascular system or kidneys of adult consumers, at current levels of lead exposure is low to negligible. In infants, children and pregnant women, there is potential concern at current levels of exposure to lead for effects on neurodevelopment. Protection of children and women of child-bearing age against the potential risk of neurodevelopmental effects should be protective for all other adverse effects of lead, in all populations.

90. The CONTAM Panel made the assumption that the developing fetus is as least as sensitive to this effect of lead as a young child. Given that the fetal/maternal cord blood lead (B-Pb) concentration ratio is approximately 0.9, the maternal B-Pb level corresponding to the $BMDL_{01}$ for effects on neurodevelopment (12 µg/L) is 13 µg/L, which is equivalent to a dietary exposure of 0.54 µg/kg b.w. per day

91. In 2013, the COT published a Statement on lead in the infant diet and agreed with the EFSA conclusion that even low exposures to lead in pregnant women, infants and children can adversely affect neurodevelopment The JECFA reached a similar conclusion and stressed that their assessment was based on dietary exposure (mainly from food) and that other sources of exposure to lead also needed to be considered (FAO/WHO, 2011). The conclusions reached by EFSA and JECFA accord with a view previously expressed by the COT that it was not possible to identify a threshold of exposure below which there was no association between lead and decrements in intelligence quotient (IQ).

Arsenic

92. EFSA reviewed arsenic in the diet in 2009. They noted that pregnant women are more efficient at methylating ingested arsenic in the third trimester and excrete more than 90 % dimethylarsinate in plasma and urine, consistent with the generally more efficient methylation of arsenic in the childbearing years. This difference is abrogated before puberty and after menopause. This indicates there are possible hormonal effects of arsenic methylation. It has been proposed that this is related to the endogenous production in women of the methyl group-donor choline that is regulated by estrogens (Fischer et al., 2007). Specific effects of arsenic on women's health have also been described. For example, a higher rate of anaemia during pregnancy has been reported in women exposed to moderate arsenic concentrations (40 µg/L) in Chile and increased age at menarche have been observed in Indian girls exposed to arsenic in drinking water (Vahter, 2009). Conversely, the more efficient metabolism of arsenic in women compared to men correlates with a lower risk of arsenic related skin lesions in women (Lindberg et al., 2008b).

93. The CONTAM Panel modelled the dose-response data from key epidemiological studies and selected a benchmark response of 1 % extra risk. A range of benchmark dose lower confidence limit ($BMDL_{01}$) values between 0.3 and 8 µg/kg b.w. As per day was identified for cancers of the lung, skin and bladder, as well as skin lesions.

Arsenic- recent findings

94. Farzan et al (2016) found an association between drinking water As and gestational diabetes mellitus and glucose intolerance that was largely limited to obese women.

95. Sun et al (2019) found that maternal exposures to vanadium, arsenic, and lead in early pregnancy were associated with decreased maternal FT3 or FT3/FT4 ratio, which was a possible mediator of the association between urinary heavy metals and reduced birth size.

Mercury

96. In their 2003 updated statement on a survey of mercury in fish and shellfish, COT agreed with the Provisional Tolerable Weekly Intake of 1.6 μg/kg bw/week for assessing methylmercury intakes by the general population previously established by JECFA.

97. COT concluded that for adults, consumption of one weekly portion of shark, swordfish or marlin could result in a mercury intake in the range of 2.2 to 3.0 mg/kg bw/week, before considering intake from the rest of the diet (upper bound mean 0.28 mg mercury/kg bw/week, not all as methylmercury). Regular intake at this level during pregnancy, or in the year leading up to pregnancy could be associated with a risk of neurodevelopmental effects in the fetus. The methylmercury intake resulting from consumption of either two 140g portions of fresh tuna or four 140g portions of canned tuna would not be expected to result in neurodevelopmental effects. Regular consumption of more than one portion of shark, swordfish or marlin per week could be associated with a risk of neurotoxicity in adults.

98. In 2012, the CONTAM Panel established a tolerable weekly intake (TWI) for inorganic mercury of 4 µg/kg b.w., expressed as mercury based on neurodevelopmental effects after prenatal dietary exposure, so it is of importance that pregnant women have dietary exposures below the TWI to protect the unborn child. For methylmercury, new developments in epidemiological studies from the Seychelles Child Developmental Study Nutrition Cohort indicated that ω-3 long-chain polyunsaturated fatty acids in fish may counteract the negative effects from methylmercury exposure. Together with the information that beneficial nutrients in fish may have confounded previous adverse outcomes in child cohort studies from the Faroe Islands, the Panel established a TWI for methylmercury of 1.3 µg/kg b.w., expressed as mercury.

99. Women aged 18 - 45 years taking part in the EFSA Comprehensive European Food Consumption Database appeared to have similar dietary exposure as the general adult population. In the adult population, the median dietary exposure among high consumers of fish was 2.08 µg Hg/kg b.w. per week, but ranged up to 6.17 µg Hg/kg b.w. per week (4.7-fold the TWI). (EFSA 2011, Merten *et al*,2011).

Mercury - recent findings

100. Vigeh et al (2018) found a negative correlation between blood mercury levels during the first and second trimesters of gestation and birth weight after adjustment for independent variables ($p = 0.006$).

Cadmium

101. The major concerns from ingestion of cadmium are chronic negative effects on the kidneys and bone density but has also been reported to mimic estradiol and thus have effects on mammary glands, ovaries and the uterus. Oral bioavailability of

cadmium is low, at 3 – 5% from food. Uptake is greater in individuals with low storage levels of iron (Gallagher et al., 2011) and is thus greater in pre-menopausal women, especially during pregnancy, than in men (COT 2018).

102. The EFSA CONTAM Panel (2009) established a tolerable weekly intake (TWI) for cadmium. Using a group meta-analysis based on urinary β2–microglobulin as a marker for kidney damage, a $BMDL_5$ of 1 μg U-Cd/ g creatinine was calculated. In order for the U-Cd concentration of the population to remain below 1 μg/ g creatinine by the age of 50 years, dietary exposure to Cd should stay below 0.36 g/kg bw/day or 2.52 μg/kg bw/week. Since Cd has a long biological half-life, CONTAM established a TWI of 2.5 μg/kg bw.

103. JECFA (2011) established a provisional tolerable monthly intake (PTMI) for cadmium of 25 μg/kg bw, equivalent to ~6 μg/kg bw/week. This was a dietary level associated with a urinary level of less than 5.24 μg Cd/g creatinine, which was not associated with increased excretion of β2- microglobulin in humans. In 2011, EFSA compared the approaches taken by itself and JECFA, and concluded (EFSA, 2011b) that the major source of variation was the choice of toxicodynamic variability function. EFSA upheld its own justification for the lower HBGV but pointed out that adverse effects were unlikely to take place in an individual at current dietary Cd levels.

Cadmium -recent findings

104. Liu et al (2019) found that in a linear model of cadmium in cord blood in a cohort of Boston women, each 1 SD (0.69 μg/L) increment of Cd was associated with 1.15 (95% CI, 0.98–1.36) times higher risk of preeclampsia.

105. Punshon et al (2019) reported that multivariable-adjusted differences in placental weight were - 7.81 g (95% CI: -15.42, -2.48) with every ng/g increase in the Cd concentration of placenta (p-Value = 0.0009). Greater decrements in placental weight and efficiency associated with placental Cd were observed for female foetuses than for males.

106. Tsuji et al (2019) found an association between metal concentrations, especially cadmium in whole blood from pregnant women and placenta malformations in the Japan Environment and Children's Study (JECS).

Legacy pesticides

107. Since 2009, 16 new Persistent Organic Pollutants have been added to the Stockholm Convention database. These include the pesticides α–, β– and γ–hexachlorocyclohexane (α–HCH, β-HCH and γ-HCH or lindane), chlordecone, pentachlorobenzene, pentachlorophenol (with its salts and esters) and endosulfan and its isomers. The acute mechanism of action is the insecticide binding at the $GABA_A$ site in the gamma aminobutyric acid (GABA) chloride ionophore complex, inhibiting the flow of chloride ions into the nerves and leading to prolonged nervous excitation.

Hexachlorocyclohexanes

108. In their statement on hexachlorocyclohexanes in the infant diet (2014), COT agreed with the approach taken to derive a TDI of 0.04 µg/kg bw for γ-HCH, based on the LOAEL from the study on lymphocyte proliferation in female mice by Meera et al. (1992, cited by EFSA, 2005). For α–HCH The COT concluded that, because its toxicity had not been well characterised, the available information was insufficient to propose a TDI, and therefore applied a margin of exposure (MOE) approach using the NOAEL of 0.1 mg/kg bw/day for hepatotoxicity as a reference point. This was supported by the findings on tumour promotion in the studies cited by EFSA (2005). The COT also applied a MOE approach for β-HCH using the LOAEL of 0.18 mg/kg bw/day based on centrilobular hypertrophy as a reference point.

109. Liop *et al* (2017) found that women in the third tertile for β-HCH in serum samples taken during the first trimester of pregnancy had lower total serum T3. The interactions between the thyroid deiodinase gene SNP DIO1 rs2235544 and β-HCH were statistically significant. There was a strong inverse association between β-HCH and freeT4 among women with CC deiodinase genotype.

Organochlorine pesticides

110. Yin *et al* (2020) found that higher plasma levels of organochlorine pesticides (OCPs) were associated with increased odds of higher plasma homocysteine after adjustment for potential confounding factors. Positive correlations were observed between plasma β-HCH and plasma homocysteine concentrations (r = 0.172, p = 0.002), which may have implications for defects of the placenta, (Chaudhry *et al* (2019).

111. The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) derived an acute reference dose (ARfD) for chlordecone of 10 µg/kg bw and an acceptable daily intake (ADI) of 0.5 µg/kg bw/ day. Using the Pesticide Residues Intake Model (PRIMo), EFSA (2020) concluded that the short- and long-term intake of chlordecone residues at the level of the proposed MRLs for animal products was not expected to exceed the toxicological reference values derived by the French authorities.

112. In 1993, Health Canada derived a TDI for pentachlorobenzene of 5 µg/kg bw/ day. This was based on a LOAEL of 5.2 mg/kg bw/ day based on minimal to moderate centrilobular hepatocellular hypertrophy and occasional necrosis of hypertrophied hepatocytes (considered to be secondary to the hypertrophy).

113. Junqoé *et al* (2020) found that the concentrations of organochlorine compounds (OCs), including pentachlorobenzene, hexachlorobenzene (HCB), hexachlorocyclohexanes (α-, β-, γ- and δ-HCH), polychlorobiphenyls (PCBs 28, 52, 101, 118, 138, 153 and 180), DDT and metabolites, in maternal serum samples collected at the first trimester of pregnancy, at delivery and in umbilical cord from a cohort of Spanish mother-newborn pairs (n = 50), were generally low. There was a small but statistically significant increase in maternal venous OCs between the first trimester and delivery. HCB, β-HCH and the PCB congeners in cord blood were

significantly correlated with their concentrations in maternal venous blood. 4,4'-DDT showed maternal-cord blood correlated with the low metabolic capacity of newborns for OC metabolism. Older maternal age correlated with maternal venous OC concentrations, and higher body mass index correlated with higher 4,4'-DDE concentrations in maternal venous blood and cord blood. In some cases, highest concentrations were found in the women with highest education level and most affluent social class. OC concentrations in the population of the same geographic area and age range had decreased between since 2002

Endosulfan

114. In their Statement of 2014, COT concluded that the concentrations of endosulfan in food were unlikely to pose a health risk to infants based on an ADI of 6 µg/kg bw established by JMPR on the basis of a no-observed adverse effect level (NOAEL) of 600 µg/kg bw/day in a two-year dietary study of the toxicity of technical grade endosulfan in rats, with a safety factor of 100. Reduced body weight and pathological findings in the kidney and lymph nodes were observed at higher doses. The ADI was supported by similar NOAEL values in other studies and species. JMPR also established an acute reference dose (ARfD) of 20 µg/kg bw/day based on a NOAEL of 2000 µg/kg bw/day in a 90-day study of neurotoxicity in rats, with a safety factor of 100.

115. Bérenger *et al* (2020) found an association between decreased body length of infants at birth and β-endosulfan concentration in the hair of mothers in a cohort of 311 French women, from whom samples were taken after they had given birth. The authors suggested that the results should be interpreted cautiously, until they were replicated or verified by further epidemiological or mechanistic studies.

Other food components

Resveratrol

116. Resveratrol is a part of the polyphenols' stilbenoids groups, that has two phenol groups linked to each other by an ethylene bridge. It can be found in the skin of red grapes, berries and peanuts. EFSA (2015) stated that daily doses of 150 mg per day of synthetic trans-resveratrol as a food supplement did not raise safety concerns. The panel concluded that resveratrol does not have a nutritionally relevant role in the human diet.

117. Maternal intakes of resveratrol have been reported to have potential beneficial effects in complicated pregnancies. Subcutaneous maternal resveratrol treatment was found to increase uterine artery blood flow in a pregnancy ewe; an increase in fetal but not cardiac growth was observed (Darby et al, 2019). Maternal resveratrol treatment (4 g/kg diet) during pregnancy resulted in the complete reversal of fetal demise in hypoxic pregnancy in a rat model (Bourque et al, 2012). A study indicated that maternal resveratrol intake caused long-term decrease in plasma cholesterol level in rat offspring (Yamasaki et al, 2020).

118. Possible harmful effects such as a sudden increase in fetal pancreatic mass and exocrine proliferation, independent of an increase in islet mass were seen in nonhuman primates, following maternal resveratrol supplementation (Roberts et al, 2015).
119. There are currently no Government dietary recommendations for pregnant women which relate to resveratrol.

Caffeine

120. In 2018 the NHS reviewed its advice on consuming caffeine in pregnancy (NHS 2018b).

121. In small doses, caffeine increases alertness, improves mood and decreases reaction times. In larger doses, caffeine leads to increased sleep latency, diuresis, nervous excitement and heart problems, especially of consumed in excess and by people with underlying cardiac disease.

122. Excess caffeine in pregnancy is associated with fetal growth restriction which in turn is associated with poorer birth outcomes. This was discussed by COT in 2008 and led to Government advice that pregnant women should not consume more than 200 mg/day caffeine (NHS, 2008).

123. In 2015 EFSA published a scientific opinion on the safety of caffeine, including reviewing the effects pregnant women. It concluded that caffeine intakes from all sources of up to 400 mg per day (about 5.7 mg/kg bw per day for a 70-kg adult) consumed throughout the day did not give rise to safety concerns for healthy adults in the general population. For pregnant women the value should be up to 200 mg per day consumed throughout the day. This amount did not give rise to safety concerns for the fetus. This conclusion was based on prospective cohort studies showing a dose-dependent positive association between caffeine intakes during pregnancy and the risk of adverse birth weight-related outcomes in the offspring.

124. In 2008, the COT noted that the basis for the Government's current advice to breastfeeding mothers on caffeine consumption was extrapolated from that provided to pregnant women (to consume no more than 200 mg of caffeine per day), and the available information did not provide a basis for refining it.

Caffeine - recent findings

125. van der Hoeven et al (2017) found that daily caffeine consumption of more than 300 mg was possibly associated with an increase in gestational age at birth. A possible relation between high tea consumption and increased risk for pregnancy induced hypertension was also observed. For most outcomes, however, no significant associations with coffee or tea intake were found. Modzelewska et al (2019) found that moderate prenatal caffeine exposure (< 200 mg/day) did not impair neonatal health, but prenatal caffeine exposure was associated with the child being born small for gestational age, which had health implications.

Phytoestrogens

126. COT Working Group on Phytoestrogens published a report in 2003 https://cot.food.gov.uk/sites/default/files/cot/phytoreport0503.pdf

127. The Working Group defined a phytoestrogen as any plant substance or metabolite that induces biological responses in vertebrates and can mimic or modulate the actions of endogenous oestrogens usually by binding to oestrogen receptors. The major phytoestrogens are the isoflavones, coumestans, lignans, and the prenylated flavonoids. There appeared to be anecdotal but little unequivocal evidence of effects of the consumption of plant material rich in phytoestrogens, for example soy bean products, on female human fertility or the development of either sex of fetus. While minor effects were seen of the consumption of soy products in premenopausal women, these were not regarded as being physiologically relevant. It was, however, regarded as possible that phytoestrogens could act in combination with reduced levels of iodine in pregnant women to affect their thyroid function sufficiently to lead to adverse effects on fetal brain development

128. Carmichael et al (2011) found that in a dietary study of 6,584 women of reproductive age, lignans contributed 65% of total phytoestrogen intake; isoflavones, 29%; and coumestrol, 5%. The highest contributors of phytoestrogen intake were vegetables (31%) and fruit (29%); for isoflavones, dairy (33%) and fruit (21%); for lignans, vegetables (40%) and fruit (29%); and for coumestans, fruit (55%) and dairy (18%). Hispanic women had higher phytoestrogen intake than other racial groups. There were indications that older mothers and mothers taking supplements had higher intake.

129. COT reported again on phytoestrogens in 2013, on risks inherent in soya in the infant diet and concluded that there was no scientific basis for a change in the current government advice. The NHS also provides advice to pregnant women about consumption of soya products (NHS 2018c). The advice states that consuming soya products during pregnancy is safe for most people and the only people who are advised to restrict soya intake on account of phytoestrogens are people with hypothyroidism, women who have been diagnosed with breast cancer and babies who have soya-based infant formula.

130. Bircsak et al (2016) found an interaction between the soy isoflavone genistein and the drug glyburide, which is used to treat gestational diabetes. Glyburide that enters cells of the placenta is normally returned to the maternal bloodstream by the action of the breast cancer resistance protein (BCRP)/ABCG2 transporter, so that the exposure of the foetus is minimised. However, dietary intake of genistein in the presence of a common genetic variant (ABCG2, C421A) inhibits the transporter, allowing increased foetal exposure to glyburide, potentially leading to hypoglycaemia, low birth weight, increased morbidity, and impaired neurological development**Summary**

131. This paper has provided background information on a range of chemicals present in food including vitamins and minerals, process contaminants, organic contaminants, legacy pesticides, heavy metals and individual components such as caffeine and resveratrol which are on the preliminary list for consideration for their effects in the maternal diet.

Questions for the Committee

132. Members are asked to consider the information provided and consider:

a) Which if any of the chemical entities described above does the Committee feel should be chosen for review regarding their effects on the health of women of childbearing age who are or plan to become pregnant?
b) Which, of any compound selected, would be a priority?
c) Of the compounds chosen, which would require single papers and which could be considered in a combined Statement?
d) Does the Committee have any other comments on this scoping paper?

Secretariat

July 2020

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Glossary

α,β,γ HCH	Hexachlorocyclohexoane isomers
ABCG2	ATP-binding cassette superfamily G member 2
ADI	Acceptable Daily Intake
AF	Aflatoxin
AI	Adequate Intake
ANSES	Agence Nationale de Securite sanitaire de l'alimentation, de l;environment et du travail
ARfD	Acute Reference Dose
As	Arsenic
BCRP	Breast Cancer Resustance Protein
BMDLx	Benchmark Dose lower confidence interval for x% adverse effect
BPA	Bisphenol A
B-Pb	Blood lead concentration
BPS	Bisphenol S
bw	bodyweight
Cd	cadmium
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
COMA	Committee on Medical Aspects of Food Policy
CONTAM	EFSA Oanel on Contaminants in the Food Chain
COT	Committee on Toxicity
DDE	Dichlorodiphenyltrichloroethene
DDT	Dichlorodiphenyltrichloroethane
DL	Dioxin-loke
DON	Deoxynivalenol

DRV	Dietary Reference Value
EFSA	European Food Safety Authority
EHMI	Equivalent Himan Monthly Intake
ECVM	Expert Committee on Vitamins and Minerals
FAO	Food and Agriculture Organization
FB	Fumonisins
FSA	Food Staandards Agency
FT3	Free triiodothyronine
FT4	Free thyroxine
HCA	Heterocyclic Amines
HCB	Hexachlorobenzene
HED	Human Equivalent Dose
Hg	Mercury
IQ	2-amino, 3-methylimidazo[4,5-f]quinolone
IQ	Intelligence Quotient
IU	International Unit
JECFA	Joint FAO.WHO Committee on Food Additives
JECS	Japan Environment and Children's Study
JMPR	Joint FAO.WHO Committee on Pesticide Residues
Kg	kilogram
L	litre
LOAEL	Lowest-Observed Adverse Effect Level
LOEL	Lowest-Observed Effect Level
MeIQ	2-amino, 3,4-dimethylimidazo[4,5-f]quinolone
MeIQx	2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline

mg	molligram
μg	microgram
MOE	Margin of Exposure
NDL	Non-dioxin-like
NHS	National Health Service
NOAEL	No-Observed Adverse Effect Level
NOEL	No-Observed Effect Level
OCP	Organochlorine Pesticide
OTA	Ochratoxin
Pb	Lead
PCB	Polychlorinated Biphenyl
PCDD	Polychlorinated dibenzodioxin
PCDF	Polychlorinated dibenzofuran
pg	picogram
PhiP	2-Amino-1-methyl-6-phenylimiazo[4,5-b]pyridine
PRI	Population Reference Intake
PRIMo	Pesticide Residues Intake Model
PTMI	Provisional Tolerable Monthly Intake
PTWI	Provisional Tolerable Weekly Intake
RI	Retinol Equivalent
SACN	Scientific Advisory Committee on Nutrition
SCF	Scientific Committee on Food
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TDI	Tolerable daily Intake

TEF	Toxic Equivalence factor
TEQ	Toxic Equivalent
t-TDI	Temporary TDI
t-TWI	Temporary Tolerable Weekly Intake
UL	Upper Limit
WHO	World Health Organization
ZEN	Zearalenone

Anex 1

The SACN Secretariat has identified a number of xenobiotics where advice from COT might be needed. . The preliminary list is given below:

Vitamins A

C

D

E

Selenium

Mycotoxins

Acrylamide

Heterocyclic amines

Resveratrol

PCBs

BPA

Dioxins

Pesticides

Heavy metals

Oily fish

Caffeine

Phytoestrogens

[i] Department of Health. Weaning and the Weaning Diet. Report of the Working Group on the Weaning Diet of the Committee on Medical Aspects of Food Policy. Report on Health and Social Subjects No 45. 1994 HMSO. London.[i]