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Annex A to TOX/2022/04

Committee on Toxicity of Chemicals in Food, Consumer products and the Environment

First draft 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

Background

1. This information presented in this annex should be read in conjunction with the main statement on the risk assessment of cow's milk in children aged 6 months to 5 years of age. The risk assessment of milk was conducted to support the work of the plant based drinks working group. This annex contains detailed supporting information for the evaluations where the COT concluded there was minimal risk to health.

Consumption data

2. The National Diet and Nutrition Survey (NDNS) rolling programme and Diet and Nutrition Survey of Infants and Young Children (DNSIYC) data were used to undertake any chronic exposure assessments in this statement, required for assessing the safety of milk from a chemical contaminant perspective, in young children aged 6 months to 5 years (Department of Health, 2011; Bates et al., 2014; Roberts et al., 2018). The data presented in Table 1 include consumption data for cow's milk consumed as a drink and used in recipes. Consumption data for children aged 6 – 12 months are derived from milk used in recipes only as cow's milk is not recommended by the NHS as a main drink for infants in this age range (NHS, 2018). Table 2 presents consumption data for milk as a drink only. As these values are only slightly lower, all exposure assessments have been undertaken using the worst case data from Table 1 only (with recipes).

Table 1. Estimated chronic consumption of cow's milk in consumers (as a drink and with recipes)

Age (months)	Number of Consumers	(g/kg bw/day) Mean	(g/kg bw/day) 97.5th percentile
6 – <12	1257	13	48
12 – <18	1275	32	75
18 – <24	157	29	79
24 – <48	351	23	59
48 – <60	618	17	46

Table 2. Estimated chronic consumption of cow's milk in consumers (as a drink without milk used in recipes)

Age (months)	Number of Consumers	(g/kg bw/day) Mean	(g/kg bw/day) 97.5th percentile
12 – <18	1148	30	71
18 – <24	147	28	73
24 – <48	337	21	54
48 – <60	585	15	42

Chemicals evaluated

Nitrate and nitrite

1. 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) day was established for sodium nitrate and the ion form of nitrate respectively. These guidance values were derived from 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

2. 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 AND Risk in both PubMed (PubMed (nih.gov) and Science Direct (ScienceDirect.com | Science, health and medical journals, full text articles and books.)

3. Three references were found that reported any 'background' contamination of nitrate in cow's milk, with no positives found for nitrite (all 'non detected'). Of the 3 papers, two reported nitrate concentrations in cow's milk outside the EU (Taiwan, USA) where agricultural practices may differ significantly to 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).

4. Potential chronic exposure to nitrate based on the consumption rates in Table 1 and the average nitrate concentration reported in Olijhoek et al. (2016), along with the % of the 3.7 mg/kg bw recommended ADI (EFSA, 2008a) are presented in Table 3.

Table 3. Nitrate exposure assessment from cow's milk consumption

Age (months	Estimated Exposure (mean) (mg/kg bw day)	Estimated Exposure (97.5th percentile) (mg/kg bw 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

5. 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 regards to dietary consumption (EFSA, 2009b).

Bisphenol A

Risk Characterisation

6. 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 day. This guidance value was determined after a benchmark dose lower confidence limit $(BMDL)_{10}$ 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 (for inter- and intra-species differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) (EFSA, 2015b).

7. 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 are currently reviewing the TDI for BPA.

Phthalates

8. 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 derived TDIs for them (EFSA, 2005a, 2005b, 2005c, 2005d, 2005e). In 2003 the World Health Organisation derived a TDI for diethyl phthalate (DEP) of 5 mg/kg bw (WHO, 2003).

9. EFSA's risk assessment and revaluation in 2019 of DBP, BBP, DEHP, DINP and DIDP for use in food contact materials re-confirmed the same critical effects and individual TDIs (mg/kg bw per day) derived 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 introducing relative potency factors.

10. 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.

11. 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.

12. 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

13. EFSA's CEP panel (2019) concluded that the Group Phthalates (expressed as DEHP equivalents) using mean consumer dietary exposure, only contributed 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 also well below the recommended TDI of 0.15 mg/kg bw per day.

14. 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.

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

15. 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).

16. 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) re-evaluated this t-TWI based on rat studies which reported reproductive effects in male offspring. Applying an overall uncertainty factor of 10 to the Lowest Observed Adverse Effect Dose (LOAEL) derived from estimated human daily intakes (EHDI) the SCF concluded that 14 pg/kg bw per week should be considered as a tolerable intake for 2,3,7,8-TCDD. COT in 2001,

recommended that a tolerable daily intake of 2 pg WHO-TEQ/kg bw per day was established 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.

17. In a recent opinion, EFSA (2018a) used toxicokinetic modelling to estimate that exposure of adolescents and adults should be less than 0.25 pg WHO-TEQ/kg bw/ day. The CONTAM panel established a TWI of 2 pg TEQ/kg bw /week, a seven-fold reduction. This was based on the critical effect of sperm concentrations that were inversely associated with serum concentration of TCDD, PCDD-TEQ and PCDD/F-TEQ in a study of Russian children whose parents had been exposed to dioxins (mainly TCDD) during manufacture of trichlorophenol and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) (Mínguez-Alarcón et al., 2017).

18. 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 Values (HBGV), the current value of 14 pg TEQ/kg bw /week having previously been shown to afford protection to the developing foetus. 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 2022, at the earliest.

Exposure Assessment and risk characterisation

19. 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).

20. To obtain published concentrations for dioxins and DL-PCBs in cow's milk a literature search was undertaken using the keywords Dioxin AND Cow AND Milk AND Risk in both PubMed and Science Direct. The results returned were for a limited number of papers with low sample numbers, except for the survey published by EFSA in 2018. The results of this survey are summarised in Table 4 and include cow's milk samples from 23 EU countries, including the UK. When converting results from the survey that have been presented on a 'per fat' basis, a value of 3.5% fat has been used as a general worst case scenario for fat content of the range of milk types, as 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 after which, semi skimmed can be introduced - but lower fat milks can be used

in cooking from the age of 1. 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.

21. Occurrence data for dioxins and DL-PCBs are presented below in Table 4. Tables 5 and 6 summarise the potential chronic exposure to dioxins plus DL-PCBs based on the cow's milk consumption rates in Table 1 using the upper bound mean and 95th percentile concentrations from the EFSA survey data (2018a) along with the % of the recommended TDI of 2 pg WHO-TEQ/kg bw per day from COT in 2001.

22. 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) presented, it is assumed that 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).

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

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

Age (months	Estimated Exposure mean) (pg WHO TEQ / kg bw day)	Estimated Exposure (97.5th percentile) (pg WHO TEQ / kg bw 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. Dioxin plus DL-PCBs exposure assessment 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 day)	Estimated Exposure (97.5th percentile) (pg WHO TEQ / kg bw 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

23. 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 (Table 4). All age ranges using the 97.5th percentile consumption data exceed this % TDI when using the 95th percentile concentration from the EFSA occurrence data (Table 5). Two age ranges using the mean consumption data and the 95th percentile concentration from the EFSA occurrence data 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 in the above assessment.

24. In the recent COT review with 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, 2019a).

Non-dioxin-like PCBs

25. 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.

26. 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).

27. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) last evaluated the NDL-PCBs in 2016 (JECFA, 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 Margin of Exposure (MOE) to provide guidance on human health risk.

28. 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 with the estimated median human body burden. For all NDL-PCBs EFSA estimated an overall body burden NOAEL of 500 µg/kg.

29. 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.

30. 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

31. From the EFSA (2005) opinion, it was concluded that the overall NOAEL 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. No overall conclusion was drawn from this opinion apart from 'A continuing effort to lower the levels of NDL-PCB in food is warranted.'

32. Considering the large European survey study 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 safety risk of NDL-PCBs from drinking cow's milk is negligible.

33. Furthermore, JECFA concluded in 2016 (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2016) that 'dietary exposures to NDL-PCBs are unlikely to be of health concern for adults and children, based on the available data.'

Polycyclic Aromatic Hydrocarbons (PAHs)

34. 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, gave a better measure for risk assessment purposes.

35. 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).

36. In contrast to dioxins and PCBs which are known as persistent and bio accumulate in animal products, PAHs can be metabolised but their interaction with the cow rumen, for example, is not well understood. (Rychen et al., 2008).

37. 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).

38. Rather than proposing a HBGV, EFSA in 2008 (EFSA, 2008b) used the US EPA BMD software (BMDS) to derive $BMDL_{10}$ values for BaP and the sum of PAH4 of 0.070 mg/kg bodyweight (bw)/day) and 0.340 mg/kg bw/day respectively. 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

39. To obtain published concentrations for PAHs in cow's milk a literature search was undertaken using the keywords PAH AND Cow AND Milk AND Risk in both PubMed and Science Direct. Results were limited to 6 small surveys within EU countries from one paper (Sun et al., 2020).

40. Due to the limited occurrence data in the literature, the UK TDS results for PAHs in 44 UK milk samples from 2012 were used for an exposure assessment (Fernandes et al., 2012). Only averages are 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 in cow's milk (whole sample basis) from UK TDS(Fernandes *et al.*, 2012)

	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

41. 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 $BMDL_{10}$ 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.

42. A MOE assessment has been undertaken using the upper bound average concentrations from the TDS 2012 data (Table 8) and consumption rates in Table 1 against the $BMDL_{10}$ 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 exposure assessment from cow's milk consumption

Age (months	Estimated Exposure (mean) (µg/kg bw day)	Estimated Exposure (97.5th percentile) (µg/kg bw day	Margin of Exposure to $BMDL_{10}$ (EFSA 2008b) (mean consumption)	Margin of Exposure to $BMDL_{10}$ (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 exposure assessment from cow's milk consumption

Age (months	Estimated Exposure (mean) (µg/kg bw day)	Estimated Exposure (97.5th percentile) (µg/kg bw day	Margin of Exposure to $BMDL_{10}$ (EFSA 2008b) (mean consumption)	Margin of Exposure to $BMDL_{10}$ (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

43. 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 there is a very low safety risk of the PAH4 from drinking cow's milk.

Lead

44. 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, 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.

45. 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.

46. 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 $BMDL_{01}$ was derived (EFSA, 2010) of 0.5 µg/kg for lead , affecting development of intellectual function, this was calculated as the level in which a 1% change in full scale IQ occurred (1 IQ point reduction). The EFSA $BMDL_{01}$ 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 a steep dose-response at low levels based on few data from a single study. This may have produced a conservative result.

Risk Characterisation

47. In EFSA (2012a) dietary exposure was calculated 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.

48. EFSA (2012a) demonstrated that in the total diet, infants were exposed to a total mean exposure of 0.83 and 0.91 µg/kg bw/day of lead in two surveys, toddlers were exposed to a total mean exposure of 1.32 µg/kg bw/day and other children were exposed to 1.03 µg/kg bw/day. These values are all above the $BMDL_{01}$ for neurological effects of 0.5 µg/kg bw/day. Whilst these exposure values do exceed the $BMDL_{01}$, the contribution of milk itself should not raise concerns, since it was not the major source of exposure; no concerns were raised in the EFSA report. Therefore, levels of lead within milk would not be expected to cause concern for human health.

49. In 2013 and 2016, the COT utilised a MOE approach to estimate the impacts of lead exposure in the diets of children aged 1-5 years. 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 led to MOEs below 1 due to other significant factors including contributions from dust and soil. A risk at the population level and to some infants and children could not be excluded. The COT did not consider any special measures were necessary for lead.

Arsenic

50. The main adverse effects of chronic inorganic arsenic consumption include skin lesions, cancer, developmental toxicity, neurotoxicity and 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 by the International Agency for Research on Cancer.

51. 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 $BMDL_{01}$ ranging between 0.3 and 8 µg/kg bw day for skin lesions as well as cancers of the lung, skin and bladder. They concluded ‘estimated dietary exposures to iAs for average and high level consumers in Europe are within the range of the $BMDL_{01}$ 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).

52. 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 $BMDL_{0.5}$ of 3 µg/kg bw day for lung cancer ranging between 2 and 7 µg/kg bw 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).

53. In 2016 the COT concluded that the JECFA $BMDL_{0.5}$ of 3 µg/kg bw/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).

54. 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

55. As in the previous 2016 COT statement, this paper focuses on inorganic arsenic due to its carcinogenic nature.

56. 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.

57. EFSA's latest 2021 evaluation of chronic iAs exposure reported that of 109 samples of cow's milk, only 3 contained any 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).

58. COT's 2016 risk assessment suggest that at mean levels of 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. The COT concluded from this

information that inorganic arsenic in cow's milk does not present a risk to health to children aged 6 months to 5 years of age.

Mercury

59. EFSA's Panel on Contaminants in the Food Chain (CONTAM) explored the toxicity of inorganic mercury in 2012. This is summarised below. The kidneys are currently thought to be the 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 exhibiting no changes. Ototoxic and reproductive and developmental effects have also been observed. Evidence for inorganic mercury induced carcinogenicity is equivocal. Epidemiological data for inorganic mercury presented effects on the immune system, liver, kidneys, immune system, endocrine systems and cyto-genotoxicity. This epidemiological data were not considered usable for establishing dose-response relationships.

60. In 2012, EFSA's CONTAM panel revaluated the previous provisional tolerable weekly intakes (PTWIs) 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 derived a tolerable weekly intake (TWI) of 4 µg/kg bw from a $BMDL_{10}$ of 60 µg/kg bw/day with an uncertainty factor of 100 to account for inter and intra species variation (EFSA, 2012c).

Risk Characterisation

61. From the 2012 EFSA CONTAM panel opinion, occurrence data for milk and dairy products was assumed to consist of 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).

62. EFSA (2012c), after taking 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/week. They stated that the majority of studies are below the TWI of 4 µg/kg bw/week however the highest UB 95th percentile dietary exposure value for toddlers at 4.06 µg/kg bw/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.

63. 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.

64. Excepting toddlers, no total inorganic mercury exposures exceeded the TWI. With cow's milk only contributing a maximum of 15% to the mean MB exposure of inorganic mercury in toddlers it is unlikely, based upon the opinion of EFSA (2012c), that mercury in cow's milk will present a risk to the health of children aged 6 months – 5 years.

65. The COT has produced a statement discussing methylmercury in the diet of infants and children aged 6 months – 5 years (COT, 2018d). For the Infant Metal 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 infant metals survey data and 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/week for inorganic mercury. The risk from inorganic mercury exposure to children is therefore low.

66. Comparing information from EFSA 2012c and the COT's consideration of TDS and infant metals survey data the COT concluded that the risk of harm to infants and children aged 6 months – 5 years from exposure to inorganic mercury in cow's milk is low.

Cadmium

67. 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 compounds background and hazards, key aspects of this hazard identification are included below (COT, 2018c).

68. Acute cadmium toxicity is largely an issue for workers involved in industrial applications. Chronic effects are a greater concern for the general population. The liver and kidneys are the main targets of cadmium chronic toxicity. Cd in the liver binds to the sulphydryl-rich protein metallothionein (MT) which is then released into the blood and filtered 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 sequestered by renal MT. As Cd concentrations increase the renal proximal cells' capacity to produce MT is exceeded and free Cd causes damage at multiple sites (COT, 2018c).

69. 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 protein damage may be reversible (Gao et al., 2016) however in later stages may be irreversible and progressive even in absence of ongoing Cd exposure (COT, 2018c).

70. Chronic cadmium exposure can induce osteoporosis and osteomalacia, with deformities and bone fragility caused by direct calcium displacement or 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, 2018c).

71. Cadmium whilst classified by the International Agency for Research on Cancer (IARC) as a group 1 human carcinogen, 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 cellular proliferation by activation of the Wnt second messenger system and mimicry of oestradiol at oestrogen receptors (IARC, 2012; COT, 2018c).

72. The COT statement in 2018 noted that there was no consistency in the epidemiological data on the carcinogenicity of cadmium and no increased incidence of tumours was seen in experimental animals.

73. 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 $BMDL_5$ of 4 µg urinary cadmium (U-Cd)/ g creatinine was calculated for an increase of the prevalence of elevated β2M. When taking 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, Cd dietary exposure should stay below 0.36 µg/kg bw/day or 2.52 µg/kg bw/week. Considering cadmium’s long biological half-life a TWI of 2.5 µg/kg bw/week was established.

74. JECFA established a provisional tolerable monthly intake (PTMI) of 25 µg/kg bw/ month (FAO/WHO, 2011b). This is equivalent to approximately 6 µg/kg bw/week or approximately 0.8 µg /kg bw/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.

75. 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/ 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.

76. 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 for its assessments (EFSA, 2011c).

Risk Characterisation

77. In 2012 EFSA published a dietary exposure assessment for the European population (EFSA, 2012a). EFSA expressed 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).

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

79. The COT 2018 statement on cadmium in the infant diet and children aged to 5 years 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 setting 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.

80. Whilst exceedances of the TWI were observed in both COT (2018c) and EFSA (2012a) exposure assessments the relative contribution of cow's milk in both of these assessments was low. Therefore, the COT concluded that cadmium in cow's milk presents a low risk to the health of infants and children aged between 6 months and 5 years.

Perchlorate

81. The EFSA CONTAM panel in 2014 decided 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 panel noted it was unknown if thyroid iodine uptake inhibition below 50% has any consequences, the CONTAM panel performed benchmark dose modelling on a study by Greer et al., (2002), previously identified by JECFA as a key study for dose-response modelling 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 $BMDL_{05}$ (5% extra risk of thyroid iodine inhibition) of 0.0012 mg/kg bw/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/day. The panel did not consider it necessary to produce a safety level for short term exposure (EFSA, 2014).

Exposure assessment and risk characterisation

82. 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. 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 3.80-5-10 µg/kg (LB-MB-UB) was also presented. Occurrence data was also provided in (EFSA, 2014)

83. In 2019 the COT reviewed the data available regarding perchlorate within the diet of infants and young children and discussed in both 2017 and 2014 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, 2019b).

84. No other European occurrence data was found through a literature search of the PubMed database using the terms "Chlorate OR perchlorate AND occurrence AND milk" with search results limited to 2001-2021.

85. An exposure assessment 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 rates from Table 1 and the TDI of 0.3 µg/kg bw/day (from EFSA, 2014). This assessment is presented in Tables 13 and 14.

Table 13. Exposure assessment 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/day)	Estimated exposure (97.5th percentile) (µg/kg bw/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 14. Exposure assessment 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/day)	Estimated exposure (97.5th percentile) (µg/kg bw/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.

86. 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 between ages 12 -< 48 months were found at the 97.5th percentile of consumption (Table 13). At the 95th percentile UB occurrence of 10 µg/kg at mean consumption levels, there were exceedances for the 12-<18 age group and exceedances at all values at the 97.5th percentile of consumption (Table 14). This, however, is an extremely conservative assessment using occurrence data presented as upper bound.

Chlorate

87. 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 in animal models. 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. Alteration to thyroid hormone levels included decreases in T3 and T4, accompanied by increases in thyroid-stimulating hormone (TSH). Long term toxicity includes formation of non- neoplastic lesions in the thyroid gland, in male and female rats and mice, bone marrow (hyperplasia) in male rats and female mice and the spleen of male rats (haemopatic cell proliferation). There is evidence of reproductive and developmental toxicity in rats.

88. In humans, acute chlorate exposure has resulted in vomiting, abdominal pain, cyanosis, methemoglobinemia, anuria and renal failure. Chronic developmental effects have been studied in humans regarding disinfection by-products, two were found to involve chlorate, one detected no congenital abnormalities in children with one study detecting congenital abnormalities at a low rate with no information regarding lifestyle habits of mothers (EFSA, 2015a).

89. 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 chlorate did not pose a genotoxic risk (EFSA, 2015a).

90. 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, 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 derived a TDI of 3 µg/kg through a read across from the 0.3 µg/kg TDI set for perchlorate based on human data and a 0.1 times potency factor for the difference in toxicity between the two compounds seen in rats (EFSA, 2015a).

Exposure assessment and risk characterisation

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

‘ 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.’

92. 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.

93. No other European occurrence data was found through a literature search of the PubMed database using the key terms "Chlorate OR perchlorate AND occurrence AND milk" with search results limited to 2001-2021.

94. An exposure assessment has been performed using the TDI of 3 µg/kg bw/day and the mean upper bound occurrence value for chlorate (17 µg/kg) from EFSA, (2015a) in addition to the consumption rates from Table 1. This assessment is presented in Table 15.

Table 15. Exposure assessment 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/day)	Estimated exposure (97.5th percentile) (µg/kg bw/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

95. 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 no exceedances of the TDI can be seen in any of the child age groups (Table 15). This provides a more detailed look at the impacts of milk than in the EFSA 2015 report where information was largely limited to 'milk and dairy products'

Insulin-like Growth Factor (IGF-1)

96. The Committee on Carcinogenicity Food, Consumer Products and the Environment (COC) released a statement on the risks of IGF-1 in cow's milk in 2018. They concluded that absorption of intact IGF-1 is unlikely. In addition, they concluded there are very few papers linking raised circulating IGF-1, diet and cancer risk and where it was investigated, dairy consumption was not linked to increased

cancer risk. The committee 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 however, this included a lack of information on diet, ethnicity of subjects and a lack of continual monitoring. Despite this the committee concluded that there was no expected increase to cancer risk from IGF-1 in the diet (COC, 2018).

97. Bovine Somatotropin (BST) treatment in 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 analysed. 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. This estimate assumes that imported milk is spread proportionally between milk intended for liquid consumption and manufacturing processes. This figure suggests that the risk of exposure to BST induced IGF-1 is likely low, further mitigating any risks presented by its presence in milk.

98. As stated by the COC in 2018 it is unlikely that IGF-1 in cow's milk poses a risk to health to infants and children aged 6 months to 5 years of age. In addition to this, milk from BST treated cows is unlikely to enter circulation into the UK in significant amounts. From this information the COT concluded that it is unlikely that IGF-1 within cow's milk poses a risk to health for children aged 6 months to 5 years of age.

Naturally occurring oestrogens in cow's milk

99. Snoj and Majdič, (2018) collated 10 studies examining occurrence of oestrogens in cow's milk however, these studies investigated US cattle. Due to differences in dairy practices between US and European cows 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 2001-2012 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. However, two papers reporting natural oestrogen levels were later found in Courant et al. (2007) and Malekinejad, Scherpenisse and Bergwerff (2006).

100. 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 the 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.

101. Hormones for use as growth-promotors in beef cattle were evaluated by JECFA in (2000). For 17β-oestradiol it was concluded that hormonal effects occur at doses lower than other toxicological responses and are 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/day 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 will be compared to this ADI.

102. Other scientific Committees have reviewed the safety of oestrogens and 17β-oestradiol for use as growth promoting hormones inn beef cattle. The Veterinary Products Committee (VPC) 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 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, whilst 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 used were conjugated oestrogens, 17β-oestradiol and its semi-synthetic esters. The COT currently considers that any genotoxic effect likely arises through an indirect mechanism such as redox cycling.

103. In the Snoj and Majdič. review and in additional information found during the literature search, it was often reported that the contribution of milk oestrogens in comparison to circulating levels of oestrogens was expected to be minimal (Pape-

Zambito, Magliaro and Kensinger, 2008; Macrina et al., 2012; Parodi, 2012; Snoj and Majdič, 2018).

Exposure assessment and risk characterisation

104. Two papers reporting EU occurrence data were found for naturally occurring oestrogens in milk. The highest occurrence was for the sum of oestrone, 17α-oestradiol, 17β-oestradiol and oestriol collected in Malekinejad, Scherpenisse and Bergwerff (2006). This consisted of 4 samples of processed milk collected from local grocery stores and a sample of organic milk. Below in Table 16, the mean concentrations of each oestrogen are presented after the milk had been enzymatically treated. Due to a lack of detections for some oestriol 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.

Table 16. Occurrence data for oestrone, α-oestradiol, β-oestradiol and oestriol in milk from Malekinejad, Scherpenisse and Bergwerff (2006)

Compound	Mean Concentration ng/L (LB - UB)
Oestrone	201.8
α-oestradiol	51.2
β-oestradiol	10.4
Oestriol	(4 - 10)
Total oestrogens	(267.4 – 273.4)

105. Two exposure assessments have been performed comparing to the JECFA ADI of 0.05 µg/kg bw/day for 17β-Oestradiol and using the mean concentration of the sum of oestrogens found within milk (267.4 – 273.4 ng/L) (LB-UB) from Malekinejad, Scherpenisse and Bergwerff, (2006) in addition to the consumption rates from Table 1. It was assumed that a litre of milk is equivalent to a kilogram. This assessment is presented in Tables 17 and 18.

Table 17. Lower Bound exposure assessment using the mean occurrence value for liquid milk from Malekinejad, Scherpenisse and Bergwerff (2006) and consumption data from the NDNS and the JECFA ADI.

Age (months)	Estimated exposure mean µg/kg bw/day	Estimated exposure 97.5th percentile µg/kg bw/day	Mean % ADI	97.5th percentile % ADI
6 – <12	0.00348	0.0128	6.95	25.7
12 – <18	0.00856	0.0201	17.1	40.1
18 – <24	0.00775	0.0211	15.5	42.3
24 – <48	0.00615	0.0158	12.3	31.6
48 – <60	0.00455	0.0123	9.09	24.6

Table 18. Upper Bound exposure assessment using the mean occurrence value for liquid milk from Malekinejad, Scherpenisse and Bergwerff, (2006) and consumption data from the NDNS and the JECFA ADI.

Age (months)	Estimated exposure mean µg/kg bw/day	Estimated exposure 97.5th percentile µg/kg bw/day	Mean % ADI	97.5th percentile % ADI
6 – <12	0.00355	0.0131	7.11	26.3
12 – <18	0.00875	0.0205	17.5	41.0
18 – <24	0.00793	0.0216	15.9	43.2
24 – <48	0.00629	0.0161	12.6	32.3
48 – <60	0.00465	0.0126	9.30	25.2

106. From occurrence data sourced from Malekinejad, Scherpenisse and Bergwerff, (2006) and NDNS consumption data no exceedances of the ADI established by JECFA in 2000 can be seen. It should be noted however that there is uncertainty regarding the role of genotoxicity in the carcinogenicity of 17β-oestradiol.

107. Regarding 17β-oestradiol, uncertainty exists, with international risk assessment groups presenting varied opinions on its genotoxicity. The now disbanded SCVPH considered the compound to be genotoxic whilst the VPC advised to consider it as a complete carcinogen until further information became available. JECFA concluded that it had genotoxic potential.

Mycotoxins

108. 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. No mention of cow's milk is present in either of these statements (COT, 2018b, 2018e) COT's 2021 statements regarding mycotoxins did not comment on mycotoxins in cow's milk (COT, 2021d, 2021a)

109. In the COT's 'Statement on the potential risk(s) of combined exposure to mycotoxins' they were unable to perform a risk assessment on the risks of 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 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).

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

Per- and polyfluoroalkyl substances (PFAS)

111. As discussed in a recent COT discussion paper (COT, 2020b) Most of the information on the fate of PFSAs and PFCAs is based on PFOS and PFOA, respectively. These compounds are readily absorbed in the gastrointestinal (GI) tract in mammals and 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 clearance. For both PFOS and PFOA, maternal transfer occurs prenatally to the foetus through placental transfer and postnatally through the consumption of maternal milk

112. Based on the high concentrations of PFAS observed in the blood of individuals exposed to contaminated water and by what is known for PFSO and PFOA, it may be assumed that the gastrointestinal (GI) absorption of most of the PFASs occurs to a significant extent in humans. PFAS are widely distributed 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. PFASs 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 PFASs 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. Short chain PFASs were found to have half-lives ranging from a few days to approximately one month, whereas PFHxS, PFOS, PFOA and PFNA estimated half-lives can exceed 3 years.

113. 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 mostly evident at higher dose concentrations. 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.

114. 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.

115. EFSA, (2020b) concluded that effects on the immune system, as decreased antibody responses, recorded at the lowest serum PFAS concentrations in both human and animal studies were critical for the risk assessment and evaluation. 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 µg/kg bw/day was derived from a $BMDL_{10}$ of 17.5 ng/ml, based on reduced antibody levels against diphtheria vaccine in 1-year old children (Abraham et al., 2020).

Risk characterisation

116. From the dietary exposure evaluation undertaken by EFSA (2020b) they 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.

117. 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.

118. 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.

Brominated flame retardants (BFRs)

Hexabromocyclododecanes (HBCDDs)

119. 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.

120. 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).

121. 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 was generated by 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. However, the COT considered that MOEs should be higher than 8 in order to provide a reasonable assurance of safety.

122. 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 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

123. From 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 also included as well as total HBCDDs.

124. 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.

125. 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.

Polybrominated biphenyls (PBB)s

126. 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) concept. 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). This is determined by the magnitude of the response that is initiated by binding with the AhR. The binding affinity, in turn, is determined by the substitution pattern of the congener, many of the most toxic congeners resemble 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).

127. 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. 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 derived 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.

128. 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 toxicity equivalences (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 toxicity equivalences (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/day.

129. With regard to the non-planar molecules, the tumour incidence in the carcinogenicity study, although possibly constitutive androstane receptor (CAR)-related, could be used to provide a reference point for the purposes of risk characterisation.

Risk characterisation

130. 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 from animal origin. The food group that contributed the most to, fatty fish, contained concentrations that would relate to approximately 6 times lower than the NOEL of 0.15 mg/kg bw. 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 ng/kg 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.

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

132. 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.

133. Within the literature, minimal levels of PBBs have been reported in milk. For example, Papke, O 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) at limits of detection (LOD)s between 3 and 60 ng/kg.

PBDEs

134. 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. This was described as a precautionary approach, as some of the congeners are expected to be less toxic than pentaBDE (COT, 2006).

135. 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 classified as the critical endpoint and $BMDL_{10}$ concentrations were derived for PBDE congeners as summarised in Table 27.

Table 27. $BMDL_{10}$ concentrations of 4 PBDEs for neurodevelopmental effects from EFSA (2011a) and COT (2015b).

PBDE	EFSA (2011b) $BMDL_{10}$ (µg/kg bw)	COT (2015c) $BMDL_{10}$ (µg/kg bw)
BDE – 47	309	172
BDE – 99	12	4.2
BDE – 153	83	9.6
BDE - 209	1,700	19,640

Risk characterisation

136. EFSA (2011a) decided that due to uncertainty regarding the data from the studies used to calculate the $BMDL_{10}$ data in Table 19, they could not be used to set 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.

137. For the 4 PDBE's evaluated by EFSA (2011b) only BDE – 99 potentially represented a safety concern from dietary exposure by any population group, with a MOE of < 2.5 for young children (1 - < 3 years). However, the 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 $BMDL_{10}$, would have resulted in an overestimation of the risk.' For liquid milk, 149 samples were included for the assessment. The milk food category represented a low % of total dietary exposure. For example, the BDE – 99 mean occurrence concentration was over 10 times higher for eggs than milk.

138. 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.

139. 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. 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.'

140. COT in 2017 issued an addendum to the 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 conclusion was 'a possible 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).

Tetrabromobisphenol A (TBBPA)

141. EFSA (2011b) published an opinion on TBBPA in food. The main toxicological target was identified as thyroid hormone regulation, with no evidence of genotoxicity or reproductive toxicity from the limited data set effect. A $BMDL_{10}$ of 16 mg/kg bw was derived for thyroid hormone homeostasis as the critical reference point.

Risk characterisation

142. EFSA (2011b) decided that due to uncertainty regarding the data from the studies used to calculate the $BMDL_{10}$ health based guidance values could not be

derived. 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.

143. From the EFSA (2011b) assessment, all dietary exposures provided large MOEs to the $BMDL_{10}$, resulting in a conclusion that 'dietary exposure to TBBPA in the European Union does not raise a health concern.' All other food stuffs, which included cow's milk, other than fish did not contain any occurrence of TBBPA above methodology reporting levels (0.02 to 0.2 µg/kg depending on the food type).

144. COT in 2019 in the '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. These 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, 2019c).

145. From the COT (2019c) assessment, the Committee concluded that all estimates of the MOE for chronic dietary TBBPA exposure (based on UK consumption data) exceed the lowest MOE values calculated by EFSA for infants and toddlers concerning exposure though ingestion 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.

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

Microplastics

147. 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.

148. The definition proposed by ECHA (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.

149. 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.

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

151. 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 gut 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)

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

153. Microplastics have been occasionally reported in cow's milk in other continents such as 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 author infers 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. 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.

Risk characterisation

154. In 2019, the European Chemical Agency (ECHA) published a restriction report in response to the European Commission's request (ECHA, 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.”

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