TOX/2018/48

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

Draft overarching statement on the potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Background

1. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risk of toxicity of chemicals in the diets of infants and young children aged 0-5 years, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to five years of age.

2. SACN is examining the nutritional basis of the advice and has asked that evidence on possible adverse effects of the diet should be considered by other advisory committees with relevant expertise.

3. The COT identified a number of chemicals in 2015[1], which might pose a risk to infants and for which advice might be needed. The following statement discusses the conclusions of the COT regarding a number of these chemicals. Chemicals identified for review and not included in this statement have been or will be subject to a full review or will be published in a second overarching statement at a later date. The remaining chemicals are listed in Annex 1.

4. The following reviews provide a brief overview of the chemicals characteristics yet focus mainly on the exposure assessment (where applicable) and the risk characterisation and conclusions.

General information

5. Unless indicated otherwise, the sources of general background information were the most recent assessments by the COT or other regulatory agencies, such as the European Food Safety Authority (EFSA), the Scientific Committee on Food (SCF), or the Expert Group on Vitamins and Minerals (EMV).

6. Exposure assessments are based on the newest occurrence data available from food surveys conducted by the Food Standards Agency (FSA). For chemicals with no available in-house data, the exposure assessment and risk characterisation have been drawn from EFSA opinions, with emphasis on UK data.

7. Consumption data (on a body weight basis) for the estimated dietary exposure were from the Diet and Nutrition Survey of Infants and Young Children

[1] https://cot.food.gov.uk/sites/default/files/TOX2015-32%20Feeding%20Review%20Scoping%20Paper.pdf

(DNSIYC) (DH, 2013) and from years 1-6 of the National Diet and Nutrition Survey (NDNS) (Bates et al., 2012 & 2014). Estimates of consumption of breast milk and infant formula vary; in this statement average and high daily intake of 800 mL and 1200 mL, respectively, were applied. This is in line with the approach taken by EFSA. Occurrence data in breastmilk were taken from the literature, preferably from the UK, where applicable.

8. Where possible, estimated exposures to chemicals were compared to health based guidance values (HBGVs) or (safe) upper limits (UL) established by the COT or other regulatory agencies, preferably EFSA.

Assessment

Alcohol

9. Alcohol is widely consumed in the UK population; levels of alcohol in breast milk are close to those in the mother's blood stream[2]. The government therefore advises breastfeeding women should not drink more than 1 or 2 units of alcohol once or twice a week.

10. In line with the 2012 statement, the COT sees no reason to change the current government advice regarding alcohol and breastfeeding.

11. As children aged 0 to 5 years would not be consuming alcohol, the current statement does not require any further assessment of alcohol in this age group.

12. The full COT statement (2012) can be found here:

https://cot.food.gov.uk/sites/default/files/cot/cotstatementoverarch201203.pdf

Caffeine

13. Back in 2008 the FSA advised pregnant women, based on a COT evaluation[3], to consume less than 200 mg per day of caffeine and provided guidance on how to achieve such intakes for different foods and beverages. In addition, the Department of Health (DH) advices pregnant and breastfeeding women "to restrict their caffeine intake to less than 200 mg a day" and "to avoid energy drinks, which can be very high in caffeine".

14. The COT previously concluded that breastfed infants can be exposed to caffeine through breastmilk. The scientific evidence does not demonstrate a health risk for infants from caffeine consumed by their mothers. COT noted in their 2012 statement, that the basis for the current government advice to breastfeeding mothers on caffeine consumption was extrapolated from data on pregnant woman and the data available at the time did not allow for refinement.

[2] http://www.drinkaware.co.uk/alcohol-and-you/family/alcohol-and-breastfeeding
[3] https://cot.food.gov.uk/sites/default/files/cot/cotstatementcaffeine200804.pdf

15. The available information does not provide a basis to refine the current Government advice regarding caffeine consumption of breastfeeding women. As children aged 1 to 5 years would not be expected to be consuming high-caffeine beverages, the COT concluded that no further assessment of caffeine for this age group is required.

16. The full COT statement (2012) can be found here:

https://cot.food.gov.uk/sites/default/files/cot/cotstatementoverarch201203.pdf

Endosulfan, Pentachlorobenzene and Chlordecone

17. In the absence of any newer data and information and given the nature and use of these chemicals, the COT decided to refer to its previous statement (2013) on endosulfane, pentachlorobenzene (PeCB) and chlordecone.

18. In brief, endosulfan is an unauthorised pesticide in the European Union since 2005 and significant residues in food are not expected. JMPR established an ADI of 0.006 mg/kg bw per day in 1998, based on a two-year dietary study in rats. An ARfD of 0.02 mg/kg bw per day was established based on a neurotoxicity study in rats.

19. No data on PeCB and chlordecone have been found in food. Even if both had been used previously in the UK, exposures would be expected to be decreasing. The US EPA established a reference dose (RfD) of 0.8 µg/kg bw per day for PeCB in 1998, based on liver and kidney damage in a sub-chronic study, Health Canada established a tolerable daily intake (TDI) of 0.5 µg/kg bw per day based on a sub-chronic study for hepatocellular hypertrophy and necrosis. No HBGVs for chlordecone are available.

20. The COT concluded, based on the available information, that there appeared to be no toxicological concern for human health; exposures were below the acceptable daily intake (ADI) or no ADI had been set, and concentrations were low and deceasing.

21. The full COT statement (2013) can be found here:

https://cot.food.gov.uk/sites/default/files/cot/tox201321.pdf

Food Additives

22. Under EU law (Regulation (EU) No. 1169/2011[4]), manufacturers must provide information about any additives used in the foods they produced. Once the additive has been assessed for safety and approved it is allocated an E number and can be used in the UK and the rest of the EU.

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[4] On the provision of food information to the consumer (FIC)
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=EN
http://www.legislation.gov.uk/uksi/2014/1855/contents/made
Specific provisions on the labelling of food additives sold as such to the manufacturer or to the final consumer are contained in Regulation (EC) No. 1333/2008.

23. The additives regulation applies to all foods produced, including foods specifically for infants and children. Therefore, the COT deemed it not necessary to assess food additives as such.

24. Previous evaluations for some food additives can be found here:

https://cot.food.gov.uk/sites/default/files/cot/cotstatementadditives.pdf

https://www.food.gov.uk/safety-hygiene/food-additives

https://cot.food.gov.uk/sites/default/files/cot/colpreschil.pdf

Legacy Pesticides

25. A number of bio-persistent pesticides, banned in the 1980s and 1990s are still present in the environment and food chain today. These compounds are collectively known as legacy pesticides, classified as persistent organic pollutants (POPs) and include aldrin, dieldrin, endrin, chlordane, heptachlor, hexachlorobenzene, mirex, toxaphene and DDT. Although they are persistent in the environment, their levels have decreased since they ceased to be used.

26. All of the legacy pesticides, except mirex and toxaphene, are on the list of EFSAs continuous call for data[5]; the data are made publicly available through summary reports, the latest on contaminant occurrence data was from 2016[6]. The last European Union report on pesticide residues in food, including POPs, was from 2015.

27. Results of the 2015 report showed that 97.2% of the samples analysed did not exceed the maximum residue levels (MRLs) permitted by EU legislation; POPs were the most frequently found pesticides at concentrations equal to or greater than the LOQ. DDT and hexachlorobenzene were the most frequently reported POPs (3% and 2.4% respectively, in chicken eggs), however levels have decreased since the 2012 report (5.8% and < 2% respectively, in chicken eggs).

28. As the levels would be expected to further decline, the COT concluded, in line with the 2012 overarching statement, that there is no indication of concern for human health.

29. The 2015 European Union report can be found here:

https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2017.4791

30. The full COT overarching statement (2012) can be found here:

https://cot.food.gov.uk/sites/default/files/cot/cotstatementoverarch201203.pdf

[5] https://www.efsa.europa.eu/en/consultations/call/180307
[6] https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/sp.efsa.2017.EN-1217

Soya phytoestrogens

31. In the absence of any newer data, the COT decided to refer to its previous statement on phytoestrogens and health (2003), soya phytoestrogens in the infant diet (2013) and effects of soya consumption on thyroid status (2014).

32. In brief, phytoestrogens are naturally produced chemicals of plant origin, notably in soya. They are structurally similar to estrogen and have been shown to influence biological processes through their ability to bind to estrogen receptiors (ER) and interfere with natural hormonal responses in animals and humans.

33. Based on the data available at the time, the COT concluded that it was not possible to determine a dose response relationship, nor to identify other risk factors with the exception of iodine deficiency. The COT therefore concluded, that individuals with hypothyroism, would still be considered a subgroup of the population with a potential concern for health. The COT however recommended that this population group, as well as general practitioners and endocrinologists, should be made aware of the potential risk of an exacerbated condition from increased consumption of soya.

34. The main toxicological concern for infants arises from the oestrogen-like activity and the potential disruption of the development and reproductive system. Other possible adverse effects include disruption of the immune and thyroid function. Due to limitations in the available data, it is not possible to set HBGVs for soya isoflavones in infants.

35. The few critical epidemiological studies available do not suggest important impacts of soya-based formula on later reproductive health in humans. However, animal studies suggest some developmental and reproductive changes. Thus, there is some uncertainty about the safety of soya-based formula. The COT concluded, that there is no substantive medical need for soya based infant formula, nor health benefits and should therefore only be used in exceptional circumstances.

36. Due to the lack of any new UK data, the COT agreed with its previous evaluation, that there is no scientific basis for a change in the current government advice.

37. The full COT statements can be found here:

https://cot.food.gov.uk/sites/default/files/cot/phytoreport0503.pdf

https://cot.food.gov.uk/sites/default/files/cot/cotstaphytos.pdf

https://cot.food.gov.uk/sites/default/files/TOX2014-41_0.pdf

Trans fatty acids

38. Public Health England (PHE) are currently consulting on draft recommendations for saturated fat and therefore no assessment of trans fatty acids by COT is required.

39. PHE has kindly provided the following information to be included in the COTs overarching statement: “While trans fats are associated with risk of heart disease, UK consumption is less than the recommended maximum intake. However, many still eat more saturated fat than recommended, which can lead to higher blood cholesterol and heart disease. Until all responses have been received, current advice (by PHE) is to consume no more than 10% of calories each day from saturated fat.”

Perchlorate

40. The data collected by the FSA on perchlorate has been submitted to and is part of the evaluation done by EFSA. The COT therefore did not consider it appropriate to undertake a full risk assessment, thus the following paragraphs provide an overview and assessment of EFSAs evaluations in 2014 and 2017.

41. Perchlorate is a chemical contaminant which is released into the environment from both, natural and anthropogenic sources. Perchlorate is further formed during the degradation of sodium hypochlorite which is used for the disinfection of water and can contaminate the water supply. Water, soil and fertiliser are considered the most likely sources for perchlorate contamination of food. Perchlorate has been reported in a wide range of foods, including vegetables, fruit, milk and dairy products, juice, beer, wine and bottled water.

42. The main adverse effects of perchlorate are on the thyroid. It competitively inhibits the uptake of iodine via the sodium-iodide symporter (NIS) in humans and rodents and therefore can possibly cause disruption of thyroid hormone synthesis and consequently lead to the development of hypothyroid symptoms. In humans, severe iodine deficiency can lead to hypothyroidism; mild to moderate iodine deficiency can lead to the development of toxic multinodular goitre, which can subsequently result in hypothyroidism.

43. EFSA concluded in their evaluation in 2012, that prolonged 50 % inhibition of thyroid iodine uptake by perchlorate may lead to goitre and multinodular goitre, even if short term exposure does not alter the thyroid function test. Therefore, using the $BMDL_{05}$ of 1.2 µg/kg bw from human dose-response data as reference point and applying an uncertainty factor (UF) of 4 to allow for inter human differences in toxicokinetics, EFSA derived a TDI of 0.3 µg/kg bw. EFSA considered a 5% inhibition of iodine uptake not to lead to adverse effects in any subgroup of the population and therefore did not apply any further UFs for interspecies differences in toxicodynamics.

44. No data are available on acute toxicity in humans; data from rodent toxicological studies is of limited use for the extrapolation to humans due to the difference in thyroid hormone physiology. A single treatment with potassium perchlorate at a concentration of 10 mg perchlorate iron/kg (assuming a 70 kg adult) used for diagnostic purposes showed no adverse effect.

45. Although acute effects in foetuses and infants have been suggested, EFSA concluded that an acute reference dose (ARfD) was not warranted on the basis that

a single day acute exposure to perchlorate at concentrations found in food and drinking water is unlikely to cause an adverse effect in both healthy humans and more vulnerable groups. In foetuses, the limitations in the reserve capacity are mitigated by the maternal supply of thyroid hormones. Neonates on the other hand rely on their own hormone synthesis and thus could be considered a more vulnerable population subgroup. However, iodine uptake with the diet may vary significantly from day to day and the thyroid system has a well developed homeostatic mechanism to take account of this. In addition, controlled human studies showed, that thyroid uptake was completely restored within 24 hours of the end of the exposure period to perchlorate. While the stores of iodine will generally be lower in individuals with mild to moderate iodine deficiency, the thyroidal iodine stores are considered to be sufficient for a one-day need. However, if the iodine inhibition continues, the situation could become critical in breast-fed infants and young children, within a week or two, especially in individuals with mild to moderate iodine deficiency. Therefore, EFSA included a short-term exposure assessment, to take into account possible adverse effects in vulnerable groups, if exposed to relatively high levels of perchlorate for a short period (two to three weeks).

46. For the total of European data, the upper bound (UB) mean and 95th percentile estimated short-term and chronic exposures exceeded the TDI of 0.3 µg/kg bw in all age groups. For UK data only, the UB mean and 95th percentile estimated short-term exposure exceed the TDI in all age groups. UB chronic estimated exposures exceed the TDI for infants and toddlers but are below the TDI in other children. Both, the chronic and short-term exposures to perchlorate are therefore of potential concern, particularly for high consumers with mild to moderate iodine deficiency and/or low iodine intake.

47. No breast milk data for perchlorate were available for the UK or Europe. Based on data from the United States, the estimated exposures for breastfed infants exceeded the TDI for both, average and high-level consumption of breastmilk. This could possibly be of concern for breastfed infants of mothers with low iodine intake, however the relevance of the estimated exposures for Europe and the UK are uncertain.

48. Overall, the COT agreed with EFSAs approach and the derivation of the HBGVs. However, EFSA themselves considered the use of the lowest $BMDL_{05}$ measured in a human volunteer study conservative in deriving the TDI and furthermore noted that there is a level of uncertainty on the length of inhibition of thyroid iodine uptake without the development of adverse effects. The COT further noted that the BMDL used to derive the TDI is based on healthy individuals. The COT also noted that EFSA established an ARfD for chlorate due to the induction of methemoglobinemia and questioned whether based on a read across from chlorate, the possibility of methaemoglobin formation by chlorate should be considered.

49. In agreement with EFSA, the COT concluded that while there are considerable uncertainties in the assessment, the chronic and short term estimated exposures for all age groups, are of potential concern, particularly in case of a mild to moderate iodine deficiency.

50. The full EFSA evaluations can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2014.3869

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.5043

Chlorate

51. The data collected by the FSA on chlorate has been submitted to and forms part of the evaluation done by EFSA in 2015. Whilst FSA and the Expert Committee on Pesticide Residues in Food (PRiF) have undertaken further data collection, also to inform the discussion on possible future MRLs under the pesticide legislation, the data are unlikely to change the (UK) exposure assessment undertaken by EFSA or conclusions drawn. The COT therefore did not consider it appropriate to undertake a full risk assessment. Thus, the following paragraphs provide an overview and assessment of the EFSA opinion on chlorate.

52. Chlorate is no longer permitted as a pesticide in the European Union (EU), due to the lack of a maximum residue level (MRL), the default MRL of 0.01 mg/kg is applicable. No maximum level for chlorate in drinking water has been set by the EU, although the World Health Organisation (WHO) set a guideline level of 0.7 mg/L.

53. Chlorate can be formed as a by-product when using chlorine, chlorine dioxide or hypochlorite and residues in food have been shown to arise from the use of chlorinated water for food processing (for example washing) and the disinfection of surfaces and food processing equipment, although in many cases they may occur simply due to the presence of chlorate in potable water used for food production.

54. The primary targets of chlorate toxicity are the thyroid gland and haematological system and like perchlorate, chlorate acts as a competitive inhibitor of iodine uptake in the thyroid leading to chronic effects such as multinodular goitre, especially in populations with mild to moderate iodine deficiency. Due to the lack of adequate epidemiological studies in humans, EFSA established a TDI of 3 µg/kg bw for chlorate based on a read across from perchlorate. When comparing the no observed adverse effect level (NOAEL) to the lowest observed adverse effect level (LOAEL) for thyroid follicular cell hypertrophy in rats, perchlorate is about 10 times more potent than chlorate. In vitro studies furthermore showed perchlorate to be the stronger inhibitor of thyroid iodine transport. Hence, the TDI for perchlorate (0.3 µg/kg bw) was multiplied by a factor of 10 to account for the different potencies of chlorate and perchlorate in rats.

55. In contrast to perchlorate, EFSA found it appropriate to establish an ARfD for chlorate, based on the acute haematological and renal toxicity of chlorate in humans. EFSA identified the formation of methaemoglobin in a 12 week controlled clinical study as a critical acute effect of chlorate and derived an ARfD of 36 µg/kg bw from the NOAEL of 36 µg/kg. No UF for more vulnerable individuals was applied in the derivation of the ARfD as EFSA concluded the difference between the NOAEL and the effect in poisoning cases, without induction of methemoglobinemia, to be sufficiently large. As with perchlorate, EFSA noted that a single acute exposure to chlorate at the concentrations found in food and drinking water would be unlikely to cause adverse effects on the thyroid, including in the more vulnerable population.

56. For the total of the European data, the TDI was exceeded for the UB 95th percentile estimated chronic exposure in all age groups; the UB mean estimated chronic exposure exceeded the TDI in infants and toddlers. The 95th percentile estimated chronic exposure for UK data only, exceeded the TDI in all age groups; all mean estimated chronic exposures were below the TDI, except for toddlers at the UB level. In all population groups exceeding the TDI, drinking water was the major contributor, with up to 40 to 60%.

57. Individuals with sufficient iodine intake are less likely to suffer adverse effects from exceedances of the TDI than foetuses, neonates and individuals with low iodine intake or individuals genetically predisposed to develop hyperthyroidism. The chronic dietary exposure is therefore of potential concern for high consumers in these age groups with mild to moderate iodine deficiency.

58. No data for acute estimated exposures on UK data only were available. The mean and 95th percentile estimated acute exposures for all European data in all age groups are below the ARfD. Single acute exposure to chlorate at levels found in food and drinking water are therefore unlikely to cause adverse effects, including vulnerable individuals. However, if drinking water would contain concentrations of 0.7 mg/L, as assumed in one of EFSAs extremely conservative additional scenarios, mean water consumption could lead to mean (infants) and 97.5th percentile (toddlers) estimated exposures similar to the ARfD, high water consumption could lead to an exceedance of up to three times the ARfD.

59. No data on concentrations of chlorate in human breastmilk were available. Based on a read across from perchlorate, applying a factor of 10 for the differences in potency, the estimated exposure from breastmilk for both, average and high-consumption of breastmilk are well below the TDI. Based on the assumptions made, the exposure of infants from breast milk is not of toxicological concern.

60. While the COT agrees with the establishment of the HBGVs, they noted some uncertainties. No human studies on inhibition of iodine uptake by chlorate were available, the TDI by EFSA is therefore based on a read across from perchlorate. The basis for the TDI of 0.3 µg/kg bw is human-dose response data, while the difference of potency is derived from animal data. EFSA therefore assumed the same potency difference of perchlorate and chlorate in humans and rats. Furthermore, different rat strains have been used for tests of the two compounds, adding additional uncertainty.

61. An ARfD was set based on a NOAEL of 36 µg/kg bw per day in a human repeat study, the NOAEL being the highest dose tested, and it is unclear as to how much higher a LOAEL would be. No UF was applied as the NOAEL was at least 300 times lower than the toxic concentration in a poisoning case without induction of methemoglobinemia. However, this difference was derived from a single poisoning case.

62. The COT agrees with the overall conclusion by EFSA. Chronic dietary exposure to chlorate is of potential concern for high consumers in all age groups, particularly to individuals with mild to moderate iodine deficiency. Drinking water was

the major contributor, at up to 40 to 60%. Single acute exposure to chlorate at levels found in food and drinking water however, are unlikely to cause adverse effects, including vulnerable individuals.

63. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4135

Furan

64. Furan and methylfurans (2-methylfuran, 3-methylfuran and 2.5-methylfuran) are volatile compounds that are formed in foods during thermal processing. Food characteristics, processing and cooking conditions, especially the preparation of the food at the level of the consumer, determines the final concentration of furan in foods as consumed. Furan can be found in a variety of foods, including coffee and canned and jarred goods.

65. In short term rodent studies (< 90 days), furan showed strong hepato- and nephrotoxicity; in long term studies, furan was associated with toxicity in the liver. Furan was unable to induce gene mutations in bacteria and results in mammalian cells in vitro were contradictory. Limited information is available on furan levels in humans. The studies available show a variety of inconsistencies and therefore do not allow for conclusions regarding the reported levels of blood and urinary furan and whether or not furan has an effect on the liver.

66. The liver has been identified as the primary target for acute and short term (< 90 days) toxicity of methylfurans in rodents; 3-methylfuran also showed indications of nephrotoxicity after long term exposure. No information on the genotoxicity of 3-methylfuran are available. 2-methylfuran and 2,5-dimethylfuran showed negative results in bacteria; some evidence however points to chromosome damage in mammalian cells in vitro.

67. The toxic potency of methylfurans were reported to be in the same order of magnitude as for furan.

68. EFSA found it not appropriate to establish a TDI due to clear evidence of indirect mechanisms in the carcinogenic mode of action (MoA) of furan and some indications of direct genotoxic mechanisms and therefore used the margin of exposure (MOE) approach. Based on the available toxicity data and taking inter- and intraspecies variations into consideration, EFSA concluded a MOE of 100 or higher to be of low health concern for non-neoplastic effects. For substances that are both genotoxic and carcinogenic, EFSA concluded a MOE of 10,000 or higher to be of low health concern, if based on a $BMDL_{10}$ from an animal carcinogenicity study.

69. UK data from the FSA long-term surveillance programme (2014-2018) forms part of the 2017 EFSA opinion, however at the time of publication, the 2017 data was not yet available. The 2017 data have since been published in the final FSA report and have been used in the COT 2018 assessment forming part of the overarching statement. No data on breast milk were available.

70. All MOEs for non-neoplastic effects of furan are greater than 100 and are therefore not of toxicological concern.

71. The mean and 97.5th percentile MOEs for neoplastic effects of furan for children ages 4 to 18 months and the 97.5th percentile MOEs for children aged 18 to 60 months, for both ready-to-eat meals and total exposure are below 10,000. The MOEs at the 97.5th percentile in children aged 4 to 18 months are lower with values of < 2500. These exposures are of potential toxicological concern. All other MOEs for neoplastic effects are greater than 10,000 and are therefore not of toxicological concern.

72. The 97.5th percentile MOEs for non-neoplastic effects of the sum of furan and the two methylfurans for children ages 4 to 18 month, for both ready-to-eat meals and total exposure, are at/below the MOE of 100. These exposures are of potential toxicological concern.

73. The lack of occurrence data on 2,5-dimethylfuran and the lack of information regarding the contribution of 2-methylfuran and 3-methylfuran, add to the uncertainties surrounding the sum of furan and methylfurans and could therefore be an over- as well as underestimation of the risk.

74. There is a level of uncertainty concerning the carcinogenic MoA and whether or not furan is directly genotoxic. The Committee acknowledges that this is a worst-case assumption and that the MOE could potentially be lowered.

75. The major contributor to the dietary exposure was ready-to-eat meals. Dietary exposure to furan of infants and young children in the UK is similar to that in other European countries and therefore not dependent on particular aspects of UK dietary habits. There have been efforts to reduce concentrations of furan (and methylfurans) in food over the recent years but the evidence so far is not sufficient to demonstrate whether there has been a decrease in dietary exposure. Therefore, efforts to reduce furan and methylfurans should continue, with respect to commercially produced food and monitoring should be continued to allow for accurate risk assessments.

Chromium

76. Chromium (Cr) is a hard, highly lustrous metal that exists in various mineral forms and is present throughout the environment. The most prevalent natural ionic form of chromium is Cr(III). Cr(VI) is present in the environment largely due to industrial activity. The general population is primarily exposed to chromium via food and drinking water. The IARC reviewed Cr(III) and Cr(VI) and their compounds. Cr(VI) and its compounds have been classified as human carcinogens that cause cancers of the lung, and paranasal sinuses after inhalation (IARC, 2012). However, the potency of the carcinogenic effect depends upon the physicochemical properties of the compound. There is currently no consistency in the data to suggest that Cr(III) compounds cause cancer in humans at concentrations to which people are exposed in food or the wider environment.

77. Food is largely a reducing environment. EFSA (2014) regard the chromium in food to be entirely Cr(III) and derived a TDI of 300 µg/kg bw/day. Drinking water,

which is purified with oxidising agents, is a source of Cr(VI). Cr(VI) is largely reduced to Cr(III) in the acidic environment of the stomach (De Flora et al, 2016, Kirman et al 2016). EFSA (2014) concluded that the levels of Cr(IV) found in drinking water were safe for all consumers but there might be a potential concern for 95th percentile consumers particularly in “Infants”, “Toddlers” and “Other children” groups, based on MOEs of <10,000. However, the CONTAM Panel concluded that the impact of the uncertainties on the risk assessment of exposure to Cr(VI) in drinking water was very large. In this estimate, therefore, only the intake of Cr(III) is considered.

78. Gastrointestinal absorption of Cr is low: The Agency for Toxic Substance and Disease Registry (ATSDR, 2012) estimates <1% for Cr(III) and 1 – 2% for Cr(IV). EFSA (2014) estimates 0.4 – 2.8% for Cr(III). WHO, (2013) estimates 2 – 8%) for Cr(VI). Absorption depends largely on the solubility of the particular compound.

79. Average- and high-level-consuming, exclusively breastfed, 0 to 6-month infants had an intake of 0.11 to 0.87 and 0.21 to 1.3% of the EFSA TDI for Cr(III) respectively. Mean intakes of chromium for non-exclusively breast fed 4 to 18-month olds relative to the TDI were 0.026 to 0.60% and 97.5th percentile exposures were 0.05 to 1.0% of the TDI.

80. In 0 to 6-month olds, intakes of chromium from ready-to-feed formula were 0 to 0.14% of the TDI in average consumers, and 0 to 0.2% of the TDI in high level consumers. Mean and high-level exposure to chromium from infant formula reconstituted with water containing chromium up to 8 µg/L (the highest limit of detection (LOD)) were up to 0.53 and 0.83% of the TDI. Total mean intakes (excluding water) of chromium from infant formulae, commercial infant foods, and other foods, for 4 to 12-month olds were 0.11 and 0.43 % of the TDI and the 97.5th percentile intakes were 0.37 to 1.2% of the TDI.

81. Based on the Infant Metals Survey (FSA, 2016a), the ranges of total mean and 97.5th percentile intakes (excluding water) of chromium from infant formula, commercial infant foods and other foods were 0.17 to 0.37 and 0.32 to 0.74% of the TDI, respectively, for children aged 12 to 18 months.

82. Based on the TDS (FSA 2016b) the total mean and 97.5th percentile intakes of chromium from a combination of all food groups for children aged 12 to 18 months the estimated chromium intakes were. 0.47 to 1.1 and 1.1 to 1.8% of the TDI respectively. For children aged 18 months to 5 years, the mean and 97.5th percentile intakes were 0.60 to 1.2 and 1.1 to 2.0 % of the TDI respectively.

<u>Soil, air and dust</u>

83. The median and 90th percentile concentrations in 5,670 topsoil samples collected between 1978 and 1982 in England and Wales. 68 and 97 mg/kg, respectively (Rawlins *et al.*, 2012). Harrison (1979) determined the levels of chromium in outside and domestic dust samples to be 11.8 ± 6.1 µg/g (Mean ± SD, n = 4, range 5.0 – 20 µg/g). Data from 23 air sampling sites across the UK have been collected by Defra. For 2007 – 2016, the lowest and highest median values were 0.8 and 8.65 and lowest and highest 99th percentiles of 1.4 and 167ng chromium/m^3 across the sites.

84. Environmental exposure to Cr(III) was calculated to be at most 0.038, 0.15 and 0.036% of the EFSA TDI for dust, soil and air respectively.

85. Estimated dietary exposures for children aged 0 to < 12 months and 1 to < 5 years do not indicate excessive chromium intake, either from breastmilk or other foods and are therefore unlikely to be of toxicological concern.

Selenium

86. 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.

87. 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).

88. Selenium compounds are readily absorbed in the small intestine. Selenium is an essential element to human health and is widely distributed throughout the body and can be detected in breast milk. It has also been reported to cross the placenta in animals. Selenium compounds are incorporated in selenoproteins, which have a variety of biological functions including antioxidant effects, T-cell immunity, thyroid hormone metabolism, selenium homeostasis and transport, and skeletal and cardiac muscle metabolism.

89. Upon absorption, selenium compounds can also bind to selenium binding proteins or, as a way of regulating selenium metabolism, form methylated metabolites in the liver. These compounds are excreted predominantly in the urine. Excretion of selenium can also occur at a smaller extend in the faeces or, for some volatile compounds in the breath (EFSA, 2014; EVM, 2003).

90. Selenium deficiency interferes with the expression and function of selenoproteins. Although the clinical manifestations are poorly defined symptoms reported from epidemiological studies in populations with low selenium intake and patients receiving selenium-free total parenteral nutrition include skeletal myopathy, cardiomyopathy and muscle weakness. Selenium deficiency is also linked to the manifestation of the degenerative Keshan and Kashin-Beck disease (SCF, 2000; EFSA, 2014).

91. High exposure to selenium can lead to acute toxicity. This is characterised by hypersalivation, emesis and garlic aroma on the breath. Other symptoms include severe vomiting and diarrhoea, hair loss, neurological disturbance and fatigue (EVM,2003).

92. Chronic toxicity, or selenosis, leads to hair and nail changes, skin lesions and clinical neurological effects such as peripheral hypoaesthesia, acroparasthaesiae, pain and hyperreflexia; numbness, convulsions and paralysis may then develop (EVM, 2003).

93. The Scientific Committee on Food (SCF) established in 2000 an UL for selenium at 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 applying an uncertainty factor of 3. The NOAEL was derived based on the absence of clinical signs in individuals with selenium levels below 1000 µg/L. In the absence of data to derive specific ULs for children, the SCF extrapolated the UL from adults to children based on reference body weights. The proposed UL values for children and adolescents were 60, 90, 130, 200 and 250 µg/day for children aged 1-3, 4-6, 7-10, 11-14 and 15-17 years respectively.

94. In their evaluation, the EVM used the same data set as the SCF to derive an UL of 450 µg/day. They considered that there were discrepancies in NOAELs in the series of studies conducted by Yang et al. and therefore used the Lowest Adverse Effect Level (LOAEL) of 900 µg/day and applied an uncertainty factor of 2 to extrapolate to a NOAEL. An uncertainty factor for inter-individual variation was not deemed necessary as they considered that the value was based on a population study.

95. Exposures estimated were calculated using consumption data from NDNS and concentrations of selemium measured in a FSA survey of metals and other elements in infant formula and foods. Mean dietary exposures to selenium for children aged 4 months to 5 years ranged from 7 µg/day (lowest lower-bound (LB)) to 46 µg/day (highest upper-bound (UB)). The corresponding 97.5th percentile exposures range from 20 to 76 µg/day.

96. Assuming a selenium concentration of 20.6 µg/L in mature breast milk (Foster et al. 1996), estimated exposures for exclusively breastfed infants (0 to 6 months) for average and high-level consumption of breast milk were 16 and 25 µg/day respectively.

97. A soil 90th percentile selenium concentration of 1.3 mg/kg (UKSO, 2017) was used to estimate exposure from soil and dust, given the absence of Se data specific to dust. The resulting exposures in infants and young children from soil and dust are at least two orders of magnitude below dietary exposures.

98. The UL for children below 1 year of age were calculated on a body weight basis using the approach used by the SCF. These were 40µg/day for children aged 4-12 months when addressing dietary exposures. The extrapolated UL would be 26 µg/day for infants 0 to <4 months and 34 µg/day for >4 to <6 months old infants.

99. Overall the COT concluded that estimated dietary exposures for children aged 4 to < 12 months and 1 to < 5 years were below the UL, either from breastmilk or other foods and are therefore unlikely to be of toxicological concern.

Zinc

100. Zinc is an essential trace element found in all plant and animal tissue. It plays a role in a wide range of biochemical and physiological functions; it's key biochemical role is in the regulation of gene expression, including transcriptional and translational control/modulation. Zinc furthermore has catalytic/structural roles in enzymes and a regulatory role in signal transduction.

101. The initial absorption of zinc occurs in the stomach, the majority however is absorbed in the upper intestine. Gastrointestinal distress, vomiting and nausea are common symptoms of acute oral exposure to zinc. Excessive chronic high zinc intakes lead to biochemical and physiological symptoms, such as secondary copper deficiency which can result in severe neurological diseases, anaemia and bone abnormalities.

102. The SCF (2003; 2006; 2017) derived a tolerable upper intake level (UL) of 25 mg per day for adults based on a NOAEL of 50 mg per day for a wide range of indicators for copper status in epidemiological studies and the application of an UF of 2 for the small number of subjects and relative short time period. In the absence of adequate data for children, the SCF chose to extrapolate from adults to children on a body weight basis, resulting in an UL of 7 mg per day for children age 1-3 years and 10 mg per day for children age 4-6 years. EVM and JECFA derived UL for adults only, while EFSA derived population reference intakes only.

103. The ULs derived by the SCF for children start at the age of 12 months and would therefore not be applicable to infants aged 4 to < 12 months. Using the same approach as SCF, the COT extrapolated an UL of 3.6 mg per day (based on a bodyweight of 9 kg for infants from DNSIYC) for infants aged 4 to < 12 months.

104. Exposure estimated were calculated using consumption data from NDNS and concentrations of zinc measured in a FSA survey of metals and other elements in infant formula and foods. For infants aged 4 to < 12 months, the mean and 97.5th percentile estimated exposures exceed the UL of 3.6 mg per day 1 and 2-fold, respectively. The mean estimated exposures for children aged 1 to < 4 years are below the UL of 7 mg per day set by SCF; the 97.5th percentile estimated exposures are at or marginally above the UL. Estimated mean and 97.5th percentile exposure for children aged 4 to < 5 years are below the UL of 10 mg per day set by SCF.

105. Assuming a zinc concentration of 3 mg/L (McCance and Widdowson, 2015) in breast milk, estimated exposures for exclusively breastfed infants (0 to 6 months) are within or at the UL of 3.6 mg per day for infants.

106. The COT concluded, that overall, estimated dietary exposure for children aged 4 to < 12 months and 1 to < 5 years do not indicate excessive zinc intakes, either from breastmilk or other foods and are therefore unlikely to be of toxicological concern.

107. However, COT noted, that all HBGVs and UL for infants and children are derived from extrapolation from adults, based on epidemiological/clinical studies in adults. It is therefore difficult to identify a HBGV or UL which is applicable for all infants and children.

Conclusions

108. In the absence of any newer information, the COT concluded that there is no requirement to change the current advice for alcohol, caffeine, endosulfane, PeCB, chlordecone and soya phytoestrogens.

109. Food additives are regulated under EU law and trans fatty acids are currently under assessment by PHE and is outside the remit of the COT. The levels for legacy pesticides are expected to further decline and the COT concluded, in line with the 2012 overarching statement, that there is no indication of concern for human health. The levels are furthermore monitored and show a declining trend based on the 2015 EU report.

110. In the absence of any UK-specific data, COT assessed perchlorate and chlorate based on the evaluations by EFSA and while the COT raised a number of uncertainties in the evaluation, overall they agreed with EFSAs approach and the HBGVs.

111. There is a level of uncertainty concerning the carcinogenic MoA and potential direct genotoxicity of furan and the COT acknowledges that its assessment is a worst case scenario. There have been efforts to reduce concentrations of furan (and methylfurans) in food over recent years but the evidence so far is not sufficient to demonstrate whether there has been a decrease in dietary exposure. The exposures in this assessment are of potential toxicological concern and efforts to reduce furan and methylfurans should continue.

112. Chromium is present in food and the environment largely as Cr(III). EFSA has derived a TDI for Cr(III) of 300 µg/kg bw/day. Estimated dietary exposures for children aged 0 to < 12 months and 1 to < 5 years do not indicate excessive chromium intake, either from breastmilk or other foods and are therefore unlikely to be of toxicological concern. Environmental exposure to Cr(III) was calculated to be at most 0.038, 0.15 and 0.036% of the EFSA TDI for dust, soil and air respectively.

113. Overall the COT concluded that estimated dietary exposures to selenium for children aged 4 to < 12 months and 1 to < 5 years were below the UL, either from breastmilk or other foods and are therefore unlikely to be of toxicological concern.

114. The COT concluded, that overall, estimated dietary exposure do not indicate excessive zinc intakes and are therefore unlikely to be of toxicological concern. However, the COT did note that all HBGVs and UL are derived from adults and it is therefore difficult to identify a HBGV or UL which is applicable for all infants and children.

Secretariat
December 2018

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Abbreviations

ADI	Acceptable daily intake
ARfD	Acute reference dose
ATSDR	Agency for Toxic Substance and Disease Registry
BMDL	Benchmark dose modelling
Bw	Body weight
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Cr	Chromium
DH	Department of Health
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
EFSA	European Food Safety Authority
EMV	Expert Group on Vitamins and Minerals
ER	Estrogen receptors
EU	European Union
FSA	Food Standards Agency
HBGVs	Health based guidance values
IARC	International Agency for Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LB	Lower bound
LOAEL	Lowest observed adverse effect level
LOD	Limit of detection
MoA	Moe of action
MOE	Margin of exposure
MRLs	Maximum residue levels
NDNS	National Diet and Nutrition Survey
NIS	Sodium-iodine symporter
NOAEL	No observed adverse effect level
PeCB	Pentachlorobenzene
PHE	Public Health England
POPs	Persistent organic pollutants
PRiF	Expert Committee on Pesticide Residues in Food
RfD	Reference dose

SACN	Scientific Advisory Committee on Nutrition
SCF	Scientific Committee on Food
TDI	Tolerable daily intake
UB	Upper bound
UF	Uncertainty factor
UKSO	UK Soil Observatory
UL	Upper level
WHO	World Health Organisation

Bisphenol A

115. Bisphenol A is currently under re-evaluation by EFSA. The COTs therefore decided to revisit their current advice following EFSAs updated evaluation.

Phthalates

116. The COT decided to assess phthalates in a separate statement after the upcoming evaluation by EFSA.

Dioxins and dioxin-like compounds

117. The COT has commented on the newest evaluation of dioxins and dioxin-like compounds by EFSA and is awaiting its publication prior to deciding if a full evaluation of its current advice is required or if the COTs assessment can be covered in a later overarching statement.

Perfluorooctanesulfonic acid (PFOS) & Perfluorooctanoic acid (PFOA)

118. The COT is currently evaluating the information provided by EFSAs scientific opinion on PFOS and PFOA, published earlier in 2018.

Monochloropropane diol (MCPD)

119. No in-house data is available for MCPD. The COT will therefore evaluate MCPD based on the most recent EFSA opinion, which includes UK data, and will be including its evaluation in a later overarching statement.

Tetrabromobisphenol (TBBPA)

120. No in-house data is available for TBBPA. The COT will therefore evaluate TBBPA based on the most recent EFSA opinion, which includes UK data, and will be including its evaluation in a later overarching statement.

Sweeteners

121. No in-house data are available for sweeteners. The COT will therefore evaluate the main sweeteners (NAMS) based on the most recent EFSA opinion and available literature and will be including its evaluation in a later overarching statement.

Mycotoxins

122. The remaining mycotoxins (NAMES) are currently under evaluation by the COT. Based on the available in-house data and conclusions, the assessment will either be covered in a later overarching statement or published as a full review.

Polycyclic Aromatic Hydrocarbons (PAHs)

123. PAHs are currently under review by the COT. Based on the available in-house data and conclusion, the assessment will either be covered in a later overarching statement or published as a full review.

Hxachlorocyclohexane (HCH)

124. No in-house data are available for HCH; the COT is currently assessing the best approach to evaluating HCHs.