

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

### **Draft 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**

#### **Introduction**

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.
2. The COT identified a number of chemicals in 2015, which might pose a risk to infants and young children and for which advice might be needed. In 2019, the COT published an Overarching Statement, reviewing a number of chemicals.
3. The following Addendum to the Overarching Statement discusses the conclusions of the COT regarding the remaining chemicals. A full list of all chemicals identified by the Committees, with the respective links to the discussion papers or Statements, where applicable, are listed in Table 1 in Annex A of the Addendum.
4. Hexachlorocyclohexanes (HCHs) and Deoxynivalenol (DON) and their acetylated and modified forms are the only chemicals that have not been finalised by the COT, prior to the presentation of the Addendum. Additional information and clarification on the discussion papers were requested by Members for both chemicals. This information will be discussed at this meeting prior to the discussion of the Addendum.
5. Therefore, in the interest of time, draft text for both, HCHs and DON have pre-emptively been included in the Addendum. Any discussions of HCHs and DON and any points/information/uncertainties the Committee would like to emphasise, will be added to the final version, should Members still be content with HCH and DON being included in the Addendum.
6. The Committee is asked to keep in mind, that all information provided in this paper, with the exception of HCH and DON, has previously been reviewed and agreed by the Committee. The Members comments are primarily sought on the text regarding its accurate reflecting of the discussions/uncertainties and main points of the discussion papers.

At this meeting, the Committee are invited to comment on the Addendum to the Overarching Statement and to consider the following questions:

- i) Do the Committee agree with the summaries if the individual chemicals?

This is a draft statement and has not been finalised. Therefore, it should not be cited.

- ii) Do the Committee agree to include HCH and DON (and their acetylated/modified form) in the Addendum and would the Members like to emphasis any points discussed prior?
- iii) Do the Committee agree with the overall conclusions of the overarching statement?
- iv) Do the Committee have any other comments?

**Secretariat**

**December 2019**

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

### Draft 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

#### Background

1. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risk of toxicity of chemicals in the diets of infants and young children aged 0-5 years, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to five years of age.
2. SACN is examining the nutritional basis of the advice and has asked that evidence on possible adverse effects of the diet should be considered by other advisory committees with relevant expertise.
3. The COT identified a number of chemicals in 2015<sup>1</sup>, which might pose a risk to young children and for which advice might be needed. In 2019, the COT published an Overarching Statement<sup>2</sup>, reviewing a number of chemicals. The following 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 are being discussed elsewhere. A full list of all chemicals identified by the Committees, with the respective links to the discussion papers or Statements, where applicable, are listed in Table 1 in Annex A.
5. The following reviews provide a brief overview of the chemicals characteristics yet focus mainly on the exposure assessment (where applicable) and the risk characterisation and conclusions, for both infants and young children.

#### General information

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

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

<sup>2</sup> [https://cot.food.gov.uk/sites/default/files/cotoverarchingstatement\\_0.pdf](https://cot.food.gov.uk/sites/default/files/cotoverarchingstatement_0.pdf)

(SCF), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) the World Health Organisation (WHO) 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 assessment and risk characterisation have been drawn from EFSA opinions, with emphasis on UK data.

8. Consumption data (on a body weight basis) for the estimated dietary exposure 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 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.

## Assessment

### *Hexachlorocyclohexane (HCH)*

10. Hexachlorocyclohexane ( $\alpha$ -,  $\beta$ -, and  $\gamma$ -HCH), are listed for elimination in Annex A of the Stockholm convention on Persistent Organic Pollutants<sup>3</sup>. Due to their lipophilic properties and persistence in the environment,  $\beta$ -HCH, and to a lesser extent,  $\alpha$ -HCH and  $\gamma$ -HCH, bioaccumulate and biomagnify in the food chain. HCHs are distributed globally, with transfer from warmer to colder regions through evaporation and condensation.

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

12. Animal studies have reported neurotoxicity in all HCHs (JMPR, 2002; ATSDR, 2005; WHO-IPCS, 1992), with there being inconclusive evidence of Parkinson's disease being related to  $\beta$ -HCH exposure in human studies (Weisskopf et al., 2010; Richardson et al., 2009, 2011; Petersen et al., 2008). Hepatotoxicity from  $\alpha$ -HCH and  $\beta$ -HCH has been demonstrated *in vivo* (Kuiper et al., 1985; EFSA, 2005; EFSA, 2012), although evidence of hepatotoxicity in humans is lacking. Renal toxicity has only been

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<sup>3</sup> <http://chm.pops.int/TheConvention/Overview/TextoftheConvention/tabid/2232/Default.aspx>

reported for  $\gamma$ -HCH (JMPR, 2002), but the mode of action (MoA) is considered irrelevant to humans (COT, 2014). Other evidence reported from animal studies include immunological toxicity (Meera et al., 1992; Wing, 2000) and immunosuppression (Kuiper et al., 1985) from  $\gamma$ -HCH and  $\alpha$ -HCH exposure, respectively. In addition to reproductive toxicity such as infertility, effects in the thymus, testes and ovaries from  $\beta$ -HCH is evident (Van Velsen et al., 1986). There is inconsistent evidence for the endocrine disrupting potential (endometriosis) of  $\beta$ -HCH (Upson et al., 2013; Buck Louis et al., 2012; Lebel et al., 1998). Additionally, evidence of reproductive effects of  $\gamma$ -HCH is inconsistent (ATSDR, 2005) and limited with regards to  $\alpha$ -HCH.

13.  $\gamma$ -HCH, which has been classified as “carcinogenic to humans” (IARC, Group 1). The mechanism by which  $\beta$ -HCH causes liver tumours in rodents was considered irrelevant to humans by the COT (2014). The Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2002) regarded  $\gamma$ -HCH as non-genotoxic and the COT (2014) concluded  $\gamma$ -HCH to be non-mutagenic and  $\alpha$ -HCH to be non-genotoxic.

14. All exposures to  $\gamma$ -HCH in breast milk were below the tolerable daily intake (TDI) of 0.04  $\mu\text{g}/\text{kg}$ , except for infants aged 0 to 4 months at high levels of consumption containing  $\gamma$ -HCH at the maximum reported concentration of 0.27  $\mu\text{g}/\text{kg}$  milk, exceeded the TDI by 1.4-fold. Exposures to  $\gamma$ -HCH in infant formula and infant food were 5 and 10-fold the TDI of 0.04  $\mu\text{g}/\text{kg}$ , respectively, for infants aged 0 to 12 months. This is likely to be an overestimation due to the limited sensitivity of the methods and actual exposures are likely lower. For children aged 1 to 5 years, there is no toxicological concern of  $\gamma$ -HCH in infant formula and complementary food.

15. For exposures to  $\alpha$ - and  $\beta$ -HCH in breast milk, infant formula and infant food the COT agreed that a margin of exposure (MOE) approach would be more appropriate, as the toxicity of  $\alpha$ - and  $\beta$ -HCH are not well characterised, and there is insufficient data to propose a TDI.

16. In 2014, the COT concluded that none of the exposures to  $\alpha$ - and  $\beta$ -HCH to infants aged 0 to 12 months were of toxicological concern. For children aged 1 to 5 years (2019), exposure to  $\alpha$ - and  $\beta$ -HCH were also of no concern. MOEs calculated for  $\beta$ -HCH in breast milk were  $> 2,500$  at mean and high-level consumption. As for  $\alpha$ -HCH, MOEs were not calculable as it was undetected in breast milk samples analysed by Woolridge et al. (2004).

17. Application of the MOE approach took into account uncertainties in the no observed adverse effect level (NOAEL) and low observed adverse effect level (LOAEL), the use of a worst-case exposure estimation for  $\alpha$ -HCH and the unusual distribution of  $\beta$ -HCH in breast milk samples reported by Kalantzi et al. (2004). In addition, the exposure values were based on breast milk samples from 15 years ago which is likely to be an overestimation of true exposures and thus underestimation of the true MOEs.

18. Further to this, the COT has previously assumed that levels of HCHs are declining. Kalantzi et al. (2004) showed levels of  $\gamma$ -HCH in UK breast milk samples to be lower in 2004 than they were in 2000, the year it was banned. As for  $\alpha$ -HCH the last analysis of UK breast milk samples by Woolridge et al. (2004) showed  $\alpha$ -HCH to

be undetected, and data showing a temporal decline of  $\beta$ -HCH in breast milk is presented in the 2014 COT statement.

19. Overall, the COT concluded that exposure to HCHs in the diets of infants aged 0 to 12 months and children aged 1 to 5 years are not of toxicological concern.

20. The full EFSA and COT evaluation 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>

#### *Monochloropropanediol (MCPD)*

21. 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.

22. 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.

23. 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 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  $\mu\text{g}/\text{kg}$  bw per day was established based on a LOAEL of 1.1 mg/kg bw per day for renal tubular hyperplasia. An uncertainty factor (UF) of 500 was used to account for the absence of a clear NOAEL and inadequacies in the reproductive toxicity studies.

24. In March 2016, EFSA selected a BMDL<sub>10</sub> value for 3-MCPD of 0.077 mg/kg bw per day for induction of renal tubular hyperplasia in male rats. The Panel derived a TDI of 0.8  $\mu\text{g}/\text{kg}$  bw per day through the application of an UF of 100. In November 2016, JECFA calculated a BMDL<sub>10</sub> of 0.87 mg/kg bw per day using the same data and software (Benchmark Dose (BMD) Software 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  $\mu\text{g}/\text{kg}$  bw per day was recommended.

25. Due to this scientific divergence in the establishment of the BMDL<sub>10</sub> 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 key effect, though a new BMDL<sub>10</sub> 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<sub>10</sub> value, a new



group TDI of 2 µg/kg bw per day for 3-MCPD and its fatty acid esters was established by applying an UF of 100 to account for intraspecies and interspecies differences.

26. 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, 2005). The T25 value is the chronic dose rate in mg/kg bw per day, which will give 25% of the animal tumours at a specific tissue site, after specific 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.

27. 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 UK data alone is likely to underestimate actual exposure. Subsequently, the following dietary exposure assessment was taken from EFSA.

28. EFSA's chronic dietary exposures were calculated for 2- and 3-MCPD and glycidol and were assessed as mean and high (95<sup>th</sup> 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) was 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 95<sup>th</sup> percentile occurrence value was calculated to be 19.1 µg/kg, leading to an exposure estimate of 3.2 µg/kg bw per day.

29. 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 95<sup>th</sup> 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 95<sup>th</sup> 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 (95<sup>th</sup> percentile occurrence value) of the TDI.

30. 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 95<sup>th</sup> percentile occurrence data resulted in a daily intake 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 95<sup>th</sup> percentile was 28.57 µg/kg, leading to an exposure estimate of 4.9 µg/kg bw per day.

31. In view of the genotoxic and carcinogenic potential of glycidol, a 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 2.5 times higher than an MOE based upon BMDL<sub>10</sub> data, i.e. 25,000 (Dybing et al., 2008). Based on this consideration, EFSA concluded that an MOE of 25,000 or larger would be of low health concern.

32. MOE estimates for the mean dietary exposures were 12,800 to 34,000 (infants), 11,300 to 5,500 (toddlers), and 11,300 to 34,000 (other children). MOE estimates for the 95<sup>th</sup> percentile dietary exposures were 4,900 to 8,500 (infants), 4,900 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 for the mean occurrence value and 2,100 for the 95<sup>th</sup> percentile occurrence value.

33. 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<sub>10</sub>, 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.

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

35. 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 concern.

36. 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>

*Polycyclic Aromatic Hydrocarbons (PAHs)*



37. Polycyclic aromatic hydrocarbons (PAHs) are organic combustion products found in vehicle exhaust, industrial processes emissions and in the diet 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.

38. EFSA (2008) 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 MoA 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.

39. The magnitude 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).

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

41. 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 that the PAHs are the causative agents of these effects (Kim et al., 2013).

42. 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<sup>4</sup>) has classified BaP as Group 1 (carcinogenic to humans, 2012), and BaA, BbF and ChR as Group 2B (possible human carcinogens, 2010).

43. EFSA derived BMDL<sub>10</sub> 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.

44. No breastmilk data for the UK were available. Using the data by Santonicola et al. (2017), which gave the highest European values for BaP (0.81 µg/kg fat) and PAH4

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<sup>4</sup> <https://monographs.iarc.fr/wp-content/uploads/2018/09/ClassificationsAlphaOrder.pdf>

(2.77 µg/kg fat), all MOEs were > 10,000, indicating that they were unlikely to be of concern.

45. Using the data on BaP in infant formula from the FSA 2003/04 survey, the MOEs for average consumption were > 10,000 and thus unlikely to be a health concern. The MOEs for BaP in the high-level consumers and all intakes of PAH4 are < 10,000. The European Medicines Agency and International Council for the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH<sup>5</sup>) 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 set as levels of low concern for health. The MOE values of < 10,000 in this assessment cover only a short period of life and are therefore unlikely to contribute significantly to the overall risk.

46. All MOEs for food are > 10,000, and thus are of low concern for health, except for the upper bound (UB) 97.5<sup>th</sup> 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

47. Younger, less mobile infants are likely to consume less soil than older children, whom are assumed to ingest 30 to 50 mg per day, (US EPA, 2011). For Principal Domain (non-urban) soils, the median (0.037 mg/kg) and the Normal Background Concentration (NBC, the upper 95% confidence level of the 95<sup>th</sup> percentile measurement, 0.5 mg/kg), give MOEs > 10,000. For the 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.

48. A Department of Environment, Food & Rural Affairs (DEFRA) map<sup>6</sup> of the BaP in UK air shows that the country in 2017 was mostly exposed to < 0.1 ng BaP/m<sup>3</sup>, with urban areas reaching 0.2 - 0.4 ng BaP/m<sup>3</sup>, although near Port Talbot, > 1.0 ng BaP/m<sup>3</sup> 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<sup>3</sup>, giving a MOE of 93,000, so exposure from air is not of concern.

49. 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 PAH. UK infants (6 to 12 months) and young children (1 to 5 years) were assumed to ingest 30 or 60 mg 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.

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<sup>5</sup> [https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-guideline-limits-genotoxic-impurities\\_en.pdf](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](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_31Mar2017.pdf)

<sup>6</sup> <https://uk-air.defra.gov.uk/data/gis-mapping>

50. 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.

51. The full EFSA evaluation can be found here:

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

#### *Tetrabromobisphenol A (TBBPA)*

52. Tetrabromobisphenol (TBBPA) is a brominated flame retardant (BFR) which is incorporated into various consumer and commercial products to improve fire resistance. TBBPA is 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.

53. 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.

54. 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 indicating enterohepatic circulation. The primary route of elimination following <sup>14</sup>C-TBBPA administration was in faeces. The plasma half-life in rats was estimated to be 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.

55. Based on the European Union (EU) draft risk assessment (ECB, 2006), the COT issued a statement on the available toxicological data of 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 deriving 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.

56. 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 are 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 derivation 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 a MOE approach and used a BMDL<sub>10</sub> of 16 mg/kg bw per day for a decrease in circulating thyroxine in female Wistar rats as the reference point.

57. The NTP published a technical report on the 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).

58. 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<sub>10</sub> of 16 mg/kg bw per day. All MOEs are greater than 1,000,000.

59. The COT concluded that the available scientific data indicates 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, 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. The Committee agreed to use the COT TDI of 1 mg/ kg bw per day for future risk assessments.

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

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

### Sweeteners

61. 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".

62. 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).

63. 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).

## Aspartame

64. Aspartame (E 951) is a dipeptide of L-phenylalanine methyl ester and L-aspartic acid bearing an amino group at the  $\alpha$ -position from the carbon of the peptide bond ( $\alpha$ -aspartame). Aspartame is a sweetener authorised as a food additive in the EU. In previous evaluations by JECFA (1980) and the SCF (1985) an ADI of 40 mg/kg bw per day was set. This has been reconfirmed in a number of occasions (JECFA 1981; SCF 1989; 2002). More recently, in 2013 EFSA have re-evaluated the safety of aspartame as a food additive and concluded that the ADI of 40 mg/kg bw per day 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.

65. 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, only subjects heterozygous for phenylketonuria (PKU) showed a somewhat reduced capacity to metabolise the phenylalanine moiety of the aspartame molecule.

66. 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  $\beta$ -aspartame, which also may be present in the sweetener as an impurity.

67. 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), the ANS Panel and the Committee on Carcinogenicity (COC). In particular, the high background incidence observed in a number of vital organs and tissues of the animals was highlighted. Additionally, the interpretation of some of the results was brought to 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 process and the reviewers did not confirm the malignant observations reported by ERF. In agreement with the EFSA concerns on the methodology, the COC in 2006 and in light of the study design limitations and the use of animals with high infection rates, concluded that no valid conclusions could be derived from the 2006 Soffritti study. The ANS Panel considered that these would also apply to the subsequent studies by Soffritti et al. that were also 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 incidents 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.

68. 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  $\mu$ M were also taken into consideration for the risk assessment.

69. The ANS Panel modelled the plasma phenylalanine levels in humans following aspartame administration. The Panel made a number of decisions 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/meal (toddlers), 18.1 - 34.2 mg/kg bw/meal (children). The highest concentration reported in children, which corresponds to 120  $\mu$ M as calculated by the dose-response output, was subtracted from the clinical guideline of 360  $\mu$ M resulting in a maximum safe plasma concentration of 240  $\mu$ M of aspartame.

70. Based on the model, a plasma phenylalanine concentration of 240  $\mu$ M 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 a sensitive sub-population (PKU patients) no further UF were applied for inter-individual variability.

71. 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.

72. 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 95<sup>th</sup> 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. 95<sup>th</sup> 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.

73. 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 intakes were 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.

74. 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.

75. 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 95<sup>th</sup> percentile exposures ranged from 2.3 - 18.0 mg/kg bw per day for Scenarios 4 and 1, respectively.

76. The COT agreed that the ADI of 40 mg/kg bw per day 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.

77. Overall, the COT concluded that there is no risk to health based on the information presented from the exposure to aspartame in children aged 0 to 5 years old.

78. The full EFSA opinion can be found here:

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

## Acesulfame K (AceK)

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

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

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

82. Initially, JECFA evaluated the safety of AceK in 1983. An ADI of 0 - 9 mg/kg bw per day was allocated based on a two-year study in dogs. The SCF established the same ADI based on the same study in 1985. In the JECFA re-evaluation in 1991, the ADI was raised to 0 - 15 mg/kg bw per day, based on a two-year carcinogenicity study in rats that was considered more representative of lifetime exposure given the lifespan of rats versus that of dogs and the fact that absorption, distribution, metabolism and excretion (ADME) data showed that AceK does not get metabolised.

83. 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.

84. 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 set at the highest dose tested (900 mg/kg bw per day and 1500 mg/kg bw per day, respectively). Taking into account toxicokinetic data, where systemic exposure has been shown to be higher in dogs than in rats, it could be assumed that systemic exposure was higher in dogs than in rats. Furthermore, they noted that there was limited evidence on the 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 per day. In 2016, EFSA received a proposal for the extension of use of AceK in foods for special medical purposes in young children (1 to 3 years). The Panel "considered that the available toxicological assessments of acesulfame K by the SCF establishing an ADI would remain valid".

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

86. 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.

87. Based on the information presented there was no concern for exposure to AceK in the diet for infants and young children.

88. The full EFSA opinion can be found here:

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

## Saccharin

89. 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.

90. The ADI of Saccharin was set at 5 mg/kg bw per day in 1993 by JECFA and in 1995 by the SCF. The SCF maintained the temporary ADI of 0 - 2.5 mg/kg bw per day established in 1977 until 1995, where the safety of saccharin was re-evaluated in light of new data. The Committee established an ADI of 0 - 5 mg/kg bw per day, expressed as 0 - 3.8 mg.kg bw per day free acid.

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

92. Based on information in a number of species including humans, rats, guinea-pigs, rabbits and monkeys, saccharin does not get metabolised. 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 form absorption rate. Following a single oral dose to adult rats, saccharin was found to be 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).

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

94. Saccharin was not found to be 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 the 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.

95. 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 equally 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 set as the NOAEL based on the lack of relevant treatment related findings at this level. An UF of 100 was applied to derive the ADI of 5 mg/kg bw per day.

96. 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.

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

98. 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.

99. Based on the information provided the COT concluded that there was no concern from exposure to saccharin in the diet for infants and young children.

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

## Sorbitol and Xylitol

101. 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).

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

103. Both sorbitol and xylitol have been allocated an ADI "not specified" following review of the available 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. At the time of the evaluation, it was concluded that consumption of up to 20 g of polyols per day would be unlikely to cause any undesirable symptoms (SCF, 1985). They noted that for both xylitol and sorbitol intake of doses  $\geq$  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).

104. Information on aggregate polyol intakes from all sources could not be located, neither 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.

105. Mean intakes were 1.3 g/meal for children aged 1 to 2 years and 1.6 g/meal for children aged 3 to 9 years old. The respective 95<sup>th</sup> percentile exposures were 3.6 g/meal and 4.7 g/meal.

106. 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, however, they are transient and not severely detrimental to human health.

107. Overall, the COT concluded that based on the information presented there was no concern from exposure to sorbitol and xylitol in the diet for infants and young children.

108. The full EFSA opinion can be found here:

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

#### Steviol Glycosides (Stevia)

109. Stevia is a relatively new 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).



110. 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.

111. JECFA have evaluated the safety of steviol glycosides multiple times, most recent in 2016. Initially a temporary ADI of 0 - 2 mg/kg bw per day was established based on a NOAEL of 2.5% in the diet, equal to 383 mg/kg bw per day expressed as steviol in a two-year study in rats and an application of an UF of 200. The additional UF of 2 was due to the need for more information on the pharmacological effects of steviol glycosides in humans. In 2008, the ADI of 0 - 4 mg/kg bw per day expressed as steviol was established and it was confirmed in 2016. New 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. The additional UF of 2 was therefore removed.

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

113. EFSA concluded that overall, stevioside and rebaudioside A did not show genotoxic potential *in vitro* or *in vivo*. Regarding carcinogenicity, based on the available data there was no indication for carcinogenic potential for 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, equivalent to 388 mg/kg bw per day of steviol glycosides) based on a lower survival rate at the highest dose (5%) compared to controls, reduced absolute kidney weights, absolute statistically significantly decreased left ovary weights, and relative brain weights were statistically significantly increased in the 5% group females compared to controls. No statistically significant neoplastic changes were reported, and EFSA noted that the tumours reported were typical of the species.

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

115. 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 calculated 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 97.5<sup>th</sup> 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 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 97.5<sup>th</sup> 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 only permitted for use 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.

116. 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.

117. Overall, the COT concluded that based on the information presented there was no concern for exposure to steviols in the diet for infants and young children.

118. 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>

## Sucralose

119. 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.

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

121. 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 for rat, man, rabbit and dog, respectively.

122. Following their first evaluation of sucralose, JECFA (1989) established a temporary ADI of 0 - 3.5 mg/kg bw per day based on a NOAEL of 750 mg/kg bw per day from a one-year dog study and an UF of 200. Further data on human metabolism, chronic toxicity and information on developmental effects as well as considerations of safety for diabetic populations were requested at the time. In 1991 and following the evaluation of newly submitted data an ADI of 0 - 15 mg/kg bw per day was set, based on a NOAEL (1500 mg/kg bw per day) 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 also recommended additional studies on immunotoxicity to assess the significance of weight changes seen in the spleen and thymus and investigate changes in lymphocyte

counts to address potential causality to 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. These recommendations were in line with the conclusions of the SCF evaluation of 1989. Additionally, the SCF 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.

123. In 2000, the SCF re-evaluated the safety of sucralose. Addressing the concerns for immunotoxicity, the Committee established 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 sensitivity of the species to high concentrations of poorly absorbed substances (sucralose absorption in rabbit was shown to be about 20%) and they were unlikely to occur in other species, including humans.

124. The SCF considered the body weight reduction seen even at low doses in rats to be the main effect for establishing an ADI. They determined that in feeding studies the reduction in body weight gain was not dose related and was attributable to the non palatability of sucralose containing diets. Based on a 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 set.

125. 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 discuss further.

126. 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.

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

128. Overall, the COT concluded that on the basis of the current 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.

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

[http://aei.pitt.edu/40830/1/21st\\_food.pdf](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](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>

### *Mycotoxins*

130. 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.

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

132. The following exposure assessments 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.

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

133. Aflatoxins are primarily produced 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.

134. 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 generally considered to occur mainly from imported materials. It is currently uncertain whether future changes in climate in the EU would lead to increased aflatoxin contamination.

135. Most of the available toxicological data relate to AFB1. Studies have consistently shown AFB1 to be 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 aflatoxin B2 (AFB2) and inadequate evidence for aflatoxin G2 (AFG2). The relative potency of aflatoxin congeners is available from bacterial mutagenicity and hepatocarcinogenic effects in the rainbow trout and rats, in the order of AFB1 > (AFG1, AFM1) >> (AFB2, AFG2).

136. 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 carcinogenic to humans (Group 1), with a role in aetiology of liver cancer, notably among subjects who are carriers of hepatitis B virus (HBV) surface antigens.

137. EFSA (2007) did not consider it appropriate to establish a HBGV since aflatoxins are both genotoxic and carcinogenic and therefore applied the MOE approach in their risk assessment. However, EFSA noted, that the available data would only be sufficient for AFB<sub>1</sub>, yet AFG<sub>1</sub> and AFB<sub>2</sub> were also shown to be carcinogenic in rodents, albeit at lower potency than AFB<sub>1</sub>. Therefore, as a conservative approach EFSA assumed the carcinogenic potency of “total aflatoxin” to be similar to AFB<sub>1</sub>. EFSA proposed a MOE of 10,000 or higher would be of low health concern, if based on a BMDL<sub>10</sub> from an animal carcinogenicity study.

138. For aflatoxins, exposure calculations were not based on measured values, all results were below the calculated LOQs. Therefore, exposures were based on lower bound (LB) (where 0 is used as the analytical value) and upper bound (UB) (the LOQ) values.

139. For aflatoxin exposures, for all age groups, the mean values were all below 0.005 µg/kg bw per day and the 97.5<sup>th</sup> percentile exposures were all below 0.019 µg/kg bw per day. The range of exposures across all age groups for AFB<sub>1</sub> is 0 - 0.12 µg/kg bw per day, for AFB<sub>2</sub>, AFG<sub>1</sub>, AFG<sub>2</sub> and AFM<sub>1</sub> the exposures are up to 0.009, 0.011, 0.019 and 0.007 µg/kg bw per day, respectively. All the results were below the calculated LOQs, which ranged from 0.13 µg/kg for AFB<sub>1</sub> in dried fruit to 2.41 µg/kg for AFG<sub>1</sub> in sugar confectionary.

140. Following EFSA's approach, the MOEs for aflatoxins were calculated using a BMDL<sub>10</sub> of 0.17 µg/kg bw per day, based on liver carcinogenicity in male rats exposed to 1 - 100 µg/kg diet of AFB<sub>1</sub> (Wogan et al., 1974). Total aflatoxin was not available as part of the TDS and due to inconsistencies in the reporting across the EU it is not certain whether total exposure could be calculated from the data available.

141. For all children aged 4 to 60 months, the MOEs are < 10,000. The mean and 97.5<sup>th</sup> percentile MOEs for AFB<sub>1</sub> are ≥ 14 to ≥ 170, the mean and 97.5<sup>th</sup> percentile MOEs for AFB<sub>2</sub>, AFG<sub>1</sub>, AFG<sub>2</sub> and AFM<sub>1</sub> are ≥ 19, 15, 8.9 and 24 to ≥ 170, respectively.

142. As previously described, the exposures, were not based on measured values, but on the LB and UB values; exposures to all aflatoxins in infants and young children were between 0 and the UB exposure. Therefore, the actual MOEs would be higher than those calculated.

143. The COT noted that there is a potential for different susceptibility of children to aflatoxins than in adults. The P450 system in neonates is less well developed than in adults and hence in many species there is a reduced capacity to activate AFB<sub>1</sub> at that age. In addition, differences in detoxifying enzymes and toxicodynamics can lead to increased susceptibility and proliferation rate of hepatocytes in neonates. However, the current data does not allow for predictions of sensitivity differences to AFB<sub>1</sub> in infants and adults. The COT was therefore not able to draw any conclusions on sensitivity differences and noted that this is a significant issue and data gap.

144. Given that aflatoxins are genotoxic and carcinogenic their presence is always undesirable and it is not possible to exclude a safety concern.

145. The full EFSA evaluation can be found here:

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

#### Citrinin

146. 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. Specific toxicokinetic studies with oral administration are not available. Experimental data indicate the occurrence of citrinin residues in edible tissues and eggs following oral exposure of animals with contaminated feed.

147. The acute lethal toxicity of citrinin ranged from 19 - 134 mg/kg bw depending on species and route of administration. Repeat dosing studies confirmed the nephrotoxicity of citrinin and again highlighted the differences in susceptibility between species. One available sub-chronic study in rats reported a NOAEL of 20 mg/kg bw per day. One available long-term feeding study in rats exposed to high dietary citrinin (initially about 70 mg/kg bw per day) identified the kidney as principal target organ and reported progressive histopathological changes and incidences of adenomas. However, the study was limited to 80 weeks, thus no conclusions on potential carcinogenicity can be drawn. Other *in vivo* studies showed the induction of chromosome abnormalities and hypodiploidy in mice bone marrow. Conventional bacterial and mammalian *in vitro* assays indicate that citrinin is not mutagenic, mutagenicity was only reported in 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 IARC's classification and concluded that it was currently not possible to confirm the carcinogenicity of citrinin.

148. Data from immunotoxicity studies were generally incomplete and did not allow for conclusions to be drawn. Data from *in vitro* and *in vivo* studies reported reproductive toxicity and teratogenic and embryotoxic effects of citrinin. However, the *in vivo* studies also reported maternal toxicity, including nephrotoxicity, indicating that the reproductive, teratogenic and embryotoxic effects may be secondary to maternal toxicity, which is in line with the COT conclusions of the available data.

149. EFSA (2012) concluded that the derivation of a HBGV would not be appropriate, given the available data on genotoxicity and the limitations and uncertainties in the current database. This was not expanded upon by EFSA which furthermore concluded, that due to the lack of human dietary exposure data a MOE approach would not be appropriate. Instead, EFSA decided to characterise the risk of citrinin and determine a level of no concern for nephrotoxicity in humans of 0.2 µg/kg bw per day based on a NOAEL of 20 µg/kg bw per day and application of an UF of 100 for interspecies and interindividual variation. A concern for genotoxicity and carcinogenicity cannot be excluded at the level of no concern for nephrotoxicity.



150. Mean and 97.5<sup>th</sup> 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 97.5<sup>th</sup> percentile exposures ranged from 0 - 0.016 and 0 - 0.041 µg/kg bw per day, respectively. Calculated mean and 97.5<sup>th</sup> 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 97.5<sup>th</sup> percentile exposures of infants and young children are below the exposure level of 0.2 µg/kg bw per day considered of no concern for nephrotoxicity in humans by EFSA.

151. The exposures reported in the TDS are not of toxicological concern for nephrotoxicity. However, the COT noted that due to lack and limitations of the available data, a concern for genotoxicity and carcinogenicity cannot be excluded.

152. The full EFSA evaluation can be found here:

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

#### Cyclopiazonic acid (CPA)

153. 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).

154. 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 human toxicity due to consumption of food contaminated with CPA.

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

156. The COT reviewed all 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 being considered for use in a MOE approach for risk characterisation.

157. The NOAEL from the Lomax et al. study, according to the authors, is 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. 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.

158. There are some uncertainties with using the Nuehring et al. study for establishing an HBGV. The main one is the unsuitability of the animals for this study, with them generally being of unknown provenance. These factors may make it difficult



to determine a LOAEL based departure point. However, a clear reduction in dose response was demonstrated. The lowest dose group, 0.1 mg/kg bw per day showed no dose related effects and was not hampered by any of the overt pre-treatment issues affecting the other groups. This could be used as a NOAEL.

159. The Lomax et al. study is only a 14-day study and additional UF would have to be factored in with its use to derive a HBGV. Overall, it was agreed that the NOAEL of 0.1 mg/kg bw per day from the Nuehring et al. study could be applied. Although there were uncertainties around the quality of the study, the NOAEL from the study by Voss et al. was 0.2 mg/kg bw per day and provided some confidence in the use of a NOAEL of 0.1 mg/kg bw per day as the basis for calculating MOEs for CPA exposures.

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

161. Mean and 97.5<sup>th</sup> 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 97.5<sup>th</sup> percentile exposures ranged from 0.001 - 0.007 and 0.005 - 0.018 µg/kg bw per day. Calculated mean and 97.5<sup>th</sup> 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.

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

163. Based on the current toxicity and exposure information, 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 and are enough 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.

#### 4,15 Diacetoxyscirpenol (DAS)

164. 4,15 Diacetoxyscirpenol (DAS) is a type A trichothecene mycotoxin from the *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 has been found to 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.

165. DAS is rapidly metabolised to a large number of metabolites *in vitro* (Yang et al., 2015). The main metabolic processes are deacylations, hydroxylations, deepoxidations and glucuronide conjugations. After oral administration in rats and mice (Conner et al., 1986; Ueno, 1983), the absorption of DAS has not been quantified but the excretion ratio between urine and faeces indicated high 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 intravenous (i.v.), the median

lethal dose (LD<sub>50</sub>) ranged from 1 - 12 mg/kg bw while the LD<sub>50</sub> ranged from 0.8 - 23 mg/kg bw after ip administration.

166. 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. 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<sup>2</sup> (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.

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

168. JECFA (2016) established a PMTDI of 0.06 µg/kg bw for T-2 and HT-2 toxin, alone or in combination, based on a LOAEL of 0.03 mg/kg bw per day associated with changes in white blood cell counts following 3 weeks of dietary exposure in pigs (Rafai et al., 1995) and the application of an UF of 500. The inclusion of DAS in the above group PMTDI of 0.06 µg/kg bw is considered to be a conservative approach when taking into consideration the observation that T-2 toxin was consistently more potent than DAS when comparing similar *in vitro* and *in vivo* endpoints.

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

170. Using these data, an 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.

171. 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.

172. 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<sub>50</sub>. 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.

173. 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 in humans. Furthermore, the application of the UF of 10 to the reference point would make it conservative and precautionary.

174. 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.

175. 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.

176. UK exposures were calculated and all the estimated mean and 97.5<sup>th</sup> percentile acute and chronic exposure levels were below the ARfD and TDI established by EFSA, respectively, and as a result, not of concern for human health.

177. The full EFSA evaluation can be found here:

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

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

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

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

180. In animals, the main effect of acute and chronic toxicity of DON is 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 oxidative stress may be involved in the mechanism rather than direct genotoxicity. Differently to other trichothecenes, DON does not show haemato- or myelotoxicity and data on neurotoxicological effects are limited.

181. 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 and no data on *in vitro* genotoxicity test with 15-Ac-DON or DON-3-glucoside or *in vivo* studies for all three forms were identified.

182. In 1999, the SCF established a temporary TDI (t-TDI) of 1 µg/kg bw per day for DON based on the NOAEL of 0.1 mg/kg bw per day from a two-year mouse study (Iverson et al., 1995) and the application of an UF of 100. In 2002, the SCF assessed the group-combined effect of common trichothecenes including T-2 and HT-2 toxins,

DON and nivalenol, and concluded that the available data were insufficient to establish a group TDI for either the combined effects or the relative potencies of the trichothecenes. Based on its assessment, the SCF decided to turn the t-TDI of 1 µg/kg bw per day for DON into a full TDI.

183. JECFA considered emesis the critical end point for acute effects as this effect has consistently been observed after DON intoxication in both experimental animals and humans.

184. In 2011, JECFA combined data from 2 studies on emesis in pigs and piglets following exposure to DON via the diet, for BMD modelling. The BMDL<sub>10</sub> ranged from 0.21 - 0.74 mg/kg bw per day, the lowest of which was used as the point of departure (POD) for establishing the ARfD. JECFA applied an UF of 25 based on the consideration that “DON-induced emesis is a systemic effect and more dependent on C<sub>max</sub> than on area under the plasma concentration–time curve (AUC)” and previous use by the JMPR for acute C<sub>max</sub>-dependent effects, and derived a group ARfD of 8 µg/kg bw for DON, 3- and 15-Ac-DON.

185. Limited data from human case reports indicate that dietary exposures up to 50 µg/kg bw per day are not likely to induce emesis.

186. In 2001, JECFA established a PMTDI for DON of 1 µg/kg bw on the basis of a NOEL<sup>7</sup> of 100 µg/kg bw per day based on decreased body weight in a two-year feeding study in mice and the application of an UF of 100. Repeat dose short-term studies considered in the 2011 evaluation indicated that this NO(A)EL of 100 µg/kg bw per day remains appropriate and JECFA reconfirmed its PMTDI. JECFA furthermore decided to convert the PMTDI for DON to a group PTMDI for DON and its acetylated derivatives (3-Ac-DON and 15-Ac-DON) as 3-Ac-DON is converted to DON and therefore contributes to the total DON-induced toxicity; the toxicity of the acetylated derivatives is considered equal to that of DON.

187. However, JECFA concluded there was insufficient information to include DON-3-glucoside in the group PMTDI or ARfD.

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

189. While the MoA and the toxicity data for 3-Ac-DON and 15-Ac-DON indicated a similar toxicity as 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 make 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 at 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.

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<sup>7</sup> At its sixty-eighth meeting (2007), the Committee decided to differentiate between NOAEL and NOEL. This NOEL would now be considered a NOAEL.

EFSA therefore decided to characterise the three forms and DON together, both for chronic and acute health effects.

190. EFSA identified vomiting as the critical acute effect in humans. Since EFSA did not consider studies based on experimental and farm animals appropriate, epidemiological studies were used as the base for the derivation of the HBGV. EFSA calculated a NOAEL of 26 µg DON/kg bw for one single eating occasion from a human outbreak in China and applied an UF of 3.16 for toxicodynamic differences in intra-human population variability to derive an ARfD of 8 µg/kg bw per eating occasion. The dose-range calculated from human urinary biomarker data supported the reference dose. The highest urinary biomarker 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 biomarkers was 36 µg DON/kg bw per day. EFSA concluded that the range of 36 - 74 µg DON/kg bw per day 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.

191. In the absence of chronic epidemiological data, EFSA identified reduced bodyweight gain in experimental animals as the critical chronic effect. EFSA calculated a BMDL<sub>05</sub> of 0.11 mg/kg bw per day based on a study in mice, the only chronic/carcinogenicity study identified (Iverson et al., 1995), and applied an UF of 100 for inter- and intra-species variability. Since the BMDL<sub>05</sub> is larger than the BMDLs calculated for reproductive and developmental toxicity, EFSA considered it sufficiently protective.

192. Acute and chronic exposures were calculated using data from the TDS. 3-Ac-DON and 15-Ac-DON were not detected in any samples above the limit of detection (LOD). A total concentration for 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.

193. Mean and 97.5<sup>th</sup> 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 per day, for all age groups and are therefore not of toxicological concern.

194. Mean and 97.5<sup>th</sup> percentile chronic exposures to 15-Ac-DON, 3-Ac-DON and DON were below the TDI of 1.0 µg/kg bw per day, for all age groups and are therefore not of toxicological concern. All mean and 97.5<sup>th</sup> percentile chronic exposure to the sum of all three forms were below the TDI, except the 97.5<sup>th</sup> percentile UB exposure in children > 12 months of age, which are at or up to 1.3-fold the TDI. This is unlikely to be of toxicological concern. However, the sum of all forms is not based on measured values but on summing the individual concentrations provided. Therefore, the estimated exposures could be an over- or underestimation of the actual values.

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



This is a draft statement and has not been finalised. Therefore, it should not be cited.

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

[http://apps.who.int/iris/bitstream/10665/44520/1/9789241660631\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/44520/1/9789241660631_eng.pdf)

## Ergot alkaloids (EAs)

196. Ergot alkaloids (EAs) infest 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.

197. EAs can act on a number of neurotransmitter receptors particularly adrenergic, dopaminergic and serotonergic receptors, 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 mutation, *in vivo* data is inconsistent but there is some evidence of clastogenicity. Tumorigenicity demonstrated in a two-year carcinogenicity study was exacerbated by a low protein diet, the absence of carcinomas and the regression indicated aetiology related to a non-genotoxic mode of action. Human data are available for the naturally occurring alkaloids used as pharmaceuticals, ergometrine and ergotamine.

198. EFSA (2012) derived a group ARfD of 1 µg/kg bw for the sum of ergot alkaloids based on a BMDL<sub>10</sub> of 0.33 mg/kg bw per day for 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.

199. EFSA derived a group TDI of 0.6 µg/kg bw per day for the sum of EAs based on the same BMDL<sub>10</sub> 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 for the derivation of the ARfD, an additional UF of 2 should be applied for the extrapolation from sub-chronic to chronic studies.

200. EFSA noted that the group ARfD is 2-fold below the lowest single dose of 2 µg/kg bw ergometrine used to induce uterine contractions and therefore the margin between this dose in a sensitive subpopulation and the group ARfD is 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. Furthermore, the group TDI is 13 times lower than the maximum recommended dose for therapeutic use of ergotamine.

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

202. The full EFSA evaluation can be found here:

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

## Fumonisin

203. Fumonisin 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).

204. Fumonisin can have significant health effects in livestock and other animals, although evidence for adverse health effects in humans is currently inconclusive. It has not been identified as acutely toxic, however, it is possibly carcinogenic to humans (Group 2B; IARC, 2002). Concerns over the exposure to fumonisin and its contribution to outcomes such as birth defects and stunting growth in children have been identified, however, human observations for reproductive and developmental toxicity have not been causally related to fumonisin exposure.

205. The human health impacts of fumonisin 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.

206. The COT considered the metabolic differences of fumonisin in adults and children since the PMTDI/TDI were based on hepatotoxic effects. They concluded that fumonisin 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, and so the kinetic profile 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.

207. All calculated exposures in the diet were below both, the EFSA TDI and JECFA PMTDI and are therefore not of toxicological concern.

208. No UK data on breast milk were available. A study by Mahoga et al., (2014) reported breast milk as a source of fumonisin in Tanzanian women. The Committee concluded that it would be unlikely that the levels of fumonisin in the breast milk in Tanzanian women, reflects that of women in the UK population, however, differences in ethnic diets should be further considered.

209. Exposure estimations showed that 6 to 9 months old infants at the 97.5<sup>th</sup> percentile whom are exclusively fed infant formula at the maximum level of 179 µg/kg exceed 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 period. In addition, the German data (Zimmer et al., 2008) on which the assessment was based may not accurately reflect the levels of fumonisin in infant formulae, in today's market. While the data was the only one available to the COT at the time, the authors of the study noted that the concentrations detected 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.

210. 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/>

Fusarenon-X (Fus-X)

211. 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.

212. The toxicological effects of Fus-X were previously evaluated by the National Institute for Public Health and the Environment (RIVM, 2002). It was identified to be acutely toxic with LD<sub>50</sub> values of 4.4 mg/kg bw in rats and 4.5 mg/kg bw in mice. The major toxicity of Fus-X is mediated through the inhibition of protein synthesis, which disrupts the process of 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.

213. RIVM were unable to establish a temporary tolerable daily intake 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.

214. Mink emesis data has been utilised for the derivatisation of benchmark doses for other trichothecene families. EFSA concluded that humans were no more sensitive than mink towards the emesis effect, since the doses of the emetine causing emesis were similar in both species.

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

216. Based on the data presented, the COT agreed that the ARfD of NIV could not be utilised as a comparative HBGV for Fus-X, since it was more acutely toxic for emetic responses. Comparison with the DON HBGV was considered more appropriate since the oral emetic potency of Fus-X relative to DON is 1.04.

217. Acute exposures of Fus-X were calculated using data from the TDS and showed no cause for concern regarding acute toxicological effects when compared against the ARfD of DON (8 µg/kg bw per day), since all MOE values were greater than 1,000. However, the COT noted that there were some uncertainties involved in the extrapolation of the data.

218. Additive acute exposures of Fus-X, DON and NIV, showed that DON made the highest contribution. Direct comparisons of the summed acute exposures (Fus-X,

DON and NIV) are below the ARfD for DON. MOE values of < 100 were observed in the upper bound values of the 97.5<sup>th</sup> percentile exposures for 12 to 60 months old infants and children for the summed acute exposure of the type B tricothecenes. However, the COT noted that the estimates of the acute exposure are highly conservative and therefore the calculated MOE values will also be conservative. Furthermore, the Committee agreed that the likelihood of co-occurrence of Fus-X with DON and NIV at these levels is low.

219. 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.

220. The full RIVM evaluation can be found here:

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

#### Moniliformin (MON)

221. 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).

222. The data on the toxicokinetics of MON in experimental animals were limited. In rats, a large portion of MON was absorbed and rapidly excreted in urine after 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 to some unknown form (Jonsson et al., 2013; 2015).

223. 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. A study in mink reported developmental and reproductive toxicity at exposure to 1.94 mg/kg bw per day, based on significant neonatal mortality and reduced offspring body weights.

224. Studies showed MON does not induce bacterial reverse mutation. MON has been shown to be clastogenic *in vitro*, inducing chromosomal aberrations and micronuclei, however no data were identified to conclude 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.

225. Due to the limitations in the available toxicity data in animals, neither acute nor chronic HBGV were established by EFSA. Therefore, a MOE approach was used to assess the level of risk.

226. For acute and sub-acute exposure to MON, EFSA identified cardiotoxicity as a 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 from 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 MOE for acute human exposures to MON.

227. Following the approach taken by EFSA, all MOEs for UK infants aged 4 to 18 months were greater than 10,000.

228. For chronic exposure to MON, EFSA identified haematotoxicity as the most sensitive endpoint measured in barrow pigs for human hazard characterisation (suitable dose-response data in other experimental animals were absent). The Panel identified a BMDL<sub>05</sub> 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 POD to calculate MOEs for chronic human exposures to MON. For UK infants aged 4 to 12 months, the smallest MOE was 1100 which occurred at the 97.5<sup>th</sup> percentile for 9 to < 12 months old. For children aged 12 to 18 months, the smallest MOE was 650, which occurred at the 97.5<sup>th</sup> percentile for 15 to < 18 months old. For young children aged 18 to 60 months, the smallest MOE was 700, which occurred at the 97.5<sup>th</sup> percentile for 18 to 24 months old.

229. The COT agreed with the MOE approach taken by EFSA for assessing the human health risk of MON. The calculated UK MOEs for both acute and chronic exposure were considered to be acceptable and adequately protective for human health. For the acute risk assessment of MON, a non-genotoxic xenobiotic, an MOE > 100 was considered to be protective. For chronic risk assessment, an MOE > 650 was considered to be protective (given the absence of long-term toxicology studies, and the exposure data being based on non-detects).

230. The full EFSA evaluation can be found here:

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

#### Nivalenol (NIV)

231. 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.

232. Generally, trichothecenes are immunotoxic and haematotoxic/myelotoxic. Several *in vivo* studies on NIV have reported an increase of immunoglobulin A (IgA) or immunoglobulin M (IgM) at higher concentrations than those reporting 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).

233. 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<sub>05</sub> 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 study duration and limitations in the reproductive and developmental toxicity data, respectively.

234. All mean and 97.5<sup>th</sup> 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.

235. The full EFSA evaluation can be found here:

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

#### Patulin (PAT)

236. 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.

237. *In vivo* animal studies demonstrated that most 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 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).

238. PAT has a strong affinity for sulfhydryl groups which in turn inhibits enzyme activity (Puel et al., 2010). In several studies, it has been concluded that the presence of reactive oxygen species (ROS) and depletion of intracellular glutathione (GSH) is key for PAT mediated toxicity and in turn the main mode of action (Barhoumi et al., 1996; Burghardt, 1992; Guo et al., 2013; Ianiri et al., 2016).

239. The oral LD<sub>50</sub> value of PAT in mice and rats varies from 20 - 100 mg/kg bw and the i.v. and ip routes are more toxic than the oral route (Pal et al., 2017).

240. Acute studies have shown that 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. PAT leads to systemic toxicity in the mammalian system including intestinal injury, intestinal ulcers, inflammation, bleeding and a decrease in transepithelial resistance. PAT causes liver inflammation (inducing a rise in alanine aminotransferase (ALT), aspartate transaminase (AST) and malondialdehyde (MDA)). PAT also causes detrimental effects on other target organs such as kidneys and thyroids.

241. Cellular and genetic material affects include DNA strand breaks, neuronal degeneration, and degeneration of glomeruli and renal tubules. In the 1986 IARC report, it stated that there was inadequate evidence for the carcinogenicity of PAT in experimental animals. This has 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".

242. The most recent evaluation of PAT was conducted by JECFA (1995). Prior to that, JECFA evaluated PAT in 1990. In this evaluation, JECFA established a provisional maximum tolerable weekly intake (PMTWI) of 7 µg/kg bw. The SCF, in 1994 agreed with the PTWI of 7 µg/kg bw established by JECFA. In 2000, the SCF produced a minute statement and endorsed the PMTDI of 0.4 µg/kg bw established by JECFA in 1995

243. The pivotal study used by JECFA (1995) to determine 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 whereas 19% of females survived until termination at 2 years. Body weights of males were reduced at the mid and high dose, but females body weights were comparable in all groups. No difference in tumour incidence was observed. The no-observed effect level (NOEL<sup>8</sup>) in this study was 0.1 mg/kg bw, administered 3 times weekly, equivalent to 43 µg/kg bw per day.

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

245. It is important to note that genotoxicity data has been published since the HBGV was calculated by JECFA. If the data are conclusive that PAT is genotoxic this would have an impact on the HBGV.

246. There has been no evaluation of PAT since the one carried out by JECFA. Therefore, reviewing recent toxicological data (1995 to 2018) the COT Members agreed that the up to date scientific data would probably not change the HBGV (excluding the genotoxicity data). The Committee concluded that the genotoxic studies were complex and suggested that they be referred to The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM). It was noted that the mode of action through reactive oxygen species (ROS) might become important when looking at genotoxicity.

247. Provisionally (draft minutes, unpublished to date) 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 details 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.

248. Based on this the COT concluded that until further testing had been carried out to the accepted standards and a conclusion on genotoxicity could be formed, the

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<sup>8</sup> [http://whqlibdoc.who.int/publications/2007/9789241209472\\_eng.pdf](http://whqlibdoc.who.int/publications/2007/9789241209472_eng.pdf)

current PMTDI of 0.4 µg/kg bw should continue to be used in the risk assessment of PAT.

249. As it stands, mean and 97.5<sup>th</sup> 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.

250. The full JECFA evaluation can be found here:

[https://ec.europa.eu/food/sites/food/files/safety/docs/cs\\_contaminants\\_catalogue\\_patulin\\_out55\\_en.pdf](https://ec.europa.eu/food/sites/food/files/safety/docs/cs_contaminants_catalogue_patulin_out55_en.pdf)

### Sterigmatocystin (STC)

251. Sterigmatocystin (STC) is produced by more than a dozen species of *Aspergillus* and a number of phylogenetically and phenotypically different fungal genera and shares its biosynthetic pathway with 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.

252. STC exhibits genotoxic effects *in vitro*, *in vivo* and *ex vivo* and carcinogenicity has been demonstrated after oral, i.p., subcutaneous and/or dermal exposure in the animal species tested.

253. EFSA (2013) evaluated a number of dose-response effects using data from available carcinogenicity bioassays in mice, rats and monkeys who had been orally administered STC. Most studies were not considered suitable for BMD modelling due to discontinuous dosing, lack of detailed tumour incident reporting, high mortality and too small a number of treatment groups. The incidents of hepatocellular carcinomas (HCC) in the study by Maekawa et al. (1979) was not considered suitable for risk characterisation by EFSA since the study combined tumours from different origins (HCC and haemangiosarcomas). However, EFSA found it appropriate to conduct BMD analysis on haemangiosarcomas as a relevant end point due to zero tumour bearing animals in the control and low dose group and one and three tumour bearing animals in the mid and high dose group, respectively.

254. The lowest BMDL<sub>10</sub> value was 0.16 mg/kg bw per day, with a BMD<sub>10</sub> 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 tumour incidence in the control group was 64%. Therefore, the BMD<sub>10</sub>/BMDL<sub>10</sub> pair is based on a limited tumourigenicity database.

255. JECFA applied BMD analysis to the same study in their 2017 evaluation and applied a BMDL<sub>10</sub> of 0.16 mg/kg bw per day as the POD for their MOE assessment.

256. EFSA was unable to apply a MOE approach in their evaluation in 2013, due to the lack of European human dietary exposure to STC. However, in general EFSA

proposed a MOE of 10,000 or higher would be of low health concern, if based on a BMDL<sub>10</sub> from an animal carcinogenicity study.

257. Mean and 97.5<sup>th</sup> percentile MOEs for infants and young children are all > 10,000. Therefore, the exposures are unlikely to be of toxicological concern to human health.

258. The full EFSA evaluation can be found here:

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

Zearalenone (ZEN)

259. 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, is commonly found in maize and also in wheat, barley, sorghum and rye.

260. 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.

261. Based on the limited evidence for carcinogenicity, EFSA (2001) applied the MOE approach using a BMDL<sub>10</sub> of 6.39 mg/kg bw per day based on incidence of pituitary adenomas in male mice exposed to concentrations of 8 and 17 mg/kg bw per day. However, EFSA also noted the wide variability in the sensitivity of species to oestrogenic effects of ZEN and that these effects are observed in pigs at doses approximately three orders of magnitude lower than doses reported to cause clastogenicity and increases in adenomas in mice. Therefore, EFSA also established a TDI of 0.25 µg/kg bw per day 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 of an UF of 4 for interspecies toxicokinetics and an UF of 10 for interhuman 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<sub>10</sub> of 6.39 mg/kg bw per day and the TDI of 0.25 µg/kg bw was in the region of 25,000. This exceeds the value of 10,000 of low concern for a genotoxic carcinogen, established by EFSA.

262. EFSA (2011) concluded oestrogenicity to be the critical effect of ZEN, as the reported genotoxicity may be related to oxidative stress mediated mechanisms and ZEN was at most a weak carcinogen.

263. Several modified forms of ZEN have been identified and characterised since the assessment on ZEN in 2011, thus EFSA decided to review the new and relevant data in 2016. There is little information on the absorption, bioavailability and metabolic fate of the metabolites and it was assumed they are as readily bioavailable as ZEN. Acute toxicity of ZEN is low and EFSA did not identify any new studies indicating the need for an ARfD or to revise the current TDI. EFSA however noted, that oestrogenicity is the common MoA for 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.

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

265. Mean and 97.5<sup>th</sup> 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.

266. The full EFSA evaluation can be found here:

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

#### *Tropane alkaloids (TAs)*

267. Tropane alkaloids (TAs) are secondary metabolites which naturally occur 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 plant seeds have been found as impurities in linseed, soybean, millet, sunflower and buckwheat and products thereof.

268. The group of TAs composes of about 200 compounds, the best-known representatives are (-)-hyoscyamine, (-)-scopolamine and atropine, a racemic mix of (-)-hyoscyamine and (+)-hyoscyamine. Unlike (+)-hyoscyamine, (-)-hyoscyamine and (-)-scopolamine are naturally formed in plants. Plant extracts containing TAs have been and are continued to be used in veterinary and human medicine, as are (-)-hyoscyamine, (-)-scopolamine and atropine.

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

270. Both compounds inhibit the muscarinic acetylcholine receptor in the central nervous system (CNS) and autonomic nervous system (ANS). However, they differ in the ability to affect the CNS, (-)-scopolamine having a more prominent effect on the CNS.

271. 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 and coma. Toxic effects of other TAs are largely unknown and only very limited data on occurrence in food and feed is available.

272. 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 data on food and feed, EFSA used these data as (-)-hyoscyamine in their evaluation of TAs.



273. EFSA establish an acute reference dose (ARfD), 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 and therefore set a group ARfD based on a human volunteer study. An UF of 10 for interindividual differences (small study, healthy male volunteers) was applied to the NOAEL of 0.16 µg/kg bw per day to derive an ARfD of 0.016 µg/kg bw per day.

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

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

276. The European Medicine Agency (EMA) and EFSA assessed the legal use of *Atropa belladonna* and atropine as authorised veterinary medicines in farm animals in 1997 and 2008. 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.

277. 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 derived by the European Commission (EC, 2016).

278. Occurrence data for the exposure assessment are from a 2014 FSA survey (Stratton et al., 2017); samples were taken 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, measured quantities of TAs were reported in only a limited number of samples. The percentage of samples with detectable levels above the limit of quantification (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 derived by the EC.

279. Following EFSA's approach, this assessment uses and reports atropine and (-)-scopolamine in food as (-)-hyoscyamine and (-)-scopolamine, respectively. The exposure assessment focused on (-)-hyoscyamine and (-)-scopolamine separately and the sum of (-)-hyoscyamine and (-)-scopolamine. 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.

280. Little to no information is available of the transfer of TAs to breast milk; the limited information available reports that only limited amounts of TAs, namely atropine,

(-)-hyoscyamine and (-)-scopolamine are excreted into breast and currently do not indicate a toxicological concern.

281. No data on the concentration of TAs in infant formula is 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.

282. In infants and young children, the UB mean and 97.5<sup>th</sup> 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 per day, established by EFSA. The only exceptions are the 97.5<sup>th</sup> percentile (UB) estimated exposures to the sum of (-)-hyoscyamine and (-)-scopolamine in cereal-based infant foods and all three food categories combined where exposures are at or close to the ARfD; however these are UB exposures, reflecting limited detection of (-)-hyoscyamine and (-)-scopolamine rather than being based on actual measured concentrations. 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.

283. Overall, all estimated acute exposures of infant 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.

284. 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 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. Overall, the total dietary exposure of infants and young children to a combination of all TAs may be substantially underestimated.

285. 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 potency estimation project/workshop and to revisit its current conclusions, should additional information become available that would warrant a re-assessment.

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

287. 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

288. The COT concluded that exposure to hexachlorocyclohexanes, diacetoxyscirpenol, ergot alkaloids, moniliformin, nivalenol, sterigmatocystin, zearalenone and sweeteners (aspartame, acesulfame K, saccharine, sorbitol and xylitol, steviols and sucralose) in the diets of infants aged 0 to 12 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 exposures 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.

289. 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 deoxynivalenol and nivalenol at the reported levels is low and that co-exposure was unlikely to result in adverse toxicological effects.

290. 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, 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 period and that the levels contributing to the high concentrations were only from one manufacturer.

291. The COT concluded that exposures to cyclopiazonic acid in the diets of infants aged 0 to 12 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 large enough.

292. 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 to 12 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 measured values but on summing the individual concentrations provided. Therefore, the estimated exposures could be an over- or underestimation of the actual values.

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

294. As it currently stands, the COT concluded that exposures to patulin in the diets of infants aged 0 to 12 months and children aged 1 to 5 years are not of toxicological concern. Based on the information provided by the COM, the COT concluded that until further testing had been carried out to the 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.

295. Given that aflatoxins are genotoxic and carcinogenic their presence is always undesirable and it is not possible to exclude a safety concern.

296. The COT concluded that the intakes of polycyclic aromatic hydrocarbons (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.

297. The COT concluded that the available scientific data 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.

298. 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 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. Overall, the total dietary exposure of infants and young children to a combination of all TAs may be substantially underestimated.

299. In the absence of any newer UK-specific data, the COT assessed 3-monochloropropanediol, 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.

## References

ATSDR (2005). Toxicological profile for alpha-, beta-, gamma-, and delta-hexachlorocyclohexane. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. 377 pp.  
<https://www.atsdr.cdc.gov/toxprofiles/tp43.pdf>

Barhoumi R, Burghardt RC (1996). Kinetic analysis of the chronology of patulin-and gossypol-induced cytotoxicity in vitro. *Toxicological Sciences*, 30(2): 290-297.

Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, Swan G (2014). National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012)  
[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/310995/NDNS\\_Y1\\_to\\_4\\_UK\\_report.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf)

Bates B, Cox L, Nicholson S, Page P, Prentice A, Steer T, Swan G (2016). National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014)  
[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/551352/NDNS\\_Y5\\_6\\_UK\\_Main\\_Text.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/551352/NDNS_Y5_6_UK_Main_Text.pdf)

BDA (The Association of UK Dietitians) (2016). Policy Statement- The Use of Artificial Sweeteners.  
[https://www.bda.uk.com/improvinghealth/healthprofessionals/policy\\_statements/sweeteners](https://www.bda.uk.com/improvinghealth/healthprofessionals/policy_statements/sweeteners)

BHF (British Heart Foundation) (2019): Are artificial sweeteners better than sugar?, *Heart Matters Magazin*.  
<https://www.bhf.org.uk/informationsupport/heart-matters-magazine/nutrition/ask-the-expert/artificial-sweeteners>

Buck Louis GM, Chen Z, Peterson CM, Hediger ML, Croughan MS, Sundaram R, Stanford JB, Varner MW, Fujimoto VY, Giudice LC, Trumble A, Parsons PJ, Kannan K (2012). Persistent lipophilic environmental chemicals and endometriosis: the ENDO Study. *Environmental Health Perspective*, 120(6):811-6.

Burdock GA, Flamm WG (2000). Review article: Safety assessment of the mycotoxin cyclopiazonic acid. *International Journal of Toxicology*, 19: 195-218.

Burghardt RC, Barhoumi R, Lewis EH, Bailey RH, Pyle KA, Clement BA, Phillips TD (1992). Patulin-induced cellular toxicity: a vital fluorescence study. *Toxicology and Applied Pharmacology*, 112(2): 235-244.

Chang PK, Ehrlich KC, Fujii I (2009). Cyclopiazonic acid biosynthesis of *Aspergillus flavus* and *Aspergillus oryzae*. *Toxins (Basel)*, 1(2): 74-99.

Chiozzotto D, Soffritti M, Falcioni L, Tibaldi E, Manservigi F, Manservigi M, Bua L and Belpoggi F (2011). Results of life span carcinogenicity bioassay on Sprague-Dawley rats exposed to aspartame since foetal life. *European Journal of Oncology*, 16: 81-97.



COC (2006). Statement on a Carcinogenicity Study of Aspartame by the European Ramazzini Foundation. Statement COC/06/S2 – December 2006.

[https://dragaonordestino.net/Drachenwut\\_Blog\\_DragaoNordestino/Ernaehrung/kohle\\_nhydrate\\_arquivos/XXX\\_aspartame.pdf](https://dragaonordestino.net/Drachenwut_Blog_DragaoNordestino/Ernaehrung/kohle_nhydrate_arquivos/XXX_aspartame.pdf)

COT (2004). COT statement on Tetrabromobisphenol A - Review of toxicological data. COT statement, 2004/02.

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

Conner MW, De Camargo J, Punyarit P, Riengropitak S, Rogers AE, Newberne PM (1986). Toxicity of anguidine in mice. *Fundamental and Applied Toxicology*, 7(1): 153-164.

Cope R., Kacew S, Dourson M (2015). A reproductive, developmental and neurobehavioral study following oral exposure of tetrabromobisphenol A on Sprague-Dawley rats. *Toxicology*, 329: 49-59.

Culp SJ, Gaylor DW, Sheldon WG, Goldstein L, Beland FA (1998). A comparison of the tumours induced by coal tar and benzo[a]pyrene in a 2-year bioassay. *Carcinogenesis*, 19: 117-124.

Cummins HA, Yallup V, Lee P, Rhenius ST and Whitney J (1983). 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside (TGS): Eight-week dietary toxicity study in rats. Life Science Research Limited, UK. Report No 11 82/MSPO21/392. Unpublished report submitted by Tate & Lyle Speciality Sweeteners, UK

Dailey RE, Blaschka AM, Brouwer EA (1977). Absorption, distribution, and excretion of [<sup>14</sup>C] patulin by rats. *Journal of Toxicology and Environmental Health, Part A*, 3(3): 479-489.

DEFRA (Department for Environment, Food and Rural Affairs) (2012). Technical Guidance Sheet on normal levels of contaminants in English soils: Benzo(a)pyrene – supplementary information. Technical Guidance Sheet No. TGS04s, Soils R&D Project SP1008.

<http://nora.nerc.ac.uk/id/eprint/19965/>

DH (Department of Health) (1994). The COMA report on Weaning and the Weaning Diet. Report on Health and Social Subjects 45. The Stationary Office London

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/743707/Weaning\\_and\\_The\\_Weaning\\_Diet\\_1994\\_.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/743707/Weaning_and_The_Weaning_Diet_1994_.pdf)

DH (2013). Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011.

<http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/>

Diggs DL, Huderson AC, Harris KL, Myers JN, Banks LD, Rekhadevi PV, Niaz MS, Ramesh A (2011). Polycyclic aromatic hydrocarbons and digestive tract cancers – a perspective. *Journal of Environmental Science and Health C, Environmental Carcinogenesis and Ecotoxicological Reviews*, 2994: 324-357.

This is a draft statement and has not been finalised. Therefore, it should not be cited.

Dybing E, O'Brien J, Renwick AG, Sanner T (2008). Risk assessment of dietary exposures to compounds that are genotoxic and carcinogenic – an overview. *Toxicology Letters*, 180: 110-117

EC (2008): Regulation (EC) No 1333/2008 on food additives. *Official Journal of the European Union* L:345/16

<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32008R1333>

EFSA (2005). Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic. *EFSA Journal*, 282: 1-31.

<https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2005.282>

EFSA (2008). Scientific opinion of the Panel on Contaminants in the Food Chain. Polycyclic aromatic hydrocarbons in food. *The EFSA Journal*, 724: 1-114.

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

EFSA (2011). Scientific Opinion on Tetrabromobisphenol A (TBBPA) and its derivatives in food. *The EFSA Journal*, 9(12): 2477.

<https://www.efsa.europa.eu/en/efsajournal/pub/2477>

EFSA (2012). Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. *The EFSA Journal*, 10, 2579.

<https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2579>

EFSA (2013). Scientific Opinion on risks for animal and public health related to the presence of nivalenol in food and feed.

<https://www.efsa.europa.eu/en/efsajournal/pub/3262>.

EFSA (2017). Risks to human and animal health related to the presence of deoxynivalenol and its acetylated and modified forms in food and feed.

<https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4718>.

EFSA (2017). Update: use of the benchmark dose approach in risk assessment. *EFSA Journal*, 15(1): 4658.

<https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2017.4658>

EFSA (2018). Risks to human and animal health related to the presence of moniliformin in food and feed. *The EFSA Journal*, 16(3): 5082.

<https://www.efsa.europa.eu/en/efsajournal/pub/5082>

EU (2011): Regulation (EU) No 1129/2011 amending Annex II to Regulation (EC) No 1333/2008. *Official Journal of the European Union* L295/1

<https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1129&from=EN>

Guo X, Dong Y, Yin S, Zhao C, Huo Y, Fan L, Hu H (2013). Patulin induces pro-survival functions via autophagy inhibition and p62 accumulation. *Cell Death & Disease*, 4(10): 822.

Harris KL, Banks LD, Manley JA, Huderson AC, Ramesh A (2013). Bioaccessibility of polycyclic aromatic hydrocarbons: relevance to toxicity and carcinogenesis. *Expert Opinion on Drug Metabolism and Toxicology*. 9(11): 1465-1480.

Health Council (2001). Lindane ( $\gamma$ -hexachlorocyclohexane). Health-based recommended occupational exposure limit. Report of the Dutch Expert Committee on Occupational Standards, a committee of the Health Council of The Netherlands. No. 2001/07OSH, The Hague, 6 December 2001.

<http://www.gezondheidsraad.nl/sites/default/files/01@07OSH.PDF>

Ianiri G, Idnurm A, Castoria R (2016). Transcriptomic responses of the basidiomycete yeast *Sporobolomyces* sp. to the mycotoxin patulin. *BMC Genomics*, 17(1): 210

IARC (1999). Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances, Saccharin and its salts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 73.

<https://monographs.iarc.fr/wp-content/uploads/2018/06/mono73-24.pdf>

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2010). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monograph Evaluating Carcinogenic Risks to Humans, 92: 1–853.

[https://www.ncbi.nlm.nih.gov/books/NBK321710/#p244\\_s3\\_102](https://www.ncbi.nlm.nih.gov/books/NBK321710/#p244_s3_102)

IARC (2002). Monographs on the evaluation of carcinogenic risks to humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. Volume 82.

<https://monographs.iarc.fr/wp-content/uploads/2018/06/mono82.pdf>

IARC (2015). DDT, lindane and 2,4-D. IARC Monographs On the evaluation of carcinogenic risk to humans

<https://monographs.iarc.fr/wp-content/uploads/2018/07/mono113.pdf>.

Iverson F, Armstrong C, Nera E, Truelove J, Fernie S, Scott P, Stapley R, Hayward S and Gunner S (1995). Chronic feeding study of deoxynivalenol in B6C3F1 male and female mice. *Teratogenesis, Carcinogenesis and Mutagenesis*, 15(6): 283-306.

JECFA (1980). Toxicological evaluation of certain food additives: aspartame, WHO Food Additives Series No 15, World Health Organization, Geneva.

<http://www.inchem.org/documents/jecfa/jecmono/v15je03.htm>

JECFA (1981). Toxicological evaluation of certain food additives: aspartame, WHO Food Additives Series No 16, World Health Organization, Geneva.

<http://www.inchem.org/documents/jecfa/jecmono/v16je03.htm>

WHO (1983). Evaluation of certain food additives and contaminants. WHO Technical Report Series 696. Twenty Seventh Report, Geneva.

<https://apps.who.int/iris/handle/10665/39165>

This is a draft statement and has not been finalised. Therefore, it should not be cited.

JECFA (1989): Toxicological evaluation of certain food additives and contaminants, WHO Food Additive Series, No 24, Cambridge University Press, Cambridge, UK.  
<http://www.inchem.org/documents/jecfa/jecmono/v024je01.htm>

JECFA (1990). Evaluation of certain food additives and contaminants. WHO Technical Report Series 789.  
<https://apps.who.int/iris/handle/10665/37651>

JECFA (1991): Toxicological evaluation of certain food additives and contaminants, WHO Food Additive Series, No 28. WHO, Geneva.  
<https://apps.who.int/iris/handle/10665/40288>

JECFA (1993). WHO Technical Report Series, no. 837. Evaluation of certain food additives and contaminants. Forty-first report, Geneva, 9-18 February 1993. Geneva.  
<https://apps.who.int/iris/handle/10665/41742>

JECFA (2001). Safety evaluation of certain mycotoxins in food. WHO Food Additives Series 47. Prepared by the Fifty-sixth  
<http://www.inchem.org/documents/jecfa/jecmono/v47je01.htm>

JECFA (2002). Evaluation of certain food additives and contaminants. WHO Technical Report Series, No. 909. Fifty-seventh report.  
[https://apps.who.int/iris/bitstream/handle/10665/42578/WHO\\_TRS\\_909.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/42578/WHO_TRS_909.pdf?sequence=1&isAllowed=y)

JECFA (2007). Evaluation of certain food additives and contaminants. WHO Technical Report Series, No. 947. Sixty-eighth report, Geneva.  
[http://whqlibdoc.who.int/publications/2007/9789241209472\\_eng.pdf](http://whqlibdoc.who.int/publications/2007/9789241209472_eng.pdf)

JECFA (2008). Compendium of Food Additive Specifications. Monograph 5. Steviol glycosides.  
<http://www.fao.org/ag/agn/jecfa-additives/details.html?id=898>

JECFA (2011). WHO Food Additives Series 74. Safety evaluation of certain contaminants in food. Eighty-third meeting.  
<https://apps.who.int/iris/bitstream/handle/10665/276868/9789241660747-eng.pdf?ua=1#page=673%22%3E>

JECFA (2012). Safety evaluation of certain food additives and contaminants. WHO Food Additives Series 65. Seventy-fourth meeting.  
[http://apps.who.int/iris/bitstream/10665/44813/1/9789241660655\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/44813/1/9789241660655_eng.pdf)

JECFA (2016). Safety evaluation of certain contaminants in food. WHO Food Additives Series 75. Eighty-third meeting.  
<https://apps.who.int/iris/bitstream/handle/10665/276868/9789241660747-eng.pdf?ua=1#page=289%22%3E>

JECFA (2016). WHO Technical Report Series no.1000. Evaluation of certain food additives, Eighty-second report.

<https://apps.who.int/iris/bitstream/handle/10665/250277/9789241210003-eng.pdf?sequence=1#page=66%22%3E>

JMPR (2002). Pesticide residues in food, Lindane, pp 181-186. FAO/WHO, Rome, Italy 16-25 September 2002.

[http://www.fao.org/fileadmin/templates/agphome/documents/Pests\\_Pesticides/JMPR/Reports\\_1991-2006/Report\\_2002.pdf](http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/Report_2002.pdf)

Jonsson M, Jestoi MN, Nathanail AV, Kokkonen UM, Anttila M, Koivisto P, Karhunen P and Peltonen K (2013). Application of OECD Guideline 423 in assessing the acute oral toxicity of moniliformin. *Food and Chemical Toxicology*, 53: 27-32.

Jonsson M, Atosuo J, Jestoi MN, Nathanail AV, Kokkonen UM, Anttila M, Koivisto P, Lilius EM and Peltonen K (2015). Repeated dose 28-day oral toxicity study of moniliformin in rats. *Toxicology Letters*, 233: 38-44.

Jung D, Becher H, Edler L, Flesch-Janys D, Gurn P, Konietzko J, Manz A, Pöpke O (1997). Elimination of beta-hexachlorocyclohexane in occupationally exposed persons. *Journal of Toxicology and Environmental Health*, 51:23-34.

Kalantzi OI, Martin FL, Thomas GO, Alcock RE, Tang HR, Drury SC, Carmichael PL, Nicholson JK, Jones KC (2004). Different levels of polybrominated diphenyl ethers (PBDEs) and chlorinated compounds in breast milk from two U.K. Regions. *Environmental Health Perspective*, 112(10):1085-91.

Kim K-H, Jahan SA, Kabir E, Brown RJC (2013). A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. *Environment International*, 60: 71-80.

Kuiper HA, den Tonkelaar EM, Van Leeuwen FXR, Franken MAM., Dormans JAMA (1985). Semi-chronic toxicity test with alpha-HCH. Bilthoven, National Institute of Public Health and Environmental Hygiene, Report No. 617917002 (full text in Dutch).

Lao JY, Xie SY, Wu CC, Bao LJ, Tao S, Zeng EY (2018). Importance of Dermal Absorption of Polycyclic Aromatic Hydrocarbons Derived from Barbecue Fumes. *Environmental Science Technology* 52(15):8330-8338 (from abstract).

Lebel G, Dodin S, Ayotte P, Marcoux S, Ferron LA, Dewailly E (1998). Organochlorine exposure and the risk of endometriosis. *Fertility and Sterility*, 69:221-228.

Lennox A, Sommerville J, Ong K, Henderson H, Allen R (2013). Diet and Nutrition Survey of Infants and Young Children.

<https://www.gov.uk/government/phighlications/diet-and-nutrition-survey-of-infants-and-young-children-2011>

Li Z, Romanoff L, Bartell S, Pittman EN, Trinidad DA, McClean M, Webster TF, Sjödin A (2012). Excretion profiles and half-lives of ten urinary polycyclic aromatic hydrocarbon metabolites after dietary exposure. *Chemical Research in Toxicology*, 26(7): 1452-1461.



This is a draft statement and has not been finalised. Therefore, it should not be cited.

Lomax LG, Cole RJ, Dorner JW (1984). The toxicity of cyclopiazonic acid in weaned pigs. *Veterinary Pathology*, 21(4):418-24.

Ma Y, Harrad S (2015). Spatiotemporal analysis and human exposure assessment on polycyclic aromatic hydrocarbons in indoor air, settled house dust and diet: a review. *Environment International*, 84: 7-16.

Mahoga H, De Meulenaer B, Kimanya M, Hipolite D, Lachat C, Kolsteren P (2014). Fumonisin B1 contamination in breast milk and its exposure in infants under 6 months of age in Rombo, Northern Tanzania. *Food and Chemical Toxicology*, 74: 112-116.

Martyn DM, Nugent AP, McNulty BA, O'Reilly E, Tlustos C, Walton J, Flynn A, Gibney MJ (2016). Dietary intake of four artificial sweeteners by Irish Pre-School Children, *Food Additives & Contaminants: Part A*, 333(4): 592-602.

Meera P, Rao PR, Shanker R, Tripathi O (1992). Immunomodulatory effects of  $\gamma$ -HCH (lindane) in mice. *Immunopharmacology and Immunotoxicology*, 14, 261-282.

Moorthy B, Chu C, Carlin DJ (2015). Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. *Toxicological Sciences*, 145(1): 5-15.

Morose G (2006). An overview of alternatives to tetrabromobisphenol A (TBBPA) and hexabromocyclododecane (HBCD). Lowell Center for Sustainable Production, University of Massachusetts, USA.

<http://www.sustainableproduction.org/downloads/AlternativestoTBBPAandHBCD.pdf>

Mortensen A (2006). Sweeteners permitted in the European Union: Safety aspects. *Scandinavian Journal of Food and Nutrition*, 50(3): 104-116.

Murphy Jr. G, Rouse RL, Polk WW, Henk WG, Barker SA, Boudreaux MJ, Floyd ZE, Penn AL (2008). Combustion-derived hydrocarbons localize to lipid droplets in respiratory cells. *American Journal of Respiratory Cell Molecular Biology*, 38: 532-540.

Nebert DW, Shi Z, Galvez-Peralta M, Uno S, Dragin N (2013). Oral benzo[a]pyrene: understanding pharmacokinetics, detoxication, and consequences – Cyp1 knockout mouse lines as a paradigm. *Molecular Pharmacology*, 84: 304-313.

NHS (National Health Service) (2018). The truth about sweeteners.

<https://www.nhs.uk/live-well/eat-well/are-sweeteners-safe/>

NTP (1990). Toxicology and carcinogenesis studies of glycidol (CAS No. 556-52-5) in F344/N rats and B6C3F1 mice (gavage studies). Technical Report Series No. 374. National Institutes of Health Publication No. 90-2829. Research Triangle Park, NC.

[https://ntp.niehs.nih.gov/ntp/htdocs/lt\\_rpts/tr374.pdf](https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr374.pdf)

NTP (2011). Summary Report of the National Toxicology Program and Environmental Protection Agency-Sponsored Review of Pathology Materials from Selected Ramazzini Institute Rodent Cancer Bioassays.

[https://ntp.niehs.nih.gov/ntp/about\\_ntp/partnerships/international/summaryrpt\\_report\\_bioassays.pdf](https://ntp.niehs.nih.gov/ntp/about_ntp/partnerships/international/summaryrpt_report_bioassays.pdf)

This is a draft statement and has not been finalised. Therefore, it should not be cited.

NTP (2014). Toxicology studies of tetrabromobisphenol A (CAS No. 79-94-7) in F344/NTac rats and B6C3F1/N mice and toxicology and carcinogenesis studies of tetrabromobisphenol A in wistar han [CrI:WI(Han)] rats and B6C3F1/N mice (gavage studies).

[https://ntp.niehs.nih.gov/ntp/htdocs/lt\\_rpts/tr587\\_508.pdf](https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr587_508.pdf)

Nuehring LP, Rowland GN, Harrison LR, Cole RJ, Dorner JW (1985). Cyclopiazonic acid mycotoxicosis in the dog. American Journal of Veterinary Research, 46(8):1670-6.

Nunes APM, Ferreira-Machado SC, Nunes RM, Dantas FJS, De Mattos JCP, Caldeira-de-Araújo A (2007). Analysis of genotoxic potentiality of stevioside by comet assay. Food and Chemical Toxicology, 45: 662-666.

Ostry V, Toman J, Grosse Y, Malir (2018). Cyclopiazonic acid: 50th anniversary of its discovery. World Mycotoxin Journal, 11(1): 135-148.

Pal S, Singh N, Ansari KM (2017). Toxicological effects of patulin mycotoxin on the mammalian system: an overview. Toxicology Research, 6(6): 764-771.

Petersen MS, Halling J, Bech S, Wermuth L, Weihe P, Nielsen F, Jørgensen PJ, Budtz-Jørgensen E, Grandjean P (2008). Impact of dietary exposure to food contaminants on the risk of Parkinson's disease. Neurotoxicology, 29:584-90.

PRiF (2014a). Pesticides residues monitoring Programme for Monitoring Programme for Quarter 1 2014.

<https://webarchive.nationalarchives.gov.uk/20151023185219/http://www.pesticides.gov.uk/Resources/CRD/PRiF/Documents/Results%20and%20Reports/2014/Q1%2014%20%20FINAL.pdf>

PRiF (2014b). Pesticides residues monitoring Programme for Monitoring Programme for Quarter 3 2014.

<https://webarchive.nationalarchives.gov.uk/20151023185139/http://www.pesticides.gov.uk/Resources/CRD/PRiF/Documents/Results%20and%20Reports/2014/Q3%2014%20FINAL.pdf>

PRiF (2018a). Report on the pesticide residues monitoring programme: Quarter 1 2018.

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/738311/pesticide-residues-quarter1-2018-report.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/738311/pesticide-residues-quarter1-2018-report.pdf)

PRiF (2018b). Report on the pesticide residues monitoring programme: Quarter 2 2018.

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/762243/pesticide-residues-quarter2-2018-report.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/762243/pesticide-residues-quarter2-2018-report.pdf)

PRiF (2018c). Report on the pesticide residues monitoring programme: Quarter 3 2018.

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/784337/pesticide-residues-quarter3-2018-report.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784337/pesticide-residues-quarter3-2018-report.pdf)

Puel O, Galtier P, Oswald I (2010). Biosynthesis and toxicological effects of patulin. *Toxins*, 2(4): 613-631

Rafai P, Bata A, Vanyi A, Papp Z, Brydl E, Jakab L, Tuboly S, Tury E (1995). Effect of various levels of T-2 toxin on the clinical status, performance and metabolism of growing pigs. *The Veterinary Record*, 136(19): 485-489.

Rapaille A, Goosens J, Heume M (2003). Sugar Alcohols. *Encyclopedia of Food Sciences and Nutrition (Second Edition)*, 5665-5671.

Richardson JR, Shalat SL, Buckley B, Winnik B, O'Suilleabhain P, Diaz-Arrastia R, Reisch J, German DC (2009). Elevated serum pesticide levels and risk of Parkinson Disease. *Achieves of Neurology*, 66(7):870-875.

Richardson JR, Roy A, Shalat SL, Buckley B, Winnik B, Gearing M, Levey AI, Factor SA, O'Suilleabhain P, German DC (2011).  $\beta$ -Hexachlorocyclohexane levels in serum and risk of Parkinson's disease. *Neurotoxicology*, 32(5):640-5.

Roberts C, Steer T, Maplethorpe N, Cox L, Meadows S, Page P, Nicholson S, Swan G (2018). National Diet and Nutrition Survey Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 – 2015/2016)

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/699241/NDNS\\_results\\_years\\_7\\_and\\_8.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/699241/NDNS_results_years_7_and_8.pdf)

Roshandel G, Semnani S, Malekzadeh R, Dawsey SM (2012). Polycyclic aromatic hydrocarbons and esophageal squamous cell carcinoma – a review. *Archives of Iranian Medicine*, 15(11): 713-722.

Santonicola S, De Felice A, Cobellis L, Passariello N, Peluso A, Murru N, Ferrante MC, Mercogliano R (2017). Comparative study on the occurrence of polycyclic aromatic hydrocarbons in breast milk and infant formula and risk assessment. *Chemosphere*, 175: 383-390.

SCF (1985). Sweeteners, Reports of the Scientific Committee for Food. Sixteenth Series, EUR 10210 EN, Commission of the European Communities, Luxembourg.

[http://aei.pitt.edu/40825/1/16th\\_food.pdf](http://aei.pitt.edu/40825/1/16th_food.pdf)

SCF (1989). Sweeteners, Reports of the Scientific Committee for Food. Twenty-first Series, EUR 11617 EN, Commission of the European Communities, Luxembourg.

[http://aei.pitt.edu/40830/1/21st\\_food.pdf](http://aei.pitt.edu/40830/1/21st_food.pdf)

SCF (1995). Saccharin and its sodium, potassium and calcium salts. Opinion expressed on 2 June 1995. Published by Commission of the European Communities. Brussels.

[https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com\\_scf\\_7\\_out26\\_en.pdf](https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_7_out26_en.pdf)

SCF (1996). Reports of the Scientific Committee for Food. Thirty-fifth series.

This is a draft statement and has not been finalised. Therefore, it should not be cited.

SCF (1999). Opinion on Fusarium toxins. Part 1: Deoxynivalenol (DON).  
[https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com\\_scf\\_out44\\_en.pdf](https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out44_en.pdf)

SCF (2000). Re-evaluation of acesulfame K with reference to the previous SCF opinion of 1991. Opinion expressed on 9 March 2000. Published by Commission of the European Communities. Brussels.

SCF (2002). Opinion of the Scientific Committee on Food: Update on the Safety of Aspartame (expressed on 4 December 2002).  
[http://ec.europa.eu/food/fs/sc/scf/out155\\_en.pdf](http://ec.europa.eu/food/fs/sc/scf/out155_en.pdf)

SCF (2000): Opinion on the Scientific Committee on Food on Sucralose. SCF/CS/ADDS/EDUL/190 Final.  
[https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com\\_scf\\_out68\\_en.pdf](https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out68_en.pdf)

SCF (2002). Opinion of the Scientific Committee on Food on Fusarium toxins. Part 6: Group evaluation of T-2 toxin, HT-2 toxin, nivalenol and deoxynivalenol.  
[https://ec.europa.eu/food/sites/food/files/safety/docs/cs\\_contaminants\\_catalogue\\_fusarium\\_out123\\_en.pdf](https://ec.europa.eu/food/sites/food/files/safety/docs/cs_contaminants_catalogue_fusarium_out123_en.pdf)

Shi Z, Dragin N, Galvez-Peralta M, Jorge-Nebert LF, Miller ML, Wang B, Nebert DW(2010). Organ-specific roles of CYP 1A1 during detoxication of dietary benzo[a]pyrene. *Molecular Pharmacology*, 78: 46-57.

Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L, Tibaldi E and Rigano A (2006). First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats, *Environmental Health Perspectives*, 114: 379-385.

Soffritti M, Belpoggi F, Tibaldi E, Degli Esposti D and Lauriola M (2007): Life-span exposure to low doses of aspartame beginning during pre-natal life increases cancer effects in rats, *Environmental Health Perspectives*, 115: 1293-1297.

Soffritti M, Belpoggi F, Manservigi M, Tibaldi E, Lauriola M, Falcioni L and Bua L (2010). Aspartame administered in feed, beginning pre-natally through life span, induces cancers of the liver and lung in male Swiss mice, *American Journal of Industrial Medicine*, 53: 1197-1206.

Stratton J, Anderson S, Leon I, Hepworth P, Chapman S, Christy J, Jardine S, Philips D, Setter R, Clough J and MacDonald S. Final report diet study (TDS) – mycotoxin analysis. FS102081. **Unpublished**

Stratton J, Clough J, Leon I, Sehlanova M, MacDonald S (2017). Final report: Monitoring of tropane alkaloids in foods. FS102116.  
<https://www.food.gov.uk/sites/default/files/media/document/fs102116finalreport.pdf>

Tennant D (2014). Potential intakes of total polyols based on UK usage survey data. *Food Additive and Contaminants, Part A: Chemical and Analytical Control Exposure Risk Assessment*, 31(4): 574–586.

Toyoda K, Matsui H, Shoda T, Uneyama C, Takada K, Takahashi M (1997). Assessment of the carcinogenicity of stevioside in F344 rats, Food and Chemical Toxicology, 35: 597-603.

Ueno Y (1983). Trichothecenes: Chemical, biological, and toxicological aspects. Volume 4. Elsevier Science Ltd.

Upton K, De Roos AJ, Thompson ML, Sathyanarayana S, Scholes D, Barr DB, Holt VL (2013) Organochlorine Pesticides and Risk of Endometriosis: Findings from a Population-Based Case-Control Study. Environmental Health Perspectives, Epub ahead of print.

US EPA (2011). Exposure Factors Handbook Chapter 5: Soil and Dust Ingestion. [https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252&CFID=69447188&CF\\_TOKEN=21916199](https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252&CFID=69447188&CF_TOKEN=21916199)

Voss KA, Norred WP, Hinton DM, Cole RJ, Dorner JW (1990). Subchronic oral toxicity of cyclopiazonic acid (CPA) in male Sprague-Dawley rats. Mycopathologia, 110(1):11-8.

Van Velsen FL, Danse LH, Van Leeuwen FXR, Dormans JA, Van Logte, MJ (1986a). The subchronic oral toxicity of the beta-isomer of hexachlorocyclohexane in rats. Fundamental and Applied Toxicology, 6(4):697-712.

Weisskopf MG, Knekt P, O'Reilly EJ, Lyytinen J, Reunanen A, Laden F, Altshul L, Ascherio A (2010) Persistent organochlorine pesticides in serum and risk of Parkinson disease. Neurology, 74(13):1055-61.

Weisskopf MG, Knekt P, O'Reilly EJ, Lyytinen J, Reunanen A, Laden F, Altshul L, Ascherio A (2010) Persistent organochlorine pesticides in serum and risk of Parkinson disease. Neurology, 74(13):1055-61.

White AJ, Bradshaw PT, Herring AH, Teitelbaum SL, Beyea J, Stellman SD, Steck SE, Mordukhovich I, Eng Sm, Engel LS, Conway K, Hatch M, Neugut AI, Santella RM, Gammon MD (2016). Exposure to multiple sources of polycyclic aromatic hydrocarbons and breast cancer incidence. Environment International, 89 – 90: 185-192.

WHO (1983). Evaluation of certain food additives. WHO Technical Report Series, 18, 12-14, Geneva.

<http://www.inchem.org/documents/jecfa/jecmono/v18je01.htm>

WHO (1991). Evaluation of certain food additives. WHO Technical Report Series, 28, 183-218, Geneva.

<http://www.inchem.org/documents/jecfa/jecmono/v28je01.htm>

WHO-IPCS (1992). Alpha- and beta-hexachlorocyclohexane, Environmental Health Criteria 123. World Health Organization, Geneva, Switzerland.

<http://www.inchem.org/documents/ehc/ehc/ehc123.htm>



Wing MG (2000). Investigation of the immunotoxic potential of lindane: Peripheral blood lymphocyte analysis on samples from mouse carcinogenicity study. Unpublished report No. CIL 024/994052 from Huntingdon Life Sciences Ltd, Huntingdon, England. Submitted to WHO by CIEL, Brussels, Belgium.

Woolridge M, Hay A, Renfrew R, Cade J, Doughty J, Law G, Madden S, McCormick F, Newell S, Roman E, Shelton N, Sutcliffe A, Wallis S (2004). SUREmilk study - Surveillance of residues in human milk: Pilot studies to explore alternative methods for the recruitment, collection, storage and management of an archive of breast milk samples. University of Leeds.

Xue W, Warshawsky D (2005). Metabolic activation of polycyclic aromatic hydrocarbons and DNA damage: a review. *Toxicology and Applied Pharmacology*, 206: 73-93.

Yang S, De Boevre M, Zhang H, De Ruyck K, Sun F, Wang Z, Cao X, Shen J, De Saeger S, Zhang S (2015). Unravelling the in vitro and in vivo metabolism of diacetoxyscirpenol in various animal species and human using ultrahigh-performance liquid chromatography-quadrupole/time-of-flight hybrid mass spectrometry. *Analytical and Bioanalytical Chemistry*, 407(28): 8571-8583.

Zimmer I, Usleber E, Klaffke H, Weber R, Majerus P, Otteneder H, Gareis M, Dietrich R, Märtlbauer E (2008). Fumonisin intake of the German consumer. *Mycotoxin Research* 24: 40-52.

## 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
ADME	Absorption, distribution, metabolism, excretion
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

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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
ER	Estrogen receptors
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

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ICH	European Medicines Agency and International Council for the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IgM	Immunoglobulin 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 <sub>50</sub>	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
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
NIS	Sodium-iodine symporter
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

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PeCB	Pentachlorobenzene
PHE	Public Health England
PKU	Phenylketonuria
PMTDI	Provisional maximum tolerable daily intake
PMTWI	Provisional maximum tolerable weekly intake
POD	Point of departure
POPs	Persistent organic pollutants
PRiF	Expert Committee on Pesticide Residues in Food
RfD	Reference dose
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
t-TDI	Temporary tolerable daily intake
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

### TOX/2019/75

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. 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 endosulfane, 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 was not applicable to the age groups assessed or the COT did not see a reason to change the current advice to government in the absence of any new data. Soya phytoestrogens are currently undergoing a separate review<sup>9</sup>, 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.

<b>Chemicals discussed in the Overarching Statement</b>	
Chlorate	<a href="https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf">https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf</a>
Chromium	<a href="https://cot.food.gov.uk/sites/default/files/tox2018-32.pdf">https://cot.food.gov.uk/sites/default/files/tox2018-32.pdf</a>
Furan	<a href="https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf">https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf</a>
Perchlorate	<a href="https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf">https://cot.food.gov.uk/sites/default/files/tox2018-31.pdf</a>
Selenium	<a href="https://cot.food.gov.uk/sites/default/files/tox2018-28.pdf">https://cot.food.gov.uk/sites/default/files/tox2018-28.pdf</a>
Vitamin A	<a href="https://cot.food.gov.uk/sites/default/files/statementaddendumvitamina.pdf">https://cot.food.gov.uk/sites/default/files/statementaddendumvitamina.pdf</a>
Zinc	<a href="https://cot.food.gov.uk/sites/default/files/tox2018-28.pdf">https://cot.food.gov.uk/sites/default/files/tox2018-28.pdf</a>
<b>Chemicals discussed in the Addendum</b>	
Hxachlorocyclohexane	<b>TO BE ADDED AFTER DECEMBER COT</b>
Monochloropropane diol	Initially presented in May 2019, paper currently not on COT website available
Mycotoxins	<a href="https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf">https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf</a>
• Aflatoxins	<a href="https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf">https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf</a>
• Citrinin	<a href="https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf">https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf</a>
• Cyclopiazonic acid	<a href="https://cot.food.gov.uk/sites/default/files/tox201964cpainthedietofinfantsand15.pdf">https://cot.food.gov.uk/sites/default/files/tox201964cpainthedietofinfantsand15.pdf</a>

<sup>9</sup> ADD LINK FOR DECEMBER PAPER

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• Deoxynivalenol	<a href="#">TO BE ADDED AFTER DECEMBER COT</a>
• 4,15-Diacetoxycirpenol	<a href="https://cot.food.gov.uk/sites/default/files/tox2018-51.pdf">https://cot.food.gov.uk/sites/default/files/tox2018-51.pdf</a>
• Ergot alkaloids	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf</a>
• Fumonisin	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-02_0.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-02_0.pdf</a> <a href="https://cot.food.gov.uk/sites/default/files/tox2019-28.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-28.pdf</a> <a href="https://cot.food.gov.uk/sites/default/files/tox201940fumonisins.pdf">https://cot.food.gov.uk/sites/default/files/tox201940fumonisins.pdf</a>
• Fusarenone	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-17.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-17.pdf</a> <a href="https://cot.food.gov.uk/sites/default/files/tox2019-33.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-33.pdf</a>
• Moniliformin	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-03.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-03.pdf</a>
• Nivalenol	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf</a>
• Patulin	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-19.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-19.pdf</a> <b>ADD LINK TO COC/Oct COT minutes</b>
• Sterigmatocystin	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf</a>
• Zearalenone	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-30.pdf</a>
Polycyclic Aromatic Hydrocarbons	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-21.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-21.pdf</a>
Sweeteners	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-36.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-36.pdf</a>
• Aspartame	<a href="https://cot.food.gov.uk/sites/default/files/tox201943steviolexposuresforchildrenaged.pdf">https://cot.food.gov.uk/sites/default/files/tox201943steviolexposuresforchildrenaged.pdf</a>
• Acesulfame K	
• Saccharine	
• Sorbitol	
• Sucralose	
• Stevia	
• Xylitol	
Tetrabromobisphenol	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-04.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-04.pdf</a>
Tropane alkaloids	<a href="https://cot.food.gov.uk/sites/default/files/tox2019-22.pdf">https://cot.food.gov.uk/sites/default/files/tox2019-22.pdf</a> <a href="https://cot.food.gov.uk/sites/default/files/tox201941taadditionalinformation.pdf">https://cot.food.gov.uk/sites/default/files/tox201941taadditionalinformation.pdf</a>
<b>Chemicals which underwent a separate full review</b>	
Acrylamide	<a href="https://cot.food.gov.uk/sites/default/files/finalacrylamidestatement.pdf">https://cot.food.gov.uk/sites/default/files/finalacrylamidestatement.pdf</a>
Aluminium	<a href="https://cot.food.gov.uk/sites/default/files/finalaluminiumaddendum_0.pdf">https://cot.food.gov.uk/sites/default/files/finalaluminiumaddendum_0.pdf</a>
Arsenic	<a href="https://cot.food.gov.uk/sites/default/files/finalstatementonarsenic_0.pdf">https://cot.food.gov.uk/sites/default/files/finalstatementonarsenic_0.pdf</a>
Bisphenol A	EFSA opinion still to be published
Copper	<a href="https://cot.food.gov.uk/sites/default/files/cotstatementoncopper.pdf">https://cot.food.gov.uk/sites/default/files/cotstatementoncopper.pdf</a>
Cadmium	<a href="https://cot.food.gov.uk/sites/default/files/cotstatementoncadmium.pdf">https://cot.food.gov.uk/sites/default/files/cotstatementoncadmium.pdf</a>
Dioxins and dioxin-like compounds	EFSA opinion <a href="https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5333">https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5333</a>
Hexabromocyclododecane	<a href="https://cot.food.gov.uk/sites/default/files/finaladdendumonhbcdds.pdf">https://cot.food.gov.uk/sites/default/files/finaladdendumonhbcdds.pdf</a>
Iodine	<a href="https://cot.food.gov.uk/sites/default/files/statementiodine0to5.pdf">https://cot.food.gov.uk/sites/default/files/statementiodine0to5.pdf</a>
Lead	<a href="https://cot.food.gov.uk/sites/default/files/finaladdendumonlead.pdf">https://cot.food.gov.uk/sites/default/files/finaladdendumonlead.pdf</a>
Manganese	Awaiting publication
Methylmercury	<a href="https://cot.food.gov.uk/sites/default/files/cotstatementonmethylmercury.pdf">https://cot.food.gov.uk/sites/default/files/cotstatementonmethylmercury.pdf</a>
Nickel	<a href="https://cot.food.gov.uk/sites/default/files/statementonpotentialrisksofnickel.pdf">https://cot.food.gov.uk/sites/default/files/statementonpotentialrisksofnickel.pdf</a>
Ochratoxin A	<a href="https://cot.food.gov.uk/sites/default/files/cotstatement-ota.pdf">https://cot.food.gov.uk/sites/default/files/cotstatement-ota.pdf</a>
Perfluorooctanesulfonic acid	EFSA opinion <a href="https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5194">https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5194</a>

This is a draft statement and has not been finalised. Therefore, it should not be cited.

and Perfluorooctanoic acid	
Phthalates	EFSA opinion <a href="http://www.efsa.europa.eu/sites/default/files/consultation/consultation/Phthalates_in_plastic_FCM_draft_opinion_for_public_consultation.pdf">http://www.efsa.europa.eu/sites/default/files/consultation/consultation/Phthalates_in_plastic_FCM_draft_opinion_for_public_consultation.pdf</a>
Polybrominated biphenyls	<a href="https://cot.food.gov.uk/sites/default/files/cotfinalminutes08dec15.pdf">https://cot.food.gov.uk/sites/default/files/cotfinalminutes08dec15.pdf</a>
Polybrominated diphenyl ethers	<a href="https://cot.food.gov.uk/sites/default/files/statementpbdes.pdf">https://cot.food.gov.uk/sites/default/files/statementpbdes.pdf</a>
T-2 toxin, HT-2 toxin and neosolaniol	<a href="https://cot.food.gov.uk/sites/default/files/cotstatement-t2ht2andneosolaniol.pdf">https://cot.food.gov.uk/sites/default/files/cotstatement-t2ht2andneosolaniol.pdf</a>