Annex A - Statement on the risk assessment of cow’s milk in children aged 6 months to 5 years, in the context of plant-based drinks evaluations

Chemicals evaluated - Annex A

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Nitrate and nitrite

3. EFSA published an Opinion on nitrate in food in 2008 (vegetables) in which an acceptable daily intake (ADI) of 5 and 3.7 mg/kg body weight (bw) per day was established for sodium nitrate and the ion form of nitrate respectively. These guidance values were based on a 125 day subchronic exposure study in dogs and a chronic study in rats, using growth retardation as the toxicological endpoint. An uncertainty factor of 100 was applied to No-Observed-Adverse-Effect Levels (NOAELs) of 500 mg/kg bw per day (sodium nitrate) and 370 mg/kg bw per day (nitrate ion). (EFSA, 2008a).

Exposure Assessment and risk characterisation

4. Only limited occurrence data for nitrate and nitrite in cow’s milk could be found from the literature. A literature search was undertaken using the keywords Nitrate OR Nitrite AND Cow AND Milk in both PubMed (PubMed (nih.gov) and Science Direct (ScienceDirect.com | Science, health and medical journals, full text articles and books.) Searches were limited to data published since 2001 and only the top 50 hits (sorted by relevance) for each reference database were reviewed.

5. Only a limited number of references were found that reported any ‘background’ contamination of nitrate or nitrite in cow’s milk. Most of the papers reported nitrate and / or nitrite concentrations in cow’s milk outside the EU (e.g.

Brazil, Taiwan, Turkey and the USA) where agricultural practices may differ significantly from the UK. Olijhoek et al. (2016) reported mean nitrate background concentrations (n = 4) of 0.13 mg/L in milk from a Danish herd (minimum and maximum values were not reported).

6. Potential chronic exposures to nitrate, based on the consumption data in Table 1 and the average nitrate concentration reported in Olijhoek et al. (2016), together with the percentage of the ADI of 3.7 mg/kg bw per day these represent, (EFSA, 2008a) are presented in Table 3.

Table 3. Nitrate risk characterisation from cow's milk consumption.

Age (months	Estimated Exposure (mean) (mg/kg bw per day)	Estimated Exposure (97.5th percentile) (mg/kg bw per day)	% ADI (mean consumption)	% ADI (97.5th percentile consumption)
6 – <12	0.00169	0.00624	0.046	0.169
12 – <18	0.00416	0.00975	0.112	0.264
18 – <24	0.00377	0.01027	0.102	0.278
24 – <48	0.00299	0.00767	0.081	0.207
48 – <60	0.00221	0.00598	0.060	0.162

7. EFSA published an Opinion in 2009 considering nitrite as an undesirable substance in animal feed. This opinion states "because of the rapid excretion of nitrite and nitrate, the likelihood of accumulation in animal tissues and products such as milk and eggs is low." The opinion also concludes that due to the extremely low concentrations of nitrite reported in fresh animal products there is no human health concern for this chemical in regard to dietary consumption (EFSA, 2009b).

8. In light of the very low percentages of the recommended ADI for nitrate that would occur through consumption of cow's milk in young children, along with the EFSA (2009) opinion's conclusion on nitrite, the COT concluded that nitrite and

nitrate contamination of cow’s milk do not pose a health risk for children aged 6 months to 5 years of age.

Bisphenol A

Risk Characterisation

9. EFSA published an Opinion in 2015 on the risks to public health related to the presence of BPA in foodstuffs in which a reduced temporary Tolerable Daily Intake (TDI) was proposed, revised from 50 down to 4 µg/kg bw per day. This guidance value was determined after a benchmark dose lower confidence limit (BMDL10) of 8,960 µg/kg bw per day was calculated for changes in the mean relative kidney weight in mice, converting this to an oral human equivalent dose (HED) of 609 µg/kg bw per day and then applying a total uncertainty factor of 150 (2.5 for inter- and 10 for intra-species differences and an additional factor of 6 for uncertainty in mammary gland, reproductive, neurobehavioral, immune and metabolic system effects). Inter-species differences in toxickinetics were covered by the use of the HED (EFSA, 2015b).

10. EFSA’s (2015b) comprehensive review of BPA exposure and toxicity concluded that BPA posed no health concern for consumers of any age group (including unborn children, infants and adolescents) at current dietary exposure levels; although the Panel noted some uncertainty regarding BPA exposure from non-dietary sources. EFSA have recently undertaken a new review of the TDI for BPA.

11. In EFSA’s (2023) re-evaluation of BPA, they established a TDI of 0.2 ng/kg bw per day. The critical effect identified was on Th17 immune cells in mice. For this critical effect, EFSA identified a reference point of 8.2 ng/kg bw per day expressed as a human equivalent dose. EFSA then conducted uncertainty analysis, which assessed a probability of 57-73% that the lowest benchmark dose for other health effects was below the reference point that was identified for Th17 cells. From this, EFSA used an uncertainty factor of 2. This was combined with an uncertainty factor of 2.5 for inter-species toxicodynamic differences and an additional uncertainty factor of 10 for intra-human variation in toxicokinetics and toxicodynamics. This produced a total uncertainty factor of 50, which was applied to the reference point to produce the TDI of 0.2 ng/ kg bw per day. EFSA applied this new TDI to their 2015 exposure assessment and concluded that mean and 95 th percentile dietary exposures exceeded the new TDI by two to three orders of magnitude for all populations (EFSA, 2023).

12. The COT had a number of reservations about EFSA's evaluation and has agreed to conduct its own assessment. The Committee is in the process of producing an interim position paper, capturing its views and proposed next steps following EFSA's updated scientific opinion (EFSA, 2023). Whilst the COT considered it possible that the TDI for BPA may need to be revised to account for new evidence and ensure it was sufficiently protective, on balance the weight of evidence did not support the conclusions drawn by EFSA, or a TDI as low as that established by EFSA in 2023. The Committee previously agreed with EFSA's assessment of the safety of BPA in 2007, 2008 and 2015 (EFSA, 2007, 2008c, 2015). Based on the 2015 opinion, the COT do not currently consider that levels of BPA within cow's milk present a risk to health for children aged 6 months to 5 years of age.

Phthalates

13. In 2005, EFSA performed risk assessments on a small range of the most widely used phthalates, namely, di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2- ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and diisodecylphthalate (DIDP) and established TDIs for them (EFSA, 2005a, 2005b, 2005c, 2005d, 2005e). In 2003 the World Health Organisation established a TDI for diethyl phthalate (DEP) of 5 mg/kg bw, based on increased maternal adrenal and kidney weights, and decreased fetal weight in a developmental toxicity study in mice, with a NOAEL of 1600 mg/kg bw per day. An overall safety factor of 300 was used, an additional factor of 3 being included because of the incompleteness of the database (WHO, 2003).

14. EFSA's risk assessment and revaluation in 2019 of DBP, BBP, DEHP, DINP and DIDP for use in food contact materials confirmed the same critical effects and individual TDIs (mg/kg bw per day) established in 2005, i.e. reproductive effects for DBP (0.01), BBP (0.5), DEHP (0.05), and liver effects for DINP and DIDP (0.15 each). Based on a plausible common mode of action (i.e. reduction in fetal testosterone) underlying the reproductive effects of DEHP, DBP and BBP, the Panel considered it appropriate to establish a group-TDI for these phthalates, taking DEHP as an index compound as a basis for calculating relative potency factors.

15. The EFSA 2019 panel on Food Contact Materials, Enzymes and Processing Aids (CEP) (EFSA, 2019) noted that DINP also affected fetal testosterone levels at doses around three-fold higher than those associated with liver effects and therefore considered it prudent to include it within the group-TDI. To account for the different potencies towards the hepatic and reproductive

endpoints an additional factor of 3.3 was used in the relative potency factor for DINP to ensure that it would not exceed the TDI derived from hepatic effects.

16. DIDP was not included in the group-TDI as its reproductive effects (i.e. decreased survival rate in the F2 generation) are not considered to be associated with anti-androgenicity. Therefore, DIDP maintained its individual TDI for liver effects of 0.15 mg/kg bw per day.

17. The group-TDI from EFSA's CEP (2019) opinion was calculated by means of relative potency factors, with DEHP taken as the index compound, as it has the most robust toxicological dataset. The relative potency factors were calculated from the ratio of the TDI for DEHP to the HBGVs of the three other phthalates. ('Group Phthalates concentration expressed as DEHP equivalents ([GPDEq], µg/kg food) = DEHP*1 + DBP*5 + BBP*0.1 + DINP*0.3.') The group-TDI was established to be 0.05 mg/kg bw per day, expressed as DEHP equivalents.

Risk Characterisation

18. EFSA's CEP panel (2019) concluded that the Group Phthalates (expressed as DEHP equivalents) using mean consumer dietary exposure, contributed only up to a maximum of 14% of the recommended group-TDI, with the high (P95) consumers up to a maximum of 23%. Additionally, they concluded that the DIDP dietary exposure estimates for both mean and high (P95) consumers were well below the recommended TDI of 0.15 mg/kg bw per day.

19. In May 2011, COT produced a statement (COT, 2011) on dietary exposure to phthalates DBP, BBP, DEHP, DINP, DIDP and DEP using data from the UK Total Diet Study (TDS), and concluded that the levels of phthalates that were found in samples from the 2007 TDS did not indicate a risk to human health from dietary exposure, either when the compounds were assessed alone or in combination.

20. In the recent COT review of EFSA' s public consultation on the EFSA Opinion "Draft update of the risk assessment of dibutylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isonylphthalate (DINP) and diisodecylphthalate (DIDP) for use in food contact materials", the COT were content that for DBP, BBP, DEHP and DINP the exposures estimated by EFSA did not indicate a health concern using the group TDI (COT, 2019).

21. From this information the COT concluded that phthalates at the levels within cow's milk do not present a risk to health for children aged 6 months to 5 years of age.

Dioxin and Dioxin-Like polychlorinated biphenyls (DL-PCBs)

22. Dioxins have a range of toxic effects on cells and in laboratory animal studies and 2,3,7,8- tetrachlorodibenzyl dioxin (TCDD) is regarded as the most toxic of the group. The toxicities of other congeners are related to that of TCDD by Toxic Equivalency Factors (TEFs). The toxicity of mixtures of dioxins and dioxin-like PCBs are quantified by the product of the concentration of each congener in the mixture and a TEF to yield a Toxic Equivalent (TEQ) value (Van den Berg et al., 2006).

23. The COT evaluated dioxins and dioxin-like PCBs in 2001 (COT, 2001). The COT agreed with the evaluation of the EU Scientific Committee on Food (SCF, 2000) who, in 2000, recommended a temporary Tolerable Weekly Intake (t-TWI) of 7 pg WHO-TEQ/kg bw. The SCF (2001) then re-evaluated this t-TWI based on rat studies, which reported reproductive effects in male offspring. Applying an overall uncertainty factor of 10 (factors of 3.2 for interindividual variations in human toxicokinetics and 3 for use of a LOAEL were used, and the result rounded) to the estimated human daily intake (EHDI) of 20 pg/kg bw per day, equivalent to the body burden in rats at the Lowest Observed Adverse Effect Level (LOAEL), the SCF concluded that 14 pg/kg bw per week should be considered as a tolerable weekly intake for 2,3,7,8-TCDD. The COT in 2001, established a tolerable daily intake of 2 pg WHO-TEQ/kg bw per day based upon effects on the developing male reproductive system mediated via the maternal body burden. It was also considered that this TDI was adequate to protect against other possible effects, such as cancer and cardiovascular effects.

24. In a recent opinion, the EFSA CONTAM Panel (EFSA, 2018a) used toxicokinetic modelling to estimate that long term exposure of adolescents and adults should be less than 0.25 pg WHO-TEQ/kg bw per day to ensure that serum levels of dioxins and DL-PCBs in boys remain below the NOAEL for effects on sperm concentrations. The CONTAM panel expressed this on a weekly basis, with rounding, to establish a TWI of 2 pg TEQ/kg bw per week, a seven-fold reduction in their t-TWI from 2001. The TWI was based on the critical effect of changes in sperm concentrations that were inversely associated with serum concentration of TCDD, PCDD-TEQ and PCDD/F-TEQ in a study of Russian children whose parents had been exposed to dioxins (mainly TCDD) during manufacture of trichlorophenol and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) (Mínguez-Alarcón et al., 2017).

25. The COT reviewed the new EFSA TWI for dioxins, setting out their views in a position paper (COT, 2021c). The Committee concluded that EFSA’s

estimation was based upon weak data sets and provided little justification for such a reduction in the Health Based Guidance Value (HBGV), the current value of 14 pg TEQ/kg bw per week having previously been shown to afford protection to the developing fetus. The European Commission (EC) has not yet adopted EFSA's new TWI due to ongoing work at the international level to review the basis and values of the WHO toxic equivalent factors (TEFs). The review of the TEFs and a finalised assessment by the EC are not expected until sometime in 2023, at the earliest.

Exposure Assessment and risk characterisation

26. It has been reported that dioxins and DL-PCBs will readily transfer through milk into the food chain. It is estimated that up to 90% of human exposure to dioxins and PCBs is derived from foodstuffs of animal origin (Food Safety Authority of Ireland, 2009).

27. To obtain occurrence data for dioxins and DL-PCBs in cow's milk the survey published by EFSA in 2018 was used. This was used rather than other published occurrence data as it is comprehensive, covering 935 cow's milk samples from 23 EU countries, including the UK, providing UB and LB data as WHO TEQ units (making the results more easily comparable to the HBGV). The results of this survey are summarised in Table 4. When converting results from the survey that have been reported on a 'per fat' basis, a value of 3.5% fat has been used as a general worst case for fat content of the range of milk types, as this is the minimum legal requirement for fat content of whole milk in the UK (Dairy UK, 2018). This is a worst case scenario as the chemical contaminants will reside in the fat portion of the milk, i.e. the higher the fat content the greater potential of contamination. The NHS recommend that children should only consume cow's milk as a drink from the age of 1 year. Whole cow's milk should be used until the age of 2 years after which, semi skimmed can be introduced - but lower fat milks can be used in cooking from the age of 1 year. Therefore, although the youngest children would potentially be more exposed to any dioxin contamination, this will reduce as lower fat milks replace whole milk in the diet.

28. Tables 5 and 6 summarise the potential chronic exposure to dioxins plus DL-PCBs based on the cow's milk consumption data in Table 1, using the upper bound mean and 95th percentile concentrations from the EFSA survey data (2018a), together with the percentage of the recommended TDI of 2 pg WHO-TEQ/kg bw per day from COT in 2001 that this represents.

29. The upper bound occurrence value is calculated by assuming that where levels of contaminants were below the level of detection (LOD) or limit of quantification (LOQ) reported, the contaminant is present at that concentration. In a lower bound scenario, it is assumed that any levels below the LOD or LOQ reported are 0.

Table 4. Summary of Dioxins plus DL-PCBs concentrations in cow's milk (whole sample basis) from EFSA (2018a).

Sample details	pg WHO TEQ / g
Number of samples	935
Mean concentration, Lower Bound	0.026
Mean concentration, Upper Bound	0.032
95^{th} percentile, Lower Bound	0.063
95^{th} percentile, Upper Bound	0.070

Table 5. Risk characterisation of Dioxin plus DL-PCBs from cow's milk consumption using the upper bound mean concentration from EFSA (2018a).

Age (months	Estimated Exposure mean) (pg WHO TEQ / kg bw per day)	Estimated Exposure (97.5th percentile) (pg WHO TEQ / kg bw per day)	% TDI (mean consumption)	% TDI (97.5th percentile consumption)
6 – 12	0.416	1.54	20.8	76.8
12 – 18	1.02	2.40	51.2	120
18 – 24	0.928	2.53	46.4	126

24 – 48	0.736	1.89	36.8	94.4
48 – 60	0.544	1.47	27.2	73.6

Table 6. Risk characterisation of Dioxin plus DL-PCBs from cow's milk consumption using the upper bound 95th percentile concentration from EFSA (2018a).

Age (months	Estimated Exposure mean) (pg WHO TEQ / kg bw per day)	Estimated Exposure (97.5th percentile) (pg WHO TEQ / kg bw per day)	% TDI (mean consumption)	% TDI (97.5th percentile consumption)
6 – 12	0.91	3.36	45.5	168
12 – 18	2.24	5.25	112	263
18 – 24	2.03	5.53	102	277
24 – 48	1.61	4.13	80.5	207
48 – 60	1.19	3.22	59.5	161

30. Based on the 97.5th percentile consumption data, two age ranges exceed the TDI of 2 pg WHO-TEQ/kg bw per day when using the upper bound mean concentration from the EFSA occurrence data, by around 20-25% (Table 5). No age ranges exceeded the TDI when the mean consumption data were used in this calculation (Table 5). All age ranges using the 97.5th percentile consumption data exceed this TDI when using the 95th percentile concentration from the EFSA occurrence data, by up to 3-fold (Table 6). Two age ranges using the mean consumption data and the 95th percentile concentration from the EFSA occurrence data slightly exceeded the TDI (Table 6). However, given the added safety margin of using the upper bound occurrence concentrations along with the worst-case assumption of all the milk from the EFSA survey containing 3.5% fat, it is suggested that, in practice, dioxins plus DL-PCBs in cow's milk represent a

lower safety risk than suggested by the above assessment.

31. In the recent COT review for SACN on the risk of toxicity of chemicals in the diets of infants and young children the COT agreed to undertake its own new assessment of dioxin and dioxin-like compounds. However, in the meantime the Committee did not consider it necessary to alter its existing advice. Any action now would take several years to be reflected in changes in body burden, due to the long half-life of dioxins (COT, 2020a).

32. The current view of the COT from the exposure assessments conducted in this annex is that the levels of dioxins and dioxin-like PCBs within cow's milk do not present a risk to health for children aged 6 months to 5 years of age.

Non-dioxin-like PCBs

33. The COT concluded in 1997 (COT, 1997) that any carcinogenesis caused by PCBs in animal studies was likely to be due to a "non-genotoxic" mechanism and accepted the advice of the COM and COC that it would be prudent to assume that all PCB congeners are potential human carcinogens. The Committee noted that preliminary work indicated that current human body burdens of PCBs may be affecting thyroid hormone levels. Further work was thought to be needed to develop an approach for assessing the health risks of the non-coplanar PCB congeners, but it was felt unlikely that there was a health risk from current intakes of PCBs from food. PCBs were likely to persist as contaminants of the environment for many years and the Committee recommended that levels in food and in human milk should continue to be monitored at regular intervals to confirm that the downward trend continued. Otherwise, a further review would be recommended to determine how human exposure could be reduced.

34. EFSA published a scientific opinion on non-dioxin-like PCBs in feed and food in 2005 concluding that "no health-based guidance value for humans can be established for NDL-PCB because simultaneous exposure to NDL-PCB and dioxin like compounds hampers the interpretation of the results of the toxicological and epidemiological studies, and the database on the effects of individual NDL-PCB congeners is rather limited. There are, however, indications that subtle developmental effects, being caused by NDL-PCB, DL-PCB, or polychlorinated dibenzo-pdioxins/polychlorinated dibenzofurans alone, or in combination, may occur at maternal body burdens that are only slightly higher than those expected from the average daily intake in European countries. Because some individuals

and some European (sub)-populations may be exposed to considerably higher average intakes, a continued effort to lower the levels of NDL-PCB in food is warranted." (EFSA, 2005).

35. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) last evaluated the NDL-PCBs in 2016 (FAO/WHO, 2016).). Six of these (PCB 28, PCB 52, PCB 101, PCB 138, PCB 153 and PCB 180) are often called "indicator PCBs" or 'ICES- 6'. The Committee focused on the six indicator PCBs, as there were sufficient data (toxicological, biomonitoring, occurrence and dietary exposure) available for review. National and international estimates of dietary exposure to the sum of the six indicator PCBs ranged, for mean exposure, from 1 to 82 ng/kg bw per day and, for high percentile exposure, from 1 to 163 ng/kg bw per day. None of the available studies for four of the six indicator PCBs was suitable for derivation of health-based guidance values or for assessment, so a comparative approach using the minimal effect doses was used to estimate Margins of Exposure (MOE) to provide guidance on human health risk.

36. In the 2005 opinion, EFSA stated 'the absence of mutagenicity indicates that a threshold approach is appropriate for the hazard characterisation, the toxicological database, however, was considered to be too limited to allow the establishment of HBGVs for NDL-PCBs. The Panel therefore decided to perform its health risk characterisation on the basis of a margin of exposure approach'. This was using a NOAEL for liver and thyroid toxicity in a 90 day rat study and applying an estimated 'body burden' margin of exposure approach (MoBB), calculated by dividing the estimated rat body burden NOAEL of 400, 800, and 1,200 µg/kg bw for PCB 28, 128, and 153, respectively by the estimated median human body burden. For all NDL-PCBs EFSA estimated an overall body burden NOAEL of 500 µg/kg.

37. The EFSA CONTAM Panel noted in its Scientific Opinion of 2005, that the sum of the six indicator PCBs represents approximately 50% of the total NDL-PCB in food.

38. The ICES- 6 NDL-PCBs are regulated in the EU (1259/ 2011), which states these should not be present as a summed concentration above 1 µg/kg for foods intended for young children.

Risk characterisation

39. From the EFSA (2005) opinion, it was concluded that the overall MOE for all NDL-PCBs MoBB was approximately 10. Although this margin appears low it is conservative due to the potential influence of dioxins and DL-PCBs

contamination of the assessment, as these have the same toxicological endpoints but greater potency. No overall conclusion was drawn in this opinion apart from ‘A continuing effort to lower the levels of NDL-PCB in food is warranted.’

40. Considering the large European survey undertaken by EFSA (2010a) (5,640 samples from 23 EU countries, including the UK), where the upper bound mean and 95th percentile occurrence concentrations (0.32 and 0.56 µg/kg respectively assuming a 3.5% whole milk sample basis) were less than the regulatory value of 1 µg/kg for foods intended for young children, it is suggested that the risk of NDL-PCBs from drinking cow’s milk is negligible.

41. Furthermore, JECFA concluded in 2016 (FAO/WHO2016) that ‘dietary exposures to NDL-PCBs are unlikely to be of health concern for adults and children, based on the available data.’

42. The COT concluded, based on the above evidence that there was no risk to health from the levels of NDL-PCBs within cow’s milk for children aged 6 months to 5 years of age.

Polycyclic Aromatic Hydrocarbons (PAHs)

43. In 2008 EFSA reviewed PAHs in food (EFSA, 2008b). Considering the large number of possible members in the group, they concluded that although benzo[a]pyrene (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, provided a better measure for risk assessment purposes.

44. Short term PAH exposure appears to cause eye and skin irritation, nausea and vomiting, and local inflammation but since PAHs occur as mixtures that may also include other non-PAH components, it is difficult to ascertain that the PAHs are the causative agents of these effects (Kim et al., 2013). Exposure to PAHs has also been associated with increased risk of cancer of various tissues including the oesophagus (Roshandel et al., 2012), gastrointestinal tract (Diggs et al., 2011) and lung (Moorthy, Chu and Carlin, 2015).

45. Animal feed can potentially be contaminated with PAHs through air, water or soil. Cows can therefore be exposed, and the contaminants transferred to the milk. PAHs are lipophilic and, as persistent organic pollutants, widely distributed in the environment, hence would be expected to occur in milk as contaminants (Sun et al., 2020).

46. In contrast to dioxins and PCBs which are resistant to metabolism in animal species, PAHs can be metabolised but their interaction with the cow rumen, for example, is not well understood. (Rychen et al., 2008).

47. Rather than proposing a HBGV, EFSA in 2008 (EFSA, 2008b) used MOEs, for which they derived BMDL10 values for BaP and the sum of PAH4 of 0.070 mg/kg bodyweight (bw) per day) and 0.340 mg/kg bw per day respectively using the US EPA BMD software (BMDS). EU regulatory limits, (EU) 835/ 2011 have been set for milk intended for infants of 1 µg/kg for BaP and 1 µg/kg for the sum of the PAH4.

Exposure assessment and risk characterisation

48. To obtain concentrations for PAHs in cow's milk a literature search was undertaken using the keywords PAH AND Cow AND Milk in both PubMed and Science Direct. Searches were limited to data published since 2001 and only the top 50 hits (sorted by relevance) for each reference database were reviewed.

49. Data retrieved were limited to 6 small surveys within EU countries from one paper (Sun et al., 2020), a study which investigated 9 samples of pasteurised Italian milk (Naccari et al., 2011) and a study investigating 18 samples of pasteurised Italian cow's milk (Girelli, Sperati and Tarola, 2014).

50. Due to the limited occurrence data in the literature, the UK TDS results for PAHs in 44 UK milk samples from 2012 were used in the exposure assessment as it was considered that they were more representative of UK milk (Fernandes et al., 2012). Only averages were provided in the report for lower and upper bound concentrations, not maximum or upper percentile values. The data are summarised below in Table 7.

Table 7. Summary of PAHs concentrations in cow's milk (whole sample basis) from UK TDS (Fernandes et al., 2012).

Sample information	µg/kg
Number of samples	44
Mean concentration BaP, Lower Bound	0.04

Mean concentration BaP, Upper Bound	0.04
Mean concentration PAH4, Lower Bound	0.01
Mean concentration PAH4, Upper Bound	0.1

51. For assessment, the EFSA panel (EFSA, 2008b) used a MOE approach based on dietary exposure for average and high level consumers to benzo[a]pyrene and PAH4 respectively and their corresponding BMDL10 values derived from the two coal tar mixtures that were used in the carcinogenicity studies of Culp et al., (1998). The panel concluded that 'The resulting MOEs for average consumers (average estimated dietary exposure) were 17,900 for benzo[a]pyrene (and) 17,500 for PAH4. For high level consumers, the respective MOEs were 10,800 and 9,900. These MOEs indicate a low concern for consumer health at the average estimated dietary exposures.' However, the MOEs are close to or below 10,000 for higher level consumers indicating potential safety concern.

52. A MOE assessment has been undertaken using the upper bound average concentrations from the TDS 2012 data (Table 8) and consumption data in Table 1 and the BMDL10 values from EFSA (2008b). This assessment is presented in Tables 8 and 9 for benzo[a]pyrene and PAH4, respectively.

Table 8. Benzo[a]pyrene risk characterisation for cow's milk consumption.

Age (months	Estimated Exposure (mean) (µg/kg bw per day)	Estimated Exposure (97.5th percentile) (µg/kg bw per day	Margin of Exposure to BMDL10 (EFSA 2008b) (mean consumption)	Margin of Exposure to BMDL10 (EFSA 2008b) (97.5th percentile consumption)
6 – 12	0.00052	0.00192	134,615	36,458
12 – 18	0.00128	0.0030	54,688	23,333
18 – 24	0.00116	0.00316	60,345	22,152

24 – 48	0.00092	0.00236	76,087	29,661
48 – 60	0.00068	0.00184	102,941	38,043

Table 9. PAH4 risk characterisation for cow’s milk consumption.

Age (months	Estimated Exposure (mean) (µg/kg bw per day)	Estimated Exposure (97.5th percentile) (µg/kg bw per day	Margin of Exposure to BMDL10 (EFSA 2008b) (mean consumption)	Margin of Exposure to BMDL10 (EFSA 2008b) (97.5th percentile consumption)
6 – 12	0.0013	0.0048	261,538	70,833
12 – 18	0.0032	0.0075	106,250	45,333
18 – 24	0.0029	0.0079	117,241	43,038
24 – 48	0.0023	0.0059	147,826	57,627
48 – 60	0.0017	0.0046	200,000	73,913

53. The MOEs presented are all above 10,000 for both average and high-level consumers across all age ranges of young children, based on the UK TDS from 2012. These high MOEs indicate that concern for any adverse health effects of B[a]P or PAH4 from consumption of cow’s milk by children aged 6 months to 5 years of age is low.

Lead

54. Colic is a characteristic early symptom of acute lead poisoning after high exposures. Other symptoms include constipation, nausea, vomiting and anorexia. Lead can cause encephalopathy in children and adults, and chronic exposure can lead to neurological, neurodevelopmental, cardiovascular and renal

toxicity and potential allergenicity. This is described in further detail in the COT's 2013 statement.

55. Lead can enter the dairy chain through bovine ingestion of flaking lead paint, vehicle and electric fence batteries, soils containing high levels of geological lead, ash from fires containing lead residues and spent lead shot from shooting. In the general environment lead is present due to historic emissions from leaded petrol.

56. The COT, the Joint FAO/WHO Committee on Food Additives (JECFA) in 2011 and the European Food Safety Authority (EFSA) in 2010 have expressed the view that it is not possible to identify a threshold below which there is no association between lead and decrements in intelligence quotient (IQ) (EFSA, 2010b; FAO/WHO, 2011b; COT, 2013, 2016a). However, a BMDL01 was calculated, (EFSA, 2010) of 0.5 µg/kg for lead, for effects on development of intellectual function. This was based on a 1% change in full scale IQ (1 IQ point reduction), i.e. as the benchmark response. The EFSA BMDL01 was selected by the COT as a reference point for use in their 2013 statement and as the basis for MOE calculations in 2016 (COT, 2013, 2016a). The COT noted that the steep dose-response at low levels was based on only a few data from a single study. This may have produced a conservative result.

Risk Characterisation

57. In EFSA (2012a) dietary exposure was estimated for lead. It was found that for infants (1 year), cow's milk contributed less than 2% to the overall middle bound mean lead dietary exposure, representing the 13th highest contributor. For toddlers (1- 3 years), cow's milk contributed less than 5% representing the 6th highest contributor and for other children (3- 10 years) it was less than 4% representing the 6th largest contributor.

58. EFSA (2012a) estimated from two surveys that in the total diet, infants were exposed to a total mean of 0.83 and 0.91 µg/kg bw per day of lead, toddlers were exposed to a total mean of 1.32 µg/kg bw per day and other children were exposed to 1.03 µg/kg bw per day. These values exceed the BMDL01 for neurological effects of 0.5 µg/kg bw per day by a maximum of 2.6-fold. Whilst these exposure values do exceed the BMDL01, the contribution of milk itself should not raise concerns, since it was not the major source of exposure, contributing not more than 5%; no concerns were raised in the EFSA report.

59. In 2013 and 2016, the COT utilised a MOE approach to estimate the potential impacts of lead exposure in the diets of children aged 1-5 years (COT,

2013, 2016b). In the 2016 addendum, using data from the 2014 Infant Metals Survey (FSA, 2016a) and the Total Diet Study (TDS) (FSA, 2016b), the diet was observed as contributing little to lead exposure for older infants and young children (>6 months). However, overall exposures resulted in MOEs below 1 due to major contributions from other sources including dust and soil. A risk at the population level and to some infants and children could not be excluded. The COT emphasised the need for continued efforts to control lead in the environment but did not consider any special measures were necessary.

60. Based on the information provided in EFSA (2012a) and the evaluation by the COT in 2013 and 2016 the Committee concludes that it is unlikely that the levels of lead in cow's milk would pose a risk to the health of infants and children from the ages of 6 months to 5 years.

Arsenic

61. The main adverse effects of chronic inorganic arsenic consumption include skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism and diabetes (EFSA, 2009c; COT, 2016b). There is some evidence of neurobehavioral effects in children, however, more research is required. Arsenic is classified as a group 1 carcinogen (carcinogenic to humans) by the International Agency for Research on Cancer.

62. JECFA in 1988 established a provisional tolerable weekly intake (PTWI) of 15 µg/kg bw (JECFA, 1989a). EFSA in 2009 noted the PTWI of 15 µg/kg bw (2.1 µg/kg bw per day) was in the region of a BMDL01 ranging between 0.3 and 8 µg/kg bw per day for skin lesions as well as cancers of the lung, skin and bladder in humans. They concluded 'estimated dietary exposures to iAs for average and high level consumers in Europe are within the range of the BMDL01 values identified, and therefore there is little or no margin of exposure and the possibility of a risk to some consumers cannot be excluded.' (EFSA, 2009c).

63. JECFA in their own evaluation in 2011 noted that the PTWI of 15 µg/kg bw (2.1 µg/kg bw per day) for iAS is in the region of the BMDL0.5 of 3 µg/kg bw per day for lung cancer ranging between 2 and 7 µg/kg bw per day. They concluded therefore that the previous HBGV was no longer appropriate (no margin of exposure), and the Committee withdrew the previous PTWI (FAO/WHO, 2011c).

64. In 2016 the COT concluded that the JECFA BMDL0.5 of 3 µg/kg bw per day identified for lung cancer should be used in the characterisation of the potential risks from exposure to inorganic arsenic in food using a margin of

exposure (MOE) approach. This was because the JECFA risk assessment was based on more robust and recent evidence than that available to EFSA in 2009 (COT, 2016b).

65. The COT noted that ‘as there is no precedent for interpreting MOEs that have been calculated based on a BMDL derived from an epidemiological study and relating to a low cancer incidence, such interpretation must be done on a case-by-case basis. The JECFA BMDL used in this case was based on human data and a 0.5% increased incidence of lung cancer in a well-conducted prospective cohort study, in which the risk of cancer increased with duration of exposure, over several decades. Taking this into account, together with the fact that inorganic arsenic does not appear to be directly genotoxic, the Committee concluded that in this instance an MOE of 10 or above would be considered a low concern.’ (COT, 2016b).

Risk Characterisation

66. As in the previous 2016 COT statement, this paper focuses on inorganic arsenic as this is the form that is of most toxicological concern.

67. In 2016 the COT concluded ’Total exposure to inorganic arsenic, from dietary and non-dietary sources, in infants and young children aged 4 to 12 months and 1 to 5 years generally generated MOEs of less than 10 and could therefore pose a risk to health’. This statement used occurrence data from the Total Diet Study and Infant Metals Survey (FSA, 2016b, 2016a). The COT also noted that dietary sources of exposure were more significant than non-dietary sources.

68. EFSA’s latest 2021 evaluation of chronic iAs exposure reported that of 109 samples of cow’s milk, only 3 contained any detectable iAs. These values were all below 0.3 µg/kg. In addition to this, EFSA stated that ‘Food of animal origin contains typically low levels of iAs as animals, similar to humans, extensively methylate the ingested iAs and the excess is excreted in the urine together with the methylated forms (Cubadda et al., 2017).’ (EFSA, 2021a).

69. COT’s 2016 risk assessment suggested that at mean levels of food consumption, for infants aged 4 months to 5 years the MOE’s were below 10, therefore a risk to health may exist from dietary exposure. However, in EFSA’s recent 2021 evaluation cow’s milk was shown to contain minimal amounts of iAs.

70. The COT concluded from this information that levels of inorganic arsenic in cow’s milk do not present a risk to health to children aged 6 months to

5 years of age.

Mercury

71. EFSA’s Panel on Contaminants in the Food Chain (CONTAM) explored the toxicity of inorganic mercury in 2012 (EFSA, 2012c). This is summarised below. The kidneys are the primary target organ for acute mercury toxicity, observed in rats and mice. At higher doses, haematological and hepatic effects have been documented and at very high doses gastrointestinal damage has been reported. Sub-acute and chronic toxicity induces further renal effects, which have been observed in rats and mice, with females being less sensitive than males. Ototoxic and reproductive and developmental effects have also been observed. Evidence for inorganic mercury induced carcinogenicity is equivocal. Epidemiological data for inorganic mercury indicated effects on the immune system, liver, kidneys, endocrine systems and genotoxicity. These epidemiological data were not suitable for establishing dose-response relationships.

72. In 2012, EFSA’s CONTAM panel revaluated the previous provisional tolerable weekly intake (PTWI) for inorganic mercury. The CONTAM panel agreed with a JECFA 2010 evaluation that the HBGV for inorganic mercury should be based upon kidney weight changes in rats (FAO/WHO, 2010). They established a tolerable weekly intake (TWI) of 4 µg/kg bw from a BMDL10 of 60 µg/kg bw per day with an uncertainty factor of 100 to account for inter and intra species differences (EFSA, 2012c).

Risk Characterisation

73. From the 2012 EFSA CONTAM panel opinion, based on the evidence reviewed, occurrence data for milk and dairy products was assumed to represent solely inorganic mercury and not methylmercury. From 8 surveys, liquid milk was found to contribute a maximum of 15% to the mean middle bound (MB) exposure to inorganic mercury for toddlers (1 year - 3 years) and 11 % for other children (3-10 years) from 12 surveys. No information was provided on the percentage contribution of liquid milk to inorganic mercury exposure in infants (1 year).

74. EFSA (2012c), after considering data from 9 European dietary surveys, stated that the highest mean exposure value (Upper Bound, UB) for inorganic mercury was for toddlers at 2.16 µg/kg bw per week. They stated that based on the majority of studies, exposure was below the TWI of 4 µg/kg bw per week, however the highest UB 95th percentile dietary exposure value for toddlers at

4.06 µg/kg bw per week was similar to the TWI. EFSA considered this an overestimate with a high level of uncertainty. This is shown by a wide Lower Bound (LB) – Upper Bound (UB) range.

75. EFSA did not consider dietary exposure to inorganic mercury to be a risk for the European population. They noted that the uncertainties would have led to a conservative risk assessment being produced.

76. Excepting toddlers, no total inorganic mercury exposures exceeded the TWI. Cow's milk contributed a maximum of only 15% to the mean MB exposure of inorganic mercury in toddlers.

77. The COT has produced a statement discussing methylmercury in the diet of infants and children aged 6 months – 5 years (COT, 2018c). For the Infant Metals Survey and the TDS, total mercury was measured (FSA, 2016a, 2016b). Apart from fish and shellfish, methylmercury does not contribute significantly to other food categories. Regarding total mercury, exposure to total mercury was below the TWI for inorganic mercury based on the Infant Metals Survey data and the Total Diet Survey data. Utilising TDS data, exposure to total mercury for children aged 1 – 5 years were within the TWI of 4 µg/kg bw per week for inorganic mercury. The risk from inorganic mercury exposure to children is therefore negligible, as the exposure estimates comprise essentially only the inorganic form.

78. Comparing information from EFSA 2012c and the COT's consideration of TDS and Infant Metals Survey data the Committee concluded that there is no health concern for infants and children aged 6 months – 5 years from exposure to inorganic mercury in cow's milk.

Cadmium

79. Cadmium has previously been evaluated in a statement by the COT on potential risks to infants and children aged 0-5 years, which provides further detail on the background and hazards of the compound; key aspects of this hazard characterisation are included below (COT, 2018b).

80. Acute cadmium toxicity is largely of concern in workers involved in industrial applications. In the general population, chronic effects are a greater concern. The liver and kidneys are the main targets of cadmium chronic toxicity. Cd in the liver binds to the sulfhydryl-rich protein metallothionein (MT), which is then released into the blood, filtered in the kidney by the glomerulus and reabsorbed by the cells of the proximal convoluted tubule. This leads to cadmium

accumulation in the kidneys and to a lesser extent in the liver. The MT-Cd complex is degraded in lysosomes and some of the Cd released is sequestered by renal MT. As Cd concentrations increase the renal proximal tubular cells' capacity to produce MT is exceeded and free Cd causes damage at multiple sites (COT, 2018b).

81. Low molecular weight proteinuria (particularly of β2-microglobulin) is an early sign of renal toxicity. This is followed by reduced filtration rate, necrosis of the nephron and high-molecular-weight proteinuria. Cadmium-induced tubular damage may be reversible (Gao et al., 2016), however in later stages it may be irreversible and progressive even in absence of ongoing Cd exposure (COT, 2018b).

82. Chronic cadmium exposure can induce osteoporosis and osteomalacia, with deformities and bone fragility caused by direct calcium displacement or by inhibiting hydroxylation of vitamin D in the kidney, disrupting calcium and phosphorous metabolism. Cadmium can also affect a number of second messengers, enzymes and indirectly induce oxidative stress. Oxidative stress plays a role in kidney and bone damage as well as in cadmium induced carcinogenesis (COT, 2018b).

83. Cadmium whilst classified by the International Agency for Research on Cancer (IARC) as a group 1 human carcinogen, based on studies in those exposed via inhalation, does not appear to be directly genotoxic. It can instead inhibit DNA repair mechanisms and lead to DNA modifications including production of 8-oxo-2'-deoxyguanosine and changes in the degree of 2'-deoxycytosine methylation. Other proposed mechanisms of cadmium induced carcinogenicity include increased cellular proliferation by activation of the Wnt second messenger system and mimicry of oestradiol at oestrogen receptors (IARC, 2012; COT, 2018b).

84. The COT statement in 2018 noted that there was no consistency in the epidemiological data to suggest that cadmium compounds can cause cancer at additional sites or by additional routes, and no increased incidence of tumours was seen in experimental animals following oral administration.

85. In 2009 the EFSA CONTAM panel established a TWI for cadmium using group-meta-analysis based on urinary β-2-microglobulin (β2M) as a marker for kidney damage (EFSA, 2009a). A BMDL5 of 4 µg urinary cadmium (U-Cd)/ g creatinine was calculated for an increase of the prevalence of elevated β2M. In order to take into account inter-individual variation of urinary cadmium levels within the study populations this was reduced to 1 µg U-Cd/ g. For the U-Cd concentration of 95% of the population to remain below 1 µg/kg creatinine by the

age of 50 years, Cd dietary exposure should stay below 0.36 µg/kg bw per day or 2.52 µg/kg bw per week. Considering cadmium's long biological half-life a TWI of 2.5 µg/kg bw per week was established.

86. JECFA established a provisional tolerable monthly intake (PTMI) of 25 µg/kg bw per month (FAO/WHO, 2011b). This is equivalent to approximately 6 µg/kg bw per week or approximately 0.8 µg /kg bw per day. This dietary level was associated with a urinary level of less than 5.24 µg Cd/g creatinine, which was not associated with increased β2-microglobulin excretion in humans.

87. In 2011 EFSA evaluated the approaches taken by itself and JECFA which had resulted in differing outcomes (EFSA, 2011c). They concluded that the main source of variation was the choice of toxicodynamic variability function. EFSA upheld its lower value of 2.5 µg/kg bw per week, stating this was: 'in order to ensure a high level of protection of consumers, including subgroups of the population such as children, vegetarians and people living in highly contaminated areas.' They also noted that adverse effects were unlikely to occur in an individual at current dietary Cd levels.

88. In 2018 the COT discussed the HBGVs generated by the EFSA panel (2009a), JECFA (2011c) and EFSA's subsequent analysis of these values, and utilised the EFSA TWI (EFSA, 2011c) in its assessments (COT, 2018b).

Risk Characterisation

89. In 2012 EFSA published a dietary exposure assessment for the European population (EFSA, 2012a). EFSA concluded that liquid milk contributed 1.59% for infants (1 year), 1.78% for toddlers (1- 3 years) and 2.28% for other children (3- 10 years) of total dietary cadmium exposure (EFSA 2012a).

90. EFSA merged the collected surveys and weighted them to the years individuals spent in each age bracket from an average 77 year lifespan. This resulted in mean average upper bound weighted lifetime exposure values as follows: infants 3.50 µg/kg bw per week, toddlers 5.90 µg/kg bw per week and other children 4.69 µg/kg bw per week. Comparing these average lifetime exposure values to the TWI of 2.5 µg/kg bw per week, exceedances are evident at mean exposure levels for infants, toddlers, and other children.

91. The COT 2018 statement on cadmium in the infant diet and children aged to 5 years (COT, 2018b) noted that there were some exceedances from dietary exposure (a 260% maximum) of the EFSA (2011c) TWI. This statement used occurrence data from the Total Diet Study (FSA, 2016b) and Infant Metals

Survey (FSA, 2016a). This exceedance was not expected to remain at these levels over the decades of bioaccumulative exposure considered by EFSA in establishing their HBGV. The COT concluded that cadmium exposure did not present a health concern, however efforts to reduce cadmium exposure should continue. Cow's milk was not identified as a key contributing food group in this assessment.

92. Whilst exceedances of the TWI were observed in both COT (2018b) and EFSA (2012a) exposure assessments, this was at most 2.6-fold and the relative contribution of cow's milk in both of these assessments was low. Therefore, the COT concluded that the levels of cadmium in cow's milk present no risk to the health of infants and children aged between 6 months and 5 years.

Perchlorate

93. The EFSA CONTAM panel in 2014 concluded that a prolonged 50% inhibition by NIS (Na+/I− symporter) inhibiting compounds like perchlorate may result in goitre and multinodular toxic goitre even if short term exposure does not alter thyroid function tests. Although the CONTAM panel noted it was unknown whether thyroid iodine uptake inhibition below 50% has any adverse consequences, they performed benchmark dose modelling on a study by Greer et al., (2002), previously identified by JECFA as a key study for dose-response modelling, using a benchmark response of 5%, based on inhibition of radiolabelled iodine uptake by the thyroid (FAO/WHO, 2011a; EFSA, 2014). The CONTAM panel selected the 95% lower confidence limit of the BMDL05 (5% extra risk of thyroid iodine inhibition) of 0.0012 mg/kg bw per day as a reference point. From this an uncertainty factor of 4 was applied to account for inter-human toxicokinetic variation producing a TDI of 0.3 µg/kg bw per day. The panel did not consider it necessary to establish a safety level for short term exposure (EFSA, 2014).

Exposure assessment and risk characterisation

94. EFSA (2017a) performed a dietary exposure assessment for perchlorate. This report lacked an exposure assessment for liquid milk. However, occurrence data from this report for milk was utilised to perform an exposure assessment for the COT statement. A mean occurrence of 0.56 - 3.07 - 5.58 µg/kg (LB-MB-UB) was calculated from 166 samples of liquid milk. A 95th percentile value of 3.80-5.0-10.0 µg/kg (LB-MB-UB) was also calculated. Occurrence data was also provided in (EFSA, 2014)

95. In 2019 the COT reviewed the data available regarding perchlorate within the diet of infants and young children and discussed in both 2014 and 2017 EFSA assessments on perchlorate in the total diet. The COT previously concluded that there are considerable uncertainties in EFSA's assessment of perchlorate in the total diet and that in both long and short term exposure scenarios for all age groups there is potential concern, particularly in the case of individuals with mild-moderate iodine deficiency (COT, 2019a).

96. No other EU /UK perchlorate occurrence data were found through a literature search of the ScienceDirect and PubMed databases using the terms "(Chlorate OR perchlorate) AND occurrence AND milk" and with search results limited to 2001-2021. One additional source of EU/UK perchlorate occurrence data was found through a literature search of the ScienceDirect and PubMed databases using the terms "(Chlorate OR perchlorate) AND milk" with search results limited to 2001-2021 and for the former database, sorted for the first 200 relevant results. No perchlorate was detected, with a limit of detection of 0.0010 mg/kg, in mid lactation or late lactation from two samples respectively of whole cow's milk from silos in an Irish powdered milk production plant (Paludetti et al., 2019). Other studies were identified from countries such as the US, Turkey and Japan.

97. A risk characterisation has been undertaken using the mean and 95th percentile upper bound occurrence values of 5.58 and 10.0 µg/kg respectively for liquid milk (EFSA, 2017a), the consumption data from Table 1 and the TDI of 0.3 µg/kg bw per day (from EFSA, 2014). This assessment is presented in Tables 10 and 11.

Table 10. Perchlorate risk characterisation using the mean UB occurrence value for liquid milk from EFSA, (2017a), consumption data from the NDNS (Table 1) and the EFSA TDI (EFSA, 2014).

Age (months)	Estimated exposure (mean) (µg/kg bw per day)	Estimated exposure (97.5th percentile) (µg/kg bw per day)	Mean %ADI	97.5th percentile %ADI
6 – 12	0.0725	0.268	24.2	89.2

12 – 18	0.179	0.419	59.6	140
18 – 24	0.162	0.441	54.0	147
24 – 48	0.129	0.329	42.8	110
48 – 60	0.0949	0.257	31.6	85.6

Table 11. Perchlorate risk characterisation using the 95th percentile UB occurrence value for liquid milk from EFSA (2017a), consumption data from the NDNS (Table 1) and the EFSA TDI (EFSA, 2014).

Age (months)	Estimated exposure (mean) (µg/kg bw per day)	Estimated exposure (97.5^{th} percentile) (µg/kg bw per day)	Mean %TDI	97.5th percentile %TDI
6 – 12	0.130	0.480	43.3	160
12 – 18	0.320	0.750	107	250
18 – 24	0.290	0.790	96.7	263
24 – 48	0.230	0.590	76.7	197
48 – 60	0.170	0.460	56.7	153.

98. Using the mean UB occurrence value of 5.58 µg/kg for ‘liquid milk’ from EFSA’s 2017 study, no exceedances were found at mean consumption levels. However, exceedances of up to 1.5-fold, between ages 12 - 48 months, were found at the 97.5th percentile of consumption (Table 10). At the 95th percentile UB occurrence of 10 µg/kg, at mean consumption levels there were

slight exceedances for the 12-18 age group and exceedances, by up to 2.6-fold, in all age groups at the 97.5th percentile of consumption (Table 11). This, however, is an extremely conservative assessment using occurrence data presented as upper bound.

99. Based on the exposure assessment presented here, which showed that the TDI was unlikely to be exceeded from consumption of cow's milk in a realistic scenario, and their previous conclusions, the COT concluded that perchlorate levels in cow’s milk do not represent a significant health risk to children aged 6 months to 5 years. However, milk is a significant contributor to total perchlorate exposure levels.

Chlorate

100. The EFSA CONTAM panel undertook an evaluation of chlorate toxicity in 2015 (EFSA, 2015a). In summary, they stated that in experimental animals chlorate exhibits both acute and chronic toxicity. Acute toxicity is targeted towards the thyroid and haematological system. This includes a reduction in erythrocytes, haemoglobin and haematocrit. Histopathological changes to the thyroid in rats included follicular cell hypertrophy, increase in colloid depression and follicular cell hyperplasia. Alterations to thyroid hormone levels included decreases in T3 and T4, accompanied by increases in thyroid-stimulating hormone (TSH). Long term toxicity included formation of non- neoplastic lesions in the thyroid gland, in male and female rats and mice, effects on bone marrow (hyperplasia) in male rats and female mice and the spleen of male rats (haemopatic cell proliferation). There was evidence of reproductive and developmental toxicity in rats.

101. In humans, acute chlorate exposure has resulted in vomiting, abdominal pain, cyanosis, methemoglobinemia, anuria and renal failure. A number of epidemiological studies have investigated possible associations between exposure to chlorination disinfection by-products and developmental effects, but only two reported information on chlorate levels in water. One of these found no association between exposure to chlorate and adverse pregnancy outcomes. The other reported an association between chlorate and a low incidence of several congenital abnormalities but there were a number of limitations in this study, including a lack of information on the lifestyle habits of the mothers (EFSA, 2015a).

102. There is equivocal evidence for carcinogenicity in female B6C31 mice and no evidence in males. There was some evidence of sodium chlorate induced

carcinogenicity in female and male F344/N rats. There is mixed in vitro and in vivo evidence of genotoxicity, however the EFSA CONTAM panel concluded that chlorate is not of concern with regard to genotoxicity (EFSA, 2015a).

103. In 2015, EFSA considered there to be currently no chronic exposure studies of chlorate in humans or adequate epidemiological studies. The CONTAM panel considered the critical effect of chlorate exposure to be competitive inhibition of the thyroid Sodium-Iodide Symporter (NIS), as is the case with perchlorate. The panel commented that whilst humans are less sensitive to compounds that alter thyroid homeostasis than rats, there are no available *in vivo* studies on human thyroid iodine uptake inhibition for perchlorate. Therefore, they established a TDI of 3 µg/kg through a read across from the 0.3 µg/kg TDI established for perchlorate based on human data and a potency factor of 0.1 for the difference in toxicity between the two compounds seen in rats (EFSA, 2015a).

Exposure assessment and risk characterisation

104. In 2019 the COT discussed EFSA's 2015 opinion on exposure to chlorate, summarising as follows (COT, 2019a):

'The COT agrees with the overall conclusion by EFSA. Chronic dietary exposure to chlorate is of potential concern for high consumers in all age groups, particularly to individuals with mild to moderate iodine deficiency. Drinking water was the major contributor, at up to 40 to 60%. Single acute exposures to chlorate at levels found in food and drinking water however, are unlikely to cause adverse effects, including in vulnerable individuals.'

105. In EFSA's 2015 scientific opinion on the risks of chlorate, the mean occurrence of chlorate in liquid milk was calculated at 10-17 µg/kg (LB-UB) from 38 samples. There was no higher or maximum occurrence value provided. The COT considered that this number of samples was low.

106. No other European occurrence data was found through a literature search of the PubMed and ScienceDirect databases using the key terms "(Chlorate OR perchlorate) AND occurrence AND milk" with search results limited to 2001-2021. One additional source of EU/UK chlorate occurrence data was found through a literature search of the ScienceDirect and PubMed databases using the terms "(Chlorate OR perchlorate) AND milk" with search results limited to 2001-2021, and for the latter database, sorted for the first 200 relevant results. This paper reported levels of 0.0010 (±0.0000) mg/kg in mid lactation and 0.0025 (±0.0000) mg/kg in late lactation from two samples respectively of whole cow's milk from silos in an Irish powdered milk production plant (Paludetti et al., 2019).

107. A risk characterisation has been performed using the TDI of 3 µg/kg bw per day and the mean upper bound occurrence value for chlorate (17 µg/kg) from EFSA, (2015a) in addition to the consumption data from Table 1. This assessment is presented in Table 12.

Table 12. Chlorate risk characterisation using the mean UB occurrence value for liquid milk from EFSA, (2015a), consumption data from the NDNS (Table 1) and the EFSA TDI (EFSA, 2015a).

Age (months)	Estimated exposure (mean) (µg/kg bw per day)	Estimated exposure (97.5th percentile) (µg/kg bw per day)	Mean %TDI	97.5th percentile %TDI
6 – 12	0.221	0.816	7.37	27.2
12 – 18	0.544	1.28	18.1	42.5
18 – 24	0.493	1.34	16.4	44.8
24 – 48	0.391	1.00	13.0	33.4
48 – 60	0.289	0.782	9.63	26.1

108. From the mean UB occurrence value of 17 µg/kg chlorate in liquid milk obtained from EFSA 2015 and the exposure data provided in this report there are no exceedances of the TDI in any of the child age groups with either mean or 97.5th %ile consumption (Table 12). This represents a more detailed assessment of the impact of milk consumption than in the EFSA 2015 report, where information was largely limited to ‘milk and dairy products’

109. From this information and that within the main statement, the COT concluded that levels of chlorate in cow’s milk do not pose a risk to health of infants and children aged 6 months – 5 years.

Insulin-like Growth Factor (IGF-1)

110. IGF-1 levels in cows can be artificially increased to improve milk production by treatment with Bovine Somatotropin (BST). BST treatment of cows is illegal within the EU and UK, however, milk from BST treated cows is not. Table 8.6 (page 90) of the 2020 Agriculture in the UK report by the Department for Environment, Food and Rural Affairs (DEFRA) (2021) has been checked. Looking at the ratio of imported milk to total supply and applying this to the total supply for liquid consumption only, as a percentage 1% of UK drinking milk was sourced from imports between 2018-2020, with an unknown amount (if any) from BST-treated animals. This estimate assumes that imported milk is spread proportionally between milk intended for liquid consumption and food production processes. This figure suggests that the risk of exposure to BST-induced IGF-1 is likely low, thus mitigating any risks from its possible presence in milk.

111. The Committee on Carcinogenicity Food, Consumer Products and the Environment (COC) produced a statement on the risks of IGF-1 in cow's milk in 2018. They concluded that there was insufficient evidence to draw any firm conclusions as to whether dietary IGF-1 is associated with increased incidence of cancer in consumers, but that absorption of intact IGF-1 is unlikely. In addition, they concluded there are very few papers on whether raised circulating IGF-1, diet and cancer risk are linked and where this had been investigated, no link was found between dairy consumption and an increased cancer risk. The COC also stated that whilst elevated IGF-1 had been observed in cancer patients, a causative relationship could not be established as tumours can produce growth factors themselves. Many of the sourced papers had considerable limitations, which included a lack of information on diet, ethnicity of subjects and a lack of continual monitoring. From this information the COC concluded that the risk, if any, is likely to be low (COC, 2018).

112. Regarding cow's milk specifically, the COC conducted a literature review finding that naturally present IGF-1 within cow's milk ranged from 1-1850 ng/ml. Postpartum milking produces 'colostrum', which contains the highest levels of IGF-1. This is rarely consumed by humans. The COC concluded that the highest IGF-1 levels in milk consumed by humans are unlikely to exceed 100 ng/ml.

113. In their 2018 statement, the COC conducted a chronic dietary exposure assessment for IGF-1 in Milk and Meat (including poultry) and their products for toddlers aged 1-3 years and adults aged 19 years and older. An extract of this assessment specifically for milk including recipes is included below in table 13.

Table 13: Chronic exposure assessment for IGF-1 in milk extracted from a chronic exposure assessment in milk and meat (including poultry) (COC, 2018) for UK Toddlers aged 1 – 3 years.

Number of Consumers	Consumer mean exposure (µg/kg bw per day)	Consumer P97.5 exposure (µg/kg bw per day)	Consumer max exposure (µg/kg bw per day)
595	2.54	7.04	22.35

114. The COC considered their exposure assessment conservative, utilising an occurrence level of 101 µg/kg (the highest reported concentration in milk from the 5th post-partum milking of Ayrshire cows) for all products. The COC states from their exposure assessment that high level dietary exposure would be below 1% of an adult's endogenous production (128 µg/kg bw per day) (COC, 2018; VPC 1999). The COC noted that toddlers are likely to have a higher exposure to IGF-1 relative to endogenous production due to a higher proportion of milk in their diet and small body size. However, there are no data on endogenous production in toddlers so this cannot be compared to dietary exposure.

115. The COC reports a number of studies suggesting that variation in circulating levels of IGF-1 could be associated with diet. The COC noted a study by Arjmandi et al. (2009) suggesting that milk protein intake was associated with elevated circulating IGF-1 and that soy protein supplementation in the diet was associated with a greater increase in circulating IGF-1 than cow's milk. However, the COC noted that there were few studies that had conducted a direct comparison between the effects of different proteins and in other studies soy was not shown to significantly affect IGF-1 levels (COC, 2018).

116. As stated by the COC in 2018 it is unlikely that IGF-1 in cow's milk poses a risk to health in infants and children aged 6 months to 5 years of age. In addition to this, milk from BST treated cows is unlikely to enter into circulation in the UK in significant amounts. From this information the COT concluded that that the levels of IGF-1 within cow's milk pose no concern for the health of children aged 6 months to 5 years of age.

Naturally occurring oestrogens in cow's milk

117. Oestrogens are naturally present in milk. The most prevalent oestrogen is oestrone (E1) in its conjugated (oestrone sulphate) and free forms.

17β-Oestradiol (E2) is also present in milk (Pape-Zambito, Magliaro and Kensinger, 2008). Concern has been raised due to the presence of elevated endogenous oestrogens in pregnant dairy cow's blood and milk due to milking during the second half of pregnancy (Ganmaa and Sato, 2005). Associated potential risks of exposure to oestrogens with regard to children include developmental effects in the urogenital, hormonal and central nervous systems and mammary glands (Snoj and Majdič, 2018). There have been differences in conclusions of risk assessment bodies on the genotoxicity of 17β-oestradiol and the role of its genotoxicity in its carcinogenicity.

118. Hormones for use as growth-promotors in beef cattle were evaluated by JECFA in (2000). Note that this use is not permitted in the EU or the UK. For 17β-oestradiol it was concluded that hormonal effects occur at doses lower than other toxicological responses and were a more appropriate basis for evaluating its safety. 17β-Oestradiol was considered to have genotoxic potential but its carcinogenic effects were considered most likely due to hormone receptor interaction. JECFA established an ADI of 0.05 µg/kg bw based on a NOEL for multiple hormone dependent parameters in postmenopausal women. A total uncertainty factor of 100 was applied, which included a factor of 10 to allow for interindividual variation and a further factor of 10 to protect sensitive population subgroups. Exposure to the sum of all oestrogens found in the occurrence data should be compared to this ADI.

119. Other scientific Committees have reviewed the safety of oestrogens and 17β-oestradiol for use as growth promoting hormones in beef cattle. The Veterinary Products Committee (VPC) in 2006 considered, as an intermediate conclusion, that 17β-oestradiol should be considered a 'complete' carcinogen (having both tumour initiating and tumour promoting properties) until further evidence was available on its mode of action (VPC, 2006). The European Scientific Committee on Veterinary measures relating to Public Health (SCVPH) concluded in 2002 that there were convincing data demonstrating the pro-genotoxicity of 17β-oestradiol through metabolic activation to reactive quinones. 17β-Oestradiol had been found to induce mutations in various cell cultures whilst the metabolite oestradiol-3,4-quinone, but not oestradiol itself, was found to cause DNA-adducts in mouse skin in vivo. Catechol-oestrogen-quinones were found to form DNA adducts in vitro and in vivo in mouse skin (SCVPH, 2002). IARC, in its assessments in 2008 of oestrogen-only menopausal therapy and combined oestrogen-progestogen menopausal therapy, concluded that receptor-mediated responses are a plausible and probably necessary mechanism for oestrogen carcinogenesis. In addition, there is support for a genotoxic effect of oestrogenic hormones or

their by-products such as reactive oxygen species. It is entirely possible that both mechanisms contribute to and are necessary for oestrogen carcinogenesis (IARC, 2012). The main oestrogens investigated were conjugated oestrogens, 17β-oestradiol and its semi-synthetic esters. The COT's current position is that any genotoxic effect arises through an indirect mechanism such as redox cycling and would therefore have a threshold.

Exposure assessment and risk characterisation

120. Snoj and Majdič, (2018) collated 10 studies examining the natural occurrence of oestrogens in cow's milk, however, these studies investigated US cattle. Due to differences in dairy practices between US and Europe it was not considered appropriate for this occurrence data to be used to perform a risk assessment. No other occurrence data from studies in the 2001-2021 period was found during a literature search of the PubMed database using the terms, "hormone AND cows AND milk AND human AND risk" and "Cows AND milk AND hormone AND human health", with search results limited to 2001- 2021.

121. A further search examining the terms: "Hormone AND milk AND cow AND human" utilising the PubMed database and the first 400 results of the ScienceDirect database sorted for relevance did not identify any studies not previously found using the previous search terms.

122. Two papers reporting EU occurrence data were later found for naturally occurring oestrogens in cow's milk, Courant et al. (2007) and Malekinejad et al. (2006). The highest occurrence was for the sum of oestrone, 17α-oestradiol, 17β-oestradiol and oestriol reported in Malekinejad et al. (2006). This was for 4 samples of processed milk collected from local grocery stores and a sample of organic milk. Below in Table 14, the mean concentrations of each oestrogen are presented after the milk had been treated enzymatically to hydrolyse any conjugates present. Due to a lack of detection of oestriol in some samples, where no oestriol was detected, for the LB scenario the concentration was assumed to be 0 whilst in the UB scenario it was assumed that concentrations were at the limit of detection of 10 ng/L. Where the signal was obscured by interference, the concentration was assumed to be the limit of detection in both scenarios.

123. A paper reporting levels of oestradiol, oestriol and progesterone within human breast milk from women in China was found. The mean values for mature human breast milk (day 42 after delivery) have been reported below in table 14 (Lu et al., 2017).

Table 14. Occurrence data for oestrone, α-oestradiol, β-oestradiol and oestriol in cow's milk from Malekinejad et al. (2006) and oestradiol and progesterone in human breastmilk at day 42 after delivery (Lu et al. 2017).

Compound	Mean Concentration in cow's milk ng/L (LB - UB)	Mean Concentration in mature human breast milk ng/L (± SD)
Oestrone	201.8	No information
α-oestradiol	51.2	1260 ± 480 (Total oestradiol)
β-oestradiol	10.4	See row above
Oestriol	(4 - 10)	4640 ± 2150
Progesterone	No information	1700 ± 2420
Total oestrogens	(267 – 273)	6340 ± 4570

124. In the Snoj and Majdič review, and in additional information found during the literature search, it was often reported that the contribution of oestrogens ingested in milk to circulating levels of oestrogens was expected to be minimal. There are multiple reasons for this, such as a low occurrence level relative to circulating hormone levels and a low bioavailability of orally ingested bioactive oestrogens due to metabolism in the intestinal mucosa and first pass metabolism in the liver (Pape-Zambito et al. 2008; Macrina et al., 2012; Parodi, 2012; Snoj and Majdič, 2018). However, estimation of circulating hormone levels in young children is a contentious area. In the past, such levels have been measured using radioimmunoassay methods with insufficient sensitivity. Subsequently, much lower circulating levels of oestrogens in prepubertal children have been reported using more sensitive methods, including gas chromatography-tandem mass spectrometry (Andersson and Skakkebaek, 1999; Courant et al., 2010).

125. In Courant et al. (2010) levels of conjugated and unconjugated 17β-oestradiol in prepubertal boys (testicular volume ≤3 mL, mean age 8.4 years) were extremely low to undetectable, with a median value of <1.01 ng/L, whilst for prepubertal girls (Tanner breast stage 1, public hair stage 1, mean age 8.4 years) 17β-oestradiol was present at a median level 2.61 ng/L. The median level of estrone for prepubertal boys was 12.7 ng/L and for prepubertal girls it was 23.5 ng/L.

126. In Ankarberg-Lindgren et al. (2018) levels of oestrone and 17β-oestradiol were reported for girls and boys at different stages of puberty. The values for boys with a testicular volume of 1-2 mL and girls in Tanner breast stage 1 were selected as representing the prepubertal stage for this statement. Median17-β-oestradiol serum concentration in prepubertal boys was 0.816 ng/L and for oestrone was 3.24 ng/L. For prepubertal girls 17β-oestradiol was present at levels of <0.544 ng/L and oestrone at 4.32 ng/L.

127. It is possible that the higher levels reported by Courant et al. (2010) than by Ankarberg-Lindgren et al. (2018) was because of slight differences in the categorisations of prepubertal stage or in the ages of the prepubertal children studied, since when Courant et al. (2010) separated the prepubertal children by age <8 years compared to >8 years they found lower concentrations of 17β-oestradiol and oestrone in the younger prepubertal girls and lower concentrations of oestrone in the younger prepubertal boys compared to the older prepubertal children.

128. The concentrations of circulating oestrogens from the two aforementioned sources are provided below in table 15.

Table 15: Combined circulating levels of reported oestrogens as presented by (Courant et al., 2010) and (Ankarberg-Lindgren et al. 2018).

Population group	Median serum concentration of total oestrogens ng/L in prepubertal boys
Prepubertal boys (From Courant et al. (2010)	12.7-13.7 (LB-UB)
Prepubertal girls (From Courant et al. (2010)	26.1

Prepubertal boys (From Ankarberg-Lindgren, Dahlgren and Andersson, (2018)	4.01
Prepubertal girls (From Ankarberg-Lindgren, Dahlgren and Andersson, (2018)	4.35-4.86 (LB-UB)

129. Previously in 2000, JECFA presented production rates for total oestrogens, calculated from the levels of circulating oestrogens and clearance rate in differing populations This included prepubertal boys and girls under the age of 8 as shown in table 16.

Table 16: Levels of circulating oestrogens, metabolic clearance rate and total daily production of oestrogens extracted from JECFA (2000).

Age/phase	Serum concentration (pg/ml)	Metabolic Clearance (L/day)	Total daily production (mg/day)
Prepubertal males	< 10	1400	< 0.014
Females <8 years of age	< 7	1400	< 0.01

130. JECFA’s production rates have been compared to different age groups’ exposure to oestrogens from cow’s milk, calculated from consumption data from table 1 and occurrence data from Malekinejad et al. (2006). This is presented in table 17.

Table 17: A comparison of the JECFA 2000 production rate for oestrogens for prepubescent boys and girls under 8 with the exposure of different age populations to oestrogens from cow’s milk derived from consumption data from table 1 and the lower and upper bound occurrence for total oestrogens from Malekinejad et al. (2006).

Age group	Total daily production of oestrogens (male) (mg/day)	Total daily production of oestrogens (female) (mg/day)	Exposure (mean consumption) mg/person/day (LB - UB)	Exposure (97.5th percentile of consumption) mg/person/day (LB - UB)
6 – 12	0.014	0.01	0.0000321 - 0.0000328	0.000123 - 0.000126
12 – 18	0.014	0.01	0.0000936 - 0.0000957	0.000211 - 0.000216
18 – 24	0.014	0.01	0.0000936 - 0.0000957	0.000225 - 0.000230
24 – 48	0.014	0.01	0.0000856 - 0.0000875	0.000206 - 0.000211
48 – 60	0.014	0.01	0.0000776- 0.0000793	0.000209 - 0.000213

131. Using the upper bound occurrence value, at mean consumption levels estimated exposures could be >0.957% of the endogenous daily production for prepubertal girls, whilst at the 97.5th percentile of exposure, the estimated exposures could be >2.3% of the endogenous daily production for prepubertal girls. There is uncertainty in the total daily production estimates presented by JECFA. Past estimates have been criticised in the literature (Andersson and Skakkebaek, 1999). This was due to uncertainty in the circulating oestrogen levels, which were estimated using methodologies now considered to be of insufficient sensitivity and often inaccurately reported values that were at or close to limits of detection. Circulating levels are likely lower than stated in table 16, as indicated by the lower concentrations presented in more recent work by Ankarberg-Lindgren Andersson et al. (table 15). In addition to this, a clearance rate for oestrogens has not been established for children and thus JECFA applied adult clearance rates, in L/day, to calculate daily production rates in prepubertal children, without adjustments for body weight or for the higher concentrations of

sex hormone binding globulin (SHBG) in prepubertal children, which would be expected to reduce clearance (Andersson and Skakkebaek, 1999).

132. Table 17 indicates that the exposure to oestrogens is potentially lower than the endogenous production rates of the above population groups. However, since JECFA only estimated upper bounds for the endogenous production rates, there is uncertainty in the circulating levels and in the metabolic clearance rates in prepubertal children, it is unclear how much lower endogenous production rates are from these estimates. Risk characterisations of oestrogens has been performed by comparing exposures estimated using the mean concentration of the sum of oestrogens found within milk (267.4 – 273.4 ng/L) (LB-UB) from Malekinejad et al. (2006) and the consumption data from Table 1 with the JECFA ADI of 0.05 µg/kg bw for 17β-oestradiol. It was assumed that a litre of milk is equivalent to a kilogram. This assessment is presented in Table 18.

Table 18. Risk characterisation of oestrogens in cow's milk using the lower bound and upper bound mean occurrence values for liquid milk from Malekinejad et al. (2006) and consumption data from the NDNS, and the JECFA ADI.

Age (months)	Estimated exposure mean µg/kg bw per day (LB - UB)	Estimated exposure 97.5 th percentile µg/kg bw per day (LB - UB)	Mean % ADI (LB - UB)	97.5th percentile % ADI (LB - UB)
6 – 12	0.00348 - 0.00355	0.0128 - 0.0131	6.95 - 7.11	25.7 - 26.3
12 – 18	0.00856 - 0.00875	0.0201 - 0.0205	17.1 - 17.5	40.1 - 41.0
18 – 24	0.00775 - 0.00793	0.0211 - 0.0216	15.5 - 15.9	42.3 - 43.2
24 – 48	0.00615 - 0.00629	0.0158 - 0.0161	12.3 - 12.6	31.6 - 32.3

48 – 60	0.00455 - 0.00465	0.0123 - 0.0126	9.09 - 9.30	24.6 - 25.2

133. From occurrence data reported in Malekinejad et al. (2006) and NDNS consumption data no exceedances of the ADI established by JECFA in 2000 are found in age group of children at either mean or 97.5th percentile consumption.

134. From the information in the main statement and that discussed above, the COT concluded that there is no exceedance of the JECFA 2000 ADI from exposure to oestrogens in cow's milk, and that the levels of oestrogens within cow's milk do not present a risk to health for children aged 6 months to 5 years of age.

Mycotoxins

135. EFSA have stated in various scientific opinions and reports that fumonisins (EFSA, 2018b), ochratoxin A (OTA) (EFSA, 2020a), zearalenone and its metabolites (EFSA, 2016) and trichothecenes such as deoxynivalenol (DON) and T2 and HT-2 (EFSA, 2017c, 2017b) have not been found to carry over from the blood to milk in ruminants at levels that could significantly impact dietary exposure. The COT in 2018 reviewed the potential risks of T-2, HT-2 and OTA in the diet of infants and children aged 0 – 5 years. There is no mention of cow's milk in either of these statements (COT, 2018a, 2018d). COT's 2021 statements regarding mycotoxins did not comment on mycotoxins in cow's milk (COT, 2021d, 2021a).

136. In the COT's 'Statement on the potential risk(s) of combined exposure to mycotoxins' the Committee was unable to perform a risk assessment on the co-occurrence of mycotoxins due to a lack of harmonised approaches/methodologies and data analysis/modelling for toxicological investigations, unelucidated mechanisms and a lack of co-occurrence data and UK exposure data. They commented 'The possibility of co-exposures from breastmilk and weaning foods also need to be considered for infants and young children' (COT, 2021d).

137. No studies were found by EFSA regarding the carry-over of the following metabolites of DON: (3-acetyldeoxynivalenol (3-Ac-DON)), 15-acetyldeoxynivalenol (15-Ac-DON) and deoxynivalenol-3-glucoside (DON-3-glucoside) to milk. In addition to this, no further information was found in a further literature review.

138. The COT concluded that the literature currently suggests that ochratoxin (OTA) zearalenone and its metabolites, trichothecenes including deoxynivalenol (DON) and T2 and HT-2 are unlikely to transfer into cow's milk from feed and do not present a risk to health for children aged 6 months to 5 years of age from the consumption of cow's milk. However, no specific information could be found regarding the transfer of 3-Ac-DON, 15-Ac-DON and DON-3-glucoside to cow's milk, therefore risk cannot be excluded, although transfer of these seems unlikely, particularly of DON-3-glucoside, given their hydrophilicity.

Per- and polyfluoroalkyl substances (PFAS)

139. As discussed in a recent COT paper (COT, 2020b), most of the information on the fate of perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAs), the two main classes of PFAS, is based on PFOS and PFOA, respectively. These compounds are readily absorbed in the gastrointestinal (GI) tract in mammals and initially distribute predominantly to the plasma and liver. PFOS and PFOA are not metabolised and are excreted in both urine and faeces. They may be subject to extensive enterohepatic recirculation. Serum elimination half-lives for PFOS in rats and mice were slightly longer than one month and in rabbits and monkeys were 3-4 months. Significant sex differences are observed in the elimination of PFOA in some species such as rats, for which half-lives may vary from a few hours in females, to several days in males. These differences in biological half-lives are mainly due to differences in renal re-uptake. For both PFOS and PFOA, maternal transfer occurs prenatally to the fetus through placental transfer and postnatally through the consumption of maternal milk.

140. Based on the high concentrations of PFAS observed in the blood of individuals exposed to contaminated water and from what is known for PFOS and PFOA, it may be assumed that gastrointestinal (GI) absorption of most of the PFASs occurs to a significant extent in humans. PFAS are widely distributed throughout the body, with the highest concentrations found in blood, liver and kidney. PFAS in blood bind to albumin. PFSA and PFCA metabolism has never been observed, however, precursor compounds such as fluorotelomer alcohols (FTOHs) and polyfluorinated phosphate esters (PAPs) can be biotransformed in humans to PFCAs and other metabolites. PFAS are eliminated in urine and faeces, and breast milk is also a substantial route of excretion. Shorter chain PFCAs are preferentially excreted in urine, whereas longer chain PFAS are preferentially eliminated through the bile and faeces. Extensive uptake from enterohepatic circulation and reabsorption by organic anion transporters (OATs) in the kidneys

are believed to be more active processes in humans compared to rodents, slowing down the excretion of these substances. In humans, short chain PFAS were found to have half-lives ranging from a few days to approximately one month, whereas for PFHxS, PFOS, PFOA and PFNA estimated half-lives can exceed 3 years.

141. The most consistent and sensitive endpoint for PFCAs following repeated exposures was increased relative liver weight, especially in male rodents. Disturbances in lipid metabolism, hepatotoxic effects and signs of cholestasis were evident mostly at higher doses. For some PFCAs increased relative kidney weight, alterations of the nasal cavity and olfactory epithelium and disturbed thyroid hormone levels were among the most sensitive endpoints.

142. The most sensitive endpoint for PFHxS and PFOS was an elevated absolute and relative liver weight. At higher dose levels, disturbed lipid metabolism, necrosis and inflammation in the liver were observed. Alterations in the kidney and disturbed thyroid hormones were repeatedly documented.

143. EFSA, (2020b) concluded that effects on the immune system should form the basis of the risk assessment and evaluation, as decreased antibody responses were observed at the lowest serum PFAS concentrations in both human and animal studies. This was considered a robust conclusion, as a reduced immune response was seen consistently for PFOS and PFOA in humans and rats. A TWI of the sum of PFHxS, PFOS, PFOA and PFNA of 4.4 ng/kg bw per day was derived from a BMDL10 of 17.5 ng/ml for the sum of the four PFASs in serum, based on reduced antibody levels against diphtheria vaccine in 1-year old children (Abraham et al., 2020).

Risk characterisation

144. From the dietary exposure evaluation undertaken by EFSA (2020b) it was concluded that fruit, fish and eggs (and all associated products) were the main contributors to PFAS exposure. Overall, the mean dietary LB exposure to PFHxS, PFOS, PFOA and PFNA in toddlers (1 - 3 years) and ‘other children’ (> 3 - 10 years) ranged from 6 to 46 ng/kg bw per week, with the 95th percentile from 19 to 96 ng/kg bw per week.

145. Up to 236 liquid milk samples were analysed for one or more of the 4 PFAS compounds (PFHxS, PFOS, PFOA and PFNA) evaluated by EFSA (2020b). No milk samples returned a quantifiable positive result above methodology reporting levels.

146. Kowalczyk et al., (2013) in in their absorption, distribution, metabolism and excretion (ADME) study of PFAS contaminated feed in dairy cows concluded ‘the kinetics of PFOA were similar to those of PFBS and substantially differed from those of PFHxS and PFOS. The very low concentration of PFBS in plasma and milk, the relatively high urinary excretion, and only traces of PFBS in liver (0.3 ± 0.3 µg/kg ww) and kidney (1.0 ± 0.3 µg/kg ww) support the conclusion that PFBS does not accumulate in the body of dairy cows’. Hill et al., (2021) in their survey of 13 cow’s milk samples in the US concluded that overall ‘the uptake of perfluoroalkyl acids (PFAA) from dairy milk in the U.S. is considered low.’ PFAA would cover both the PFCA and PFSA classes of PFAS.

147. Considering the lack of reported quantifiable amounts of PFHxS, PFOS, PFOA and PFNA in all liquid milk sample data presented by EFSA (2020b) plus the conclusions from Kowalczyk et al. (2013) and Hill et al. (2021) discussed further within the main statement, the COT concluded that PFAS exposures via cow’s milk are not of health concern to infants and children aged 6 months to 5 years.

Brominated flame retardants (BFRs)

Hexabromocyclododecanes (HBCDDs)

148. Studies in laboratory animals have shown that, following oral administration, HBCDDs can be detected in adipose tissue, liver and muscle. Longer-term exposure shows HBCDDs have the potential to bioaccumulate.

149. In the COT (2015c) statement on potential risks from HBCDDs in the infant diet, the Committee concluded that a MOE approach should be taken for the risk assessment, in which estimated exposures to HBCDDs were compared to a reference point of 3 µg/kg bodyweight (bw)/day. This was derived from a study in which neonatal mice were given a technical mixture of HBCDDs by a single gavage administration and behavioural changes were observed in adulthood (Eriksson et al., 2006).

150. Within the COT 2015 statement, the COT discussed the EFSA view that MOEs greater than 8 would indicate that there was no concern for health. This comprised a factor of 2.5 to cover inter-species differences and a factor of 3.2 to cover uncertainties in the elimination half-life in humans producing an MOE of 8, above which there is adequate reassurance that there is no health concern regarding the toxic effect of HBCDDs. The COT agreed in 2015 with EFSA that interspecies differences in toxicokinetics were accounted for by the body burden

approach and using data relating to a critical period of neurological development reduced the toxicodynamic uncertainty. However, the COT considered that MOEs should be rather higher than 8 in order to provide a reasonable assurance of safety, to take account of possible inter-individual differences on toxicodynamics.

151. EFSA (2021b) also concluded that the critical effect of HBCDDs was neurodevelopmental, as seen in behavioural studies in mice (Eriksson et al., 2006). However, effects were also noted in the immune system, reproductive system, the liver and on thyroid hormone homeostasis. A lowest observed adverse effect level (LOAEL) of 0.9 mg/kg bw was considered the Point of Departure regarding behaviour in mice and this equated to a body burden concentration of 0.75 mg/kg bw. In humans, this is equivalent to a chronic intake of 2.35 µg/kg bw per day.

Risk characterisation

152. In a dietary exposure evaluation by EFSA (2021b), 6,857 occurrence values from 2,287 samples were compiled to assess the HBCDD presence in foods. This included approximately 500 values from the UK. In this assessment, data for the stereoisomers α, β and γ-HBCDD were included as well as total HBCDDs.

153. From this dietary exposure assessment, EFSA (2021b) presented data that showed the largest contributing food groups for HBCDDs exposure were fish, poultry, livestock meat and eggs. From the 198 milk analyses undertaken as part of this assessment, the mean LB concentration was 0.01 µg/kg.

154. COT in 2015 concluded that the margins of exposure to HBCDDs by dietary intake of breast milk, infant formula, commercial infant food, fish oil and food in general are at least 400 and not a cause for concern for any age group, as they are considerably greater than 8.

155. In light of the (EFSA, 2021b) and (COT, 2015c) conclusions, the COT concluded that the levels of HBCDDs in cow’s milk do not pose a health risk to infants and children aged 6 months to 5 years.

Polybrominated biphenyls (PBB)s

156. Individual PBB congeners vary in their pattern of toxicity. PBBs have been categorised on a similar structural basis as the PCBs, with category I comprising congeners lacking ortho substituents (coplanar PBBs). Coplanar PCBs are dioxin like with regards to their toxicity and are included in the toxicity

equivalency factor (TEF) approach. A number of PBB effects are dioxin-like and consistent with the aryl hydrocarbon receptor (AhR)-mediated mechanism of action, including altered vitamin A homeostasis, thymic atrophy, dermal and ocular effects (e.g. chloracne and inflammation of eyelids), and body weight changes (wasting syndrome). The magnitude of the response is determined by binding affinity for the AhR. The binding affinity, in turn, is determined by the substitution pattern of the congener, many of the most toxic congeners resembling the structural configuration of 2,3,7,8-TCDD. The dioxin-like coplanar PBB-169 (3,3’,4,4’,5,5’-hexaBB) has been found to be the most toxic congener in several test systems (COT, 2006).

157. In EFSA's (2010c) opinion on PBBs in the food chain they described them as not directly genotoxic, with the main toxicity targets as the reproductive system, immune system, thyroid hormone homeostasis and liver function. Hepatic carcinogenicity was chosen as the critical effect with a no observed effect level (NOEL) of 0.15 mg/kg bw per day. This came from a National Toxicology Programme (NTP) 2-year carcinogenicity study in rats, which included pre- and perinatal exposure of the dams (NTP, 1993). This NOEL was obtained using a technical PBB mixture that may not be representative for the mix of congeners found in the diet, therefore EFSA concluded that it was inappropriate to use this NOEL to derive a health-based guidance value.

158. For planar PBBs, as previously concluded by the COT (2006, 2015a), the World Health Organization (WHO) toxicity equivalency factors (2005 WHO-TEFs) assigned to PCBs could be applied to the corresponding PBB congeners, to determine TEQs. This would be a conservative approach since the corresponding chlorinated congeners are expected to be more toxic than their brominated counterparts due to their higher relative potencies and lower clearance. The TEQs for planar PBBs could then be added to those for other relevant compounds to give a measure of the total intake of chemicals with dioxin-like properties, which could be compared with the TDI of 2 pg WHO-TEQ/kg bw.

159. With regard to the non-planar congeners, the increase in tumour incidence in the carcinogenicity study, although possibly constitutive androstane receptor (CAR)-related and hence not relevant to humans, could be used to provide a reference point for the purposes of risk characterisation.

Risk characterisation

160. In EFSA’s dietary exposure assessment minimal concentrations of PBBs were found. Results were obtained from the analysis of 16 PBB congeners

on 794 food samples, with a focus on samples of animal origin. The food group that contributed the most, fatty fish, contained concentrations that would correspond to intakes of approximately 6 times lower than the NOEL of 0.15 mg/kg bw per day. For liquid milk (n = 51) samples, only BB-52 and BB-101 were detected and this was only in 37% of samples. Concentrations ranged from 0.55 to 6.83 pg/g fat (LB and UB) and 0.64 to 6.92 pg/g fat (LB and UB) for BB-52 and BB-101, respectively. EFSA concluded that 'the risk to the European population from exposure to PBBs through the diet is of no concern'.

161. From the 2015 COT statement on polybrominated biphenyls (PBBs) in the infant diet, the Committee concluded that data on sources of exposure to PBBs were available for only a limited number of congeners, coverage of which had varied between studies. Moreover, few measurements had been made in the UK, and there was uncertainty about the extent to which they were representative. Thus, reliable estimation of infants' exposure to PBBs was not possible, and no meaningful risk assessment could be performed.

162. COT (2015a) also stated that further research on the toxicity of PBBs is not a high priority since their use is now restricted, and exposures are likely to decrease. However, it would be useful to obtain more data on levels of the planar congeners in foods in the UK.

163. Within the literature, minimal levels of PBBs have been reported in milk. For example, Papke et al., (2010) reported on results for cow's milk samples (n=15) from Northern Europe. No PBBs were found (BB-30, -52, -101, -153 and -209), with limits of detection (LOD)s between 3 and 60 ng/kg.

164. In light of the EFSA, (2010c) conclusion, the COT 2015 statement and evidence from the literature, the COT concluded that the levels of PBBs in cow's milk do not pose a health risk to infants and children aged 6 months to 5 years.

PBDEs

165. Studies on the commercial PBDEs indicate that pentaBDE is the most toxic. The COT in 2003 therefore compared the estimated intakes of the sum of the measured PBDE congeners with the reported effect levels for pentaBDE, in their assessment of PBDEs in the Skerne-Tees river system. This was described as a precautionary approach, as some of the congeners are expected to be less toxic than pentaBDE (COT, 2006).

166. EFSA (2011a) published an opinion on PBDEs in food. Within this they described the main toxicological end points as the reproductive system, immune

system, thyroid hormone homeostasis and liver function. They also indicated a potential DNA damaging effect via the induction of reactive oxygen species. Neurodevelopmental effects were considered the critical endpoint and BMDL10 values were derived for PBDE congeners as summarised in Table 19.

Table 19. BMDL10 concentrations of 4 PBDEs for neurodevelopmental effects after a single administration. from EFSA (2011a).

PBDE	BMDL10 (µg/kg bw)	Human intake equivalent to the BMDL10 (ng/kg bw per day)
BDE – 47	309	172
BDE – 99	12	4.2
BDE – 153	83	9.6
BDE - 209	1,700	19,640*

*No value provided by EFSA (2011a), so calculated by COT (2015b), using same approach as EFSA for the other congeners.

Risk characterisation

167. EFSA (2011a) decided that due to uncertainty regarding the data from the studies used to calculate the BMDL10 values in Table 19, they could not be used to establish HBGVs. Instead, they used a MOE approach after undertaking a dietary exposure assessment using PBDE occurrence data from 3,971 food samples originating from 11 EU countries.

168. For the 4 PDBE’s evaluated by EFSA (2011b) only BDE-99 potentially represented a safety concern from dietary exposure in any population group, with a MOE of < 2.5 for young children (1 - < 3 years). However, the CONTAM panel stated ‘that the use of UB intake estimates and the application of the longest reported half-life in humans for the calculation of the dietary intake associated with the body burden at the BMDL10, would have resulted in an overestimation of

the risk.’ For liquid milk, 149 samples were included for the assessment. The milk food category contributed a low % to total dietary exposure. For example, the BDE-99 mean occurrence concentration was over 10 times higher for eggs than milk.

169. Fernandes et al., (2016) looked at PDBEs in UK food and feed. From 3 cow’s milk samples the mean concentration reported for the sum of 17 congeners was 0.05 µg/kg, this was 3 times lower than the mean result reported for eggs and over 40 times lower than the mean result for fish.

170. Pietron et al., (2021) looked at 30 cow’s milk samples alongside a selection of goat’s (n = 35) and sheep’s (n = 22) milk samples. All samples were from the EU (Poland). They concluded that the mean result found for cow’s milk of 0.23 µg/kg for the sum of 10 PDBE congeners was lower than for the other milk varieties, significantly so ($P<0.05$) for certain congener types. They also further concluded that ‘milk consumption does not pose a risk related to PBDEs.’

171. COT in 2017 issued an addendum to its 2015 statement on potential risks of PDBE’s in the infant and young children’s diet. Occurrence in breastmilk, infant formula and commercial infant foods were the main focus of the exposure assessment. However, general food consumption was also evaluated using the 2012 TDS data which includes cow’s milk. The COT concluded that there was ‘a potential concern with respect to exposure of infants to BDE-99 and (to a lesser extent) BDE-153 from food, other than commercial infant food. The current analysis indicated that exposure of young children aged 1-5 years to these congeners from such food was unlikely to be a health concern’ (COT, 2017).

172. Overall, reviewing the EFSA (2011b) and COT (2015b; 2017) conclusions, in addition to the evidence from the literature that cow’s milk contains only very low levels of PBDEs, the COT concluded that the levels of PBDEs in cow’s milk do not pose a risk to health for infants and children aged 6 months to 5 years.

Tetrabromobisphenol A (TBBPA)

173. EFSA (2011b) published an opinion on TBBPA in food in 2011. The main toxicological target was identified as thyroid hormone regulation, with no evidence of genotoxicity or reproductive toxicity from the limited data set available. A BMDL10 of 16 mg/kg bw was derived for effects on thyroid hormone homeostasis as the critical effect.

Risk characterisation

174. EFSA (2011b) decided that due to uncertainty regarding the data from the studies used to calculate the BMDL10, health-based guidance values could not be established. Instead, they used a MOE approach after undertaking a dietary exposure assessment using TBBPA occurrence data from 652 food samples from 4 EU countries (Ireland, Norway, Spain and UK). The majority of these food samples (465) were either fish or other seafood, as the most likely source of contamination.

175. From the EFSA (2011b) assessment, all dietary exposures provided large MOEs to the BMDL10, resulting in a conclusion that 'dietary exposure to TBBPA in the European Union does not raise a health concern.' All food stuffs, which included cow's milk, other than fish did not contain any TBBPA above methodology reporting levels (0.02 to 0.2 µg/kg depending on the food type).

176. COT in 2019 in its 'Review of potential risks from tetrabromobisphenol A (TBBPA) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years' undertook a chronic dietary TBBPA exposure assessment. Exposures were calculated using occurrence data from the UK 2004 Total Diet Study (TDS) (Driffield et al. 2008) and consumption data from DNSIYC and NDNS (COT, 2019b).

177. In the COT (2019c) assessment, the Committee concluded that all estimates of the MOE for chronic dietary TBBPA exposure (based on UK consumption data) were greater than the lowest MOE values calculated by EFSA for infants and toddlers for exposure though consumption of breast milk and cow's milk, respectively. The UK MOE values appear to be adequately protective and indicate minimal risk from estimated chronic dietary exposures.

178. Papke et al., (2010) reported on results for cow's milk samples (n=15) from Northern Europe. Mean values were < 0.005 µg/kg.

179. In light of the EFSA (2011b) and COT (2019c) conclusions and evidence from the literature that levels in cow's milk are very low, so that the MOEs are not of concern, the COT concluded that levels of TBBPA in cow's milk do not pose a risk to health for infants and children aged 6 months to 5 years.

Microplastics

180. Currently there is no internationally agreed definition of a microplastic, however, publications by Verschoor and de Valk, (2016) and

Hartmann et al., (2019) have proposed criteria and considerations to be included in the definition of microplastics. In Europe, the European Chemicals Agency (ECHA) has proposed a regulatory definition for a microplastic under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation.

181. The definition proposed by ECHA (European Chemicals Agency, 2019) for a microplastic is a “material consisting of solid polymer-containing particles, to which additives or other substance(s) may have been added, and where ≥ 1% w/w have (i) all dimensions 1 nm ≤ x ≤ 5 mm or (ii) for fibres, a length of 3 nm ≤ x ≤ 15 mm and length to diameter ratio of >3. Polymers that occur in nature that have not been chemically modified (other than by hydrolysis) are excluded, as are polymers that are (bio)degradable.” Note that this definition covers nanoplastics.

182. In 2019, the European Chemical Agency (ECHA) published a restriction report in response to the European Commission’s request (European Chemicals Agency, 2019). In this, ECHA identified four concerns stemming from the potential environmental and human health risks posed by the presence of microplastics in the environment. These were; ‘their size, small (typically microscopic) making them readily available for ingestion and potentially liable to transfer within food chains, very resistant to environmental (bio)degradation, (bio)degrade in the environment progressively via fragmentation, and are practically impossible to remove from the environment after release.”

183. Microplastics are persistent environmental contaminants and have been detected in both the aquatic (e.g. oceans, freshwater rivers and lakes) and terrestrial (e.g. landfills, agricultural land from utilisation of plastic mulch, wastewater, sewage sludge, compost and anaerobic digestate) environments.

184. Due to their widespread presence in the environment, microplastics also occur in food (e.g. seafoods, salt, honey, vegetables) and drinks (e.g. bottled water, milk, soft drinks, tea, beer) (Toussaint et al., 2019).

185. As described in a recent COT statement (COT, 2021b) there are four morphological and chemical characteristics of microplastics, i.e. physicochemical properties, which influence their potential hazards. These are:

i) Physical (e.g. bulk), which could lead to intestinal blockage, as observed in aquatic and avian species.

ii) Chemical composition, e.g. unbound monomers, additives, sorbed chemicals from the environment e.g. persistent organic pollutants and heavy metals.

iii) Metabolism or degradation to form monomers or other derivatives, some of which could be chemically reactive (e.g. isocyanates from polyurethane).

iv) The presence of biofilms (attachment and colonisation of microorganisms on the plastics).

186. Orally ingested microplastics in mammalian species either remain confined in the gastrointestinal tract (GI), translocate from the GI tract into organs or tissues (via endocytosis by M cells and paracellular persorption), and/or are excreted.

Risk characterisation

187. Microplastics have been occasionally reported in cow's milk in other continents, such as in a study in Mexico (Kutralam-Muniasamy et al., 2020; Shruti et al., 2021), where the authors stated that 'thermoplastic sulfone polymers (polyethersulfone and polysulfone) were common types of microplastics in milk samples, which are highly used membrane materials in dairy processes.' The authors infer that the origin of microplastics in cow's milk lies in the processing and packaging of the milk, rather than originating from dairy cows and could be limited by increased controls and preventative measures during processing. The COT concurs with this conclusion. The authors found the presence of microplastics at low levels (1 – 14 particles / Litre) in all 23 cow's milk samples analysed.

188. The current view of the COT from the above information and that included in the main statement is that the levels of microplastics in cow's milk do not represent a risk to health for children aged 6 months to 5 years of age.