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

Addendum to the 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

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. At a joint meeting of the COT and SMCN Secretariat, a list of chemicals was proposed, taking into account likelihood of exposure, availability of new data and toxicological significant of the chemicals. The list was brought to the COT in the form of a scoping paper in 2013[1] and again in 2015[2]. From this list the COT identified a number of chemicals, which might pose a risk to young children and for which advice might be needed. In 2019, the COT published an Overarching Statement[3], reviewing a number of chemicals. The current paper is an Addendum to the Overarching Statement, discussing the conclusions of the COT regarding the remaining chemicals.

4. Chemicals identified for review and not included in the Overarching Statement or the Addendum have been subject to a full review or were considered to either be outside the remit of the COT or for it to be unnecessary to change its existing advice to government in the absence of any new data. A full list of all chemicals identified by the Committees, with the respective links to the discussion papers or Statements, where applicable, is provided in Table 1 in Annex A.

5. The following reviews provide a brief overview of the characteristics of the chemicals but focus mainly on the exposure assessment (where applicable) and the risk characterisation and conclusions, for both infants and young children.

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[1] https://cot.food.gov.uk/sites/default/files/cot/tox201203.pdf
[2] https://cot.food.gov.uk/sites/default/files/TOX2015-32%20Feeding%20Review%20Scoping%20Paper.pdf
[3] https://cot.food.gov.uk/sites/default/files/cotoverarchingstatement_0.pdf

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Assessment

6. Unless indicated otherwise, the sources of general background information were the most recent assessments by the COT or other risk assessment bodies, such as the European Food Safety Authority (EFSA), the Scientific Committee on Food (SCF), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the World Health Organisation (WHO) International Programme on Chemical Safety (IPCS) or the Expert Group on Vitamins and Minerals (EMV).

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

8. Consumption data (on a body weight basis) for the estimated dietary exposures were from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013) and from years 1-8 of the National Diet and Nutrition Survey (NDNS) (Bates et al., 2014; 2016; Roberts et al., 2018). Estimates of consumption of breast milk and infant formula vary; in this statement, in the absence of specific data, 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.

9. 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 risk assessment bodies, preferably EFSA.

10. The margin of exposure (MOE) approach has been applied for genotoxic carcinogens or chemicals with genotoxic and carcinogenic potential. Following EFSAs guidance and unless otherwise indicated, an MOE of > 100 is considered protective for non-neoplastic effects, an MOE > 10,000 is considered of low health concern for neoplastic effects from a genotoxic carcinogen, if based on a $BMDL_{10}$ from an animal carcinogenicity study.

11. For ease of reading, the assessment has been split into three sections; section 1 provides information on contaminants and process contaminants, section 2 provides information on the most common sweeteners in the UK and section 3 provides information on several natural toxins. Table 1 provides a brief overview of the main conclusions by the COT, grouping chemicals of no concern, chemicals of concern and chemicals for which a potential concern cannot be excluded, due to a gap in the current data.

Table 1 Brief overview of the main conclusions by the COT

Chemicals of no concern The estimated dietary exposures are below the respective HBGVs or above the respective acceptable MOEs and	Hexachlorocyclohexane Polycyclic aromatic hydrocarbons Tetrabromobisphenol Cyclopiazonic acid

are therefore not of toxicological concern.	Diacetoxyscirpenol Ergot alkaloids Fumonisins Fusarenon-X Moniliformin Nivalenol Sterigmatocystin Zearalenone Aspartame Acesulfame K Saccharine Sorbitol and xylitol Stevia Sucralose
Chemicals of concern The estimated dietary exposures are above the respective HBGVs or below the respective acceptable MOEs and are therefore of toxicological concern.	Monochloropropanediol, its fatty acid esters and glycidol Aflatoxins
Chemicals of potential concern A potential health effect can currently not be excluded due to data gaps and limitations.	Deoxynivalenol and its acetylated/ modified forms Citrinin Patulin Tropane alkaloids

1 Contaminants and process contaminants

1.1 Hexachlorocyclohexane (HCH)

12. Hexachlorocyclohexanes (α-, β-, and γ-HCH), are listed for elimination of production and use in Annex A of the Stockholm convention on Persistent Organic Pollutants[4] (POPs). Due to their lipophilic properties and persistence in the environment, β-HCH, and to a lesser extent, α-HCH and γ-HCH, bioaccumulate and biomagnify in the food chain. HCHs are distributed globally, with transfer from warmer to colder regions through evaporation and condensation.

13. HCHs in the diets of infants aged 0 to 12 months underwent a separate full review (COT, 2014) from HCHs in the diets of children aged 1 to 5 years, which was a shorter review (COT, 2019). In both reviews, the COT concluded that exposure to HCHs are of no toxicological concern. The COT has previously concluded that levels of HCHs are declining, as the Kalantzi et al., 2004 study showed levels of γ-HCH in

[4] http://chm.pops.int/TheConvention/Overview/TextoftheConvention/tabid/2232/Default.aspx

UK breast milk samples to be lower than they were in 2000, the year it was banned. As for α-HCH, the last analysis of UK breast milk samples was by Woolridge et al., 2004, where α-HCH was undetected; and data showing a temporal decline of β-HCH in breast milk is presented in the 2014 COT statement (COT, 2014).

14. γ-HCH is extensively and rapidly absorbed. It is widely distributed in the body and its absorption via dermal routes has been demonstrated (FAO/WHO, 2002). α-HCH and β-HCH are almost completely absorbed from the gastrointestinal tract and are predominantly distributed to the liver, kidney, brain, muscle and adipose tissue (WHO-IPCS, 1992). The half-life for elimination for γ-HCH from plasma is 8 to 10 days (Health Council, 2001), whereas the half-life for α-HCH is unknown (WHO-IPCS, 1992) and for β-HCH is estimated to be up to 7.6 years (Jung et al., 1997). The metabolites of γ-HCH and α-HCH are excreted mainly in the urine, and a smaller proportion is eliminated in the faeces (FAO/WHO, 2002; WHO-IPCS, 1992). In contrast, for β-HCH faecal excretion is of more importance (WHO-IPCS, 1992).

15. In animal studies, neurotoxicity has been reported for all HCHs (FAO/WHO, 2002; ATSDR, 2005; WHO-IPCS, 1992), with inconclusive evidence of Parkinson's disease related to β-HCH exposure in human studies (Weisskopf et al., 2010; Richardson et al., 2009, 2011; Petersen et al., 2008). Hepatoxicity from α-HCH and β-HCH has been demonstrated in vivo (Kuiper et al., 1985; EFSA, 2005a; EFSA, 2012), although evidence of hepatoxicity in humans is lacking. Renal toxicity has been reported only for γ-HCH (FAO/WHO, 2002), and the mode of action (MoA) is considered irrelevant to humans, as it involves binding to male rat specific α-2u-globulin (COT, 2014). Other effects with evidence from animal studies include immunotoxicity (Meera et al., 1992; Wing et al., 2002) and immunosuppression (Kuiper et al., 1985) from γ-HCH and α-HCH exposure, respectively. With β-HCH, in addition to reproductive toxicity such as infertility, effects in the thymus, testes and ovaries are evident (Van Velsen et al., 1986). There is inconsistent evidence for endocrine disrupting potential (endometriosis) of β-HCH (Upson et al., 2013; Buck Louis et al., 2012; Lebel et al., 1998). Additionally, evidence of reproductive effects of γ-HCH is inconsistent (ATSDR, 2005) and limited with regards to α-HCH.

16. The Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2002) regarded γ-HCH as non-genotoxic. Since the JMPR evaluation Kalantzi et al. (2004a) have reported one positive result of genotoxicity in a comet assay. However, the COT concluded that the overall balance of evidence indicated that γ-HCH is non-mutagenic (COT, 2014). γ-HCH has been classified by IARC as "carcinogenic to humans", being able to cause non-Hodgkin lymphoma (IARC, Group 1).

17. The COT concluded that α-HCH is a non-genotoxic liver carcinogen, by a MoA (most likely CAR activation) not relevant to humans (COT, 2014).

18. As for β-HCH, the COT concluded that it is a non-genotoxic liver carcinogen in rodents, although the MoA for liver tumour formation is considered irrelevant to humans, as it likely involves CAR activation (COT, 2014).

19. All exposures to γ-HCH in breast milk were below the tolerable daily intake (TDI) of 0.04 µg/kg bw, except for infants aged 0 to 4 months at high levels of consumption (1200mL per day) containing γ-HCH at the maximum reported

concentration of 0.27 µg/kg milk, which exceed the TDI by 1.4-fold. Exposures to γ-HCH in infant formula and infant food were 5 and 10-fold the TDI of 0.04 µg/kg bw, respectively, for infants aged 0 to 12 months. However, this is very likely to be an overestimation, as γ-HCH was below the detection limit in all samples and actual exposures are likely to be lower. For children aged 1 to 5 years, there is no toxicological concern of γ-HCH in infant formula and complementary food.

20. For exposures to α- and β-HCH in breast milk, infant formula and infant food the COT agreed that an MOE approach would be more appropriate, as the toxicity of α- and β-HCH are not well characterised, and there is insufficient data to propose a TDI.

21. In 2014, the COT concluded that none of the exposures of α- and β-HCH to infants aged 0 to 12 months were of toxicological concern (COT, 2014). For children aged 1 to 5 years, MOEs were calculated only for β-HCH in breast milk, which were > 2,500 at the 97.5th percentile and are therefore of no toxicological concern (COT, 2019). For all other diets/foodstuffs, where α- and β-HCH were not detected above their limit of detection/limit of quantification (LODs/LOQs), MOEs (based on lower-bound (LB) and upper-bound (UB) exposure estimates) were not calculated as HCHs are legacy pesticides and the COT previously concluded that levels have been declining over time (COT, 2014).

22. Interpretation of the MOEs in both reviews took into account the uncertainties in toxicological reference points and exposure estimates. For α-HCH, the toxicological reference point was the no observed adverse effect level (NOAEL) of 0.1 mg/kg bw per day for hepatoxicity. The endpoint was liver hypertrophy and its use in risk characterisation is therefore conservative, as liver enlargement in the absence of signs of hepatic damage is considered adaptive and not adverse. As for the exposure, a worst-case estimate was used in the 2014 review. For β-HCH the toxicological reference point was the lowest observed adverse effect level (LOAEL) of 0.18 mg/kg bw per day for centrilobular hypertrophy in the 2014 COT review, and a NOAEL of 0.1 mg/kg bw per day based on liver hypertrophy in the 2019 review, again an endpoint of questionable toxicological significance. The exposure estimates in both reviews were based on data from the Kalantzi et al. (2004) study, where the distribution of β-HCH concentrations in breast milk samples reported was atypical. Ultimately, these breast milk samples were analysed 15 years ago, which is likely to result in an overestimation of current exposures and thus underestimation of the MOEs.

23. The full EFSA and COT evaluations can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2005.250

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

1.2 Monochloropropanediol (MCPD)

24. 2- and 3- monochloropropanediol (MCPD) and their esters are contaminants of soy sauce and processed vegetable oils. Glycidyl ester (GE) is produced from

fatty acids present in vegetable oil, particularly diacylglycerol (DAG) upon heating to temperatures > 200°C which occurs during the deodorisation stage of refining.

25. EFSA did not undertake a risk characterisation for 2-MCPD and its esters due to a lack of toxicological information and insufficient data for dose-response assessments. No toxicokinetic data or long-term studies for 2-MCPD were identified; for *in vitro* genotoxicity of 2-MCPD, only limited unpublished industry data were identified. Thus, a HBGV was not established for 2-MCPD.

26. In 2002, JECFA performed a risk assessment on the presence of 3-MCPD in food. Renal tubular hyperplasia represented the critical effect in rats exposed chronically via drinking water. Data indicating a lack of genotoxicity *in vivo* led JECFA to conclude that 3-MCPD induces neoplasia in rats by a mechanism that does not involve DNA damage and requires exposure above a threshold dose. A provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg bw was established based on a LOAEL of 1.1 mg/kg bw per day for renal tubular hyperplasia seen in a long-term carcinogenicity study in rats. An uncertainty factor (UF) of 500 was used to account for the absence of a clear NOAEL and inadequacies in the reproductive toxicity studies.

27. In March 2016, the EFSA CONTAM Panel selected a $BMDL_{10}$ value for the hazard characterisation of 3-MCPD of 0.077 mg/kg bw per day, based on induction of renal tubular hyperplasia in male rats. The Panel established a TDI of 0.8 µg/kg bw through the application of an UF of 100. In November 2016, JECFA calculated a $BMDL_{10}$ of 0.87 mg/kg bw per day using the same data and software (Benchmark Dose Modelling Software (BMDS) from the US EPA). However, JECFA applied an UF of 200 (which incorporates a factor of 2 related to inadequacies in the reproductive toxicity studies), hence a TDI of 4 µg/kg bw was established.

28. Due to this scientific divergence in the establishment of the $BMDL_{10}$ reference value, and in light of the recent EFSA guidance on BMD modelling (EFSA 2017), EFSA updated its 2016 opinion for 3-MCPD and its fatty acid esters. In EFSA's revised 2018 opinion, renal tubular hyperplasia in male rats was reconfirmed as the critical effect, though a new $BMDL_{10}$ of 0.20 mg/kg bw per day for 3-MCPD was obtained using PROAST software (v64.9) with model averaging. Based on this $BMDL_{10}$ value, a new group TDI of 2 µg/kg bw for 3-MCPD and its fatty acid esters was established by applying an UF of 100 to account for intraspecies and interspecies differences.

29. No *in vivo* data were identified for GE, therefore EFSA only considered toxicity studies involving glycidol. Two-year carcinogenicity studies conducted by the National Toxicology Program (NTP, 1990) in mice (25 and 50 mg/kg bw per day) and rats (37.5 and 75 mg/kg bw per day) showed increased incidences of tumours in multiple organs from both sexes. There is strong evidence from *in vitro* data and some evidence from *in vivo* studies that glycidol is a genotoxic compound. EFSA considered the dose-response data to be inadequate for BMD modelling as only two dose levels were administered. In cases where the dose-response data are inadequate for BMD modelling, EFSA recommends the use of the T25 as the reference point for substances that are genotoxic and carcinogenic (EFSA, 2005b). The T25 value is the chronic dose rate in mg/kg bw per day, which will give 25% of

the animals tumours at a specific tissue site, after correction for the spontaneous incidence within the standard life time of that species. Thus, EFSA derived a T25 value of 10.2 mg/kg bw per day for peritoneal mesothelioma in male rats, which was used as the reference point for risk assessment.

30. UK occurrence data for 3-MCPD (only) (FSA, 2010) were reported to, and provided part of, EFSA's assessment in 2016. However, only five food product categories were analysed for 3-MCPD (biscuits, bread, breakfast cereals, roasted coffee and soy sauce), therefore a UK exposure assessment based on these data for the UK alone is likely to underestimate actual exposure. Subsequently, the following dietary exposure assessment was taken from EFSA.

31. EFSA's chronic dietary exposures were calculated for 2- and 3-MCPD and glycidol and were assessed as mean and high (95th percentile) exposures. For infant formula, an average consumption of infant formula (diluted, ready to eat) was calculated over the period from 1 to 4 months of age to be 170 g/kg bw per day. Occurrence values in infant formula (powder) were divided by 7.7 to account for dilution into liquid infant formula. The mean occurrence of 3-MCPD in diluted infant formulae was 14.03 µg/kg, leading to an exposure estimate of 2.4 µg/kg bw per day. The 95th percentile occurrence value was calculated to be 19.1 µg/kg, leading to an exposure estimate of 3.2 µg/kg bw per day.

32. The exposure assessment for 3-MCPD was based upon the level of exposure to the parent compound, regardless of the original form (i.e. as free or as ester of fatty acids) and referred to as 3-MCPD. The mean exposure to 3-MCPD was 0.5 - 1.5 µg/kg bw per day across the dietary surveys for the age groups 'infants' (0 to 12 months), 'toddlers' (1 to 3 years) and 'other children' (3 to 10 years). The 95th percentile exposure to 3-MCPD was 1.1 - 2.6 µg/kg bw per day across dietary surveys in these age groups. EFSA noted that the 95th percentile exposures for infants, toddlers and other children were up to 1.3-fold the TDI of 2 µg/kg bw per day. For infants receiving infant formulae, exposures were 1.2-fold (mean occurrence value) and 1.6-fold (95th percentile occurrence value) of the TDI.

33. Exposure to glycidol referred to the parent compound, although the original form in food products was exclusively as fatty acid esters. Across the dietary surveys for the age groups 'infants', 'toddlers' and 'other children', the mean exposure to glycidol was 0.3 - 0.9 µg/kg bw per day. Using the 95th percentile occurrence data resulted in a daily exposure estimate of 0.8 - 2.1 µg/kg bw per day across dietary surveys in these age groups. The mean occurrence of glycidol in diluted infant formulae was calculated to be 11.3 µg/kg, leading to an exposure estimate of 1.9 µg/kg bw per day. The calculated 95th percentile was 28.57 µg/kg, leading to an exposure estimate of 4.9 µg/kg bw per day.

34. In view of the genotoxic and carcinogenic potential of glycidol, an MOE approach was applied by EFSA. MOEs were calculated by dividing the T25 value of 10.2 mg/kg bw per day by the estimated European chronic exposures. According to EFSA guidance (EFSA, 2005) "a MOE of an order of magnitude of 10,000 or higher would not be considered of low health concern under circumstances where there were greater uncertainties, for example if the MOE was calculated using a T25, or if the reference point were based on a poor animal database". When the reference

point is based upon T25 data it is considered that the MOE should be at least 2.5 times higher than an MOE based upon $BMDL_{10}$ data, i.e. ≥ 25,000 (Dybing et al., 2008). Based on this consideration, EFSA concluded that an MOE of 25,000 or greater would be of low health concern.

35. MOE estimates for the mean dietary exposures were 12,800 to 25,500 (infants), 11,300 to 25,500 (toddlers), and 11,300 to 34,000 (other children). MOE estimates for the 95th percentile dietary exposures were 4,900 to 8,500 (infants), 5,100 to 10,200 (toddlers), and 6,000 to 12,800 (other children). Exposure in infants receiving formula only resulted in a MOE of 5,400 using the mean occurrence value and 2,100 using the 95th percentile occurrence value.

36. Given the limited UK occurrence data, the COT agreed that the European dietary exposure estimates could be considered to be reasonably representative of UK exposures. The Committee concluded that it is not currently possible to characterise risks for 2-MCPD due to a lack of toxicological information and insufficient data for dose-response assessments. For 3-MCPD, EFSA and JECFA had derived different values for the $BMDL_{10}$, based on renal hyperplasia in male rats, and the COT noted that consideration of best practice for BMD modelling may be required in the future for the purposes of harmonisation.

37. Overall, the Committee agreed with EFSA's evaluation of 3-MCPD and its fatty acid esters and its evaluation of glycidol.

38. The COT concluded for infants, toddlers and other children that some of EFSA's MOE values for glycidol and exceedances of the TDI for 3-MPCD are of potential health concern. As concluded by EFSA, the impacts of the uncertainties in these risk assessments for glycidol and 3-MCPD are high, for example uncertainty in the reference point used as a basis for the calculation of the MOE values for glycidol, and the long-term effects of 3-MCPD on the male reproductive system. In addition, the exposure data may not reflect occurrence in the UK.

39. The full EFSA evaluation and update can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4426

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5083

1.3 Polycyclic Aromatic Hydrocarbons (PAHs)

40. Polycyclic aromatic hydrocarbons (PAHs) are organic combustion products found in vehicle exhaust, industrial process emissions and in cooked food and cooking by-products such as oils vaporised from frying pans and smoke from barbecues. While the diet is a significant source of PAHs for non-smokers, cigarette smoke makes the major contribution to the intake for smokers.

41. EFSA (2008a) concluded that the Toxic Equivalency Factor (TEF) approach for mixtures should not be applied to PAHs, because of the lack of oral carcinogenicity data on individual PAHs, their different MoAs and the evidence of poor predictivity of the carcinogenic potency of PAH mixtures based on the currently

proposed TEF values. Rather, risk characterisation should be based upon the PAHs with carcinogenicity, i.e. for benzo[a]pyrene (BaP) and the other PAHs in the two coal tar mixtures used by Culp et al. (1998). Although BaP alone has been used as a marker for PAHs, the presence of a mixture of BaP, benz[a]anthracene (BaA), benzo[b]fluoranthene (BbF) and chrysene (ChR), designated PAH4, rather than a mixture of 8 or 16 compounds, gave a better measure for risk assessment purposes.

42. The extent of absorption of PAHs appears to be in the order of oral > dermal > inhalation (Lao et al., 2018). PAHs are taken up into the lymphatic system, in the presence of bile, with long-chain fatty acids (> 10 carbons) (Harris et al., 2013).

43. Cytochrome (CYP) 1A1, 1A2, 1B1 and 3A4 oxidise PAHs to epoxides, diols, and quinones that can form DNA adducts, either directly or following further metabolism, and lead to mutagenesis and carcinogenesis (Xue and Warshawsky, 2005). PAHs also induce CYPs and other enzymes via the aryl hydrocarbon receptor (AhR) and induce oxidative stress mechanisms (Murphy et al., 2008). CYP1A1, 1A2 and 1B1 also detoxify BaP (Shi et al., 2010; Nebert et al., 2013). Levels of PAH metabolites peak within the first hour following oral ingestion and then slowly decline, reaching pre-ingestion levels by about 24 hours. (Li et al., 2012).

44. Short term PAH exposure may cause eye and skin irritation, nausea and vomiting and local inflammation but, since PAHs occur as mixtures that may include other non-PAH components, it is difficult to ascertain the extent to which the PAHs are the causative agents of these effects (Kim et al., 2013).

45. Exposure to PAHs has been associated with increased risk of cancer including in the breast, oesophagus, GI tract and lung (Diggs et al., 2011; White et al., 2016; Roshandel et al., 2012; Moorthy et al., 2015). The International Agency for Research on Cancer (IARC[5]) has classified BaP as Group1 (carcinogenic to humans, 2012), and BaA, BbF and ChR as Group 2B (possible human carcinogens, 2010).

46. EFSA derived $BMDL_{10}$ values for BaP and PAH4 of 0.070 and 0.340 mg/kg bw per day, respectively. These values were used to derive MOEs for this risk assessment. Where only BaP data are given, or where the PAHs are regarded as a group of > 4, BaP is considered alone.

47. No breastmilk data for the UK were available. Using the data of Santonicola et al. (2017), which gave the highest European values for BaP (0.81µg/kg fat) and PAH4 (2.77 µg/kg fat), all MOEs were > 10,000 (11,00 – 21,000 for BaP and 15,000 – 29,000 for PAH4), indicating that they were unlikely to be of concern.

48. Using the data on BaP in infant formula from the FSA 2003/04 survey, the MOEs for average consumption were > 10,000 (11,000 – 14,000) and thus unlikely to be a health concern. The MOEs for BaP in the high-level consumers and all intakes of PAH4 were < 10,000 (7100 – 9300 for BaP, 4700 – 9000 for PAH4). The European Medicines Agency and International Council for the Harmonisation of

[5] https://monographs.iarc.fr/wp-content/uploads/2018/09/ClassificationsAlphaOrder.pdf

Technical Requirements for Pharmaceuticals for Human Use (ICH[6]) have published guidance on the risk assessment of shorter than lifetime exposure to genotoxic and/or mutagenic substances. For short term exposures, lower MOEs can be considered as of low concern for health. The MOE values in this assessment cover only a short period of life and are therefore unlikely to contribute significantly to the overall risk.

49. All MOEs for food were > 10,000 (11,000 – 280,000 for BaP and 15,000 – 170,000 for PAH4) and thus are of low concern for health for infants and young children aged 0 to 5 years old, except for the upper bound (UB) 97.5th percentile intakes of BaP for children aged 4 to < 6 and 6 to < 9 months (8000 and 8300, respectively). As above, exposure at this level only takes place for a short period of life and are therefore unlikely to be of concern.

Soil, Air and Dust

50. Younger, less mobile infants are likely to consume less soil than older children, who are assumed to ingest 30 to 50 mg of soil per day, (US EPA, 2011). For Principal Domain (non-urban) soils in the UK, the median (0.037 mg/kg) and the Normal Background Concentration (NBC, the upper 95% confidence level of the 95th percentile measurement, 0.5 mg/kg), give MOEs > 10,000. For urban soils, the median MOE values were 56,000 to 84,000 and thus are a low concern for health, but the NBC MOEs were 4,200 to 6,300 across the age ranges and thus may represent a risk to health. However, the NBC is very conservative, and this exposure covers only a short period of life, so these values are still unlikely to be a concern for health in most places.

51. A Department of Environment, Food & Rural Affairs (DEFRA) map[7] of BaP in UK air shows that rural areas in 2017 were mostly exposed to < 0.1 ng BaP/m^3, with urban areas reaching 0.2 - 0.4 ng BaP/m^3, although near Port Talbot, > 1.0 ng BaP/m^3 was measured. The highest possible exposure from air was 0.75 ng/kg bw per day in children aged 12 to < 15 months at an air concentration of 1.0 ng/m^3, giving an MOE of 93,000, so exposure from air is not of concern.

52. The one available paper on UK house dust (Ma and Harrad, 2015) gave a concentration of 345 µg/kg for BaP and 5095 µg/kg for the sum of PAHs. UK infants (6 to 12 months) and young children (1 to 5 years) were assumed to ingest 30 or 60 mg of dust per day, respectively (US EPA, 2011). The BaP MOEs for 6 month to 5 year-old children ranged from 43,000 to 65,000, so exposures from dust are not of toxicological concern.

53. Overall, intakes of BaP and PAH4 from human breast milk and food represent a low level of concern. Intakes from infant formula, soil and dust are not expected to contribute markedly to lifetime exposure.

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[6] https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-guideline-limits-genotoxic-impurities_en.pdf
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_31Mar2017.pdf

[7] https://uk-air.defra.gov.uk/data/gis-mapping

54. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2008.724

1.4 Tetrabromobisphenol A (TBBPA)

55. Tetrabromobisphenol (TBBPA) is a brominated flame retardant (BFR), which is incorporated into various consumer and commercial products to improve fire resistance. At times, TBBPA was the BFR with the largest worldwide production volume, representing about 60% of the total BFR market (Morose, 2006). Although TBBPA is no longer produced in the EU, products containing TBBPA are still imported into the EU from non-EU countries.

56. Approximately 90% of the total use of TBBPA is as a reactive intermediate in the manufacture of epoxy and polycarbonate resins, where it is covalently bound with the polymer. However, a portion of the TBBPA may be unreacted and can leach out of the material. TBBPA is also incorporated additively into materials such as acrylonitrile butadiene styrene (ABS) resins. Here, it is not covalently bound with the polymer, and can leach out into the environment where it has been detected in outdoor and indoor air, domestic dust and biological matrices such as fish and birds.

57. TBBPA is readily absorbed from the GI tract in rats. Systemic bioavailability of TBBPA as the parent compound is low, with most distributed directly to the liver. Glucuronide and sulphate conjugates of TBBPA were identified in bile with some evidence indicating enterohepatic circulation. The primary route of elimination following 14C-TBBPA administration was in faeces. The plasma half-life in rats was approximately 13 hours. In humans, the half-life of TBBPA-glucuronide in plasma was estimated to be between 48 and 72 hours. The main target for TBBPA toxicity is thyroid hormone homeostasis.

58. Based on the European Union (EU) draft risk assessment (ECB, 2006), the COT issued a statement on the available toxicological data for TBBPA in 2004. The highest oral dose tested in a 90-day rat study and in a two-generation rat reproductive toxicity study of 1,000 mg/kg bw per day, at which “no clear adverse effects were observed” (Cope et al., 2015), was considered to be a NOAEL and used as the basis for establishing a TDI. An UF of 100 (for intra- and inter-species variation in toxicokinetics and toxicodynamics) with an additional UF of 10 (for the absence of chronic toxicity studies) was applied. Thus, the COT recommended a TDI of 1 mg/kg bw per day.

59. At that time, no long-term carcinogenicity studies on TBBPA were identified. However, based on the absence of genotoxicity *in vitro*, no indications for proliferative changes or cytotoxicity in studies with up to 90 days repeated administration, and no immunosuppression except possibly at high doses, EFSA concluded that there were no indications that TBBPA might be carcinogenic. EFSA identified a number of limitations and uncertainties in the toxicological database which were considered to make the establishment of a HBGV inappropriate for TBBPA, such as large reported ratios between the BMD and its lower and upper confidence limits for several toxicological endpoints, indicating considerable uncertainties in the outcome of the BMD modelling. Therefore, EFSA used an MOE

approach and used a $BMDL_{10}$ of 16 mg/kg bw per day for a decrease in circulating thyroxine in female Wistar rats as the reference point.

60. In 2014, the NTP published a technical report on toxicology and long-term carcinogenicity studies of TBBPA in rats and mice administered 250, 500 or 1,000 mg TBBPA/kg bw in corn oil via gavage 5 days per week for 2 years (NTP, 2014). It was concluded that TBBPA caused cancers of the uterus in female rats and of the liver in male mice. In addition, TBBPA was found not to be mutagenic in bacterial mutagenicity assays, with or without exogenous metabolic activation. *In vivo*, no increases in micronucleated erythrocytes were observed in the peripheral blood of male or female B6C3F1/N mice following 3 months of administration of TBBPA by gavage, suggesting that TBBPA did not induce bone marrow toxicity over the dose range tested (10 - 1,000 mg/kg).

61. Following EFSA's approach, MOEs for chronic dietary exposure were calculated using UK chronic dietary exposures from the 2004 Total Diet Study (TDS) and a $BMDL_{10}$ of 16 mg/kg bw per day. All MOEs are greater than 1,000,000.

62. The COT concluded that the available scientific data indicate that the carcinogenicity of TBBPA is not mediated through a genotoxic mechanism. Given the absence of genotoxicity, tumours only at high doses, large MOEs, and conservatism of exposure estimates based on non-detects, an MOE of 100 was considered to be sufficiently protective for human health. Thus, the calculated MOEs for UK chronic dietary exposures were considered not to be cause for concern for infants and young children aged 0 to 5 years old. The Committee agreed to use the COT TDI of 1 mg/ kg bw per day for future risk assessments.

63. The full COT statement (2004) can be found here:

https://cot.food.gov.uk/sites/default/files/cot/cotstatements04tbbpa.pdf

2 Sweeteners

64. In the EU (EC 2008; EU 2011) sweeteners are referred to as food additive substances used to "impart a sweet taste to foods or in table-top sweeteners". Table-top sweeteners "shall mean preparations of permitted sweeteners, which may contain other food additives and/or food ingredients, and which are intended for sale to the final consumer as a substitute for sugars".

65. Artificial sweeteners are considered safe to consume up to the acceptable daily intake (ADI) in the general population with the exception of foods for infants and young children. In line with EU regulation, the use of sweeteners is prohibited in all foods for infants (under 12 months old) and young children (1 to 3 years old). This includes foods specifically prepared for infants and young children (i.e., "baby food") (The British Dietetic Association, 2016).

66. The safety of the most commonly used sweeteners in the UK was addressed by the COT and the outputs are presented below. These are: aspartame, acesulfame K, saccharin, sorbitol and xylitol, stevia and sucralose (NHS, 2018).

2.1 Aspartame

67. Aspartame (E 951) is a dipeptide of L-phenylalanine methyl ester and L-aspartic acid bearing an amino group at the α-position from the carbon of the peptide bond (α-aspartame). Aspartame is a sweetener authorised as a food additive in the EU. In 2013 EFSA re-evaluated the safety of aspartame as a food additive and concluded that the ADI of 40 mg/kg bw was still appropriate, following the review of new available data. The COT commented on the EFSA evaluation during its public consultation and agreed with its analysis and conclusions. The US Food and Drug Administration (FDA) has set the ADI for aspartame at 50 mg/kg bw.

68. Following oral ingestion, aspartame is hydrolysed in the GI tract to yield aspartic acid, phenylalanine and methanol. These metabolites are then absorbed and enter normal endogenous metabolic pathways. In humans, subjects heterozygous for phenylketonuria (PKU) showed a somewhat reduced capacity to metabolise the phenylalanine moiety of the aspartame molecule.

69. In its re-evaluation of aspartame, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) also considered the safety of its gut derived metabolites, methanol, phenylalanine and aspartic acid and its degradation products 5-benzyl-3,6-dioxo-2-piperazine acetic acid (DKP) and β-aspartame, which also may be present in the sweetener as an impurity.

70. EFSA reviewed the extensive literature addressing all aspects of safety of aspartame, including addressing the results reported in the studies from Soffritti et al. (2006; 2007; 2010) as well as from Chiozzotto et al. (2011). These studies reported a number of carcinomas in the test animals (both male and female rats and mice). However, on a number of occasions, as well as in 2013, the validity of the studies has been questioned by a number of EFSA scientific panels including the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (ACF), and the ANS Panel, as well as by the Committee on Carcinogenicity (COC). In particular, the high background tumour incidence observed in a number of vital organs and tissues of the animals was highlighted. Additionally, the interpretation of some of the results was called into question. For instance, the ANS Panel noted that “the increase in incidence of mammary carcinomas was not considered indicative of a carcinogenic potential of aspartame since the incidence of mammary tumours in female rats is rather high and varies considerably between carcinogenicity studies”. Moreover, there has been evidence of high rates of infection in the European Ramazzini Foundation (ERF), where the studies were performed. The NTP (2011) reviewed the original histopathological slides and reported a lack of formal quality assessment. Overall, it was concluded that many of the malignant neoplasms and lymphoid dysplasias observed by the EFR were a result of hyperplasia due to chronic infection. In agreement with the EFSA concerns on the methodology, and in light of the study design limitations and the use of animals with high infection rates, the COC in 2006 concluded that no valid conclusions could be derived from the 2006 Soffritti study. The ANS Panel considered that these concerns would also apply to the subsequent studies by Soffritti et al. that were carried out at the ERF. Regarding the 2010 Soffritti et al. study in mice, hepatocellular carcinomas and alveolar/bronchiolar carcinomas were reported. The ANS Panel in 2011 concluded that these tumours fell within their historical control ranges for

spontaneous tumours and also noted that Swiss mice are known to have high background incidence of these two particular tumour types. It was thus concluded that the results of this study do not provide evidence for carcinogenic effects of aspartame.

71. Overall, the ANS Panel considered the previous NOAEL of 4000 mg/kg bw per day from a carcinogenicity study in rats still applicable, however noted that developmental effects seen in rabbits at lower doses should not be ignored. Following a MoA analysis, it was considered that the adverse effects were attributable to the metabolite phenylalanine. The Panel noted that adverse developmental effects were seen in children born to PKU mothers and seemed to be related to maternal phenylalanine levels. The current clinical guidelines recommending that plasma levels of phenylalanine should be maintained below an average value of 360 µM were also taken into consideration for the risk assessment.

72. The ANS Panel modelled the plasma phenylalanine levels in humans following aspartame administration. The Panel made a number of assumptions that resulted in an overestimation of the potential phenylalanine exposure from the diet, as a worst-case approach. The Panel considered that the threshold utilised for comparisons to the modelling should be lowered to allow for simultaneous intake of the food additive with meals. In toddlers it was assumed that the mean daily exposure to phenylalanine from diet is taken up in five meals and in children in four meals, rendering the phenylalanine intake per kg bw and meal into 18.6 - 33.4 mg/kg bw per meal (toddlers), and 18.1 - 34.2 mg/kg bw per meal (children). The highest phenylalanine concentration reported in children, which corresponds to 120 µM as calculated by the dose-plasma phenylalanine modelling, was subtracted from the clinical guideline of 360 µM resulting in a maximum safe plasma concentration of 240 µM of aspartame.

73. Based on the model, a plasma phenylalanine concentration of 240 µM would result from the administration of a bolus dose of 103 mg aspartame/kg. For an individual heterozygous for PKU, the concentration would be reached by the administration of a bolus dose of 59 mg aspartame/kg bw. The Panel considered that given the conservative assumptions, realistic dietary intake of aspartame and the confidence intervals provided by the modelling, the peak plasma phenylalanine levels would not exceed the clinical target threshold when a normal individual consumed aspartame at levels below the current ADI of 40 mg/kg bw per day. It was concluded based on the above that the current ADI is protective of the general population and that there would not be a risk of adverse effects on pregnancy. As the modelling was based on safe concentration of aspartame in a sensitive sub-population (PKU patients) no further UF were applied for inter-individual variability. The ANS Panel noted that the ADI is not applicable to PKU patients.

74. No information on breastmilk data in the UK data was available. As sweeteners are prohibited for use in baby food, an exposure assessment of the intakes from baby formula(s) was not carried out.

75. The exposures presented to the COT were from the 2013 EFSA evaluation, for European populations. No data were submitted from the UK. Estimated exposures were assuming presence of aspartame at the maximum permitted level

(MPL) (Scenario 1) and based on reported use levels or analytical data (Scenario 2). For the first scenario, mean exposures ranged from 3.2 - 16.0 mg/kg bw per day in toddlers (12 to ≤ 35 months) and 95th percentile exposures from 11.8 - 37.0 mg/kg bw per day. For children (3 to ≤ 9 years) in the second scenario, mean refined exposures ranged from 1.6 - 16.0 mg/kg bw per day in toddlers and 1.8 - 13.0 mg/kg bw per day in children. 95th percentile exposures ranged from 7.5 - 36.0 mg/kg bw per day and 6.3 - 32.0 mg/kg bw per day for children and toddlers, respectively.

76. Additionally, a study by Martyn et. al (2016) assessed the dietary intake of four artificial sweeteners in Irish children (n = 500) aged 1 to 4 years, using information from the National Pre-School Nutrition Survey (NPNS, 2010-2011) in which food intake was recorded using a four-day weighted food diary along with anthropometric, health and lifestyle and demographic information. Food categories included cereals, desserts carbonated and non-carbonated flavoured drinks, confectionery.

77. Four exposure scenarios were presented:

-Scenario 1: Exposure using NPNS data and MPL for sweeteners assuming that where legally permitted the sweetener is always present in food.

-Scenario 2: Exposure using NPNS data and the MPL and taking into account occurrence data from the Irish National Food Ingredient Database v4 (INFID v4).

-Scenario 3: Exposure using NPNS intake data and concentrations for sweetener in foods based on the information from the National Chemical Food Sampling program, conducted by official agencies in Ireland.

-Scenario 4: Exposure using NPNS intake data and concentrations for sweeteners in food from the INFID v4.

78. The mean exposures in Irish children ranged from 0.76 mg/kg bw per day (Scenario 4) to 4.6 mg/kg bw per day (Scenario 1). The 95th percentile exposures ranged from 2.3 - 18.0 mg/kg bw per day for Scenarios 4 and 1, respectively.

79. The COT agreed that the ADI of 40 mg/kg bw, which was re-confirmed following EFSA's extensive review, is still applicable. Despite the lack of breastmilk and dietary information for children aged 0 to 1 years old, the Committee concluded that based on the available exposure information presented, and also because of the fact that sweeteners are not permitted in baby food and the lower intake of solid foods in infants aged 0 to 1 years, it would be unlikely that the ADI would be exceeded in that age group.

80. Overall, the COT concluded that there is no risk to health from the exposure to aspartame in children aged 0 to 5 years old.

81. The full EFSA opinion can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3496

2.2 Acesulfame K (AceK)

82. Acesulfame K (AceK) is an EU approved sweetener that is approximately 200 times sweeter than sucrose. Due to its high-water solubility and heat resistance it is approved for use in a wide range of products such as baked goods, candies and puddings.

83. AceK is currently on EFSA's call for data list and due to be re-evaluated.

84. AceK was rapidly absorbed and excreted unchanged in urine in both animals and humans, indicating that it does not undergo metabolism.

85. Following a submission for an extension of the ADI, the SCF (2000) re-evaluated the safety of AceK taking into account new scientific data. The Panel reaffirmed its conclusion that AceK is not mutagenic or genotoxic and endorsed previous specifications regarding impurities (specifically 5-chloro-acesulfame) for which toxicological data are limited.

86. Regarding the ADI, the SCF considered the two-year study in dogs and the two-year study in rats, where for both the NOAEL was the highest dose tested (900 mg/kg bw per day and 1500 mg/kg bw per day, respectively). Taking into account toxicokinetic data, it could be assumed that systemic exposure was higher in dogs than in rats. Furthermore, they noted that there was limited evidence for toxicokinetic differences between humans and dogs and concluded that the dog remained the most appropriate species for establishing the HBGV, thus reaffirming the ADI of 0 - 5 mg/kg bw.

87. Exposure to AceK in Irish children aged 1 to 4 years has been assessed by Martyn et al. (2016) as described in paragraph 77. Mean exposures ranged from 0.58 - 2.8 mg/kg bw per day whilst 95th percentiles ranged from 2.1 - 11.0 mg/kg bw per day for Scenarios 4 and 1, respectively.

88. Overall, the COT concluded that despite the lack of breastmilk data and dietary exposures for infants aged 0 to 1 years, it would be unlikely that the ADI would be exceeded for this age group as sweeteners are not permitted in baby foods and solid food consumption for that age group would generally be lower than that of older children.

89. Overall, the COT concluded that there was no concern for exposure to AceK in the diet for infants and young children.

90. The full EFSA opinion can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4437

2.3 Saccharin

91. Saccharin is the oldest sugar substitute. The substance and its sodium, potassium and calcium salts (E954) are authorized through the Directive 94/35/EC

as a sweetener for use in a wide variety of foodstuffs such as non-alcoholic drinks, desserts and similar products, confectionery and food supplements, at the maximum usable dose from 80 - 3000 mg/kg food, depending on the types of food.

92. The ADI of Saccharin was established at 0- 5 mg/kg bw in 1993 by JECFA and in 1995 by the SCF, expressed as 0 - 3.8 mg.kg bw free acid.

93. Saccharin and its salts are currently on EFSA's call for data list and due to be re-evaluated.

94. Based on information in a number of species including humans, rats, guinea-pigs, rabbits and monkeys, saccharin does not undergo metabolism. Studies in humans and rats indicate that the majority of saccharin administered in the diet (80 - 85%) is slowly absorbed and rapidly excreted unchanged in the urine. In humans it is likely that the rate of absorption will also depend on food intake, which affects the acidity of the stomach. In more acidic pH conditions saccharin exists as the non-ionised form, which is rapidly absorbed in comparison to the low absorption rate of the ionised form. Following a single oral dose to adult rats, saccharin was distributed to most organs, with the highest concentrations in the kidney and bladder, the organs responsible for elimination, followed by the plasma. There is no evidence of bioaccumulation of saccharin in any tissue (WHO, 1993).

95. Acutely, saccharin is of low toxicity. Saccharin is well tolerated in humans, based on single and repeated exposure studies.

96. Saccharin was not genotoxic *in vitro* or *in vivo*. IARC (1999) concluded that "sodium saccharin produces urothelial bladder tumours in rats by a non-DNA-reactive mechanism that involves the formation of a urinary calcium phosphate-containing precipitate, cytotoxicity and enhanced cell proliferation. This mechanism is not relevant to humans because of critical interspecies differences in urine composition." It was therefore classified as Group 3 by IARC (not classifiable as to their carcinogenicity to humans) and considered that there was inadequate evidence in humans for the carcinogenicity of saccharin salts used as sweeteners, sufficient evidence in experimental animals for the carcinogenicity of sodium saccharin and inadequate evidence in experimental animals for the carcinogenicity of saccharin (acid form) and calcium saccharin.

97. The ADI was based on a two-generation carcinogenicity study in male rats fed with sodium saccharin at 1%, 3%, 4%, 5%, 6.25% and 7.5% in the diet (Schoenig et al., 1985). Starting at 3%, the animals showed a marked disturbance in homeostasis, with a dose-related decrease in body weight gain despite increased food consumption. This was related to inhibitory effects of saccharin on carbohydrate and protein digestion. Bladder tumours induced by saccharin were found to be specific for the male rat and not relevant for female rats and mice, hamsters and monkeys, and not relevant for humans (WHO, 1993; SCF, 1995). The lowest dose level (1% - equivalent to 500 mg/kg bw per day) was identified as the NOAEL, based on the lack of relevant treatment related findings at this level. An UF of 100 was applied to establish the ADI of 5 mg/kg bw.

98. No data were available on the occurrence of saccharin in breastmilk in the UK. It is legally prohibited for baby foods to contain saccharin and therefore an exposure assessment for that food group was not carried out.

99. Dietary exposures to saccharin in Irish children aged 1 to 4 years were estimated by Martyn et al. (2016), as described in paragraph 77. Mean exposures ranged from 0.2 mg/kg bw per day (Scenario 4) to 0.71 mg/kg bw per day (Scenario 1). The 95th percentile exposures ranged from 0.76 - 2.5 mg/kg bw per day for Scenarios 4 and 1, respectively.

100. Overall, the COT agreed with the findings of the SCF, JECFA and IARC that the tumours seen in male rats were not biologically relevant to humans. Despite the lack of information on occurrence of saccharin in breastmilk, the Committee concluded that it would be unlikely that the ADI would be exceeded for this age group as sweeteners are not permitted in baby foods and solid food consumption for that age group would generally be lower than that of older children.

101. The COT concluded that there was no concern from exposure to saccharin in the diet for infants and young children.

102. The full SCF and JECFA evaluations can be found here:

https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_7_out26_en.pdf

https://apps.who.int/iris/bitstream/handle/10665/36981/WHO_TRS_837.pdf?sequence=1&isAllowed=y

2.4 Sorbitol and Xylitol

103. Sorbitol and xylitol are polyols, referred to as bulk sweeteners. Both sorbitol and xylitol naturally occur in some fruits and vegetables and xylitol is also formed as part of the pentose phosphate shunt during carbohydrate metabolism in humans (Mortensen, 2006).

104. They are currently on EFSA's call for data list and will be re-evaluated.

105. Both sorbitol and xylitol have been allocated an ADI "not specified" following review of the safety information in both animals and humans. Both the SCF (1985) and JECFA (1983) acknowledged that excessive consumption of polyols could produce a laxative effect and recommended that the consumption of polyols from all sources should be limited to levels below those shown to induce diarrhoea. Their laxative effect is attributed to a disturbance in osmosis across the intestinal wall due to the poor digestibility of polyols and their metabolites. Tolerability in humans varies greatly and there are also indications that younger children are more susceptible to the laxative effects than adults. It was concluded that consumption of up to 20 g of polyols per day would be unlikely to cause any undesirable symptoms (SCF, 1985). It was noted that for both xylitol and sorbitol intake of doses ≥ 50 g per day induced diarrhoea in humans. In children doses below 30 g per day are unlikely to cause gastrointestinal discomfort (Rapaille et al., 2003).

106. Information on aggregate polyol intakes from all sources could not be located, nor on occurrence in breastmilk. A study by Tennant (2014) reporting potential intake of total polyols in children based on NDNS data (2012) was identified. The exposures were based on reported use levels of polyols in the relevant food categories and it was felt that it would be more relevant to express intakes on a per meal occasion basis in relation to the development of gastrointestinal discomfort.

107. Mean intakes were 1.3 g per meal for children aged 1 to 2 years and 1.6 g per meal for children aged 3 to 9 years old. The respective 95th percentile exposures were 3.6 g per meal and 4.7 g per meal.

108. Overall, it was agreed that the main safety concern for polyols is gastrointestinal discomfort due to their laxative properties. It is unlikely that this will occur based on a regular diet, and in cases of excess the nature of these effects cause discomfort, which, however, are transient and not severely detrimental to human health.

109. Overall, the COT concluded that there was no concern from exposure to sorbitol and xylitol in the diet for infants and young children.

110. The full EFSA opinion can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2076

2.5 Steviol Glycosides (Stevia)

111. Stevia is a relatively recently introduced sugar alternative that comprises of mixtures of steviol glycosides extracted from the leaves of the stevia plant and is about 300 times sweeter than sugar. It has been assessed both by JECFA and EFSA's ANS Panel. The initial risk assessments for steviol glycosides were for mixtures of specific compositions based on the information provided by applicants, however in later opinions this has been expanded to some other compositions which are reflected in specifications on the identity and purity of steviol glycosides for use in food. In Europe, steviol glycosides are permitted for use as a sweetener in food (E 960).

112. Steviol glycosides are poorly absorbed following oral exposure, but hydrolysis occurs by the gut microflora to steviol, which is readily absorbed. The rest is excreted in the faeces. The absorbed fraction undergoes conjugation with glucuronic acid in the liver, resulting in the formation of steviol glucuronide. In humans, steviol glucuronide is excreted in urine.

113. JECFA have evaluated the safety of steviol glycosides multiple times, most recent in 2016. In 2008, an ADI of 0 - 4 mg/kg bw expressed as steviol was established and this was confirmed in 2016. Studies considered during the 2008 evaluation showed no adverse effects of steviol glycosides when taken at doses of about 4 mg/kg bw per day, expressed as steviol, for up to 16 weeks by individuals with type 2 diabetes mellitus and individuals with normal or low-normal blood pressure for four weeks.

114. In their evaluation in 2010, EFSA considered steviol glycosides, from 3 petitioners, comprising not less than 95% stevioside and/or rebaudioside A. As these two components exhibit similar toxicokinetic profiles in both rats and humans, EFSA considered the toxicological information on either chemical to be suitable for the evaluation of steviol glycosides in general.

115. EFSA concluded that overall, stevioside and rebaudioside A did not show genotoxic potential *in vitro* or *in vivo*. Regarding carcinogenicity, there was no indication for carcinogenic potential of steviol glycosides. The NOAEL was based on the only two-year study, in F344 rats, in which the test material complied with JECFA specifications (Toyoda et al., 1997). The NOAEL for this study was 2.5% (967 and 1120 mg stevioside/kg bw per day in males and females, respectively, corresponding to 388 mg/kg bw per day of steviol equivalents) based on a lower survival rate at the highest dose (5%) compared to controls, reduced absolute kidney weights, statistically significantly decreased absolute left ovary weights, and statistically significantly increased relative brain weights in the 5% group females compared to controls. EFSA noted that the tumours reported were typical of the species.

116. There was no available information on occurrence of steviol glycosides in breastmilk.

117. Exposures to steviols were estimated using recent consumption data from the NDNS Years 1 - 8 for the 1.5 to 5 years of age group. The exposures were estimated assuming that steviols are present at the MPL specified for each category by Regulation (EC) No 1333/2008. Mean exposure to steviols was 3.1 mg/kg bw per day. The 97.5th percentile exposures were estimated by either assuming a person is a high-level consumer of all food groups (9.9 mg/kg bw per day) or, using EFSA's approach, by assuming that an individual is a high-level consumer of one food category and would be an average consumer of the others. In line with the EFSA approach, this estimate was refined by selecting a group that made one of the highest contributions to exposure. Fruit nectar was one of the major contributors to 97.5th percentile exposure, so adding the exposure from this group to mean exposures from the rest of the groups resulted in a high-level exposure estimate of 4.5 mg/kg bw day. According to relevant regulation, steviol glycosides are permitted for use only in "energy reduced" or "no added sugar" commodities, however regular food commodities have been used as surrogates in the instances where a "no added sugar" alternative was not available within the NDNS food codes database. The COT agreed that this was likely to produce an additional degree of conservatism in the estimates.

118. Overall, the COT highlighted the conservatism in the exposure estimates for children 1.5 to 5 years of age. Despite the lack of information on dietary exposures for infants aged 0 to 1 years, it would be unlikely that the ADI would be exceeded for this age group as sweeteners are not permitted in baby foods and solid food consumption for that age group would generally be lower than that of older children.

119. Overall, the COT concluded that there was no concern for exposure to steviols in the diet for infants and young children.

120. The full EFSA evaluations can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2010.1537

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.1972

2.6 Sucralose

121. Sucralose is an artificial sweetener, about 600 times sweeter than sugar. It is approved for use in the EU (E955) and due to its heat stability can be found in a wide range of products including baked goods, pre-sweetened breakfast cereals, beverages, chewing gums and desserts. Both JECFA and the SCF have evaluated sucralose and established a TDI of 0–15mg/kg bw (JECFA, 1991; SCF, 2000).

122. Sucralose is currently on EFSA's call for data list and due to be re-evaluated.

123. In humans, orally administered sucralose is absorbed at levels ranging from 8 - 22%. It is rapidly excreted unchanged in urine. Following administration of single oral doses, the terminal elimination half-life was around 5, 25, 39 and 79 hours in rat, human, rabbit and dog, respectively.

124. In 1991, and following the evaluation of newly submitted data, an ADI of 0 - 15 mg/kg bw was established, based on a NOAEL (1500 mg/kg bw per day, the highest dose tested) from a two-year study in rats that included exposure *in utero* and the application of an UF of 100. The reduction in body weight gain in all treated groups was considered secondary to the reduced food consumption due to the impalpability of high sucralose concentrations in the diet. JECFA recommended additional studies on immunotoxicity to assess the significance of weight changes seen in the spleen and thymus and to investigate changes in lymphocyte counts to address potential causality from exposure to sucralose. These were based on observations in a study by Cummins et al. (1983) where rats were exposed to sucralose in the diet for either 4 or 8 weeks. Additionally, the SCF IN 1989 highlighted the weak mutagenic activity of 1,6-dichloro-1,6-dideoxyfructose (1,6-DCF), a hydrolysis product of sucralose. This was considered of potential relevance as 1,6-DCF could be formed in the acidic pH of soft drinks. They were however satisfied that the sweetener as such did not possess genotoxic or carcinogenic potential and had not shown serious target-directed organ toxicity.

125. In 2000, the SCF re-evaluated the safety of sucralose. Addressing the concerns for immunotoxicity, the Committee identified a NOAEL of 3000 mg/kg bw per day for any effects on lymphoid organs and the immune system that might occur, whether caused directly by sucralose, or indirectly via stress and/or dietary factors. New studies on the mutagenicity of 1,6-DCF *in vitro* and *in vivo* indicated no cause of concern. Addressing the NOAEL of 350 mg/kg bw per day for maternal gastrointestinal effects in rabbits, the SCF concluded that these were attributable to the particular sensitivity of this species to high concentrations of poorly absorbed substances (sucralose absorption in rabbit was about 20%) and they were unlikely to occur in other species, including humans.

126. The SCF noted that the reductions in body weight gain seen at low doses in feeding studies in rats were not dose related and were attributable to the non-palatability of sucralose containing diets. Reduced body weight gain in rats at higher doses was considered the critical effect on which to establish the ADI. Based on an overall NOAEL of 1500 mg/kg bw per day from dietary and gavage studies for this endpoint and the application of an UF of 100, an ADI of 0 - 15 mg/kg bw per day was established.

127. The COT was aware of reports on the potential formation of chlorinated organic compounds from the heat degradation of sucralose during cooking and baking, however due to the lack of data at the time of reviewing they were unable to assess this further.

128. No UK information on the occurrence of sucralose in breastmilk could be located. It is legally prohibited for baby foods to contain sucralose and therefore an exposure assessment for that food group was not carried out.

129. Dietary exposures to sucralose in Irish children aged 1 to 4 years were estimated by Martyn et al. (2016) as described in paragraph 77. Mean exposures ranged from 0.65 - 2.5 mg/kg bw per day and 95th percentile exposures from 2.0 - 9.1 mg/kg bw per day.

130. Overall, the COT concluded that on the basis of the data available there was no concern from exposure to sucralose in the diet of infants and young children aged 0 to 5 years old, however this is pending the completion of the EFSA evaluation and further information on the heat degradation of sucralose.

131. The full SCF and JECFA evaluations can be found here:

http://aei.pitt.edu/40830/1/21st_food.pdf

https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out68_en.pdf

http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=2340

3 Natural toxins

132. The following sections provide an overview of the assessment of several mycotoxins and tropane alkaloids.

3.1 Mycotoxins

133. 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). There are currently no Government dietary recommendations for infants and young children which relate to mycotoxin levels.

134. The COT agreed that co-exposure to mycotoxins is an important area and should be further considered. An in-depth scoping paper on this will be prepared by the Secretariat at a later date and therefore the following paragraphs focus on exposures and risk characterisation of individual mycotoxins.

135. The following exposure estimates were calculated using the data from the FSA survey on mycotoxins in relevant foods in the 2014 TDS (Stratton et al., unpublished), unless otherwise indicated.

3.1.1 Aflatoxin (B1, B2, G1, G2 and M1)

136. Aflatoxins are produced primarily by two species of *Aspergillus* fungus and can be found in foods as a result of fungal contamination both pre- and postharvest, with the rate and degree of contamination dependent on temperature, humidity, soil and storage conditions. Aflatoxins are most commonly associated with groundnuts, tree nuts, dried fruit, spices, figs, crude vegetable oils, cocoa beans, maize, rice, cottonseed and copra.

137. Aflatoxin M1 (AFM1) is a major metabolite of aflatoxin B1 (AFB1) in humans and animals. It may be present in milk from animals fed on AFB1 contaminated feed and also in human breast milk. For the UK, exposure to aflatoxins is considered to occur mainly from imported materials. It is possible that future changes in climate could lead to increased aflatoxin contamination.

138. Most of the available toxicological data relate to AFB1. AFB1 is both genotoxic and carcinogenic in experimental animals. Sufficient experimental evidence is also available for the carcinogenicity of naturally occurring mixtures of aflatoxins, and of aflatoxin G1 (AFG1) and AFM1, whereas there is only limited evidence for the carcinogenicity of aflatoxin B2 (AFB2) and inadequate evidence for aflatoxin G2 (AFG2). The relative potency of aflatoxin congeners based on data from bacterial mutagenicity testing and hepatocarcinogenic effects in the rainbow trout and rats, is in the order of AFB1 > (AFG1, AFM1) >> (AFB2, AFG2).

139. The potential carcinogenicity of aflatoxins (either total or AFB1) in humans has been examined in a large number of epidemiology studies, generally carried out in Africa and Asia, where substantial quantities of aflatoxins occur in basic foodstuffs. IARC concluded that naturally occurring aflatoxins are hepatocarcinogenic to humans (Group 1) and this is exacerbated in subjects who are carriers of hepatitis B virus (HBV) surface antigens.

140. EFSA (2007) did not consider it appropriate to establish a HBGV for aflatoxins as they are both genotoxic and carcinogenic; they therefore applied the MOE approach in their risk assessment. However, EFSA noted that the available data were sufficient to assess only AFB1, yet AFG1 and AFB2 are also carcinogenic in rodents, albeit with lower potency than AFB1. Therefore, as a conservative approach, EFSA assumed the carcinogenic potency of “total aflatoxin” to be similar to that of AFB1.

141. Following EFSAs approach, MOEs for aflatoxins were calculated using a $BMDL_{10}$ of 0.17 µg/kg bw per day, based on liver carcinogenicity in male rats

exposed to 1 - 100 µg/kg diet of AFB1 (Wogan et al., 1974) and exposures estimated from UK occurrence data from the TDS (2014).

142. Occurrence data on total aflatoxin was not available as part of the TDS and due to inconsistencies in the reporting across the EU, total exposure could not be calculated with any confidence from the data available. The assessment here therefore focused on individual aflatoxins.

143. All aflatoxin results in the TDS were below their respective calculated LOQ.

144. When exposures were calculated using 0 as the lower bound (LB) and the LOQ as the upper bound (UB), the MOEs for AFB1, AFB2, AFG1, AFG2 and AFM1 for all groups ranged from infinity to substantially less than 10,000. Hence, whilst there is no evidence that exposures are such that they are of concern, equally it is not possible to exclude this possibility. The COT therefore noted that there is a need for improved methods to measure actual aflatoxin values.

145. While estimated concentrations between the LOD and the LOQ are less reliable than concentrations measured above the LOQ, the COT noted that it would still be of value for such concentrations to be reported, as they would be preferred when assessing exposure, as opposed to using 0 or the LOQ as an estimate.

146. The COT also noted that there is a potential difference in susceptibility of children to aflatoxins compared to adults. Neonatal mice are more sensitive than adult mice to the hepatocarcinogenicity of AFB1. The levels of a number of detoxifying enzymes are lower and the proliferation rate of hepatocytes is higher in neonates than in adults, which would tend to increase susceptibility. However, the P450 system in neonates is less well developed than in adults and hence there is a reduced capacity to activate AFB1 at that age, which would tend to reduce susceptibility. The available data do not allow for the overall difference in susceptibility to AFB1 between infants and adults to be estimated, as it is not possible to extrapolate quantitatively from the findings in mice to humans. The COT was therefore not able to draw any conclusions on sensitivity differences and noted that this is a significant issue and data gap.

147. Given that aflatoxins are genotoxic and carcinogenic their presence is always undesirable and given the uncertainties in this assessment it is not possible to exclude a safety concern without additional information.

148. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2007.446

3.1.2 Citrinin

149. Citrinin is produced by several species of the genera *Aspergillus*, *Penicillium*, and *Monascus*. and is normally formed under harvest and storage conditions. It occurs predominantly in grains but also in other plant products such as beans, fruit and herbs and spices. It is also found in red mould rice (RMR), used as a food colourant and preservative in Asian foods. Experimental data indicate the occurrence

of citrinin residues in edible tissues and eggs following oral exposure of animals with contaminated feed. Toxicokinetic studies with oral administration are not available.

150. The acute lethal dose of citrinin ranged from 19 - 134 mg/kg bw, depending on species and route of administration. In repeat dosing studies citrinin was nephrotoxic and these again highlighted the differences in susceptibility between species. In a sub-chronic study in rats a NOAEL of 20 mg/kg bw per day was identified. In a long-term feeding study in rats exposed to high dietary citrinin levels (initially about 70 mg/kg bw per day), the kidney was identified as the principal target organ and progressive histopathological changes with an increased incidence of renal adenomas were observed. However, the study was limited to 80 weeks, thus no conclusions on potential carcinogenicity could be drawn. Other *in vivo* studies showed the induction of chromosome abnormalities and hypodiploidy in mouse bone marrow following administration of citrinin. Conventional bacterial and mammalian *in vitro* assays with citrinin showed no evidence of mutagenicity; positive results were reported in only one study, using rat hepatocytes as the activation system in the Ames test. IARC concluded that citrinin is not classifiable as to its carcinogenicity to humans (Group 3). The COT agreed with IARCs classification and concluded that it was currently not possible to assess the carcinogenicity of citrinin with confidence.

151. Results from immunotoxicity studies were generally inconclusive and/or non-specific and did not allow for conclusions to be drawn. Citrinin showed evidence of teratogenicity and embryotoxicity *in vivo*. However, these effects occurred only in the presence of maternal toxicity, including nephrotoxicity, indicating that they may be secondary to maternal toxicity, a conclusion shared by the COT, on reviewing the available data. Treatment of male mice with citrinin intraperitoneally resulted in reproductive toxicity. The Committee was unable to determine the toxicological significance to dietary exposure of findings by this route of administration.

152. EFSA (2012) concluded that establishment of a HBGV would not be appropriate, given the available data on genotoxicity and the limitations and uncertainties in the current database, including on the carcinogenic potential of citrinin. EFSA furthermore concluded that, due to the lack of human dietary exposure data an MOE approach would not be possible. Instead, to provide risk managers with some indication of the possible risk, EFSA decided to estimate the critical citrinin concentration in grains and grain-based products that would result in an exposure equal to the level of no concern for nephrotoxicity in humans. Based on an overall NOAEL of 20 µg/kg bw per day for nephrotoxicity in rats, and application of an UF of 100 for interspecies and interindividual variation, a level of no concern for nephrotoxicity in humans of 0.2 µg/kg bw per day was determined. A concern for genotoxicity and carcinogenicity could be excluded at the level of no concern for nephrotoxicity.

153. Mean and 97.5th percentile exposures for infants aged 4 to 12 months ranged from 0 - 0.009 and 0 - 0.025 µg/kg bw per day, respectively. For young children aged 12 to 18 months the mean and 97.5th percentile exposures ranged from 0 - 0.016 and 0 - 0.041 µg/kg bw per day, respectively. Mean and 97.5th percentile dietary exposures for young children aged 18 to 60 months ranged from 0 - 0.019 and 0 - 0.044 µg/kg bw per day, respectively. All mean and 97.5th percentile exposures of

infants and young children are below the exposure level of 0.2 µg/kg bw per day considered by EFSA of no concern for nephrotoxicity in humans.

154. The exposures reported in the TDS are not of toxicological concern for nephrotoxicity in infants and young children aged 0 to 5 years old. However, the COT noted that due to lack and limitations of the available data, a concern for genotoxicity and carcinogenicity cannot be excluded.

155. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2605

3.1.3 Cyclopiazonic acid (CPA)

156. Cyclopiazonic acid (CPA) is produced by several species of *Aspergillus* and *Penicillium* and is widespread in agricultural raw materials. CPA is normally formed under storage conditions and may be found alongside aflatoxin in the food and feed chain. CPA has been found in a range of food types including seeds, grains, cheeses, meat products, eggs and cow's milk (Burdock and Flamm, 2000; Chang *et al*., 2009).

157. After ingesting CPA-contaminated feeds, test animals display GI and neurological effects. Organs affected include the liver, kidney, heart, and digestive tract, which show degenerative changes and necrosis (Ostry *et al*. 2018). There is little evidence available for toxicity in humans due to consumption of food contaminated with CPA.

158. Due to the limited availability of relevant toxicity data, there are currently no risk assessments or evaluations of CPA by European or International agencies or committees such as EFSA, JECFA and IARC.

159. The COT reviewed the available toxicity studies for CPA. Three of the studies, a 90-day dog study by Nuehring et al. (1985), a 90-day rat study by Voss et al. (1990) and a 14-day pig study by Lomax et al. (1984) were discussed in more depth as they were considered potentially most appropriate for use in an MOE approach for risk characterisation.

160. The NOAEL from the Lomax et al. study in pigs, according to the authors, was 0.01 mg/kg bw per day, which is 10-fold lower than the NOAEL of 0.1 mg/kg bw per day from the Nuehring et al. study in dogs. However, the GI effects that were observed in a minimal number of animals from the 0.1 and 1.0 mg/kg bw per day treatment groups are common in pigs of that age. The Committee therefore concluded that the NOAEL for this study was 1 mg/kg bw per day.

161. There are some uncertainties in using the Nuehring et al. study for establishing an HBGV. The main one is the suitability of the animals for this study, as they were generally of unknown provenance. However, a clear dose response was demonstrated. The 0.1 mg/kg bw per day dose group showed no dose related effects and could be considered the NOAEL for the study.

162. The Lomax et al. study was only of 14 days duration, whereas the Nuehring et al. study was for 90 days, with a lower NOAEL. Overall, it was agreed that the NOAEL of 0.1 mg/kg bw per day from the Nuehring et al. study should be used in hazard characterisation. Although there were uncertainties around the quality of this study, the NOAEL from the 90-day rat study of Voss *et al*. was 0.2 mg/kg bw per day and thus provided some support for the use of a NOAEL of 0.1 mg/kg bw per day as the basis for calculating MOEs for CPA exposures.

163. There was no information available regarding levels of CPA in breast milk or infant formulae.

164. Mean and 97.5th percentile exposures from the rest of the diet for infants aged 4 to 12 months ranged from 0 - 0.004 and 0.001 - 0.011 µg/kg bw per day, respectively. For young children aged 12 to 18 months the mean and 97.5th percentile exposures ranged from 0.001 - 0.007 and 0.005 - 0.018 µg/kg bw per day. Mean and 97.5th percentile dietary exposures for young children aged 18 to 60 months ranged from 0.002 - 0.009 and 0.007 - 0.022 µg/kg bw per day.

165. MOEs for the UB estimates of exposure were calculated using the NOAEL of 0.1 mg/kg bw per day. The MOEs ranged from 4,500 to 100,000.

166. Based on the available information on toxicity and exposure, the margin between the NOAEL of 0.1 mg/kg bw per day from the Nuehring et al. study and estimated UK exposures all exceed 1,000 (an additional factor of 10 was applied to allow for the fact that the NOAEL was from a sub-chronic study) and are sufficient to suggest that CPA present in the diet does not pose a health concern for infants aged 0 to 12 months and children aged 1 to 5 years.

3.1.4 4,15-Diacetoxyscirpenol (DAS)

167. 4,15-Diacetoxyscirpenol (DAS) is a type A trichothecene mycotoxin from *Fusarium* species. It is found in cereals and cereal-based products including wheat, barley, rice, rye, maize, oats and sorghum. In addition, it has been found in coffee beans. DAS can co-occur with many other mycotoxins in grains and grain-based products, in particular Fusarium toxins, including other type A and type B trichothecenes, and zearalenone.

168. DAS is rapidly metabolised to a large number of metabolites (Yang et al., 2015). The main metabolic processes are deacylations, hydroxylations, de-epoxidations and glucuronide conjugations. After oral administration in rats and mice (Conner et al., 1986; Ueno, 1983), the absorption of DAS was not quantified but the excretion ratio between urine and faeces indicated extensive absorption. DAS was rapidly distributed to most organs. Tissue concentrations decreased rapidly with no apparent accumulation in any tissue and more than 90% of radiolabelled DAS was excreted within 24 hours. Haematological effects such as anaemia, leukopenia and thrombocytopenia were observed. When administered intravenously (i.v.), the median lethal dose (LD_{50}) ranged from 1 - 12 mg/kg bw while after i.p. administration the LD_{50} ranged from 0.8 - 23 mg/kg bw.

169. Data from when DAS was tested as a cytostatic anticancer drug (named anguidine) in phase I and phase II clinical trials on cancer patients by i.v. administration demonstrated adverse health effects in humans. Nausea and vomiting were the most relevant acute adverse health effects of DAS when administered i.v. with a NOAEL at 1.2 mg/m^2 (equivalent to 32 µg DAS/kg). Haematotoxicity (with a NOAEL of 65 µg/kg bw) and myelosuppression were the most frequently observed and persistent adverse effects observed in the phase I studies when DAS was given repeatedly.

170. Increase in levels of gut satiety hormones (e.g. cholecystokinin (CCK)) is considered the mechanism of DAS (and other trichothecenes) induced anorexia. *In vitro* studies indicated cytotoxic properties on haematopoietic progenitors which could be due to stimulation of apoptosis or inhibition of protein synthesis.

171. Due to the limitations in the available data set, EFSA established human acute and chronic HBGVs based on data obtained in clinical trials of DAS as an anticancer agent (anguidine).

172. Using these data, an acute reference dose (ARfD) of 3.2 µg/kg bw and a TDI of 0.65 µg/kg bw were established by EFSA. The TDI was more than 10-fold higher than that established by JECFA.

173. The COT noted the limited toxicity data available in experimental animals via i.v., i.p. and oral routes. The COT agreed that it was appropriate to use the human studies with DAS (anguidine) administered i.v. as a cytostatic anticancer drug in the hazard characterisation.

174. The COT discussed the toxicity data comparing i.v. with oral exposure in relation to GI toxicity. It was noted that very few data were available using the oral route. The only direct oral/i.v. comparison was for the rat, where there was a 5-fold difference in LD_{50}. Hence, this suggested that the use of a NOAEL after i.v. dosing would likely over-estimate risk and should reasonably be expected to protect against oral exposure. Taking all this into consideration, the COT agreed with the use of i.v. data to establish the HBGVs.

175. The COT agreed with the EFSA establishment of an ARfD for DAS, the use of the clinical trial data, and the application of an UF of 10 to account for differences in toxicokinetics and toxicodynamics among individuals. Furthermore, the application of the UF of 10 to the reference point would make it conservative.

176. The COT also agreed with the method EFSA used to establish a TDI for DAS, based on the NOAEL for haematotoxicity and myelotoxicity from the clinical trial data. The Committee discussed the establishment of the PMTDI by JECFA and noted that inclusion of DAS in the group PMTDI for T-2 and HT-2 was quite conservative, given that the JECFA group PTMDI was 0.06 µg/kg bw, whilst the EFSA TDI for DAS was 0.65 µg/kg bw. The JECFA PMTDI was not based on DAS data.

177. Based on their discussions of the HBGVs established by EFSA and JECFA, the COT recommended the use of the EFSA ARfD and TDI values, rather than the PMTDI established by JECFA, for future UK risk assessments for DAS.

178. UK exposures were calculated and all the estimated mean and 97.5th percentile acute and chronic exposure levels were below the ARfD and TDI established by EFSA, respectively, and as a result, not of health concern for infants and young children aged 0 to 5 years old.

179. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5367

3.1.5 Deoxynivalenol (DON), 3-acetyldeoxynivalenol (3-Ac-DON), 15-acetyldeoxynivalenol (15-Ac-DON) and deoxynivalenol-3-glycoside (DON-3-glycoside)

180. Deoxynivalenol (DON) is produced by *Fusarium* species growing on cereal crops, typically at temperate climates. 3-Acetyldeoxynivalenol (3-Ac-DON) and 15-acetyldeoxynivalenol (15-Ac-DON) are fungal metabolites of DON, and deoxynivalenol-3-glycoside (DON-3-glycoside) is a plant metabolite of DON. Consequently, these four chemicals have been found in cereal crops and in cereal-based foods such as bread, pasta and biscuits.

181. In humans, an estimated 70% of ingested DON was excreted to urine, mainly as glucuronide conjugated DON.

182. In animals, the main effects of acute and chronic exposure to DON are characterised by feed refusal and decreased body weight gain. DON has further been reported to impact the immune response, have developmental and reproductive toxicity and is known to cross the placental barrier. DON is genotoxic *in vitro*; available data suggest however that the mechanism involves oxidative stress rather than direct genotoxicity. Different to other trichothecenes, DON does not show haemato- or myelotoxicity and data on neurotoxicological effects are limited.

183. For 3-Ac-DON, 15-Ac-DON and DON-3 glucoside no data could be identified on chronic toxicity, haemato- and myelotoxicity, neurotoxicity and carcinogenicity. 3-Ac-DON was inactive in a bacterial mutation assay but no data on *in vitro* genotoxicity tests with 15-Ac-DON or DON-3-glucoside or *in vivo* studies for all three forms were identified.

184. In 2017, EFSA established a group ARfD of 8 µg/kg bw per eating occasion and a group TDI of 1 µg/ kg bw per day.

185. While the MoA and the toxicity data for 3-Ac-DON and 15-Ac-DON indicated similar toxicity to that of DON, toxicity data for DON-3-glucoside were limited and *in vivo* data on chronic toxicity were missing with the consequence that EFSA could not reach a firm conclusion on the hazard of DON-3-glucoside and could also not compare it with that of DON and its two acetylated forms. Therefore, EFSA applied a conservative approach assuming that 1) 3-Ac-DON, 15-Ac-DON and DON-3-

glucoside are all metabolised to DON and absorbed to the same extent as DON, 2) the acetylated forms of DON induce the same acute and chronic adverse health effects as DON and 3) similar health effects of DON-3-glucoside as DON cannot be excluded. EFSA therefore decided to characterise the three forms and DON together, both for acute and chronic health effects.

186. Since EFSA did not consider the studies in experimental and farm animals suitable, epidemiological studies were used as the base for establishing the HBGV. EFSA identified vomiting as the critical acute effect in humans. EFSA calculated a NOAEL of 26 µg DON/kg bw for one single eating occasion from a human outbreak in China and applied the default UF of 3.16 for toxicodynamic differences for intra-human population variability to establish an ARfD of 8 µg/kg bw per eating occasion. The dose-range calculated from human urinary biomarker data supported the reference dose; single and multiple biomarker approaches showed strong correlation between total DON in urine and dietary intake. The highest urinary biomarker level was reported for a healthy pregnant woman from which an exposure of 74 µg DON/kg bw was back calculated. The next highest exposure based on urinary biomarker levels was 36 µg DON/kg bw. EFSA concluded that the range of 36 - 74 µg DON/kg bw would represent a range of NOAELs at which adverse effects (vomiting) would not be expected to occur in humans. However, EFSA did note a number of uncertainties such as the inconsistency between urinary DON biomarker levels using different methods, neglecting the variation of DON excretion and urine volume amongst individuals and inconsistent reporting. EFSA noted however, that the calculated NOAEL of 26 µg DON/kg bw per eating occasion is not in disagreement with the calculations based on human data by JECFA.

187. In the absence of chronic epidemiological data, EFSA identified reduced bodyweight gain in experimental animals as the critical chronic effect. EFSA calculated a $BMDL_{05}$ of 0.11 mg/kg bw per day based on a study in mice, the only chronic toxicity/carcinogenicity study identified (Iverson et al., 1995), and applied an UF of 100 for inter- and intra-species differences to establish a group TDI of 1 µg/kg bw. Since the $BMDL_{05}$ is lower than the BMDLs calculated for reproductive and developmental toxicity, EFSA considered it sufficiently protective for these effects.

188. Acute and chronic exposures were calculated using data from the TDS; measurements were performed for DON, 3-AC-DON and 15-AC-DON, no measurements were available for 3-DON-glycoside. 3-Ac-DON and 15-Ac-DON were not detected in any samples above the limit of detection (LOD). A combined concentration for the sum of 15-Ac-DON, 3-Ac-DON and DON was not provided to the FSA as part of the TDS, thus the sum used in the exposure assessment was estimated by summing the individual concentrations of all three forms.

189. Mean and 97.5th percentile acute exposures to 15-Ac-DON, 3-Ac-DON and DON and the sum of all three forms were below the group ARfD of 8.0 µg/kg bw, for all age groups and are therefore not of toxicological concern for infants and young children aged 0 to 5 years old.

190. Mean and 97.5th percentile chronic exposures to 15-Ac-DON, 3-Ac-DON and DON were below the TDI of 1.0 µg/kg bw, for all age groups and are therefore not of toxicological concern. All mean and 97.5th percentile chronic exposures to the sum

of all three forms were below the TDI, except the 97.5th percentile UB exposure in children > 12 months of age, which were at or up to 1.3-fold the TDI. This is unlikely to be of toxicological concern. Further, the sum of all forms is not based on individual measured values but on summing the respective averages of the concentrations provided. Therefore, exposure estimates might be conservative.

191. The full EFSA and JECFA evaluations can be found here:

https://www.efsa.europa.eu/en/efsajournal/pub/4718

http://apps.who.int/iris/bitstream/10665/44520/1/9789241660631_eng.pdf

3.1.6 Ergot alkaloids (EAs)

192. Ergot alkaloids (EAs) infest a number of plant species including commercially important grains such as rye, wheat, rice, corn, barley, millet and oat. More than 50 different EAs have been identified but the total amounts and patterns vary between fungal strains, geographic regions and host plants.

193. EAs can act on a number of neurotransmitter receptors particularly adrenergic, dopaminergic and serotonergic receptors, and the effects of these receptor interactions may be acute or long-term. Data for the genotoxic potential of EAs other than ergotamine are limited/insufficient. The available *in vitro* data did not indicate bacterial or mammalian mutagenicity, *in vivo* data are inconsistent but there is some evidence of clastogenicity. Tumorigenicity (neurofibromas on the ears) observed in a two-year carcinogenicity study of crude ergot was exacerbated by a low protein diet. The absence of carcinomas and the regression of tumours on cessation of ergot indicated an aetiology related to a non-genotoxic mode of action. Human data are available for the naturally occurring alkaloids used as pharmaceuticals, ergometrine and ergotamine.

194. EFSA (2012) established a group ARfD of 1 µg/kg bw for the sum of ergot alkaloids based on a $BMDL_{10}$ of 0.33 mg/kg bw per day for an increased incidence of tail muscular atrophy in a 13-week rat feeding study of ergotamine (Spieijers et al., 1993) and application of an overall UF of 300, comprised of the default UF of 100 for intra- and interspecies differences and an UF of 3 for deficiencies in the database.

195. EFSA established a group TDI of 0.6 µg/kg bw for the sum of EAs based on the same $BMDL_{10}$ of 0.33 mg/kg bw per day, as for the derivation of the ARfD, and application of an overall UF of 600. EFSA concluded that in addition to the UF of 300 used in establishing the ARfD, an additional UF of 2 should be applied for extrapolation from a sub-chronic study to chronic exposure.

196. EFSA noted that the group ARfD is 2-fold lower than the lowest single dose of 2 µg/kg bw ergometrine used to induce uterine contractions and therefore considered the margin between this dose in a sensitive subpopulation and the group ARfD as adequate. The lowest prescribed dose of ergotamine used in the treatment of migraine is approximately 10 to 20 times higher than the group ARfD and 20 to 40 times higher than the group TDI.

197. The mean and 97.5th percentile acute exposures of infants and young children to total EAs are all below the ARfD of 1 µg/kg bw, and the mean and 97.5th percentile chronic exposures are all below the TDI of 0.6 µg/kg bw. Exposure to EAs are therefore not of toxicological concern.

198. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2798

3.1.7 Fumonisins

199. Fumonisins are common contaminants of maize and have also been found in rice, grapes, green coffee beans, onions, mango, corn and other cereals, peanuts and dried fruits. There are three main sub-types; fumonisin FB1 (FB1), fumonisin B2 (FB2) and fumonisin B3 (FB3).

200. Fumonisins can have significant health effects in livestock and other animals, although evidence for adverse health effects in humans is currently inconclusive. FB1 is not acutely toxic, however, it is possibly carcinogenic to humans (Group 2B; IARC, 2002). Concerns over exposure to fumonisins and their contribution to outcomes such as birth defects and stunting growth in children have been identified, however, reproductive and developmental effects observed in humans have not been causally related to fumonisin exposure.

201. The human health impacts of fumonisins have more recently been evaluated by JECFA in 2017 and by EFSA in 2018. JECFA established a PMTDI of 2 µg/kg bw for all sub-types, alone or in combination. EFSA established a lower TDI, of 1 µg/kg bw for all sub-types. Both HBGVs were based on the induction of megalocytic hepatocytes in male mice with an UF of 100. The difference in values was due to different results from the BMD modelling.

202. The COT considered possible metabolic differences of fumonisins between adults and children since the PMTDI/TDI was based on hepatotoxic effects in adult animals. Members concluded that fumonisins are poorly absorbed and metabolised by hydrolysis and acetylation, the metabolites being excreted mainly in the faeces. These metabolic reactions are generally well developed at birth, which, together with the predominantly biliary excretion suggests that there should not be marked differences in plasma levels in infants; however, the Committee acknowledged that there is a lack of specific information.

203. No UK data on levels in breast milk were available. A study by Mahoga et al., (2014) reported fumonisins levels in breast milk in Tanzanian women. The Committee concluded that it would be unlikely that these levels would reflect levels in women in the UK population; however, differences in ethnic diets should be further considered.

204. All calculated exposures in the TDS were below both the EFSA TDI and JECFA PMTDI for all infant groups aged 0-12 months (except those aged 6-9 months; where an exceedance was observed, refer to following paragraph) and children aged 1-5 years.

205. The 97.5th percentile exposure estimates for 6 to 9 months old infants in whom it was assumed feeding was exclusively with infant formula and that fumonisins were present at the maximum level of 179 µg/kg, exceeded both the EFSA TDI and JECFA PMTDI, at 3.0 µg/kg bw per day. However, exposure to infant formulae is considered short when compared to a lifetime. In addition, the German data (Zimmer et al., 2008) on which the assessment was based may not accurately reflect the levels of fumonisins in infant formulae, in today's market. While the data were the only ones available to the COT at the time, the authors of the study noted that the concentrations reported have been declining and only one manufacturer was contributing to the high concentrations observed. The COT concluded that occasional exceedances are unlikely to result in adverse toxicological effects as the HBGVs were based on repeat-dose effects.

206. The full EFSA and JECFA evaluations can be found here:

https://www.efsa.europa.eu/en/efsajournal/pub/5172

http://www.who.int/foodsafety/publications/technical-report-series-1002/en/

3.1.8 Fusarenon-X (Fus-X)

207. Fusarenon-X (Fus-X) is a type B trichothecene that can be present alone or in combination with other mycotoxins in cereals such as wheat, barley, oats, rye, rice, sorghum, millet and maize.

208. The toxicological effects of Fus-X were previously evaluated by the National Institute for Public Health and the Environment (RIVM) (Pronk et al, 2002). It is acutely toxic, with oral LD_{50} values of 4.4 mg/kg bw in rats and 4.5 mg/kg bw in mice. Like other trichothecenes, Fus-X is ribotoxic, resulting in inhibition of protein and DNA synthesis. Furthermore, Fus-X has been shown to induce apoptosis in *in vitro* and *in vivo* animal studies. The target organs of Fus-X are those that contain actively proliferating cells *e.g*. thymus, spleen, small intestine, testes and the bone marrow.

209. RIVM were unable to establish a temporary TDI in their 2002 evaluation due to data insufficiencies, especially the limited number of oral studies, their limitations and the lack of carcinogenicity data. Furthermore, no HBGV has been established by EFSA, JECFA or any EU Member State.

210. Emesis in mink has been used as the basis for determining benchmark doses for the risk characterisation of other trichothecene families. EFSA concluded that humans were no more sensitive than mink towards the emetic effect, since the doses of emetine causing emesis were similar in both species. The COT did note that there was some residual uncertainty as to whether this would equally apply to Fus-X.

211. Comparative toxicity data for Fus-X suggests that it is more toxic when other type B trichothecenes (DON, 3-Ac-DON, 15-Ac-DON and NIV) in eliciting emesis when administered orally. It had lower relative oral emetic potency compared to some type A trichothecenes (HT-2 and T-2).

212. The COT agreed that it was not appropriate to use the ARfD for NIV as a comparative HBGV for Fus-X, since it was more potent at inducing an acute emetic response. Comparison with the HBGV for DON was considered more appropriate, since the oral emetic potency of Fus-X relative to DON is 1.04.

213. Acute exposures to Fus-X were estimated using data from the TDS and these showed no cause for concern with regard to acute toxicological effects when compared with the ARfD for DON (8 µg/kg bw per day, based on human data by EFSA and on emesis in pigs by JECFA). However, the COT noted that there were some uncertainties involved in the extrapolation of the data.

214. Additive acute exposures of Fus-X, DON and NIV, showed that DON made the largest contribution and hence comparison was with the ARfD for DON. The summed acute exposures (Fus-X, DON and NIV) for all age groups were below the ARfD for DON. The COT noted that the estimates of acute exposure were highly conservative and that the likelihood of co-occurrence of Fus-X with DON and NIV at these levels is low.

215. The COT concluded that acute co-exposure of Fus-X with DON and NIV was unlikely to result in adverse toxicological effects in infants and young children.

216. The full RIVM evaluation can be found here:

https://www.rivm.nl/bibliotheek/rapporten/388802024.pdf.

3.1.9 Moniliformin (MON)

217. Moniliformin (MON) is a mycotoxin with low molecular weight produced by several *Fusarium* species and *Penicillium melanoconidium*. It occurs predominantly in cereal grains and subsequently cereal products. This risk characterisation for MON made use of a scientific opinion from EFSA (2018).

218. The data on the toxicokinetics of MON in experimental animals were limited. In rats, MON was extensively absorbed and rapidly excreted in urine after oral administration. The authors noted, however, that the fate of at least half of the amount ingested remained unknown in the study, and tissue concentrations were not measured. The authors speculated that MON might be biotransformed and then excreted in urine in some unknown form (Jonsson et al., 2013; 2015).

219. MON showed no evidence of inducing reverse mutation in bacteria. MON was clastogenic *in vitro*, inducing chromosomal aberrations and micronuclei, however no data were identified to determine on whether this is caused by a direct or indirect mechanism. No *in vivo* genotoxicity data or carcinogenicity data were identified in the published literature.

220. Adverse acute effects in rodents included ultrastructural myocardial lesions, decreased myocardial contractile force, ventricular arrhythmia and congestive heart failure. EFSA identified one subacute study in rats, where indications of cardiotoxicity were observed at 9 mg/kg bw per day. One sub-chronic study with a limited number

of rats was identified in which cardiotoxicity and mortality were induced at 32.5 mg/kg bw per day. Data on haematotoxicity and immunotoxicity were too scarce to conclude on the hazard of MON in experimental animals. In a study in mink developmental and reproductive toxicity were observed at a dose of 1.94 mg/kg bw per day, based on significant neonatal mortality and reduced offspring body weights. Due to the limitations in the available toxicity data in animals, neither an acute nor a chronic HBGV was established by EFSA, thus an MOE approach was used in their risk assessment.

221. For acute exposure to MON, EFSA identified cardiotoxicity as the critical adverse health effect. Heart failure was observed at 15 mg/kg bw per day and indications of cardiotoxicity were seen at 9 mg/kg bw per day in a subacute study in rats. EFSA used the NOAEL of 6 mg/kg bw, identified from this study, as the reference point to calculate the MOEs for acute human exposures to MON.

222. For chronic exposure to MON, EFSA identified haematotoxicity observed in barrow pigs as the most sensitive endpoint for human hazard characterisation (suitable dose-response data in other experimental animals were absent). EFSA determined a $BMDL_{05}$ of 0.20 mg/kg bw from the dose-response data on the decrease of haematocrit and haemoglobin levels from a 28-day study in pigs. This value was used as the point of departure (POD) to calculate MOEs for chronic human exposures to MON.

223. The COT agreed with the MOE approach taken by EFSA for assessing the human health risk of MON. The MOE approach was used to assess the level of risk for UK infants and young children aged 4 to 60 months from estimated dietary exposures. For acute estimated exposures for UK infants aged 4 to 18 months, all MOEs were greater than 10,000. In respect of estimated chronic exposures for UK infants aged 4 to 12 months, the lowest MOE was 1100 which occurred at the 97.5th percentile for 9 to < 12 months old. For children aged 12 to 18 months, the lowest MOE was 650, which occurred at the 97.5th percentile for 15 to < 18 months old. For young children aged 18 to 60 months, the lowest MOE was 700, which occurred at the 97.5th percentile for 18 to 24 months old.

224. The calculated UK MOEs for both acute and chronic exposure were considered to be adequately protective for human health in infants and young children aged 0 to 5 years old. For the acute risk assessment of MON, a non-genotoxic xenobiotic, an MOE > 100 was considered to be protective. Furthermore, use of the NOAEL from a repeat-dose study in rats as the reference point in these comparisons was considered to be conservative. For chronic risk assessment, an MOE > 650 was considered to be protective. In addition to a margin of 100, a factor of up to 10 was considered necessary to ensure protection given the absence of long-term toxicity studies; however, because exposure estimates were based on non-detects, an additional factor of less than 10 was considered to be sufficiently protective.

225. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5082

3.1.10 Nivalenol (NIV)

226. Nivalenol (NIV) is a type B trichothecene produced by fusarium species under moist and cool conditions and predominantly found in cereal grains and cereal-based products.

227. Generally, trichothecenes are immunotoxic and haematotoxic/myelotoxic. Several *in vivo* studies on NIV have reported an increase of immunoglobin A (IgA) or immunoglobin M (IgM) at higher levels than those causing haematotoxic effects such as neutropenia or leukopenia. IARC concluded in 1993 that “there is inadequate evidence in experimental animals for the carcinogenicity of nivalenol” and that NIV was not classifiable as to its carcinogenicity to humans (Group 3).

228. As NIV is unlikely to be genotoxic, EFSA (2013) considered it appropriate to establish a TDI of 1.2 µg/kg bw based on a $BMDL_{05}$ of 0.35 mg/kg bw per day for haematological disturbances in white blood cell (WBC) counts observed in rats and the application of an overall UF of 300, consisting of the default UF of 100 for intra- and interspecies differences and additional UFs of 2 and 1.5 for extrapolation from sub-chronic to chronic duration and limitations in the reproductive and developmental toxicity data, respectively.

229. All mean and 97.5th percentile exposures of infants and young children aged 4 to 60 months are below the TDI of 1.2 µg/kg bw established by EFSA and therefore the exposures to NIV are not of toxicological concern.

230. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3262

3.1.11 Patulin (PAT)

231. Patulin (PAT) is a mycotoxin produced by certain species of the genera *Aspergillus* and *Penicillium*, including *A. clavatus*, *P. expansum*, P*. patulum*, *P. aspergillus* and *P. byssochlamys*. *P. expansum* is a common spoilage microorganism in apples. The major potential dietary sources of patulin are apples and apple juice made from affected fruit.

232. *In vivo* animal studies demonstrated that most of an orally administered dose was eliminated within 48 hours in faeces and urine, less than 2% being expired as carbon dioxide. No other metabolites have been identified. About 2% of the administered dose was still present in the body after 7 days. It was concluded that the major retention sites of PAT are erythrocytes and blood-rich organs (spleen, kidney, lung and liver) (Dailey et al., 1977).

233. PAT has a strong affinity for sulfhydryl groups which in turn leads to depletion of intracellular glutathione (GSH) and inhibition of enzyme activity (Puel et al., 2010). There is an associated increase in the formation of reactive oxygen species (ROS). These key events contribute to the main mode of action of PAT mediated toxicity (Barhoumi et al., 1996; Burghardt, 1992; Guo et al., 2013; Ianiri et al., 2016).

234. The oral LD_{50} values of PAT in mice and rats vary from 20 - 100 mg/kg bw and it is more toxic by the i.v. and ip routes than the oral route (Pal et al., 2017).

235. Acute administration of PAT causes haemorrhages, formation of oedema and dilation of the intestinal tract in experimental animals (McKinlet et al., 1980). In sub-chronic studies, hyperaemia of the duodenal epithelium and kidney function impairment were observed as the main effects. Additional effects in the intestine included ulceration, inflammation, distension, haemorrhage and a decrease in transepithelial resistance. PAT also causes liver inflammation (inducing a rise in alanine aminotransferase (ALT), aspartate transaminase (AST) and malondialdehyde (MDA)) and detrimental effects on other organs such as the testes and thyroid.

236. Cellular and genetic material affects include DNA strand breaks, neuronal degeneration, and degeneration of glomeruli and renal tubules. JECFA (1995) noted that patulin was genotoxic in most mammalian cell assays but was largely negative in bacterial assays. Whilst these effects might be due to its reaction with sulfhydryl groups, thus inhibiting enzymes involved in DNA replication, JECFA concluded that, based on the available data, patulin should be considered genotoxic. In the 1986 IARC report, it is stated that there was inadequate evidence for the carcinogenicity of PAT in experimental animals. These conclusions have been restated in a factsheet by the WHO (2018) which states that: “Patulin is considered to be genotoxic however a carcinogenic potential has not been demonstrated”.

237. The pivotal study used by JECFA (1995) to establish an HBGV was a combined reproductive toxicity, long-term toxicity/carcinogenicity study. Rats derived from the F1 generation showed increased mortality in both sexes at the highest dose. All males had died by 19 months and only 19% of females survived until termination at 2 years. Mortality was due to dilatation of the gut and/or pneumonia, most probably secondary to antibiotic-like effects of patulin leading to a selective growth advantage to pathogenic Gram-negative bacteria. Body weights of males were reduced at the mid and high dose, but female body weights were comparable in all groups. No difference in tumour incidence was observed. The no-observed effect level (NOEL[8]) for effects on body weight was 0.1 mg/kg bw, administered 3 times weekly, equivalent to 43 µg/kg bw per day.

238. Based on this NOEL and using an UF of 100, JECFA established a PMTDI of 0.4 µg/kg bw.

239. It is important to note that additional genotoxicity data have been published since the HBGV was established by JECFA. If the data show conclusively that PAT is genotoxic this would have an impact on the HBGV.

240. There has been no evaluation of PAT since the one carried out by JECFA. However, reviewing recent toxicological data (1995 to 2018), COT Members agreed that this information would probably not change the HBGV (excluding the genotoxicity data). The Committee concluded that the genotoxic studies were complex and suggested they be referred to The Committee on Mutagenicity of

[8] http://whqlibdoc.who.int/publications/2007/9789241209472_eng.pdf

Chemicals in Food, Consumer Products and the Environment (COM). It was noted that the ability of patulin to induce reactive oxygen species (ROS) might be relevant when looking at its genotoxicity.

241. Provisionally (draft minutes[9]) the COM concluded that the *in vitro* and *in vivo* genotoxicity studies were inadequate. There was some evidence of positive results (particularly *in vitro*, but also *in vivo*), but this was from non-standard tests with insufficient detail on how they were conducted. Therefore, the observed positive responses could not be interpreted, but were also difficult to discount. It was suggested that standard regulatory genotoxicity tests should be conducted to acceptable standards (i.e. Ames test and *in vitro* micronucleus test) and that it would also be useful to investigate whether any positive response was due to oxidative stress.

242. Based on this, the COT concluded that until further genotoxicity testing had been carried out to accepted standards and a conclusion on genotoxicity could be formed, the current PMTDI of 0.4 µg/kg bw should continue to be used in the risk assessment of PAT.

243. Mean and 97.5th percentile exposures of infants aged 0 to 12 months and young children aged 12 to 60 months are all below the PMTDI of 0.4 µg/kg bw per day, therefore, the levels of PAT measured in the food groups are not of toxicological concern for infants and young children aged 0 to 5 years old. This conclusion is contingent on resolution of the issue of the genotoxic potential of PAT.

244. The full JECFA evaluation can be found here:

https://apps.who.int/iris/bitstream/handle/10665/37246/WHO_TRS_859.pdf

3.1.12 Sterigmatocystin (STC)

245. Sterigmatocystin (STC) is produced by more than a dozen species of *Aspergillus* and a number of other phylogenetically and phenotypically different fungal genera and shares its biosynthetic pathway with that of aflatoxins. STC is generally produced in storage, rather than in the field, and has been found in grains and grain-based products, green coffee beans, spices, beer, peanuts, crispbread, rye, rice, white bread, muesli, chilli and cheese.

246. STC exhibits genotoxic effects *in vitro, in vivo* and *ex vivo* and carcinogenicity has been observed after oral, i.p., subcutaneous and/or dermal exposure.

247. EFSA (2013) evaluated the suitability of the data from available carcinogenicity bioassays in mice, rats and monkeys for dose-response modelling of the carcinogenicity of STC following its oral administration. Most studies were not considered suitable for BMD modelling due to discontinuous dosing, lack of detailed tumour reporting, high mortality and too small a number of treatment groups. The incidences of liver tumours in the study by Maekawa et al. (1979) was not considered suitable for hazard characterisation by EFSA since the study combined

[9] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/866372/COM_Meeting_200220.zip

tumours from different origins (hepatocellular carcinomas (HCC), haemangiosarcomas and 1 tumour not specified). The incidence of HCC (with only one tumour-bearing animal at the highest dose) was not suitable for dose-response modelling. However, EFSA found it appropriate to conduct BMD analysis on the incidence of haemangiosarcomas, which is a relevant endpoint, as there were zero tumour bearing animals in the control and low dose groups and one and three tumour bearing animals in the mid and high dose groups, respectively.

248. The lowest $BMDL_{10}$ value was 0.16 mg/kg bw per day, with a BMD_{10} of 0.36 mg/kg bw per day. However, EFSA noted that only 11% of the total number of tumour bearing animals had haemangiosarcomas and that the overall tumour incidence in the control group was 64%. Therefore, the BMD_{10}/$BMDL_{10}$ pair is based on a limited tumourigenicity database.

249. JECFA applied BMD analysis to the same study data set in their 2017 evaluation and used the $BMDL_{10}$ of 0.16 mg/kg bw per day as the POD in their MOE assessment.

250. EFSA was unable to apply an MOE approach in their evaluation in 2013, due to the lack of European human dietary exposure data for STC.

251. Mean and 97.5th percentile MOEs for UK infants and young children, based on the $BMDL_{10}$ of 0.16 mg/g bw per day, are all > 10,000. Therefore, the exposures are unlikely to be of toxicological concern.

252. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3254

3.1.13 Zearalenone (ZEN)

253. Zearalenone (ZEN) is produced by several fusarium species, can grow and invade crops in moist cool field conditions and post-harvest under poor storage conditions, and is commonly found in maize and also in wheat, barley, sorghum and rye.

254. IARC has classified ZEN as not classifiable as to carcinogenicity in humans (Group 3) based on the limited evidence in experimental animals. ZEN does not cause gene mutations in bacterial test systems, however it has been reported as clastogenic and aneugenic *in vitro* and clastogenic *in vivo* in the mouse.

255. EFSA (2011) concluded that oestrogenicity was the critical effect of ZEN, as the reported genotoxicity may be mediated by oxidative stress and ZEN was at most a weak carcinogen; the oestrogenic effects of ZEN are observed in pigs at doses approximately three orders of magnitude lower than doses reported to cause clastogenicity and increases in the incidence of adenomas in the liver and pituitary of mice.

256. EFSA established a TDI of 0.25 µg/kg bw based on a NOAEL of 10.4 µg/kg bw per day for oestrogenic effects in female pigs and the application of an overall UF

of 40, comprising an UF of 4 for interspecies toxicokinetics and 10 for interindividual human variability; EFSA decided not to use the UF of 2.5 for interspecies toxicodynamics as human females would not be more sensitive to the effects of oestrogen than female pigs. The margin between the $BMDL_{10}$ of 6.39 mg/kg bw per day for pituitary adenomas in male mice and the TDI of 0.25 µg/kg bw was in the region of 25,000. This exceeds the value of 10,000 considered of low concern for a genotoxic carcinogen, established by EFSA.

257. Acute toxicity of ZEN is low and EFSA did not identify any studies indicating the need for an ARfD.

258. There is little information on the absorption, bioavailability and metabolic fate of the metabolites and modified forms of ZEN and it was assumed they are as readily bioavailable as ZEN. EFSA noted that oestrogenicity is the common MoA for the toxicity of ZEN and its metabolites and therefore found it appropriate to establish a group HBGV. To account for the differences in the oestrogenic potencies *in vivo*, each modified form of ZEN was assigned a potency factor relative to ZEN, the assumption being made that the oestrogenic effects of the various modified forms are additive. EFSA confirmed the TDI of 0.25 µg/kg bw for ZEN as a group TDI for ZEN and its modified forms.

259. However, EFSA did note that the overall uncertainty associated with its assessment is high and it probably overestimates the risk of modified ZEN.

260. Mean and 97.5th percentile UK exposures of infants and young children are all below the group TDI of 0.25 µg/kg bw per day and are therefore not of toxicological concern.

261. The full EFSA evaluation can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2197

3.2 Tropane alkaloids (TAs)

262. Tropane alkaloids (TAs) are secondary plant metabolites (i.e. they are not essential for functioning of the plant), which occur naturally in several plant families, such as *Brassicaceae*, *Solanaceae* and *Erythroxylaceae*. TAs are found in all parts of the plant and are responsible for the toxic effects of those plants. The respective plant seeds have been found as impurities in linseed, soybean, millet, sunflower and buckwheat and products thereof.

263. The group of TAs comprises about 200 different compounds, the best-known representatives of which are (-)-hyoscyamine, (-)-scopolamine [(-)-hyoscine] and atropine, a racemic mix of (-)-hyoscyamine and (+)-hyoscyamine. Unlike (+)-hyoscyamine, (-)-hyoscyamine and (-)-scopolamine are formed naturally in plants. (+)-Hyoscyamine is formed by the racemisation of (-)-hyoscyamine. Plant extracts containing TAs have been and continue to be used in veterinary and human medicine, as are (-)-hyoscyamine, (-)-scopolamine and atropine. The pharmacology active moiety in atropine is (-)-hyoscyamine.

264. TAs are readily absorbed from the GI tract and distributed into tissues; excretion is predominantly via urine.

265. (-)-Hyoscyamine and (-)-scopolamine inhibit muscarinic acetylcholine receptors in the central nervous system (CNS) and the autonomic nervous system (ANS). However, they differ in the ability to affect the CNS, (-)-scopolamine having the more pronounced effect.

266. In humans, toxic effects of (-)-hyoscyamine and (-)-scopolamine include inhibition of saliva, bronchial and sweat gland secretion, dilation of pupils and paralysis of accommodation, change in heart rate, inhibition of urination, reduction in GI tone and inhibition of GI secretion. In extreme cases, toxic effects can include hallucination, delirium, coma and ultimately death. Toxic effects of other TAs are largely unknown and only very limited data on occurrence in food and feed is available.

267. EFSA (2013) performed a risk assessment on (-)-hyoscyamine and (-)-scopolamine, the TAs for which both occurrence and toxicity data were available. When atropine was reported in food and feed, EFSA used the values as if they were for (-)-hyoscyamine in their evaluation of TAs.

268. EFSA established an ARfD for the two compounds, as the pharmacological effects of (-)-hyoscyamine and (-)-scopolamine occur within a short time period after administration. EFSA assumed equivalent potency of (-)-hyoscyamine and (-)-scopolamine, due to their common MoA, albeit there is some difference on their potency in the CNS. EFSA therefore established a group ARfD based on bradycardia and CNS effects in a human volunteer study of a combination of (-)-hyoscyamine and (-)-scopolamine. An UF of 10 for interindividual differences (small study, healthy male volunteers) was applied to the overall NOAEL of 0.16 µg/kg bw per day to establish a group ARfD of 0.016 µg/kg bw (16 ng/kg bw), expressed as the sum of (-)-hyoscyamine and (-)-scopolamine, assuming equivalent potency.

269. The group ARfD is approximately two orders of magnitude lower than the lowest single therapeutic dose of (-)-hyoscyamine and (-)-scopolamine.

270. EFSA considered the ARfD to be protective against long term exposure due to the lack of bioaccumulation, genotoxicity and chronic toxicity of these TAs.

271. The European Medicines Agency (EMEA, now EMA, 1998a, 1998b) and EFSA (2008) assessed the legal use of *Atropa belladonna* and atropine as authorised veterinary medicines in farm animals in 1997 and 2008, respectively. Since atropine is used infrequently and readily absorbed and eliminated, it was not considered necessary to establish a maximum residue limit (MRL) as animals are unlikely to be sent to slaughter immediately after treatment. EMA and EFSA both concluded it was unlikely that residues of TAs in edible tissues (meat, milk, eggs) would be of risk to consumers.

272. Based on EFSA's conclusions that toddlers might significantly exceed the group ARfD through the diet and the fact that it is not always possible to distinguish between the enantiomers of hyoscyamine, a maximum level for atropine (reflecting

the occurrence of (-)-hyoscyamine)) and (-)-scopolamine of 1.0 µg/kg in cereal-based food for infants and young children was established by the European Commission (EC, 2016). The Commission noted that as the synthesis of tropane alkaloids in plants leads to (-)-hyoscyamine but not (+)-hyoscyamine, analytical results on atropine in food of plant origin reflects the occurrence of (-)-hyoscyamine.

273. Occurrence data for the exposure assessment were taken from a 2014 FSA survey (Stratton et al., 2017); samples were obtained from a wide variety of food groups and analysed for as many TAs for which reliable standards were available (24 in total). Overall, the concentrations of TAs found in the survey were low, measurable quantities of TAs were reported in only a limited number of samples. The percentage of samples with detectable levels above the LOQ e.g. in cereal-based infant food, ranged from 0% (scopine and scopoline) to 26% (tropine). The average levels reported were below the permitted maximum level of 1.0 µg/kg in cereal based food for infants and young children established by the EC.

274. Following EFSAs approach, this assessment uses and reports atropine in food as (-)-hyoscyamine and assumes that values reported as (-)-scopolamine are enantiomerically pure (-)-scopolamine. The exposure assessment focused on (-)-hyoscyamine and (-)-scopolamine separately and their sum. Consumption of commercial infant and young children foods, breakfast cereals and teas (dry product) are assumed to be highest at the age groups of interest (children aged 4 to 18 months and 18 to 60 months) and therefore cover all other food groups.

275. Little to no information is available of the transfer of TAs to breast milk; the limited information available, on atropine, (-)-hyoscyamine and (-)-scopolamine, indicate that only limited amounts of TAs are excreted into breast milk and currently do not indicate a toxicological concern.

276. No data on the concentration of TAs in infant formula are available; given the source of TAs and the assessment by the EMA and EFSA that it is unlikely for residues of TAs in milk to be of risk to the consumer, it is highly unlikely that TAs would be detected in infant formula or that levels reported would be of risk to infants.

277. In infants and young children, the UB mean and 97.5th percentile estimated dietary acute exposures to (-)-hyoscyamine and (-)-scopolamine and the sum of (-)-hyoscyamine and (-)-scopolamine were below the ARfD of 16 ng/kg bw, established by EFSA. The only exceptions are the 97.5th percentile (UB) estimated exposures to the sum of (-)-hyoscyamine and (-)-scopolamine in cereal-based infant foods and all three food categories combined, where exposures were at or close to the ARfD; however these are UB exposure estimates, reflecting detectable levels of (-)-hyoscyamine and (-)-scopolamine in only a limited number of samples with levels in the remainder assumed to be at the LOQ/LOD, rather than being based on actual measured concentrations in all samples. In addition, the ARfD is based on a human (male) volunteer study and derived from a NOAEL with the application of an UF of 10 for interindividual differences.

278. Overall, all estimated acute exposures of infants and young children to (-)-hyoscyamine and (-)-scopolamine or the sum of (-)-hyoscyamine and (-)-

scopolamine are close to or below the ARfD of 16 ng/kg bw per day. The exposures are unlikely to be of toxicological concern.

279. The COT noted that although numerous TAs have been tested for and reported in the FSA report (Stratton et al., 2017), due to the lack of toxicity data, this risk assessment focused only on (-)-hyoscyamine and (-)-scopolamine. A number of TAs of unknown potency were present at higher concentrations than (-)-hyoscyamine and (-)-scopolamine with some of these reported at quantifiable levels in up to 26% of the cereal-based samples. In the absence of any toxicological data and HBGVs on these TAs there is a high degree of uncertainty as to the risks associated with total TAs in the diet.

280. In the current absence of in-house expertise on potential structure related pharmacological effects of other TAs, the COT agreed to include TAs in an upcoming dose-response project/workshop and to revisit its current conclusions, should additional information become available that would warrant a re-assessment.

281. The COT further noted that insufficient data on the racemisation and degradation of TAs under conditions used for food preparation, as well as on the consequences of *in vivo* racemisation or potential toxicity of degradation products further add to the overall uncertainty regarding the total dietary risk.

282. The full EFSA evaluation and external scientific report can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3386

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2016.EN-1140

Conclusions

283. The COT concluded that exposure to hexachlorocyclohexanes, diacetoxyscirpenol, ergot alkaloids, moniliformin, nivalenol, sterigmatocystin, zearalenone and sweeteners (aspartame, acesulfame K, saccharine, sorbitol and xylitol, stevia and sucralose) in the diets of infants aged 0 to12 months and children aged 1 to 5 years are not of toxicological concern. For sweeteners, the COT noted furthermore that despite the lack of breastmilk data and dietary exposure information for infants aged 0 to 1 years, it would be unlikely that the HBGVs would be exceeded for this age group as sweeteners are not permitted in baby foods and solid food consumption for that age group would generally be lower than that of older children.

284. The COT concluded that exposures to fumonisins in the diets of infants aged 0 to 12 months and children aged 1 to 5 years are not of toxicological concern, possible occasional exceedances through consumption of infant formula, are unlikely to result in adverse toxicological effects. The COT noted that exposure to infant formulae is considered short when compared to a lifetime, concentrations of fumonisins in infant formula have been declining and the levels contributing to the high concentrations reported were from only one manufacturer.

285. The COT concluded that exposures to fusarenon-X in the diets of infants aged 0 to 12 months and children aged 1 to 5 years are not of toxicological concern.

However, the COT noted that there were some uncertainties involved in the extrapolation of the data. The Committee agreed that the likelihood of co-occurrence of fusarenon-x with other type B trichothecenes, deoxynivalenol and nivalenol, at the reported levels is low and that acute co-exposure was unlikely to result in adverse toxicological effects.

286. The COT concluded that exposures to cyclopiazonic acid in the diets of infants aged 0 to12 months and children aged 1 to 5 years do not pose a health concern as the margin between the NOAEL of 0.1 mg/kg bw per day and estimated UK exposures is sufficient large.

287. The COT concluded that exposures to deoxynivalenol (DON), 15-Ac-DON, 3-Ac-DON, and the sum of all three forms in the diets of infants aged 0 to12 months and children aged 1 to 5 years are unlikely to be of toxicological concern. However, the COT noted that the sum of all forms is not based on individual measured values but on summing the respective averages of the concentrations provided. Therefore, the estimated exposures could be an overestimation of the actual values.

288. The COT concluded that exposures to citrinin are not of toxicological concern for nephrotoxicity. However, it was noted that due to lack and limitations of the available data, a concern for genotoxicity and carcinogenicity cannot be excluded.

289. The COT concluded that exposures to patulin (PAT) in the diets of infants aged 0 to 12 months and children aged 1 to 5 years are not of toxicological concern, but this is contingent on resolution of the genotoxic potential of PAT. In the absence of definitive conclusions on this, the COT recommends that the current PMTDI of 0.4 µg/kg bw should continue to be used in the risk assessment of PAT.

290. Aflatoxin levels in all samples in the TDS were below their respective LOQ. However, given that aflatoxins are genotoxic and carcinogenic their presence in food is always undesirable and when exposure was estimated based on their LOQs, it was not possible to exclude a safety concern.

291. The COT concluded that the intakes of polycyclic aromatic hydrocarbons (BaP and PAH4) from human breast milk and food are of low concern for health for infants and young children aged 0 to 5 years old. Intakes from infant formula, soil and dust are not expected to contribute markedly to lifetime exposure.

292. The COT concluded that the available information indicates that the carcinogenicity of tetrabromobisphenol A is not mediated through a genotoxic mechanism. Given the absence of genotoxicity, tumours only at high doses, large MOEs, and conservatism of exposure estimates based on non-detects, a MOE of 100 was considered to be sufficiently protective for human health. Thus, the calculated MOEs for UK chronic dietary exposures were considered not to be cause for concern for infants and young children aged 0 to 5 years old.

293. Overall, all estimated acute exposures of infant and young children to (-)-hyoscyamine and (-)-scopolamine or the sum of (-)-hyoscyamine and (-)-scopolamine are unlikely to be of toxicological concern. However, the Committee noted that a number of other tropane alkaloids of unknown potency were present at

higher concentrations than (-)-hyoscyamine and (-)-scopolamine, with some of these reported at detectable levels in up to 26% of the cereal-based samples. In the absence of any toxicological data and HBGVs on these TAs there is a high degree of uncertainty to the risks associated with total TAs in the diet.

294. Given the limited UK-specific occurrence data, the COT assessed 3-MCPD, its fatty acid esters and glycidol based on the latest EFSA evaluation. Overall, the Committee agreed with EFSA's evaluation and that some of EFSA's MOE values for glycidol and exceedances of the TDI for 3-MPCD are of potential concern. However, as concluded by EFSA, the impacts of the uncertainties in these risk assessments for glycidol and 3-MCPD are high, for example uncertainty in the reference point used as a basis for the calculation of the MOE values for glycidol, and the long-term effects of 3-MCPD on the male reproductive system, as well as in the occurrence data.

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Abbreviations

ABS	Acrylonitrile butadiene styrene
Ace K	Acesulfame K
ACF	EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
ADI	Acceptable daily intake
AFB1	Aflatoxin B1
AFB2	Aflatoxin B2
AFG1	Aflatoxin G1
AFM1	Aflatoxin M1
AhR	Aryl hydrocarbon receptor
ALT	Alanine aminotransferase
ANS	Autonomic nervous system
ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
ARfD	Acute reference dose
AST	Aspartate transaminase
ATSDR	Agency for Toxic Substances and Disease Registry
BaA	Benz[a]anthracene
BaP	Benzo[a]pyrene
BbF	Benzo[b]fluoranthene
BFR	Chrysene
BMD(L)	Benchmark dose modelling
CCK	Cholecystokinin
ChR	Chrysene
CNS	Central nervous system
COC	Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
COM	Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

CPA	Cyclopiazonic acid
CYP	Cytochrome
DAS	4,15 Diacetoxyscirpenol
1,6-DCF	1,6-dichloro-1,6-dideoxyfructose
DEFRA	Department of Environment, Food and Rural Affairs
DH	Department of Health
DKP	5-benzyl-3,6-dioxo-2-piperazine acetic acid
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
DON	Deoxynivalenol
3-Ac-DON	3-acetyldeoxynivalenol
15-Ac-DON	15-acetyldeoxinivalenol
EA	Ergot alkaloids
EC	European Commission
EFSA	European Food Safety Authority
EMA	European Medicine Agency
EMV	Expert Group on Vitamins and Minerals
ERF	European Ramazzini Foundation
EU	European Union
FSA	Food Standards Agency
GI	Gastrointestinal
GSH	Glutathione
HBGVs	Health based guidance values
HBV	hepatitis B virus
HCC	Hepatocellular carcinomas
HCH	Hexachlorocyclohexane
IARC	International Agency Research on Cancer
ICH	European Medicines Agency and International Council for the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA	Immunoglobin A
IgM	Immunoglobin B

INFID	Irish National Food Ingredient Database v4
ip	intraperitoneal
IPCS	International Programme on Chemical Safety
iv	intravenous
JECFA	Joint FAO/WHO Committee on Food Additives
LB	Lower bound
LD_{50}	Mean lethal dose
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues
LOAEL	Lowest observed adverse effect level
LOD	Limit of detection
LOQ	Limit of quantification
MCPD	Monochloropropanediol
MDA	malondialdehyde
MoA	Mode of action
MOE	Margin of exposure
MRLs	Maximum residue levels
NBC	Normal Background Concentration
NDNS	National Diet and Nutrition Survey
NIV	Nivalenol
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NPNS	National Pre-School Nutrition Survey
NTP	National Toxicology Program
PAHs	Polycyclic aromatic hydrocarbons
PAT	Patulin
PeCB	Pentachlorobenzene
PKU	Phenylketonuria
PMTDI	Provisional maximum tolerable daily intake
POD	Point of departure

POPs	Persistent organic pollutants
RIVM	National Institute for Public Health and the Environment
RMR	Red mould rice
ROS	Reactive oxygen species
SACN	Scientific Advisory Committee on Nutrition
SCF	Scientific Committee on Food
STC	Sterigmatocystin
TBBPA	Tetrabromobisphenol
TDI	Tolerable daily intake
TDS	Total Dietary Study
TEF	Toxic equivalent factor
UB	Upper bound
UF	Uncertainty factor
UL	Upper level/limit
WBC	White blood cells
WHO	World Health Organisation
ZEN	Zearalenone

ANNEX A

1. Table 1 lists all chemicals reviewed by the COT in support of SACN and the Government recommendations on complementary and young child feeding.

2. Links to the full discussion papers presented to the COT are provided, where applicable; the discussion papers provide the background for the majority of chemicals discussed in the Overarching Statement and this Addendum. Note that these do not necessarily reflect the final views of the Committee. In addition, all other chemicals for which full reviews were requested by the COT are provided, links to the published Statements are included, where applicable.

3. Alcohol, caffeine, food additives, legacy chemicals (including endosulfan, pentachlorobenzene (PeCB) and chlordecone) and trans fatty acids were not subject to discussion papers as they were either outside the remit of the COT, consumption data were not applicable to the age groups assessed or the COT did not consider it necessary to change its existing advice to government in the absence of any new data. Soya phytoestrogens are currently undergoing a separate review[10], with emphasis on soya drink consumption in children aged 6 months to 5 years.

4. The Overarching Statement and accompanying lay summary can be found here:

https://cot.food.gov.uk/committee/committee-on-toxicity/cotstatements/cotstatementsyrs/cot-statements-2019/cot-overarching-statement

Table 1 List of all chemicals presented to the COT, including links to the respective COT discussion papers and Statements, where applicable.

Chemicals discussed in the Overarching Statement	
Chlorate	https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf
Chromium	https://cot.food.gov.uk/sites/default/files/tox2018-32.pdf
Furan	https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf
Perchlorate	https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf
Selenium	https://cot.food.gov.uk/sites/default/files/tox2018-28.pdf
Vitamin A	https://cot.food.gov.uk/sites/default/files/statementaddendumvitamina.pdf
Zinc	https://cot.food.gov.uk/sites/default/files/tox2018-28.pdf
Chemicals discussed in the Addendum	
Hexachlorocyclohexane	https://cot.food.gov.uk/sites/default/files/tox01969hch.pdf https://cot.food.gov.uk/sites/default/files/cot/cotstatmhchs.pdf
Monochloropropane diol	https://cot.food.gov.uk/sites/default/files/tox201920mcpd_0.pdf
MYCOTOXINS	https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf
Aflatoxins	https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf
Citrinin	https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf

[10] https://cot.food.gov.uk/sites/default/files/tox201971discussionpaperonsoyadrink.pdf

Cyclopiazonic acid	https://cot.food.gov.uk/sites/default/files/tox201964cpainthedietofinfantsand15.pdf
Deoxynivalenol	https://cot.food.gov.uk/sites/default/files/tox20196805donadditionalinformation.pdf
4,15-Diacetoxyscirpenol	https://cot.food.gov.uk/sites/default/files/tox2018-51.pdf
Ergot alkaloids	https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf
Fumonisins	https://cot.food.gov.uk/sites/default/files/tox2019-02_0.pdf https://cot.food.gov.uk/sites/default/files/tox2019-28.pdf https://cot.food.gov.uk/sites/default/files/tox201940fumonisins.pdf
Fusarenon-x	https://cot.food.gov.uk/sites/default/files/tox2019-17.pdf https://cot.food.gov.uk/sites/default/files/tox2019-33.pdf
Moniliformin	https://cot.food.gov.uk/sites/default/files/tox2019-03.pdf
Nivalenol	https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf
Patulin	https://cot.food.gov.uk/sites/default/files/tox2019-19.pdf
Sterigmatocystin	https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf
Zearalenone	https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf
Polycyclic Aromatic Hydrocarbons	https://cot.food.gov.uk/sites/default/files/tox2019-21.pdf
Sweeteners • Aspertame • Acesulfame K • Saccharine • Sorbitol • Sucralose • Stevia • Xylitol	https://cot.food.gov.uk/sites/default/files/tox2019-36.pdf https://cot.food.gov.uk/sites/default/files/tox201943steviolexposuresforchildrenaged.pdf
Tetrabromobisphenol	https://cot.food.gov.uk/sites/default/files/tox2019-04.pdf
Tropane alkaloids	https://cot.food.gov.uk/sites/default/files/tox2019-22.pdf https://cot.food.gov.uk/sites/default/files/tox201941taadditionalinformation.pdf
Chemicals which underwent a separate full review	
Acrylamide	https://cot.food.gov.uk/sites/default/files/finalacrylamidestatement.pdf
Aluminium	https://cot.food.gov.uk/sites/default/files/finalaluminiumaddendum_0.pdf
Arsenic	https://cot.food.gov.uk/sites/default/files/finalstatementonarsenic_0.pdf
Bisphenol A	EFSA opinion still to be published
Copper	https://cot.food.gov.uk/sites/default/files/cotstatementoncopper.pdf
Cadmium	https://cot.food.gov.uk/sites/default/files/cotstatementoncadmium.pdf
Dioxins and dioxin-like compounds	EFSA opinion https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5333
Hexabromocyclododecane	https://cot.food.gov.uk/sites/default/files/finaladdendumonhbcdds.pdf
Iodine	https://cot.food.gov.uk/sites/default/files/statementiodine0to5.pdf
Lead	https://cot.food.gov.uk/sites/default/files/finaladdendumonlead.pdf
Manganese	https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2018/statement-on-the-health-effects-of-manganese-in-the-diets-of-infants-aged-0-12-months-and-children-aged-1-5-years
Methylmercury	https://cot.food.gov.uk/sites/default/files/cotstatementonmethylmercury.pdf
Nickel	https://cot.food.gov.uk/sites/default/files/statementonpotentialrisksofnickel.pdf
Ochratoxin A	https://cot.food.gov.uk/sites/default/files/cotstatement-ota.pdf

Perfluorooctanesulfonic acid and Perfluorooctanoic acid	EFSA opinion https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5194 PFAS opinion for public consultation http://www.efsa.europa.eu/en/consultations/call/public-consultation-draft-scientific-opinion-risks-human-health
Phthalates	EFSA opinion http://www.efsa.europa.eu/sites/default/files/consultation/consultation/Phthalates_in_plastic_FCM_draft_opinion_for_public_consultation.pdf
Polybrominated biphenyls	https://cot.food.gov.uk/sites/default/files/cotfinalminutes08dec15.pdf
Polybrominated diphenyl ethers	https://cot.food.gov.uk/sites/default/files/statementpbdes.pdf
T-2 toxin, HT-2 toxin and neosolaniol	https://cot.food.gov.uk/sites/default/files/cotstatement-t2ht2andneosolaniol.pdf