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

Statement on the risk assessment of cow's milk in children aged 1 to 5 years, in the context of plant-based drinks evaluations

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Background

1. Plant-based drinks have become increasingly popular in the United Kingdom (UK) both for individuals with an allergy to cow's milk or lactose intolerance and those who wish to avoid dairy products for ethical, cultural or other reasons. Currently, the most popular alternatives to dairy are soya, oat and almond-based drinks.

2. Current UK Government advice regarding the use of plant-based drinks for infants and young children is that unsweetened calcium-fortified plant-based drinks, such as soya, oat and almond drinks, can be given to children from the age of 12 months as part of a healthy balanced diet; rice drinks should not be given due to the levels of arsenic in these products (NHS, 2018). The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has reviewed the potential for adverse effects arising from consumption of soya, oat and almond drinks by young children (aged 6 months- 5 years), at the request of the Department of Health and Social Care (DHSC), with a statement setting out the views and conclusions of the Committee published in January 2021 (COT, 2021a). Also, the Scientific Advisory Committee on Nutrition (SACN) have been considering the nutritional aspects of plant-based drinks and in order to bring together the nutritional

and chemical risk assessments of these drinks, a joint working group of SACN and COT has been established.

3. DHSC is in the process of conducting an Equalities Analysis covering both the Nursery Milk Scheme and the Healthy Start Scheme, which considers equalities issues posed by the current legislation as it pertains both to plant-based drinks, and also to animal milks other than cow's milk. DHSC is keen to ensure that this Equalities Analysis reflects the most up-to-date advice on safety and toxicity issues from COT, and on nutritional issues from SACN. Hence, this process is currently on hold whilst the joint Working Group considers plant-based drinks.

4. The COT agreed during its meeting in July 2021 that the main comparator for plant-based drinks should be cow's milk and that a discussion paper should be produced looking at the potential chemical risks from the consumption of this in the population group of interest, children aged 6 months to 5 years.

5. Most of the fresh cow's milk available in the UK is UK derived, thus the risks and relevant chemical exposures for this paper are European Union (EU) or UK focused and it is assumed that EU farming practices are similar to those in the UK.

6. This statement follows two discussion papers presented over the course of 2021 (TOX/2021/53 and TOX/2021/58), which presented exposure assessments and subsequent risk characterisations for a range of chemical compounds that could potentially occur in milk. This included a majority of chemicals that are not known to have any potential direct beneficial impacts on the health of consumers within the age category 1 – 5 years of age, and iodine, an essential nutrient which can have both beneficial and detrimental effects depending on multiple factors including dose. The full list of compounds discussed is as follows:

Part 1 (TOX/2021/53):

I. Veterinary medicines
II. Pesticides

III. Nitrate and Nitrite
IV. Bisphenol A (BPA)
V. Phthalates
VI. Dioxins and Dioxin-Like Polychlorinated Biphenyls (DL-PCBs)
VII. Non-Dioxin-Like Polychlorinated Biphenyls (NDL-PCBs)
VIII. Polycyclic Aromatic Hydrocarbons (PAHs)
IX. Isoflavones: Genistein (GEN), Daidzein (DAI), Equol (EQU, metabolite of DAI), Formononetin (FOR) and Biochanin A (BIO)

Part 2 (TOX/2021/58):

X. Heavy metals: Lead (Pb), Arsenic (As), Mercury (Hg) and Cadmium (Cd)
XI. Iodine
XII. Perchlorate and Chlorate
XIII. Mycotoxins: Aflatoxins (AFB1 and AFM1) and others including Deoxynivalenol (DON)
XIV. Hormones – Oestrogens, Insulin-Like Growth Factor 1 (IGF-1)
XV. Per- and polyfluoroalkyl substances (PFAS)
XVI. Brominated Flame Retardants (BFRs)
XVII. Microplastics

7. The Committee considered compounds in cow's milk to be of minimal risk where the evidence indicated that there was no exceedance of health-based guidance values from consumption of cow's milk. In these cases, supplementary information, including the discussion of health-based guidance values (HBGVs), detailed exposure assessments and, where relevant, risk characterisation are included in Annex A to this statement.

8. It is acknowledged from scrutiny of the historical EU RASFF (Rapid Alert System for Food and Feed) data and FSA's alert tools that occasional incidents of contamination of cow's milk with chemicals not included in the discussion papers have occurred; this has involved chemicals such as mineral oils (Montgomery, Haughey and Elliott, 2020), other plant toxins from feed contamination, other

agricultural contaminants (e.g. urease inhibitors) (Byrne *et al.*, 2020) and other contaminants (e.g. parabens). As 'one-off' incidents these are acknowledged but not discussed or evaluated in this statement as the overall risks to the population are deemed minimal.

9. Members discussed comparing the levels of particular contaminants within selected plant-based drinks and cow's milk. However, many compounds present in cow's milk may not be present at significant levels in plant-based drinks and vice versa.

Consumption data

10. 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 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 when 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 than the combined exposures in Table 1, milk as a drink dominating consumption in all age groups above 6 months, exposure assessments have been undertaken using the highest consumption estimates from Table 1.

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

Age (months)	Number of Consumers	(g/person/ day) Mean	(g/person/ day) 97.5th percentile	(g/kg bw per day) Mean	(g/kg bw per day) 97.5th percentile
6 – <12	1257	120	460	13	48

12 – <18	1275	350	790	32	75
18 – <24	157	350	840	29	79
24 – <48	351	320	770	23	59
48 – <60	618	290	780	17	46

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

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

11. Exposure assessments utilising these data cover the general population at both mean and high levels of consumption.

Chemicals assessed

Veterinary medicines

12. Veterinary medicines, for example antibiotics, are used in animal husbandry to alleviate suffering and disease. UK farmers should follow the Veterinary Medicines Directorate (VMD) recommended guidance on responsible use (VMD, 2014). This includes accurate record keeping, purchasing from authorised sources, correct administration (e.g. dose, frequency, route) and observing relevant withdrawal periods (the length of time that must pass after administration before the animal can enter the food chain for use in food production to ensure that unacceptable levels of the chemical do not enter the food chain.

13. Veterinary medicines can be present below the maximum residue limits (MRLs) following use according to good veterinary practice and this does not constitute a risk to health. However, they can on occasion be present in animal derived products above these MRLs when procedures are not followed correctly. Cow's milk is routinely monitored through ongoing surveys with the UK National Reference Laboratory (NRL).

14. Between 2015 and the end of 2020, 21,574 analyses of cow's milk samples were undertaken as part of the VMD survey covering, anthelmintics, avermectins, cephalosporins and other antimicrobials (as a screening method), chloramphenicol, dapsone, florfenicol, and non-steroidal anti-inflammatory drugs (NSAIDS) (VMD, 2015, 2016, 2017, 2018, 2019, 2020). From the analysis over this 6-year period only 0.12% (24) returned a positive result. Positive results were considered instances where medicines were above the maximum residue limit (MRL) for milk, which in itself does not necessarily mean that there is a potential health concern. Following risk assessment, it was concluded that only two of these residues, penicillin G and triclabendazole, both in 2017, represented levels in milk that were a potential health concern to the consumer, and this was before taking any dilution effect into account, e.g. from bulk tanks at dairies.

15. Based on the last 6 years UK statutory survey the COT concluded that the risk from veterinary medicine exposure from drinking cow's milk is negligible.

Pesticides

16. Pesticides primarily enter the dairy food chain via consumption of contaminated feed or water by cattle. They are routinely monitored through ongoing statutory surveillance with the UK National Reference Laboratory. When good agricultural practice is followed compounds should be below their regulated limits and would be deemed not to constitute a risk to health. However, when above these levels they can potentially present a risk to health.

17. Between 2015 and the end of 2020, 1,723 cow's milk samples were analysed and reported by The Expert Committee on Pesticide Residues in Food (PRiF) (2015, 2016, 2017, 2018, 2019, 2020). From all the samples analysed over this 6-year period only 1 returned a positive result above the Maximum Residue Limit (MRL). This residue, in 2019, was a persistent quaternary ammonium compound at 0.3 mg/kg, likely a contaminant from a cleaning product.

18. Based on the last 6 UK statutory survey results the COT concluded that the risk from pesticide exposure from drinking cow's milk is negligible.

Nitrate and nitrite

19. Nitrate and nitrite are naturally occurring chemicals that form part of the nitrogen cycle. They act as oxidising agents that can cause methemoglobinemia in animals and humans after high exposure. They occur naturally in vegetables but are also used widely as meat preservatives, are found in agricultural waste streams e.g. from fertiliser use, and as chemical contaminants from industrial processes and materials.

20. Nitrates are widely ingested by animals and humans, although nitrite is regulated as an undesirable substance in animal feed (EU 574/ 2011). In animals, the largest potential exposure to nitrite is from the in-vivo transformation of nitrate to nitrite. Feed and contaminated water can have high levels of nitrate and represent the main contributor to nitrite exposure for food-producing animals (Cockburn *et al.*, 2013).

21. An exposure assessment has been undertaken for nitrate within Annex A using UK consumption data (Table 1 above). This is presented alongside a discussion of EFSA's 2009 opinion on nitrite. Nitrate exposure was below 1% of the ADI. EFSA's 2009 opinion concluded that nitrite is present at extremely low levels in fresh animal products and therefore not of human health concern (EFSA, 2009).

22. 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 conclusion in EFSA's (2009) opinion on nitrite, the COT concluded that nitrate and nitrite contamination of cow's milk do not pose a health risk for children aged 6 months to 5 years of age.

Bisphenol A

23. Bisphenol A (BPA) is a compound used as a monomer in the production of many plastics and resins, particularly polycarbonate materials employed in the manufacture of food contact materials and food storage containers such as cans. Potentially, it can migrate from plastic containers, or resins from coatings, into food and drinks. It is also widely used in the production of non-food related products such as surface coatings, resin-based paints, flame retardants and medical devices. For cow's milk, BPA contamination may come from the mechanical milking apparatus and subsequent storage vessels in the dairy chain such as cooling tanks.

24. BPA can interfere with the regulation of hormones in the endocrine system. It may therefore have adverse effects on metabolism, growth, sexual development, stress response, insulin production, sexual behaviour, reproduction, and fetal development (Cirillo *et al.*, 2015). It may also be a contributing factor in the onset of metabolic disorders, including diabetes and obesity, and immune dysfunction (Bansal, Henao-Mejia and Simmons, 2018).

25. EFSA's 2015 opinion on BPA, discussed in Annex A, advised a reduced temporary tolerable daily intake (t-TDI), based on changes in relative kidney weight in mice, but concluded that dietary exposure to BPA does not pose a health risk for consumers at any age group (EFSA, 2015b).

26. EFSA's 2023 opinion on BPA, discussed in Annex A, advised a reduced TDI based on an effect on TH17 immune cells. Applying the new TDI to their 2015 exposure assessment, EFSA concluded that mean and 95th percentile dietary

exposures exceeded the new TDI by two to three orders of magnitude for all populations (EFSA, 2023)

27. In 2019, COT was asked to review the risk of toxicity of chemicals in the diets of infants and young children aged 0-5 years, in support of a review by SACN of Government recommendations on complementary and young child feeding (COT, 2019b, 2020) and BPA was considered as part of that review. In light of the recent opinion from EFSA, the COT has reconsidered BPA. The Committee has 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 the COT's 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, 2008c and 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

28. Phthalates are esters of the aromatic dicarboxylic acid phthalic acid that have a long history of use as additives to plastics to improve their flexibility but also have wide applicability across industry, for example in pharmaceutical coatings, paints, cosmetics and food contact materials.

29. Phthalates do not form covalent bonds with the material into which they are incorporated, therefore can readily migrate into food from packaging materials. The extensive and historic use of phthalates has led to their being widely distributed in the environment and the food chain. The general population is exposed to phthalates via food (including migration from food contact materials) and drinking water, but

also through inhalation and dermal exposure (Heudorf, Mersch-Sundermann and Angerer, 2007).

30. 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, 2005b, 2005c, 2005d, 2005e, 2005f).

31. In Annex A, EFSA's 2005 and 2019 risk assessments of phthalates are discussed. In the 2019 assessment, exposure to the group of phthalates (DEHP+ DBP+ BBP+ DINP expressed as DEHP equivalents) contributed up to 14% of the recommended group TDI whilst for 95th percentile consumers exposure was a maximum of 23% of the TDI (EFSA, 2019). For DIDP both mean and 95th percentile consumers were exposed to well below the TDI.

32. In May 2011, COT produced a statement (COT, 2011) on dietary exposure to the phthalates DBP, BBP, DEHP, DINP, DIDP and diethyl phthalate (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.

33. In the recent COT review of EFSA' s public consultation on their 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 Committee was content that for DBP, BBP, DEHP and DINP the exposures estimated by EFSA did not indicate a health concern using the group TDI (COT, 2019a).

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

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

35. Formed as by-products of a number of industrial processes, polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are two groups of tricyclic planar compounds that are formed by combustion of organochlorine compounds or of non-chlorine compounds in the presence of chlorine. Of these, 75 PCDD and 135 PCDF "congeners" are known, with structures varying in the number of chlorine atoms and their positions in the rings. Only 17 of these are relatively persistent in animals and humans and therefore considered relevant (EFSA, 2018).

36. HBGVs have been established by multiple authorities and these are discussed within Annex A.

37. An exposure assessment has been undertaken for cow's milk using consumption data from Table 1 and is presented within Annex A using occurrence levels from EFSA's 2018 opinion paper (EFSA, 2018), compared against the recommended TDI of 2 pg WHO-TEQ/kg bw per day from COT in 2001 (COT, 2001). Utilising the upper bound (UB) mean occurrence levels led to exceedances of the TDI in two age groups. Factors including the worst-case assumption of a 3.5% fat content of milk and using the upper bound of the mean occurrence concentrations suggest that realistic exposure will be below the levels estimated in this exposure assessment.

38. At the 95th percentile occurrence value, exceedances of the TDI occurred for both mean and high level consumers, however, this scenario is considered to be highly conservative and unrealistic.

39. As noted in the recent COT review of chemicals in the diets of infants and young children, the Committee is reviewing the current guidance values for dioxins and dioxin like PCBs. However, the COT does not consider it necessary to update its advice until this work has been completed (COT, 2021c).

40. The current view of the COT from the exposure assessments conducted in annex A is that dioxins 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

41. Some PCBs do not share the same molecular targets as the dioxins and have different effects, for example oestrogenic and anti-oestrogenic effects, and are therefore regarded as a separate group of persistent organic chemicals that can be present in the environment and food.

42. Dietary exposure assessments by EFSA, (2005a) and JECFA, (2016) are discussed within Annex A. These surveys suggest that dietary exposure is within safe levels for young children.

43. The COT concluded, based on the above evidence, that NDL-PCBs within cow's milk do not present any risk to health for children aged 6 months to 5 years of age.

Polycyclic Aromatic Hydrocarbons (PAHs)

44. PAHs (polycyclic aromatic hydrocarbons) are organic compounds characterised by the presence of 2 or more fused aromatic rings, many of which are known carcinogens. Although naphthalene, with 2 fused rings, would technically be part of this group of compounds it is usually not regarded as a member. PAHs are common products of combustion of organic matter and are widely distributed in the environment as the result of vehicle exhaust and industrial processes and in the diet in cooked food due to their presence as cooking by-products, such as in oils vaporised from frying pans and smoke from barbecues. Production of PAHs by cooking is greater when fat expressed from the food drips directly onto the heating element or hot coals.

45. An exposure assessment for benzo[a]pyrene (BaP) and a separate assessment for PAH4 (sum of BaP, benz[a]anthracene (BaA), benzo[b]fluoranthene (BbF) and chrysene (ChR)), was undertaken. These are presented within Annex A utilising consumption data in Table 1 (above) and the UK TDS from 2012 (Fernandes *et al.*, 2012).

46. The resulting margins of exposure (MOEs) for the exposure to PAH4 are all above 10,000 for both average and high-level consumers across all age ranges of young children. These high MOE's indicate that it is unlikely that there will be adverse effects on human health from these chemicals from drinking cow's milk.

47. In the recent COT review with SACN on the risk of toxicity of chemicals in the diets of infants and young children, the COT concluded that the intakes of PAHs (BaP and PAH4) from human breast milk and food are of low concern for health for children aged 1 to 5 years, i.e. the margins of exposure are high (COT, 2020).

Isoflavones

48. Phytoestrogens are chemicals of plant origin that have been shown to influence biological processes, mainly through their structural similarities to oestrogens, and their ability to bind to oestrogen receptors (ERs).They can therefore potentially cause unfavourable effects such as disruptions in sexual behaviour and brain sexual differentiation, changes in hormone levels, and increases in breast cancer risk (Xiao, 2008; Socas-Rodríguez *et al.*, 2015). The largest group of phytoestrogens are flavonoids, which can be further divided into three subclasses, coumestans, prenylated flavonoids and isoflavones.

49. Isoflavones can be found in many plants, including barley, sunflower, clover, lentils, alfalfa sprout, broccoli and cauliflower. However, the richest sources of isoflavones in the human diet are foods and dietary supplements made from soya bean and soya protein (McCarver *et al.*, 2011). Soya isoflavones in foods occur mainly as carbohydrate conjugates (glycosides), the major group being the glucose conjugates (glucosides), e.g. genistein (GEN) and daidzein (DAI). The other most

commonly considered isoflavones include formononetin (FOR), biochanin A (BIO) and a metabolite of DAI, equol (EQU).

50. The phenolic and hydroxyl moieties (and the distance between them) are key structural similarities between isoflavones and17β-oestradiol, which allow them to bind to ERs. Numerous studies have indicated that GEN is the isoflavone with the greatest oestrogenic activity (McCarver et al., 2011).

51. Animal studies performed before 2003 indicated that intake of isoflavones in early life can produce oestrogenic effects, affect thyroid function, alter protein concentrations and structures in the brain, and alter some parameters of immune function, as well as sexual development in older animals. Although some animal studies indicated possible risks to humans, overall, the results of animal studies were inconsistent. The COT 2003 report noted that human data were limited, and that most of the relevant scientific information was derived from experimental studies in animals, mainly rodents. The extrapolation of such studies to humans was difficult because of inter-species differences in ADME (absorption, distribution, metabolism, and excretion), sexual development and reproductive function, and the use of relatively high doses or non-oral routes of administration.

52. *In vitro* experiments reviewed in the 2003 COT report (COT, 2003) showed that phytoestrogens could modulate the levels of sex hormone binding globulin (SHBG), inhibit enzymes involved in oestrogen biosynthesis and metabolism to modulate concentrations of endogenous oestrogens, and inhibit thyroid peroxidase activity to reduce the concentrations of thyroid hormones. GEN was found to interact with topoisomerase II and protein kinases (enzymes involved in cellular proliferation and differentiation) and to inhibit human T-cell proliferation and interleukin-2 production.

53. The 2003 COT report concludes that it is not possible to propose HBGVs for infants (COT, 2003). Reasons for this include the difficulty in extrapolation from animals to humans because of differences in toxicokinetics, uncertainty about differences between adults and infants (particularly those arising from development of the gut microflora), and the lack of dose-response data and the possibility of bias

and chance effects in the available human studies. In a more recent 2013 COT report (COT, 2013a) assessing literature since 2003, the same conclusions were reached, in that it was not possible to propose HBGVs due to limitations in the available data.

54. Other health authorities have proposed HBGVs, such as the Nordic Council in 2020 (Nordic Council of Ministers, 2020). For children they proposed 'a rounded value of 0.07 mg/kg bw per day of GEN. This corresponds to 2.1 mg genistein per day for a person weighing 30 kg'. This value was derived from the Li *et al.*, (2014) rat study taking the LOAEL of 20 mg/kg bw and applying a further uncertainty factor of 3 on top of the factors of 10 x 10 for interspecies differences and intraspecies variation.

55. Isoflavones are known to be transferred to cow's milk after digestion of plant-based feed stuffs (Bláhová *et al.*, 2016). Occurrence in the milk is dependent on the feed. Milk phytoestrogen concentration is strongly influenced by silage plant composition. Feed with either deliberate addition of, or inadvertently contaminated with, red clover for example will have greatly increased concentrations of isoflavones (Höjer *et al.*, 2012).

Risk Characterisation

56. To obtain information on the concentrations for isoflavones in cow's milk a literature search was undertaken using the keywords Isoflavone AND Cow AND Milk AND Risk in both PubMed and Science Direct. A large number of results with very varied isoflavone concentrations was returned from European countries. Data for the UK data only are summarised below (Table 3) from (Nørskov *et al.*, 2019).

Table 3. Summary of mean isoflavone concentrations (all µg/kg) GEN, EQU, FOR and DAI from differing cow's milk types in the UK (µg/kg).

Milk Type	Number of samples	GEN	EQU	FOR	DAI	Sum

Conventional	48	0.83	63.6	0.08	0.95	67.7
Organic	48	2.32	411	1.10	2.69	417
Free range	24	0.85	66.4	0.09	0.96	70.4

57. An additional source reported a total isoflavone concentration of 60 µg/kg wet weight within whole milk (Kuhnle *et al.*, 2008).

58. As noted above, COT have not established a HBGV for isoflavones for young children and the significance of the concentrations summarised in Table 3 and in paragraph 57 are uncertain.

Lead

59. Lead is a well-studied heavy metal and pollutant which can cause multiple negative health effects in humans. Its impact on the health of infants was evaluated by the COT in their statement on the potential risks from lead in the infant diet COT, (2013b) and its addendum (COT, 2016a).

60. EFSA's 2012 opinion on lead and the COT's 2013 and 2016 statements on lead exposure in the diets of infants and children have been considered (Annex A). Whilst exceedances of the benchmark dose lower confidence limit ($BMDL_{01}$) of 0.5 µg/kg bw per day were observed in EFSA's total dietary exposure estimate for infants aged <1 year (0.83 and 0.91 µg/kg bw per day in two surveys), toddlers aged 1-<3 years (1.32 µg/kg bw per day) and other children aged 3-<10 years (1.03 µg/kg bw per day), at most this was 3-fold and as the contribution of cow's milk to total middle bound lead exposure did not exceed 2% for infants, 5% for toddlers and 4% for other children, lead within cow's milk never exceeds a 20^{th} of total exposure and is therefore not a concern (EFSA, 2012b). The COT's statement found diet contributed little to lead exposure compared to other sources of exposure (COT, 2013b, 2016a).

61. Based on the information provided in EFSA (2012b) and the evaluation by the COT in 2013 and 2016, the COT concludes that it is unlikely that lead would pose a

risk to the health of infants and children from the ages of 6 months to 5 years from consumption of cow's milk.

Arsenic

62. Inorganic arsenic (iAs) is the focus of this evaluation as it was with the previous COT statement, as this is the form that is of most toxicological concern (COT, 2016b).

63. The COT's 2016 statement and EFSA's 2021 evaluation have been considered in Annex A. The COT's 2016 risk assessment suggested that at mean levels of consumption, for infants aged 4 months to 5 years the MOE's for the overall diet 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 (EFSA, 2021a).

64. The COT concluded from the above 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

65. Mercury is a metal released from both anthropogenic and natural sources. It is found as elemental mercury (Hg^0), inorganic mercury (mercurous and mercuric cations (Hg^+ and Hg^{2+} respectively)) and organic mercury. Methylmercury is the most abundant organic mercury compound in the food chain (COT, 2018c).

66. The toxicity of mercury varies depending on whether the mercury is in an organic or inorganic form. The focus of this paper is inorganic mercury, as in EFSA's 2012 opinion evidence was presented that almost all of the mercury within cow's milk was inorganic in nature (EFSA, 2012c).

67. The COT's 2018 statement on methylmercury in the diets of infants and children and EFSA's 2012 opinion have been considered in Annex A. EFSA did not consider total dietary exposure to inorganic mercury to be a risk for the European population. For all age groups, excepting toddlers, the TWI for inorganic mercury was not exceeded. Cow's milk contributed a maximum of 15% to this total exposure. The COT in 2018 found no exceedances of the inorganic mercury TWI using either TDS or infant metals survey data for the assessment.

68. From the above information the COT concluded that there is no health concern for infants and children aged 6 months – 5 years from exposure to inorganic mercury from consumption of cow's milk.

Cadmium

69. Cadmium (Cd) is a soft, silver-white or blue-white metal existing in various mineral forms and is present throughout the environment. It is used in many processes such as electroplating, alloy production, paints and pigments and is found in a wide range of industrial and consumer products. Environmental cadmium concentrations are reflective of natural sources such as volcanic activity as well as anthropogenic sources, for example non-ferrous metal smelting.

70. Exposure assessments performed by (EFSA, 2012a) and the COT have been considered. This information can be found within Annex A. Whilst exceedances of the TWI were observed with both COT, (2018b) and EFSA, (2012a) exposure assessments, the relative contribution of cow's milk in both of these assessments was low.

71. In the EFSA exposure assessment (EFSA, 2012a), collected surveys were merged and the results from the different age groups weighted according to the number of years included out of an average life span of 77 years, producing mean average upper bound lifetime exposures. For infants aged <1 year this was 3.50 µg/kg bw per week, for toddlers aged 1-< 3 years this was 5.9 µg/kg bw per week and for other children aged 3-<10 years this was 4.69 µg/kg bw per week. These all

exceed the EFSA (2011c) TWI of 2.5 µg/kg bw per week. For infants, liquid milk contributed 1.59% to total dietary cadmium exposures whilst for toddlers it contributed 1.78%, and for other children 2.28%.

72. In COT (2018b) exposures up to 260% of the EFSA 2011 TWI were estimated but cow's milk was not identified as one of the key contributing food groups.

73. The COT concluded from the above information that the levels of cadmium in cow's milk present no concern to health for infants and children aged between 6 months and 5 years.

Iodine

74. Iodine is an essential micronutrient necessary to produce thyroid hormones. The COT released a statement (COT, 2017b) discussing in depth the potential risks of excess iodine in the diets of infants and children aged 0-5 years. Milk is a considerable source of iodine in the diet. This may be due to fortification of animal feed with iodine compounds and teat dipping with iodine-containing sterilising preparations prior to milking.

75. Iodine excess is generally well tolerated by healthy individuals. For some it may cause hypothyroidism, hyperthyroidism, goitre and/or thyroid autoimmunity. Individuals with iodine deficiency or pre-existing thyroid disease may be more vulnerable to iodine excess-induced thyroid disorders (Farebrother, Zimmermann and Andersson, 2019).

76. In 1989 the Joint Expert Committee on Food Additives (JECFA) established a provisional Maximum Tolerable Daily Intake (PMTDI) for iodine of 17 µg/kg bw from all sources (FAO/WHO, 1989). No safety factors were used as these studies encompassed a relatively large number of subjects (FAO/WHO, 1989).The JECFA PMTDI was utilised to perform a risk assessment in the COT's 2000 statement on iodine in cow's milk (COT, 2000). Based on the same human studies as used by JECFA, the European Scientific Committee on Food (SCF) in 2002 established a

TUL of 600 µg/day for adults, scaled according to body weight for children, recorded in EFSA, (2006).

77. The COT (2017b) stated “Excess iodine has considerably varied effects between individuals. The adult thyroid gland secretes about 80 µg thyroxine per day which requires a dietary intake of between 100 and 150 µg/day of iodine. Humans have a number of mechanisms by which they can counter an excess of iodine. These include the sodium-iodide symporter which blocks the transport of iodine into the thyroid cells and the Wolff-Chaikoff effect, more details of which can be found in the review by Bürgi, (2010). Most people can tolerate a chronic excess of iodine of up to 2 g of iodine per day but there will be some individuals who experience effects at much lower levels, close to the upper recommended limit for intake (Bürgi, 2010).”

78. In the COT’s 2017 statement on the risks of excess iodine exposure to infants and young children they assessed three HBGVs. This assessment is paraphrased below.

79. The Expert Group on Vitamins and Minerals (EVM) looked in detail at the metabolism of iodine and the effects of excess iodine, in 2003 (EVM, 2003). The EVM concluded that there were insufficient data to establish a Safe Upper Level (SUL) for iodine. For guidance purposes, they indicated that a level of 0.5 mg/day of supplemental iodine in addition to the background intake of 0.43 mg/day would be unlikely to cause adverse effects in adults based on slight alterations in serum thyroid hormone levels at supplemental doses of ≤2 mg/day in a range of human studies. From these data the EVM proceeded to set a guidance level for iodine at 15 µg/kg bw per day for adults.

80. In 2002, the SCF published an opinion on the tolerable upper intake levels of vitamins and minerals, recorded in EFSA, (2006). For iodine, they established a tolerable upper level (TUL) of 600 µg/day for adults, reduced on a body surface area (body weight$^{0.75}$) basis for children to 200 µg/day for ages 1-3 years and 250 µg/day for ages 4-6 years. This TUL was based on dose-response studies of short duration in humans, which showed changes in serum thyroid hormone levels at dose levels of 1800 µg/day and was supported by longer term studies with approximately similar

doses that did not show any adverse effects but lacked detailed iodine intake data. An uncertainty factor of 3 was used to account for these uncertainties. These values were endorsed by EFSA (2006).

81. In 2017 the COT established HBGVs based on the EFSA (2006) endorsed TULs in their statement assessing the risks of excess iodine in the diet of infants and young children. This resulted in different TULs for different age groups based on different mean bodyweights. This approach has been followed below in Table 4 using mean age specific bodyweight data supplied by the FSA's exposure assessment team to produce derived TULs for the selected age ranges (EFSA, 2006; Department of Health, 2013; Bates *et al.*, 2014, 2016, 2020; Roberts *et al.*, 2018).

Table 4: Table displaying the age adjusted TULs from EFSA 2006, mean bodyweight for each age group supplied from NDNS data and the TULs derived from these data (EFSA, 2006; Department of Health, 2013; Bates *et al.*, 2014, 2016, 2020; Roberts *et al.*, 2018).

Age group	0-<12 months	12-<18 months	18-<24 months	24-<48 months	48 –<60 months
EFSA adjusted TUL (µg/day)	No tolerable upper limit (TUL) specified for this group	200	200	200	250
Average bodyweight (kg bw)	N/A	10.9	12.2	15.3	19.4

Derived TUL µg/kg bw per day	N/A	18.4	16.4	13.1	12.9

Exposure Assessment and Risk Characterisation

82. The 2016 infant metals survey provided comprehensive occurrence information for iodine in UK milk. Iodine was found to be present at a mean level of 271 µg/kg (FSA, 2016).

83. In addition to the infant metal survey, occurrence levels were found through an interrogation of the PubMed database using the terms “iodine AND cows AND milk” and “Iodine AND excess AND milk” with search results limited to 2001-2021.

84. A review article by Reijden et al., collated iodine occurrence data from 30 European and 1 United States (US) studies including 2 from the UK in 2012 and 2016 (Reijden, Zimmermann and Galetti, 2017). The 2012 UK study presented a median iodine level in conventional milk of 250 µg/kg from 80 samples whilst the 2016 study presented a mean value of 458 µg/kg from 24 samples (Bath, Button and Rayman, 2012; Payling *et al.*, 2015).

85. Bath *et al* (2017) also documented iodine at median levels of 438 µg/kg in conventional (non-organic) milk. Sample numbers were restricted to 5 samples, taken at a single time in winter. Due to the seasonal variation in iodine levels this may have resulted in increased levels of iodine in these samples as winter milk is often recorded as having higher iodine levels (Bath et al., 2017; Reijden, Zimmermann and Galetti, 2017).

86. A study by O’Kane et al. investigating seasonal variation in iodine and selenium concentration in milk found year-round mean (± SD) (standard deviation) iodine levels of 475.9 (± 63.5) µg/kg in pasteurised UK milk (O’Kane *et al.*, 2018).

This mean was obtained from the analysis of 36 samples. 95th percentile or maximum occurrence data were not presented in this study. The highest seasonal mean concentration was 543.3 (± 53.7) µg/kg from 9 samples of milk collected in spring.

87. An additional study was identified recording iodine at levels of 437 (± 155.2) µg/L in 11 samples of whole milk from collection tankers used by an Irish powdered milk production plant and at levels of 135.5 (±7.6) µg/L at mid-lactation and 419 (±2.8) µg/L at late lactation from 2 samples each of whole milk from silos in the plant (it is not clear how the SDs were determined from 2 samples) (Paludetti et al., 2019).

88. The highest UK year-round mean iodine concentration reported was found in O'Kane et al. (475.9 µg/kg). Using this occurrence value, the JECFA 1989 PMTDI of 17 µg/kg bw per day and the consumption rates in Table 1, a risk characterisation was undertaken which is presented in Table 5.

Table 5: Risk Characterisation for iodine from cow's milk consumption using the annual mean iodine occurrence in O'Kane et al. (2018), the consumption data from the NDNS (Table 1) and JECFA's PMTDI (FAO/WHO, 1989).

Age (months)	Estimated exposure mean µg/kg bw per day	Estimated exposure 97.5th percentile µg/kg bw per day	Mean % guidance value	97.5th percentile % guidance value
6 – <12	6.19	22.8	36.4	134
12 – <18	15.2	35.7	89.6	210
18 – <24	13.8	37.6	81.2	221
24 – <48	10.9	28.1	64.4	165
48 – <60	8.09	21.9	47.6	128

89. Comparing exposure to the JECFA PMTDI as in Table 5, there were no exceedances at mean levels of consumption in any of the selected populations. For

the 97.5th percentile of consumption there were exceedances, of up to 2.2-fold, in all populations.

90. Using the consumption data in Table 1, occurrence data from O'Kane et al. (475.9 µg/kg) and the EVM, (2003) guidance value of 15 µg/kg bw per day, a risk characterisation was undertaken which is presented in Table 6.

Table 6. Risk characterisation for iodine from cow's' milk consumption using annual mean iodine occurrence in O'Kane et al. (2018), consumption data from the NDNS (Table 1) and the EVM 2003 guidance value (EVM, 2003).

Age (months)	Estimated exposure mean µg/kg bw per day	Estimated exposure 97.5th percentile µg/kg bw per day	Mean % guidance value	97.5th percentile % guidance value
6 – <12	6.19	22.8	41.2	152
12 – <18	15.2	35.7	102	238
18 – <24	13.8	37.6	92.0	251
24 – <48	10.9	28.1	73.0	187
48 – <60	8.09	21.9	54.0	146

91. Average consumers in the age group 12 - < 18 months marginally exceed the guidance value of 15 µg/kg bw per day set by the EVM in 2003. High consumer exposures exceed the guidance value for all age groups, by up to 2.5-fold.

92. Using the derived SCF/EFSA TULs presented in Table 4, occurrence data from O'Kane et al. (475.9 µg/kg) and the consumption data in Table 1 a risk characterisation for was undertaken which is presented in Table 7.

Table 7: Risk characterisation for cow's milk consumption using annual mean iodine occurrence in O'Kane et al. (2018), consumption data from the NDNS (Table 1) and

TUL's derived from EFSA's 2006 values (EFSA, 2006; Department of Health, 2013; Bates *et al.*, 2014, 2016, 2020; Roberts *et al.*, 2018).

Age (months)	Estimated exposure mean µg/kg bw per day	Estimated exposure 97.5th percentile µg/kg bw per day	Mean % guidance value	97.5th percentile % guidance value
6 – <12	No TUL	No TUL	No TUL	No TUL
12 – <18	15.2	35.7	83.00	195
18 – <24	13.8	37.6	84.2	229
24 – <48	10.9	28.1	83.7	215
48 – <60	8.09	21.9	62.8	170

93. Comparing consumption to the SCF/EFSA TULs, at mean levels of consumption none of the selected populations exceeded derived TULs whilst at the 97.5th percentile of consumption all populations exceeded the TULs, by up to 2.3-fold.

94. In the COT's 2000 paper, a survey of UK cow's milk from 1998-9 was discussed and it was reported that the overall mean iodine concentration in cow's milk was 311 µg/kg, with a lower mean concentration in summer (200 µg/kg). These values were used to estimate exposure and safety was assessed against guidance values calculated from the JECFA PMTDI of 0.017 mg/kg bw per day (17 µg/kg bw per day) which was available at the time. At mean levels of consumption of the total diet, exceedance of the guidance values was observed for the age group 1½ - 2½ years at 221 µg/day. For the age groups 2½ - 3½, and 3½ - 4 years iodine exposure approached the guidance level at 215 and 204 µg/day respectively. For high level consumers, exceedances for the 3 age groups 1 ½ - 2 ½, 2 ½ - 3 ½, and 3 ½ - 4 ½ years were observed, with exposures of 362, 379 and 330 µg/day respectively. For milk consumption alone, exceedances of the guidance values calculated from the previously adopted PMTDI were present in high level consumers (97.5th percentile)

for the groups aged 1 ½ - 2 ½ and 2 ½ - 3 ½ years. The COT concluded that iodine in cow's milk was unlikely to pose a risk to health even in children who are high level consumers (COT, 2000). In part, this was based on the reassurance provided by a study in which 1-11 year old children received doses of iodide up to 1000 µg /day for four months without signs of toxicity. This corresponds to 59-94 µg /kg bw per day in children aged 1 ½ - 4 ½ years, which is more the three times the JECFA PMTDI.

95. The COT's 2000 conclusion was reaffirmed in the COT 2017b paper on the risk of excess iodine in the diets of infants and young children arguing:

> 'These HBGVs are based on limited data. In all cases the relevant studies on which the HBGV was established did not allow an accurate estimation of dietary intakes. The response to high iodine intakes can be highly variable between individuals and will depend on iodine status. Individuals with a low iodine status who are suddenly exposed to high iodine levels are more likely to experience adverse effects than those with an adequate iodine status.
>
> For many of the parameters of thyroid function normally assessed, it is difficult to distinguish between adverse effects and normal homeostatic changes due to iodine. Further, the RNI and the guidance levels/tolerable daily intakes are of a similar order of magnitude. These two factors, together with the fact that the relevant available studies are all in adult populations, make it difficult to identify a safe upper level which is applicable for all infants and children.'

96. In the COT paper of 2000 on iodine in cow's milk, exceedances were identified for 97.5th percentile consumers. This was mirrored in the exposure assessments produced in this paper with high level consumers of milk exceeding the EVM guidance level, TULs derived from EFSA and the JECFA PMTDI. For mean level consumers however, iodine exposure approached the 2003 EVM guidance level of 15 µg/kg bw per day for the group 12- <18 months. COT's 2000 and 2017 statements stated that iodine levels in cow's milk were considered to pose no toxicological concern as exceedances of the HBGV occurred only at the 97.5 %ile estimates, these were at most 2.5-fold, and for the additional reasons discussed above. With similar results from the current exposure assessment, the COT

concluded that the risk to health to children aged 6 months to 5 years of age from iodine from consumption of cow's milk is likely to be low.

Perchlorate

97. Perchlorate ($ClO4^-$) has both natural and anthropogenic sources. Previous biomonitoring studies have suggested it is most likely to be a ubiquitous environmental contaminant. It is present in the environment due to use of sodium nitrate (also known as Chilean nitrate) fertilisers and industrial emissions such as from the use of ammonium perchlorate in solid rocket fuel propellants, explosives, fireworks, flares, air-bag inflators, and in other industrial processes, and formation during the degradation of chlorine-based cleaning products. Within the EU, likely sources include use of nitrate (fertiliser) leading to accumulation in plants. Plant protection products and water disinfection could slightly increase exposure (EFSA, 2014).

98. Perchlorate acts on the thyroid, inhibiting iodine uptake via the sodium-iodide symporter protein. This leads to depletion in levels of thyroid hormones leading to hypothyroid effects in individuals with a moderate iodine deficiency; this was discussed in a paper in 2018 by the COT (COT, 2018a).

99. An exposure assessment is presented within Annex A using occurrence data for liquid milk from EFSA's 2017 exposure assessment and NDNS consumption data. For the mean UB occurrence, there were no exceedances of the TDI of 0.3 µg/kg bw per day (from EFSA, 2014) at mean levels of consumption for any age group. In 97.5th percentile consumers, for the age range 12-<48 months there were exceedances, with exposures ranging from 110-140% of the TDI. Using the 95th percentile UB occurrence value, there was a slight exceedance of the TDI, at 107%, in the age group 12-<18 months at mean consumption, and for all assessed age groups at high level (97.5th percentile) consumption levels, ranging from 153-263% of the TDI. This, however, is an extremely conservative assessment due to the use of upper bound occurrence values in addition to high consumption levels (97.5th percentile).

100. The COT (2019b) discussed EFSA's assessments (EFSA, 2014, 2017) in 2019. The COT concluded that in both long and short term exposure scenarios for all age groups, while there were considerable uncertainties in the assessment, there was potential concern from total dietary exposure to perchlorate, particularly in the case of individuals with mild to moderate iodine deficiency.

101. Based on the exposure assessment presented in Annex A which showed that the TDI was unlikely to be exceeded from consumption of cow's milk in a realistic scenario, and on 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

102. Chlorate is formed as a by-product of chlorine, chlorine dioxide and hypochlorite usage in disinfecting drinking water, water for plant production and food contact surfaces. Chlorine washing of animal derived products is illegal within the EU however plant derived foods can be washed.

103. The EFSA CONTAM panel concluded in their 2015 opinion that the majority of chlorate enters the food chain by washing of food and food contact surfaces. Chlorate is likely to enter milk from cleaning of surfaces and sterilisation of containers (EFSA, 2015a).

104. COT's previous statement on the infant diet (2019b), which included chlorate, discussed EFSA's 2015 opinion and stated that chlorate levels in the total diet were of potential concern for high consumers particularly for individuals with iodine deficiency.

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. An exposure assessment was performed using the mean UB occurrence of chlorate in liquid milk from EFSA (2015a) and is presented in Annex A. No exceedances of the TDI of 3 µg/kg bw per day were observed for any age group for both mean and higher level (95th percentile) consumers.

107. From this information the COT concluded that the 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)

108. IGF-1 is a hormone naturally present in both cow's milk and human breast milk. Through treatment with bovine somatotropin (BST), IGF-1 levels in cows can be artificially increased to improve milk production. BST treatment of cows is illegal within the UK and EU, however milk from BST treated cows can be legally imported. IGF-1 in the diet has been discussed in the scientific literature due to concern over its potential links to cancer.

109. Based on data from DEFRA (DEFRA, 2021), liquid drinking milk from BST treated cows is unlikely to enter circulation into the UK in significant amounts. This is discussed in further detail in Annex A.

110. The COC's 2018 'Statement on possible carcinogenic hazard to consumers from insulin-like growth factor-1 (IGF-1) in the diet' (COC, 2018) is discussed in annex A. Naturally occurring levels in milk are considered, with the COC stating that the levels in milk consumed by humans are unlikely to exceed 100 ng/ml. The COC concluded there was 'insufficient evidence to draw any firm conclusions as to whether exposure to dietary IGF-1 is associated with an increased risk of cancer in consumers. However, the data indicate that the levels of IGF-1 consumed are likely to be low and that IGF-1 is likely to be broken down in the gut and not absorbed to any significant extent. Thus, the risk, if any, is likely low.'.

111. From the information above and that presented in annex A the COT concluded that the levels of IGF-1 in 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

112. Endogenous oestrogens are oestrogens that are naturally present within cows and humans as well as other animals. They are naturally present within cow's milk. Supplementation of cows with oestrogens is illegal within the UK. There is discussion in the literature over the potential effects of ingested oestrogens on the hypothalamic-pituitary-gonadal axis (HPG axis).

113. Regarding 17β-oestradiol, opinions from the Veterinary Products Committee (Veterinary Products Committee, 2006), JECFA (FAO/WHO, 2000) and the European Scientific Committee on Veterinary Measures Relating to Public Health (SCVPH, 2002) have been discussed within annex A. There are varied regulatory opinions on the genotoxicity of 17β-oestradiol, however the COT considers that any genotoxic effect is due to an indirect mechanism.

114. Within annex A is a comparison of exposure to oestrogens naturally found in cow's milk to endogenous production rates of oestrogens in prepubescent boys and girls under the age of 8, presented by JECFA in 2000 (FAO/WHO, 2000). Exposure values were generated from occurrence data from Malekinejad, Scherpenisse and Bergwerff (2006) and NDNS consumption data for children aged 6 months to 5 years of age (Table 1). This was to assess the common claim within the literature that levels of oestrogens within cow's milk would be markedly below the levels produced endogenously within children. The significant uncertainties regarding the endogenous daily production rates in prepubertal children are discussed. From this assessment it was shown that whilst levels within cow's milk are potentially lower than the total daily production of oestrogens it is unclear by how much.

115. In addition, an exposure assessment has been performed and is presented within Annex A, which compares exposures to the JECFA (2000) ADI of 0.05 µg/kg bw, based on hormonal effects for 17β-oestradiol. No exceedance of the ADI was seen in any population group.

116. From the above information and that discussed further in Annex A, the COT concluded that there is no exceedance of the JECFA 2000 ADI from exposure to oestrogens in cow's milk, and 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

117. Mycotoxins are a group of fungal-derived compounds, some of which are highly toxic. Cow's milk can be contaminated with multiple mycotoxins. A wealth of information exists regarding occurrence of aflatoxin M_1, a major metabolite of aflatoxin B_1, in milk. Regarding other mycotoxins, contamination studies have shown variation in the extent to which fumonisins, zearalenone, ochratoxin and trichothecenes and their metabolites transfer from feed to dairy cows and then subsequently into milk. The scientific literature contains far less information on these other mycotoxins and their occurrence in milk.

118. Discussion of mycotoxins other than aflatoxins can be found in Annex A, with the literature currently suggesting that ochratoxin (OTA), zearalenone and it 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. 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.

Aflatoxins

119. Aflatoxins can enter cow's milk through feed contaminated with fungi such as Aspergillus flavus and Aspergillus parasiticus. Aflatoxin AFB_1 is the most common

aflatoxin found in feed. This is converted within the bovine liver via P450 mediated hydroxylation to form the major metabolite AFM_1. AFM_1 is the most commonly reported and researched mycotoxin within milk, however, AFB_1 has also been detected albeit in non-European countries after cattle were exposed to very high levels of AFB_1, a scenario which is highly unlikely in UK and EU dairy cattle (Scaglioni *et al.*, 2014; Becker-Algeri *et al.*, 2016). Other aflatoxins include aflatoxins B_2, G_1, G_2 and M_2 (AFB_2, AFG_1, AFG_2 and AFM_2) and these have also been detected in milk, however, far less information is available on these compounds (EFSA, 2020a).

120. Chronic aflatoxin exposure can lead to immunotoxic effects due to impaired DNA duplication in bone marrow resulting in low leukocyte counts and immunodeficiency, as well as carcinogenic and mutagenic effects. Non-specific inhibition of cell division can also affect other cell types with effects particularly apparent within the gastrointestinal tract. The liver is the primary target of aflatoxin toxicity. This results in bile duct proliferation, hepatic lesions, centrilobular necrosis and fatty acid infiltration. This often progresses to liver cancer (Ráduly *et al.*, 2020). AFB_1 and some other aflatoxins are also directly mutagenic, which contributes to their carcinogenic effects.

121. Aflatoxins were reviewed by the SCF in 1996, and EFSA in 2007 and 2020. They have also been evaluated by JECFA in 1998, 2001 and AFM_1 was also reviewed in 2018. EFSA's most recent risk assessment produced by the CONTAM panel concluded that the chronic endpoint of liver carcinogenicity in rats was the most relevant effect (EFSA, 2020a). They considered the Wogan et al, study of 1974 to be the most satisfactory for dose response modelling (Wogan, Paglialunga and Newberne, 1974). The resulting BMD value was also used in the COT's 2021 statement on plant-based drinks (see below).

122. The COT's (2021a) overarching statement on consumption of plant-based drinks in children aged 6 months to 5 years of age describes the Wogan, et al. (1974) study as follows: "Groups of male Fisher (sic) rats were administered diets containing 0, 1, 5, 15, 50, or 100 µg/kg diet of AFB_1 (purity >95%) until clinical deterioration of animals was observed, at which time all survivors in that treatment

group were killed. EFSA converted the dietary concentrations of AFB_1 into daily intakes assuming that an average adult male rat consumed 40 g diet per kg body using weight per day. EFSA also adjusted the daily intake to 104 weeks in order to compensate for the shorter study duration in some of the AFB_1 groups. In the modelling of the results from the Wogan et al. (1974) study the highest dose was omitted because this dose resulted in a 100% tumour incidence. Using model averaging, the $BMDL_{10}$ for AFB_1 was 0.4 µg/kg bw per day".

Risk Characterisation

123. EFSA calculated the contributions of individual food categories in the collected surveys using the mean LB occurrence value in their 2020 risk assessment. It was reported that 'milk and dairy products' were the most substantial contributor to AFM_1 exposure for all age groups. However, it should be noted that there was a high percentage of non-detects (up to 90% or more) and the median LB was 0. For the group other children (≥ 36 months to < 10 years old), liquid milk was found to account for up to 89% of exposure to AFM_1. Liquid milk also contributed up to 49% of total exposure for infants < 12 months old and up to 74% of total exposure for toddlers (≥ 12 months to < 3 years old). In addition to this, in situations of high exposure, liquid milk could contribute up to 89% of total exposure to AFM_1. Liquid milk is therefore a significant contributor to AFM_1 exposure levels. However, exposure to AFM1 from milk at these levels will usually be limited to a short period in life.

124. Analysing the information within EFSA's 2020 risk assessment 'milk and dairy products' contributed <1% of total AFB_1 exposure in all surveys. This suggests that there is unlikely to be any health concern from AFB_1 exposure from milk to children aged 6 months to 5 years of age.

125. EFSA also concluded that liquid milk was an important source of exposure of AFM_1 + AFT (the sum of AFB_1, AFB_2, AFG_1 and AFG_2) for infants, toddlers and children. However, this is driven by high AFM_1 contributions.

126. In 2020 EFSA utilised both an animal derived $BMDL_{10}$ and human epidemiological data to perform two risk characterisations; the animal derived $BMDL_{10}$ approach and the subsequent total dietary exposure assessment are discussed below, as this is easier to communicate and was in line with the conclusions drawn from the human data.

127. In (EFSA, 2020a), for AFM_1 a 0.1 potency factor was applied to account for the fact that in a study on Fischer rats, AFM_1 was found to induce liver cancer with a potency of 0.1 of that of AFB_1. This produced a value of 4.0 µg/kg bw per day for use in an MOE approach to assess AFM_1 (EFSA, 2020a). For mean total dietary AFM_1 exposure, MOE values were below 10,000 for infants (< 12 months old) in median and maximum exposure groups, all exposure groups for toddlers (≥ 12 months to < 36 months old) and median UB exposure values and maximum exposure for other children (≥ 36 months to < 10 years old). For the 95th percentile of total dietary exposure, all populations within relevant groups ('infants', 'toddlers' and 'other children') exhibited MOE values below 10,000. EFSA commented that this is a health concern however it was noted that high levels of milk exposure may occur only for a short period in a child's life. For total AFT + AFM_1 dietary exposure, all age groups and exposure levels exhibited MOEs below 10,000 suggesting there is a potential health concern from the total diet. MOEs for AFM_1 exposure for total dietary exposure are presented below in Tables 9 through to 12. MOEs for AFT + AFM_1 for total dietary exposure are presented below in Tables 13 through to 16.

Table 9. MOEs at the lower bound of the minimum, median and maximum mean exposure levels in the total diet to AFM1 from (EFSA, 2020a).

Age group	Minimum MOE	Median MOE	Maximum MOE
Infants	28571	7018	2564
Toddlers	8889	5882	2817
Other Children	22222	11429	5128

Table 10. MOEs at the upper bound of the minimum, median and maximum at mean exposure levels to AFM1 in the total diet from EFSA (EFSA, 2020a).

Age group	Minimum MOE	Median MOE	Maximum MOE
Infants	19048	4938	2020
Toddlers	6250	3810	2210
Other Children	14286	7692	4000

Table 11. MOEs at the lower bound of the minimum, median and maximum at 95th percentile exposure levels to AFM1 in the total diet from (EFSA, 2020a).

Age group	Minimum MOE	Median MOE	Maximum MOE
Infants	6061	2703	642
Toddlers	3810	2721	1053
Other Children	9302	5000	1852

Table 12. MOEs at the upper bound of the minimum, median and maximum at 95th percentile exposure levels to AFM1 in the total diet from (EFSA, 2020a).

Age group	Minimum MOE	Median MOE	Maximum MOE
Infants	4082	1942	508
Toddlers	2685	1835	825
Other Children	6452	3175	1465

Table 13. MOEs at the lower bound of the minimum, median and maximum at mean exposure levels to AFT + AFM_1 in the total diet from (EFSA, 2020a).

Age group	Minimum MOE	Median MOE	Maximum MOE
Infants	2222	952	396
Toddlers	541	325	195
Other children	460	328	208

Table 14. MOEs at the upper bound of the minimum, median and maximum at mean exposure levels to AFT + AFM_1 in the total diet from (EFSA, 2020a).

Age group	Minimum MOE	Median MOE	Maximum MOE
Infants	455	155	40
Toddlers	79	44	32
Other children	75	46	32

Table 15. MOEs at the lower bound of the minimum, median and maximum at 95th percentile exposure levels to AFT + AFM_1 in the total diet from EFSA (EFSA, 2020a).

Age group	Minimum MOE	Median MOE	Maximum MOE
Infants	615	345	122
Toddlers	310	172	90
Other children	235	174	91

Table 16. MOEs at the upper bound of the minimum, median and maximum at 95th percentile exposure levels to AFT + AFM_1 in the total diet from (EFSA, 2020a).

Age group	Minimum MOE	Median MOE	Maximum MOE
Infants	99	54	14
Toddlers	48	26	15
Other children	53	25	17

128. In light of EFSA's latest risk assessment it is unlikely that AFB_1 in liquid milk presents a risk to children aged 6 months to 5 years of age. Cow's milk was, however, found to contribute significantly (up to 89%) to total dietary exposure of AFM_1 and AFM_1 + AFT in 'infants', 'toddlers' and 'other children'. As total dietary exposures to AFM_1 and AFM_1 + AFT produced MOEs below 10,000 in these populations at estimated mean exposure levels, a risk to human health cannot be excluded for infants and children aged 6 months to 5 years.

129. From the above information, the COT concluded that a risk to health from aflatoxin M_1 from consumption of cow's milk by children aged 6 months to 5 years of

age cannot be excluded. A risk to health also cannot be excluded for total aflatoxins within milk, however the low MOEs present are largely driven by levels of AFM_1 within cow's milk. Other aflatoxins did reduce the MOE further. It was noted that there was a high percentage on non-detects in the milk and dairy samples, which would affect the way in which exposure is best calculated.

Per- and polyfluoroalkyl substances (PFAS)

130. PFAS are a range of synthetic compounds that contain multiple fluorine atoms. They possess excellent surfactant properties and are widely used in consumer products such as paints, polishes and stain repellents. Thet are also used, or have been used, in firefighting foams. The Organisation for Economic Co-operation and Development (The Organisation for Economic Co-operation and Development OECD, (2021) define PFAS as:

> 'fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), i.e. with a few noted exceptions, any chemical with at least a perfluorinated (–CF3) or a perfluorinated (–CF2–) is a PFAS.'

131. The 2 main classes of PFAS are perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAs). In 2020 EFSA undertook a risk assessment of the potential effects on human health related to the presence of perfluoroalkyl substances in food, focussing on four of the PFAS. These were two PFCAs: perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and two PFSAs: perfluorohexane sulfonic acid (PFHxS) and perfluorooctane sulfonic acid (PFOS) (EFSA, 2020b).

132. Further information on establishment of HBGVs and on risk characterisation have been provided in Annex A. Within EFSA's 2020 dietary exposure evaluation no samples tested positive for the four PFAS compounds above the analytical method reporting levels.

133. In an article by Hill, Becanova and Lohmann, (2021), 13 milk samples were taken from US cattle in areas of concern. These were farms which reported biosolid amendments on cropland or were located within proximity to aqueous film forming foam (AFFF) contaminated soils. No perfluoroalkyl acids (PFAAs) were detected, with the authors concluding that uptake of PFAAs into dairy milk within the U.S. is low.

134. Kowalczyk *et al.*, (2013) in their study of absorption, distribution, metabolism and excretion (ADME) of PFAS contaminated feed in dairy cows concluded that the kinetics of PFOA were similar to PFBS and differed from PFHxS and PFOS. Low levels of PFBS were detected in milk, plasma and trace amounts were detected in the kidneys and liver. Coupled with a high urinary excretion the authors concluded that PFBS does not accumulate in dairy cows.

135. Considering the lack of reported quantifiable amounts of PFHxS, PFOS, PFOA and PFNA in all liquid milk sample data presented by EFSA (2020c) plus the conclusions from Kowalczyk et al. (2013) and Hill, Becanova and Lohmann (2021), the COT concluded that the levels of PFAS in cow's milk are not of health concern to infants and children aged 6 months to 5 years.

Brominated flame retardants (BFRs)

136. Brominated flame-retardants (BFRs) are structurally diverse chemicals used in plastics, textiles and other materials to enhance their flame-retardant properties. There are 5 main classes of BFRs:

i) Hexabromocyclododecanes (HBCDDs), example uses include thermal insulation.
ii) Polybrominated biphenyls (PBBs), example uses include in consumer appliances, textiles and plastic foams.
iii) Polybrominated diphenyl ethers (PBDEs), example uses include in electronic circuitry, casings and textiles.

iv) Tetrabromobisphenol A (TBBPA) and other phenols, example uses include in electronic circuitry and within thermoplastics in TV sets.

v) Other brominated flame retardants.

137. Some BFRs, including polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD) are mixed into polymers rather than being chemically bound to them and can leach out of the products/materials in which they are used and into the environment.

138. The use of many of the BFRs is restricted or prohibited within the EU, nevertheless due to their persistent nature they are widely distributed in the environment such as within water systems, air and soil. BFRs can therefore readily enter the food chain primarily through animal products such as milk and meat.

Hexabromocyclododecanes (HBCDDs)

139. HBCDDs are non-aromatic, brominated cyclic alkanes used primarily as additive flame retardants in materials such as styrene resins. The commercial product consists of three diastereoisomers α, β and γ-HBCD. Although technical HBCD typically consists primarily of γ-HBCD, the relative proportions of the isomers vary depending on product application.

140. A discussion of the MOE approach taken by EFSA, COT's 2015 opinion on this work, in addition to additional work by EFSA is presented within Annex A (EFSA, 2011a, 2021b; COT, 2015c).

141. Regarding risk characterisation, in EFSA's 2021 assessment the mean LB concentration of HBCDDs within milk was < 0.01 µg/kg. The COT concluded that the MOEs 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. (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 were multiplied. This produces a value of 8. For MOEs above this level there is adequate reassurance that there is no health concern.)

142. In light of the (EFSA, 2021b) and (COT, 2015c) conclusions (see Annex A) 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

143. (PBBs) are brominated hydrocarbons formerly used as additive flame retardants. As such these substances were added, rather than chemically bound, to plastics used in a variety of consumer products, such as computer monitors, televisions, textiles and plastic foams, and were able to migrate from the plastic and enter the environment. They are structurally similar compounds in which 2-10 bromine atoms are attached to the biphenyl molecular structure. In total, as with the structurally similar polychlorinated biphenyls (PCBs), 209 different PBB congeners are possible.

144. EFSA concluded that 'the risk to the European population from exposure to PBBs through the diet is of no concern.' Levels in milk were 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, 2010). This is discussed further in Annex A.

145. In 2015 the COT concluded that a reliable estimation of infants' exposures to PBBs was not possible due to limitations within data sources such as the number of congeners covered and a lack of UK data. In spite of this they considered it a low priority due to the restriction on their use (COT, 2015a). Within the literature (discussed in Annex A), minimal levels of PBBs have been reported in milk.

146. In light of the EFSA, (2010) 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

147. PBDEs are produced by direct bromination of diphenyl ether. There are 209 individual PBDE congeners, each of which is identifiable by a unique congener number. Three commercial PBDE flame-retardants, pentabromodiphenyl ether (pentaBDE), octabromodiphenyl ether (octaBDE) and decabromodiphenyl ether (decaBDE) have been available in the UK. The commercial PBDEs are not pure products but a mixture of various diphenyl ethers with varying degrees of bromination.

148. EFSA's 2011 exposure assessment (discussed further in Annex A) determined that the only safety concern was for young children aged 1- < 3 years Milk contributed a low percentage to their total dietary exposure.

149. A review of the literature for occurrence of PBDEs in milk did not show a concern for health as concentrations were low (discussed in Annex A).

150. The COT concluded in 2015 that there 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 (COT, 2015b). An addendum to this statement was produced in 2017 that further concluded that '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, 2017a).

151. Reviewing the EFSA (2011b) and COT (2015b; 2017a) conclusions in addition to the evidence from the literature that cow's milk contains only very low levels, 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)

152. Worldwide, TBBPA is the most widely used BFR and approximately 90% of TBBPA, manufactured by bromination of bisphenol A, is used as a reactive

intermediate in the manufacture of epoxy and polycarbonate resins. In this case it is covalently bound to the polymer and is unlikely to escape into the environment. The remaining 10% is used as an additive flame retardant, where it does not react chemically with the other components of the polymer and may therefore leach out of the matrix into the environment.

153. (EFSA, 2011b) and the COT (2019c) concluded that there was no risk to health from TBBPA. EFSA found that dietary exposures resulted in large MOEs, with cow's milk not containing any TBBPA above reporting levels. The work by COT in 2019 resulted in MOEs greater than those reported in EFSA's 2011 evaluation. The COT concluded that with respect to cow's milk exposure, the MOEs were adequately protective. This is further discussed in Annex A.

154. In light of the EFSA (2011b) and COT (2019c) conclusions and evidence from the literature (further discussed in Annex A) that levels in cow's milk were very low, so that the MOEs were 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

155. Plastic pollution has been widely recognised as a global environmental problem (Villarrubia-Gómez, Cornell and Fabres, 2018). The adverse effects of plastic litter have been widely documented for marine animals (e.g. entanglement, ingestion and lacerations); however, the potential risks from exposure to smaller plastic particles i.e. micro- and nanoplastics in humans are yet to be fully understood.

156. 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) (Jin *et al.,* 2021; Toussaint *et al.*, 2019). The occurrence of microplastics in milk will likely be due to contamination from dairy machinery and / or packaging rather than the cow itself.

157. ECHA in 2019 listed the four major concerns posed by the presence of microplastics in the environment, considered in Annex A (ECHA, 2019).

158. (COT, 2021b) stated that a full risk assessment on the potential toxic effect(s) of microplastics could not be carried out. This was due to the lack of toxicokinetic and toxicity data in general, the paucity of currently available data for levels of microplastics in different food types and the difficulty of performing an accurate exposure assessment. However, whilst risks from microplastics cannot be quantified currently, microplastic contamination in milk is likely to be lower than in other foodstuffs.

159. The current view of the COT from the above information and that included in Annex A, is that exposure to microplastics from the consumption of cow's milk does not represent a risk to health for children aged 6 months to 5 years of age.

Summary

160. To aid in the risk assessment of the chemicals described in this statement three tables are included (Tables 17, 18 and 19), providing a summary of the conclusions and where appropriate to this paper, the HBGV for each substance and highest age range-estimated exposure via the diet, based on mean consumption data.

Conclusions

161. The COT reviewed an extensive range of chemical compounds that could be present incidentally or as contaminants in cow's milk to allow comparison with plant-based dairy alternatives.

162. As can be seen in the summary tables, the vast majority of these potential contaminants present no risk of adverse health effects in children aged 6 months to 5 years of age at the levels observed within cow's milk.

163. The exceptions are iodine, BaP and PAH4, AFM_1 specifically and total aflatoxins due to the contribution of AFM_1, for which any risk to health in children aged 6 months to 5 years of age is unlikely but cannot be completely excluded. The possible risks to health in these age groups from exposure to isoflavones in cow's milk is unknown, as no HBGVs have been established for these compounds in young children and hence there is a lack of knowledge on the toxicological significance of the levels that might be found in milk.

Table 17. Summary of risk assessment conclusions for selected compounds and their occurrence levels within cow's milk based on previous authority opinions.

Compound (s)	**HBGV, (endpoint)**	**Effect (s)**	**Authority**	**COT Conclusion: Health risk from cow's milk**
Nitrite	n/a	Methemoglobinemia	EFSA	No health concern
Bisphenol A	4 µg/kg bw (Increase in mouse kidney weight.	Kidney weight; endocrine perturbation with potential effects on metabolism, growth, sexual development, stress response, insulin production, gender behaviour, reproduction, and fetal development.	EFSA	Currently, no health concern (However, the COT is currently in the process of producing an interim position paper capturing the COT's views and next steps following EFSA's 2023 updated position on BPA.).
DBP, BBP, DEHP, DINP (Summed as	0.05 mg/kg bw (reproductive effects in rats).	Reproductive effects, hepatic effects.	EFSA / COT	No health concern.

DEHP equivalents)				
DEP	5 mg/kg bw (maternal adrenal and kidney weight changes, fetal weight in mice).	Increased maternal adrenal and kidney weights, decreased fetal weight.	WHO / COT	No health concern.
NDL-PCBs	n/a. Minimal effect dose of 2 mg/kg bw per day, expressed as body burden (liver and thyroid in rat).	Liver and thyroid effects.	JECFA	No health concern.
Isoflavones GEN, EQU, FOR, DAI	0.07 mg/kg bw (GEN only) (accelerated pubertal development in female mice).	Endocrine effects (oestrogenic effects) effecting thyroid and immune function and sexual development.	Nordic Council	Any risk to health is uncertain as HBGVs have not been established for young children.
Lead	None, $BMDL_{01}$ of 0.5 µg/kg bw per day ((development of intellectual function).	Multiple toxic effects.	EFSA/COT	Unlikely to be a health concern.
Inorganic Arsenic	None. $BMDL_{0.5}$ of 3 µg/kg bw per day JECFA / COT (lung cancer).	Multiple toxic effects including carcinogenicity.	EFSA/COT	No health concern.
Inorganic Mercury	TWI – 4 µg/kg (kidney weight change in rats).	Multiple toxic effects including renal, haematological, hepatic and gastrointestinal effects.	EFSA / COT	No health concern.

Cadmium	TWI – 2.5 µg/kg (urinary β-2-microglobulin (B2M) as a marker for kidney damage).	Multiple toxic effects including renal toxicity, hepatotoxicity, osteoporosis and osteomalacia.	EFSA / COT	No health concern.
AFM_1	None. Guidance value of 4 µg/kg bw per day derived from a $BMDL_{10}$ based on liver tumour incidence for AFB1 in rats with a 0.1 potency factor applied.	Multiple effects such as immunotoxicity, carcinogenicity and mutagenicity.	EFSA / COT	Health risk cannot be excluded, but exposure estimate uncertain.
AFB_1	None. $BMDL_{10}$ of 0.4 µg/kg bw per day based on liver tumour incidence in rats after AFB1 exposure.	Multiple effects such as immunotoxicity, carcinogenicity and mutagenicity.	EFSA / COT	Health concern unlikely, rarely detected.
Total aflatoxins	None. $BMDL_{10}$ of 0.4 µg/kg bw per day based on liver tumour incidence in rats after AFB1 exposure.	Multiple effects such as immunotoxicity, carcinogenicity and mutagenicity.	EFSA / COT	Health risk cannot be excluded, but exposure estimate uncertain, driven by AFM1 occurrence in milk.

PFAS (PFHxS, PFOS, PFOA and PFNA)	TWI of 4.4 ng/kg bw (reduced antibody levels against diptheria vaccine in 1-year old children).	increased relative liver weight, effects on the immune system.	EFSA	No health concern.
HBCDDs	None. Human equivalent body burden of 2.35 µg/kg corresponding to LOAEL in mice (neurodevelopmental effects).	Neurodevelopmental, immune system effects, reproductive system effects, liver effects and effects on thyroid hormone homeostasis.	EFSA	No health concern.
PBBs	None. NOEL of 0.15 mg/kg bw per day (hepatic carcinogenicity).	Multiple effects (dioxin like) such as altered vitamin A homeostasis, chloracne and body weight changes, carcinogenicity.	EFSA	No health concern.
PBDEs	None. Range of $BMDL_{10}$ s between 12 and 1,700 µg/kg bw per day (neurodevelopmental effects).	Neurodevelopmental, immune system effects, reproductive system effects, liver effects and thyroid hormone homeostasis.	EFSA	No health concern.

TBBPA	None. $BMDL_{10}$ of 16 mg/kg bw per day (thyroid hormone homeostasis).	Thyroid hormone regulation.	EFSA	No health concern.

Table 18. Summary of risk assessment conclusions on potential chemical contaminants of cow's milk, a comparing the highest estimated mean exposures (occurrence and consumption) to their health-based guidance values, from exposure assessments presented in this paper and its annex.

Compound (s)	**HBGV, (endpoint)**	**Authority**	**Highest Exposure (mean consumption), kg bw per day**	**% HBGV or MOE**	**Highest exposure age range (months)**	**Effect**	**Conclusion: Health risk from cow's milks**
Nitrate	3.7 mg/kg bw per day (growth retardation in dogs and rats).	EFSA	0.00416 mg	0.112	12 – <18	Methemoglobinemia	No health concern.
Dioxins plus DL-PCBs	2 pg/kg WHO-TEQ, (reproductive effects in rats).	EFSA	1.024 pg	51.2	12 – <18	Range of toxic effects including chloracne and reproductive effects.	Current view, no health concern.

							However, re-evaluation of dioxins is pending.
Benzo[a]pyrene (BaP)	None, $BMDL_{10}$ of 70 µg/kg bw per day (total tumour-bearing animals)	EFSA	0.00128 µg	54,688 (MOE)	12 – <18	Carcinogenic	Low health concern, but cannot be completely excluded
Sum of BaP, BbF,ChR and BaA (PAH4)	None, $BMDL_{10}$ of 340 µg/kg bw per day (total tumour-bearing animals).	EFSA	0.0032 µg	106,250 (MOE)	12 – <18	Carcinogenic	Low health concern, but cannot be completely excluded.
Iodine	EVM: Guidance level of 15 µg/kg bw per day EFSA: TUL of 200-250 µg/day.	COT / EVM / EFSA / JECFA	15.2 µg	102 (EVM guidance value).	12 – <18	Varied effects dependent on previous exposure to iodine.	Low health concern, but cannot be completely excluded.

	JECFA: PMTDI 17 µg/kg bw per day (Alterations in serum thyroid hormone levels from human studies).						
Perchlorate	0.3 µg/kg (inhibition of radiolabelled iodine uptake by the thyroid).	EFSA	0.179 µg	59.6	12 – <18	Inhibition of iodine uptake, depletion of thyroid hormones.	No health concern.
Chlorate	TDI of 3 µg/kg bw per day. (Read across from perchlorate with a 0.1 potency factor, inhibition of radiolabelled iodine	EFSA	0.544 µg	18.1%	12 – <18	Inhibition of iodine uptake, depletion of thyroid hormones.	No health concern.

	uptake by the thyroid).						
Naturally occurring oestrogens within cow's milk.	ADI – 0.05 µg/kg bw per day for 17β-oestradiol (NOEL based on multiple hormone dependent parameters in postmenopausal women. To protect sensitive population subgroups an uncertainty factor of 10 was applied.).	JECFA	0.0875 µg	17.5%	12 – <18	Suggested effects in children include developmental effects in the urogenital, hormonal and central nervous systems and mammary glands. The COT considers any genotoxicity of 17β-oestradiol to be indirect in nature.	No health concern.

Table 19. A summary of information for compounds within cow's milk where a formal risk assessment could not be performed.

Compound (s)	**Literature evaluation**	**Effect**	**Conclusion: Health risk**

			from cow's milk
Veterinary Medicines	Between 2015 and the end of 2020, only 24 of 21,574 samples of cow's milk analysed returned a positive result (above the maximum residue level). Only 2 of these were considered to pose a potential health risk but this was without taking any dilution effect e.g. from bulk tanks, into account.	Various effects	No health concern.
Pesticides	Between 2015 and the end of 2020 only 1 of 1,723 samples of cow's milk returned a positive result (above the maximum residue level). The risk from residues of pesticides from drinking cow's milk is negligible.	Various effects	No health concern.
IGF-1	IGF-1 supplementation is unlikely to generate a risk to consumer health. In addition milk from IGF-1 treated cow's is unlikely to enter the UK as fresh milk in significant quantities.	No substantiated carcinogenic effects	No health concern.
Other mycotoxins	Milk is considered unlikely to contain significant amounts of other mycotoxins. Specific information was not available for the transfer of 3-Ac-DON, 15-Ac-DON and DON-3-glucoside to cow's milk, but transfer of these seems unlikely, given their hydrophilicity.	Effects including immunotoxicity, carcinogenicity and mutagenicity.	Health concern considered unlikely, though specific information on some

			metabolites is lacking.
Microplastics	A lack of toxicokinetic and toxicity data in general, the paucity of currently available data for microplastics in different food types and difficulties in performing an accurate exposure assessment, however levels of microplastics in milk are lower than in other areas of the diet.	Various, depending on type.	No known health concern.

Abbreviations and Technical Information

ADI	Acceptable Daily Intake
15-Ac-DON	15-Acetyldeoxynivalenol
3-Ac-DON	3-Acetyldeoxynivalenol
ADME	Absorption, Distribution, Metabolism and Excretion
AFB_1	Aflatoxin B1
AFB1	Aflatoxin B_1
AFB2	Aflatoxin B2
AFFF	Aqueous Film Forming Foam
AFG1	Aflatoxin G1
AFM_1	Aflatoxin M1
AFM1	Aflatoxin M_1
AFM2	Aflatoxin M2
AFT	Sum of AFB1, AFB2, AFG1 and AFG2
AhR	Aryl Hydrocarbon Receptor
As	Arsenic
BaA	Benz[a]anthracene
BaP	Benzo[a]pyrene
BbF	Benzo[b]fluoranthene
BBP	Butyl-benzyl-phthalate
BFR	Brominated Flame Retardants
BIO	Biochanin A
BMDL	Benchmark Dose Lower Confidence Limit
BPA	Bisphenol A
Br	Bromine
BST	Bovine Somatotropin
bw	Body Weight
CAR	Constitutive androstane receptor

Cd	Cadmium
CEP	EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
CF2	Perfluorinated Methylene Group
CF3	Perfluorinated Methyl Group
ChR	Chrysene
Cl	Chlorine
COC	The Committee on Carcinogenicity Food, Consumer Products and the Environment
CONTAM	EFSA Panel on Contaminants in the Food Chain
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
DAI	Daidzein
DBP	Di-butylphthalate
DecaBDE	Decabromodiphenyl ether
DEFRA	Department for Environment, Food and Rural Affairs
DEHP	Bis(2- ethylhexyl)phthalate
DHSC	Department of Health and Social Care
DIDP	Di-isodecylphthalate
DINP	Di-isononylphthalate
DL-PCBs	Dioxin-Like Polychlorinated Biphenyls
DL-PCBs	Dioxins and Dioxin-Like Polychlorinated
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
DON	Deoxynivalenol
DON-3-glucoside	Deoxynivalenol-3-Glucoside
E1	Oestrone
E2	17β-Oestradiol
EC	European Commission
ECHA	European Chemical Agency
EFSA	European Food Safety Authority

EHDI	Estimated Human Daily Intakes
EQU	Equol (metabolite of DAI)
ERs	Oestrogen Receptors
EU	European Union
EVM	Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organisation
FDA	Food and Drug Administration
FOR	Formononetin
FSA	Food Standards Agency
FSH	Follicle Stimulating Hormone
FTOHs	Fluorotelomer alcohols
GEN	Genistein
GH	Growth Hormone
GI	Gastrointestinal
H	Hydrogen
HBCD	Hexabromocyclodecane
HBGV	Health Based Guidance Value
HED	Human Equivalent Dose
Hg	Mercury
Hg^{+}	Mercurous cation
Hg^{0}	Elemental mercury
Hg^{2+}	Mercuric cation
HPG axis	Hypothalamic-Pituitary-Gonadal Axis
I	Iodine
IARC	International Agency for Research on Cancer
iAS	Inorganic Arsenic
ICES- 6	Indicator PCBS: 28, 52, 101, 138, 153 and 180
IGF-1	Insulin-like Growth Factor 1
IGFBP-3	Insulin Growth Promoting Factor Binding Protein 3
IQ	Intelligence quotient
JECFA	Joint FAO/WHO Expert Committee on Food Additives

LB	Lower Bound– - Lower bound and upper bound approaches are utilised in order to assess left censored data (Occurrence values below the limits of detection or quantification). The lower bound refers to situations where a zero value has been assigned to occurrence values below the limit of detection or limit of quantification.
LH	Luteinising Hormone
LOD	Limit of Detection
MB	Middle Bound - The middle bound is and approach for assessing left censored data. Any values below the limit of detection (LOD) or limit of quantification (LOQ) are assigned the value LOD/2 or LOQ/2 respectively.
mg	Milligram
mm	Millimetre
MoBB	Margin of Body Burdens
MOE	Margin Of Exposure
MRL	Maximum Residue Limit
MT	Metallothionein
NDL-PCBs	Non-Dioxin-Like Polychlorinated Biphenyls
ng	Nanogram
NHS	National Health Service
NIS	Na^+/I^- symporter
nm	Nanometre
NOAELs	No-Observed-Adverse-Effect Levels
NOEL	No Observed Effect Level
NRL	National Reference Laboratory
NSAIDS	Non-Steroidal Anti-inflammatory drugs
OctaBDE	Octabromodiphenyl Ether
OECD	The Organisation for Economic Co-operation and Development
OTA	Ochratoxin A
PAHs	Polycyclic Aromatic Hydrocarbons

PAPs	Polyfluorinated Phosphate Esters
Pb	Lead
PBB-169	3,3',4,4',5,5'-hexaBB
PBBs	Polybrominated Biphenyls
PBDEs	Polybrominated Diphenyl Ethers
PCBs	Polychlorinated Biphenyls
PCDDs	Polychlorinated Dibenzodioxins
PCDFs	Polychlorinated Dibenzofurans
PE	Polyethene
PentaPBDE	Pentabromodiphenyl Ether
PFAAs	Perfluoroalkyl Acids
PFAS	Per- and polyfluoroalkyl substances
PFBS	Perfluorobutanesulfonic Acid
PFCAs	Perfluoroalkyl Carboxylic Acids
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic Acid
PFOA	Perfluorooctanoic Acid
PFOS	Perfluorooctane Sulfonic Acid
PFSAs	Perfluoroalkane Sulfonic Acids
pg	picograms
PHE	Public Health England
PMTDI	Provisional Maximum Tolerable Daily Intake
PP	Polypropene
PTMI	Provisional tolerable Monthly Intake
PTWI	Provisional Tolerable Weekly Intake
RASFF	Rapid Alert System for Food and Feed
SACN	Scientific Advisory Committee on Nutrition
SCF	Scientific Committee on Food
SCF	European Scientific Committee on Food
SCVPH	Scientific Committee on Veterinary measures relating to Public Health

SD	Standard Deviation
SUL	Safe Upper Level
TBBPA	Tribromobisphenol A
TCDD	2,3,7,8-Tetrachlorodibenzyl Dioxin
TDI	Tolerable Daily Intake
TDS	UK Total Diet Study
TEF	Toxicity Equivalency Factor
TEQ	Toxic Equivalent Value
TSH	Thyroid-Stimulating Hormone
TUL	Tolerable Upper Level
TWI	Tolerable Weekly Intake
UB	Upper Bound - Lower bound and upper bound approaches are utilised in order to assess left censored data (Occurrence values below the limits of detection or quantification). In the upper bound approach any occurrence levels below the limit of detection or limit of quantification (left censored data) are assigned the value of the limit of detection or the limit of quantification.
U-Cd	Urinary Cadmium
UK	United Kingdom
US	United States
US-EPA	United States Environmental Protection Agency
VMD	Veterinary Medicines Directorate
VPC	Veterinary Products Committee
WHO	World Health Organisation
β2M	β-2-microglobulin
µg	microgram

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