**TOX/2021/58**

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

# Discussion paper for the risk assessment of cow's milk in children aged 1 to 5 years, in the context of plant-based drinks evaluations – Part 2

## Background

1. Plant-based drinks have become increasingly popular in the United Kingdom (UK) both for individuals with an allergy to cows' milk or lactose intolerance and those who wish to avoid dairy products for other ethical or cultural reasons.

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). As Members are aware, the (COT) reviewed three of the drinks, with a statement being published earlier this year at the request of the Department of Health and Social Care (DHSC). The Scientific Advisory Committee on Nutrition (SACN) have also been considering the nutritional aspects of these drinks and in order to bring together the nutritional and chemical risk assessments of plant-based 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 the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), and on nutritional issues from the Scientific Advisory Committee on Nutrition (SACN). However, this process is currently on hold whilst the joint working group considers plant-based drinks.

4. The Committee was asked to consider the potential for adverse effects arising from the consumption of plant drinks by young children (aged 6 months- 5 years) who were following a plant-based diet. The drinks considered were soya, oat and almond; rice drinks were not reviewed since there is existing advice that these should not be given to young children due to their arsenic content. The statement setting out the views and conclusions of the Committee was published in January 2021 (COT, 2021a).

5. The Committee agreed during their meeting of July 2021 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 in the consumption of this over the identical population group of interest, children aged 6 months to 5 years.

6. Most of the fresh cow's milk available in the UK is UK derived, 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 the UK.

7. The following potential chemical contaminants of cow's milk were assessed. The Committee may decide whether this should constitute the exhaustive list or whether other compounds, or class of compounds, should be added. The list was derived after a literature review and evaluating historical records (back to March 2019) from the Food Standards Agency (FSA) incident dashboard. This paper (part 2 of 2) covers the chemicals X to XVII, part 1 presented at October's COT meeting has covered the remainder.

This is a paper for discussion and does not reflect the views of the Committee.
It should not be cited.

Chemicals covered in the previous paper (part 1)

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)

Chemicals covered in this paper (part 2):

X. Heavy metals: Lead (Pb), Arsenic (As), Mercury (Hg) and Cadmium (Cd)

XI. Iodine

XII. Chlorate and perchlorate

XIII. Mycotoxins: Aflatoxins ($AFB_1$ and $AFM_1$) 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

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 occasionally other chemical contamination incidents will occur 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 industrial contaminants (e.g. Parabens). As 'one-off' incidents these are acknowledged but not discussed or evaluated in this paper as the overall risks are negligible

**Lead**

9. Lead is a well-known 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 (2013) in their statement on the potential risks from lead in the infant diet and their addendum COT (2016a).

10. Colic is a characteristic early symptom of acute lead poisoning after high exposures. Other symptoms include constipation, nausea, vomiting and anorexia. Lead can cause encephalopathy in children and adults, chronic exposure can lead to neurological, neurodevelopmental, cardiovascular and renal toxicity and potential allergenicity. This is described in further detail in the COT's 2013 statement.

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

12. The COT, the Joint FAO/WHO Committee on Food Additives (JECFA) in 2011 and the European Food Safety Authority (EFSA) in 2010 have expressed the view that it is not possible to identify a threshold below which there is no association between lead and decrements in intelligence quotient (IQ) (EFSA, 2010a; FAO/WHO, 2011b; COT, 2013, 2016a). However, a benchmark dose level $(BMDL)_{01}$ was derived (EFSA, 2010) of 0.5 µg/kg for lead , affecting development of intellectual function, this was calculated as the level in which a 1% change in full scale IQ occurred (1 IQ point change). The EFSA $BMDL_{01}$ was selected by the COT as a reference point for use in their 2013 statement and as the basis for MOE calculations in 2016 (COT, 2013, 2016a). The COT noted a steep dose-response at low levels based on few data from a single study. This may have produced a conservative result.

Risk Characterisation

12. In EFSA (2012a) dietary exposure was calculated for lead. It was found that lead from milk and dairy products contributed 10.6% to lead exposure across all age groups. However, for infants (<1 year) they contributed a mean value of 21.8% (21.5 - 38.4%) for toddlers (1-< 3 years) 20% (13.7 - 29.1) and for other children (3-<10 years) 18.2% (6.5 - 26.9%). In spite of this, for infants, cow's milk contributed less than 2% to the overall middle bound mean lead dietary exposure, representing the 13$^{th}$ highest contributor. For toddlers, cow's milk contributed less than 5% representing the 6$^{th}$ highest contributor and for other children it was less than 4% representing the 6$^{th}$ largest contributor.

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

report. Therefore, levels of lead within milk would not be expected to cause concern for human health.

14. In 2013 and 2016, the COT utilised a MOE approach to estimate the impacts of lead exposure in the diets of children aged 1-5 years. In the 2016 addendum using data from the 2014 infant metals survey (FSA, 2016a) and the Total Diet Study (TDS) (FSA, 2016b), the diet was observed as contributing little to lead exposure for older infants and young children (>6 months) however, overall exposures led to MOEs below 1 due to other significant factors including contributions from dust and soil. A risk at the population level and to some infants and children could not be excluded. The COT did not consider any special measures were necessary for lead.

15. Based on the information provided in EFSA 2012a and the evaluation by the COT in 2016 it is suggested that it is unlikely that lead in cow's milk would provide a risk to infants and children from the ages of 6 months to 5 years.

**Arsenic**

16. Arsenic (As) is a metalloid found in the environment in multiple forms due to both natural and anthropogenic activity. The risks of arsenic to infants and young children were evaluated by the COT (2016b). Organic arsenic compounds are generally accepted as less toxic than their inorganic counterparts which are usually found in fish, seafood and other marine organisms (arsenobetaine, arsenosugars, and arsenolipids) (EFSA, 2009a). Environmental inorganic arsenics (iAs) mostly comprise of arsenic species in the pentavalent and trivalent states. It is also present as thiol complexes.

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

18. JECFA in 1988 established a provisional tolerable weekly intake (PTWI) of 15 µg/kg bw (JECFA, 1989a). EFSA in 2009 noted the PTWI of 15 µg/kg bw (2.1 µg/kg bw per day) was in the region of a $BMDL_{01}$ ranging between 0.3 and 8 µg/kg bw day for skin lesions as well as cancers of the lung, skin and bladder. They concluded 'estimated dietary exposures to iAs for average and high level consumers in Europe are within the range of the $BMDL_{01}$ values identified, and therefore there is little or no margin of exposure and the possibility of a risk to some consumers cannot be excluded.' (EFSA, 2009a).

19. JECFA in their own evaluation in 2011 noted that the PTWI of 15 µg/kg bw (2.1 µg/kg bw per day) for iAS is in the region of the $BMDL_{0.5}$ of 3 µg/kg bw day for lung cancer ranging between 2 and 7 µg/kg bw day. They concluded therefore that the previous health based guidance value (HBGV) was no longer appropriate (no margin of exposure), and the Committee withdrew the previous PTWI (FAO/WHO, 2011c).

20. In 2016 the COT concluded that the JECFA $BMDL_{0.5}$ of 3 µg/kg bw/day identified for lung cancer should be used in the characterisation of the potential risks from exposure to inorganic arsenic in food using a margin of exposure (MOE) approach. This was because the JECFA risk assessment was based on more robust and recent evidence than that available to EFSA in 2009 (COT, 2016b).

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

Risk characterisation

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

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

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

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

**Mercury**

26. 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, 2018d).

27. Mercury toxicity 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

report it was assumed the majority of mercury within milk was inorganic in nature (EFSA, 2012b).

28. EFSA's Panel on Contaminants in the Food Chain (CONTAM) explored the toxicity of inorganic mercury in 2012. This is summarised below. The kidneys are currently thought to be the target organ for acute mercury toxicity observed in rats and mice. At higher doses, haematological and hepatic effects have been documented and at very high doses gastrointestinal damage has been documented. Sub-acute and chronic toxicity induces further renal effects which have been observed in rats and mice with females exhibiting no changes. Ototoxic and reproductive and developmental effects have also been observed. Evidence for inorganic mercury induced carcinogenicity is equivocal. Epidemiological data for inorganic mercury presented effects on the immune system, liver, kidneys, immune system, endocrine systems and cyto-genotoxicity. This epidemiological data were not considered usable for establishing dose-response relationships.

29. In 2012, EFSA's CONTAM panel revaluated the previous provisional tolerable weekly intakes (PTWIs) for inorganic mercury. The CONTAM panel agreed with a JECFA 2010 evaluation that the HBGV for inorganic mercury should be based upon kidney weight changes in rats (FAO/WHO, 2010). They derived a tolerable weekly intake (TWI) of 4 µg/kg bw from a $BMDL_{10}$ of 0.06 mg/kg bw/day with an uncertainty factor of 100 to account for inter and intra species variation (EFSA, 2012b).

Risk Characterisation

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

31. EFSA (2012b), after taking data from 9 European dietary surveys, stated that the highest mean exposure value (Upper Bound, UB) for inorganic mercury was for toddlers at 2.16 µg/kg bw/week. They stated that the majority of studies are below the TWI of 4 µg/kg bw/week however the highest UB 95$^{th}$ percentile dietary exposure value for toddlers at 4.06 µg/kg bw/week was similar to the TWI. EFSA considered this an overestimate with a high level of uncertainty. This is shown by a wide Lower Bound (LB) – Upper Bound (UB) range.

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

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

34. The COT has produced a statement discussing methylmercury in the diet of infants and children aged 6 months – 5 years (COT, 2018d). For the Infant Metal Survey and the TDS, total mercury was measured (FSA, 2016a, 2016b). Apart from fish and shellfish, methylmercury does not contribute significantly to other food categories. Regarding total mercury, exposure to total mercury was below the TWI for inorganic mercury based on infant metals survey data and total diet survey data. Utilising TDS data, exposure to total mercury for children aged 1 – 5 years were within the TWI of 4 µg/kg bw/week for inorganic mercury. The risk of inorganic mercury exposure to children is therefore low.

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

**Cadmium**

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

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

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

39. Chronic cadmium exposure can induce osteoporosis and osteomalacia, with deformities and bone fragility caused by direct calcium displacement or inhibiting hydroxylation of vitamin D in the kidney, disrupting calcium and phosphorous metabolism. Cadmium can also affect a number of second messengers, enzymes

and indirectly induce oxidative stress. Oxidative stress plays a role in kidney and bone damage as well as in cadmium induced carcinogenesis (COT, 2018c).

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

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

42. In 2009 the EFSA CONTAM panel established a TWI for cadmium using group-meta-analysis based on urinary β-2-microglobulin (β2M) as a marker for kidney damage (EFSA, 2009b). A $BMDL_5$ of 4 µg urinary cadmium (U-Cd)/ g creatinine was calculated for an increase of the prevalence of elevated β2M. When taking into account inter-individual variation of urinary cadmium levels within the study populations this was reduced to 1 µg U-Cd/ g. For the U-Cd concentration of 95% of the population to remain below 1 µg/kg creatinine by the age of 50, Cd dietary exposure should stay below 0.36 µg/kg bw/day or 2.52 µg/kg bw/week. Considering cadmium's long biological half-life a TWI of 2.5 µg/kg bw/week was established.

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

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

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

Risk Characterisation

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

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

48. The COT 2018 statement on cadmium in the infant diet and children aged to 5 years noted that there were some exceedances from dietary exposure (a 260% maximum) of the EFSA (2011a) TWI. This statement used occurrence data from the total diet study (FSA, 2016b) and infant metals survey (FSA, 2016a). This exceedance was not expected to remain at these levels over the decades of bioaccumulative exposure considered by EFSA in setting their HBGV. The COT

concluded that cadmium exposure did not present a health concern, however efforts to reduce cadmium exposure should continue. Cow's milk was not identified as a key contributing food group in this assessment.

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

**Iodine**

50. Iodine is an essential micronutrient necessary to produce thyroid hormones. The COT released a statement (2017a) 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 sterilising compounds prior to milking.

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

52. 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/day from all sources, based on the same longer term studies in adults used by the European Scientific Committee on Food (SCF) in 2002 in support of their TUL, recorded in EFSA, (2006). No safety factors were used as these studies encompassed a relatively large number of subjects (JECFA, 1989b).

53. The COT (2017a) 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)."

54. The COT published a statement on the risks of excess iodine exposure to infants and young children in 2017 where they assessed three HBGVs, This assessment is paraphrased below (paragraphs 55 - 58) (COT, 2017a).

55. 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 set a Safe Upper Level (SUL) for iodine. For guidance 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 0 - 2 mg/day in a range of human studies. From this data the EVM proceeded to set a guidance level for iodine at 15 µg/kg bw/day for adults. This value is utilised in an exposure assessment in this paper due to its conservative nature.

56. In 2002, the SCF published an opinion on the tolerable upper intake levels of vitamins and minerals, recorded in EFSA, (2006). For iodine, they set 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 adverse effects, but lacked detailed iodine intake data. An uncertainty factor of 3 was used. These values were endorsed by EFSA (2006).

57. In 2017 the COT calculated new HBGVs based on the EFSA (2006) endorsed values in their statement assessing the risks of excess iodine in the diet. This used differing mean bodyweights for separate age groups based on different mean bodyweights. These HBGVs are displayed in Table 1.

Table 1: Table displaying the HBGVs generated using EFSA endorsed values and mean bodyweight for age found in (COT, 2017a).

| Age group | 0-<12 months | 12-<15 months | 15-<18 months | 18-<24 months | 24-<60 months |
|---|---|---|---|---|---|
| HBGV | No tolerable upper limit (TUL) specified for this age group | 18.9 µg/kg bw/day TUL | 17.9 µg/kg bw/day TUL | 16.7 µg/kg bw/day TUL | 15.5 µg/kg bw/day TUL |

Exposure assessment and risk characterisation

58. 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 a chronic exposure assessment in young children aged 6 months to 5 years (Department of Health, 2011; Bates et al., 2014; Roberts et al., 2018). Cow's milk consumption was used as a proxy for plant-based milk. The data presented in Table 2 includes consumption data for cow's milk consumed as a drink and with recipes. Consumption data for children aged 6 – 12 months are derived from recipes only as cow's milk is not recommended by the National Health Service (NHS) as a main drink for infants in this age range (NHS, 2018). Table 3 presents consumption data without recipes. As these values are only slightly lower, all exposure

assessments have been undertaken using the worst case data from Table 2 only (with recipes).

Table 2: Estimated chronic consumption of cow's milk in consumers (as a drink and with recipes)

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

Table 3: Estimated chronic consumption of cow's milk in consumers (as a drink without recipes)

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

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

60. 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.

61. A review article by Reijden et al., collated iodine occurrence data from 30 European and 1 United States (US) study 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 at 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).

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

63. A study by O’Kane et al. investigating seasonal variation in iodine and selenium concentration in milk found mean (± SD) (standard deviation) iodine levels were 475.9 (± 63.5) µg/kg in pasteurised Northern Irish milk (O’Kane et al., 2018). This mean was obtained from the analysis of 36 samples. 95$^{th}$ percentile or maximum occurrence data were not presented in this study. The highest recorded mean concentration was 543.3 (± 53.7) µg/kg from 9 samples of milk collected in spring.

64. The highest found UK mean iodine concentration was found in Kane et al. (475.9 µg/kg). Using the consumption rates in Table 2 and the EVM, (2003) guidance value of 15 µg/kg bw /day, an exposure assessment was undertaken which is presented in Table 4.

Table 4: Exposure assessment from cows' milk consumption using mean iodine occurrence in O'Kane et al. (2018), consumption data from the NDNS and the EVM 2003 guidance value (EVM, 2003).

| Age (months) | Estimated exposure mean µg/kg bw/day | Estimated exposure 97.5$^{th}$ percentile µg/kg bw/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 |

65. Average consumers in the age group 12 - < 18 months slightly exceed the guidance value of 15 µg/kg bw/day set by the EVM in 2003. High consumer exposures exceed the guidance value for all age groups.

66. In the COT's 2000 paper, a survey of UK cows' milk from 1998-9 was discussed which identified overall mean iodine concentration at cow's milk to be 311 µg/kg with a lowered mean concentration in summer (200 µg/kg). These values were used to generate exposure data and their safety assessed against guidance values calculated from the JECFA PMTDI of 0.017 mg/kg bw/day (17 µg/kg bw 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 at 362, 379 and 330 µg/day were observed. For milk consumption alone, exceedances of the guidance values calculated from the previously adopted PTWI were present in high level consumers (97.5$^{th}$ percentile) for the groups aged 1 ½ - 2

½, 2 ½ - 3 ½ years. The COT concluded that iodine in cows' milk was unlikely to pose a risk to health even in children who are high level consumers (COT, 2000). This conclusion was reaffirmed in the COT 2017 paper on the risk of excess iodine in the diets of infants and young children.

67. In the COT paper of 2000 on iodine in cows' milk exceedances were identified for 97.5$^{th}$ percentile consumers. This was mirrored in the exposure assessment produced in this paper with high level consumers of milk exceeding the TDI. For mean level consumers however, iodine exposure approached the 2003 EVM's 15 µg/kg bw/day TDI for the group 12-<18 months. COT's 2000 and 2017 statements stated that iodine levels in cows' milk were seen to pose no toxicological concern. With similar results in this exposure assessment it is suggested that the risk to health from iodine in cows' milk is likely to be low.

**Perchlorate**

68. Perchlorate ($ClO_4^-$) has both natural and anthropogenic sources. Previous biomonitoring studies have suggested it is most likely to be a ubiquitous compound. It is present in the environment due to Chilean fertilisers and industrial emissions such as ammonium perchlorate in solid rocket fuel propellants and formation of perchlorate from degradation of chlorine-based cleaning products. Within the EU likely sources include Chilean nitrate (fertiliser) leading to accumulation in plants. Plant protection products and water disinfection could slightly increase exposure (EFSA, 2014).

69. 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 however in individuals with a moderate iodine deficiency, this was discussed in a discussion paper from 2018 from the COT (COT, 2018a).

70. The EFSA CONTAM panel in 2014 decided a prolonged 50% inhibition by NIS ($Na^+/I^-$ symporter) inhibiting compounds like perchlorate may result in goitre and multinodular toxic goitre even if short term exposure does not alter thyroid function

tests. Although the panel noted it was unknown if thyroid iodine uptake inhibition below 50% has any consequences, the CONTAM panel performed benchmark dose modelling on a study by Greer et al., (2002), previously identified by JECFA as a key study for dose-response modelling based on inhibition of radiolabelled iodine uptake by the thyroid (FAO/WHO, 2011a; EFSA, 2014). The CONTAM panel selected the 95% lower confidence limit of the $BMDL_{05}$ (5% extra risk of thyroid iodine inhibition) of 0.0012 mg/kg bw/day as a reference point. From this an uncertainty factor of 4 was applied to account for inter-human toxicokinetic variation producing a TDI of 0.3 µg/kg bw/day. The panel did not consider it necessary to produce a safety level for short term exposure (EFSA, 2014).

Exposure assessment and risk characterisation

71. EFSA (2017a) performed a dietary exposure assessment for perchlorate. This report lacked an exposure assessment for liquid milk. Occurrence data from this report for milk was utilised to perform a exposure assessment. A mean occurrence of 0.56 - 3.07 - 5.58 µg/kg (LB-MB-UB) was calculated from 166 samples of liquid milk. A 95$^{th}$ percentile value of 3.80-5-10 µg/kg (LB-MB-UB) was also presented. Occurrence data was also provided in (EFSA, 2014)

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

73. An exposure assessment has been undertaken using the mean and 95$^{th}$ percentile upper bound occurrence values of 5.58 and 10.0 µg/kg respectively for liquid milk (EFSA, 2017a), the consumption rates from Table 2 and the TDI of 0.3 µg/kg bw/day (from EFSA, 2014). This assessment is presented in Tables 5 and 6.

Table 5: Exposure assessment using the mean UB occurrence value for liquid milk from EFSA, (2017a), consumption data from the NDNS (Table 2) and the EFSA TDI (EFSA, 2014).

| Age (months) | Estimated exposure (mean) (µg/kg bw/day) | Estimated exposure ($97.5^{th}$ percentile) (µg/kg bw/day) | Mean %ADI | 97.5th percentile %ADI |
|---|---|---|---|---|
| 6 – <12 | 0.0725 | 0.268 | 24.2 | 89.2 |
| 12 – <18 | 0.179 | 0.419 | 59.6 | 140 |
| 18 – <24 | 0.162 | 0.441 | 54.0 | 147 |
| 24 – <48 | 0.129 | 0.329 | 42.8 | 110 |
| 48 – <60 | 0.0949 | 0.257 | 31.6 | 85.6 |

Table 6: Exposure assessment using the 95th percentile UB occurrence value for liquid milk from EFSA (2017a), consumption data from the NDNS (Table 2) and the EFSA TDI (EFSA, 2014).

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

74. Using the mean UB occurrence value of 5.58 µg/kg for 'liquid milk' from EFSA's 2017 study no exceedances were found at mean consumption levels. However, exceedances between ages 12 -< 48 months were found at the 97.5$^{th}$ percentile of consumption (Table 5). At the 95$^{th}$ percentile UB occurrence of 10 µg/kg at mean consumption levels there were exceedances for the 12-<18 age group and exceedances at all values at the 97.5$^{th}$ percentile of consumption (Table 6). This however is an extremely conservative assessment using occurrence data presented as upper bound.

75. From the exposure assessment presented, it appears that perchlorate levels in milk do not represent a significant health risk. However, milk is a significant contributor to total perchlorate levels.

**Chlorate**

76. Chlorate is formed as a by-product of chlorine, chlorine dioxide or hypochlorite usage in disinfecting drinking water, water for plant production and food surface contacts. Chlorination of animal derived products is illegal within the EU however plant derived foods can be washed.

77. The 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 by cleaned surfaces and sterilised containers (EFSA, 2015).

78. EFSA undertook an evaluation of chlorate toxicity in 2015. In summary they stated that in experimental animals chlorate exhibits both acute and chronic toxicity. Acute toxicity is targeted towards the thyroid and haematological system in animal models. This includes a reduction in erythrocytes, haemoglobin and haematocrit. Histopathological changes to the thyroid in rats include follicular cell hypertrophy, increase in colloid depression and follicular cell hyperplasia. Alteration to thyroid hormone levels included decreases in T3 and T4 accompanied by increases in thyroid-stimulating hormone (TSH). Long term toxicity includes formation of non-

neoplastic lesions in the thyroid gland, in male and female rats and mice, bone marrow (hyperplasia) in male rats and female mice and the spleen of male rats (haemopatic cell proliferation). There is evidence of reproductive and developmental toxicity in rats.

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

80. There is equivocal evidence for carcinogenicity in female B6C31 mice and no evidence in males. There was some evidence of sodium chlorate induced carcinogenicity in female and male F344/N rats. There is mixed in vitro and in vivo evidence of genotoxicity however the EFSA CONTAM panel concluded chlorate did not pose a genotoxic risk (EFSA, 2015).

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

Exposure assessment and risk characterisation

82. 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.

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

84. An exposure assessment has been performed using the TDI of 3 µg/kg bw/day and the mean upper bound occurrence value for perchlorate (17 µg/kg) from EFSA, (2015) in addition to the consumption rates from Table 2. This assessment is presented in Table 7.

Table 7: Exposure assessment using the mean UB occurrence value for liquid milk from EFSA (2015) and consumption data from the NDNS and the EFSA TDI (2015)

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

85. From the mean UB occurrence value of 17 µg/kg chlorate in liquid milk obtained from EFSA 2015 and the exposure data provided in this report no exceedances of the TDI can be seen in any of the child age groups (Table 7). This provides a more detailed look at the impacts of milk than in the EFSA 2015 report where information was largely limited to ‘milk and dairy products’ Therefore this suggests that chlorate in cow’s milk is unlikely to pose a risk to health to infants and children aged 6 months – 5 years.

**Insulin-like Growth Factor (IGF-1)**

86. IGF-1 originating from the treatment of cows with bovine somatotropin (BST) is discussed in the scientific literature due to concern over its potential links to cancer.

87. The Committee on Carcinogenicity Food, Consumer Products and the Environment (COC) released a statement on the risks of IGF-1 in cows' milk in 2018. They concluded that absorption of intact IGF-1 is unlikely. In addition, they concluded there are very few papers linking raised circulating IGF-1, diet and cancer risk and where it was investigated dairy consumption was not linked to increased cancer risk. The committee also stated that whilst elevated IGF-1 had been observed in cancer patients, a causative relationship could not be established as tumours can produce growth factors themselves. Many of the sourced papers had considerable limitations however, this included a lack of information on diet, ethnicity of subjects and a lack of continual monitoring. Despite this the committee concluded that there was no expected increase to cancer risk from IGF-1 in the diet (COC, 2018).

88. Bovine Somatotropin (BST) treatment in cows is illegal within the EU and UK however milk from BST treated cows is not. Table 8.6 (page 90) of the 2020 Agriculture in the UK report by the Department for Environment, Food and Rural Affairs (DEFRA) (2021) has been analysed. Looking at the ratio of imported milk to total supply and applying this to the total supply for liquid consumption only as a percentage, <1% of UK drinking milk was sourced from imports between 2018-2020. This estimate assumes that imported milk is spread proportionally between milk intended for liquid consumption and manufacturing processes. This figure suggests that the risk of exposure to BST induced IGF-1 is likely low, further mitigating any risks presented by its presence in milk.

89. As stated by the COC in 2018 it is unlikely that IGF-1 in cows' milk poses a risk to health to infants and children aged 1-5 .

**Endogenous Oestrogens**

90. Exogenous endocrine disrupting chemicals have been suggested as potential sources for a range of developing health issues. This has arisen due to a mimicry between them, and hormones naturally produced by individuals and potential effects this may cause due to effects on the hypothalamic-pituitary-gonadal axis (HPG axis). This has raised concerns about endogenous oestrogens and their consumption.

91. A large amount of information within this discussion paper relating to endogenous oestrogens is drawn from a recent comprehensive review by Snoj and Majdič, (2018) which encompassed a large amount of literature.

92. Snoj and Majdič, (2018) collated 10 studies examining estrone; however, these studies investigated US cattle. Due to differences in dairy practices between US and European cows it was not considered appropriate for this occurrence data to be used to perform a risk assessment. No other occurrence data from studies in the 2001-2012 period was found during a literature search of the PubMed database using the terms, “hormone AND cows AND milk AND human AND risk” and “Cows AND milk AND hormone AND human health” with search results limited to 2001-2021. However, two papers reporting natural oestrogen levels were later found in Courant et al. (2007) and Malekinejad, Scherpenisse and Bergwerff (2006).

93. Endogenous oestrogens are naturally present in milk. The most prevalent oestrogen is oestrone (E1) in its conjugated (oestrone sulphate) and free forms. 17β-Oestradiol (E2) is also present in milk (Pape-Zambito, Magliaro and Kensinger, 2008). Concern has been raised due to the presence of elevated endogenous oestrogens in pregnant dairy cows blood and milk due to the milking during the second half of pregnancy (Ganmaa and Sato, 2005). Health concerns regarding endogenous oestrogens generally stem from the effects of endocrine disruptors. Hormone mimicking xenobiotics have been suggested to impact reproductive, neurological, developmental behavioural disorders. As an extension of this, questions have been raised on the impact of endogenous hormones in foodstuffs. The associated potential risks of exposure to oestrogens with regard to children

include developmental effects in the urogenital, hormonal and central nervous systems and mammary glands (Snoj and Majdič, 2018). There have been differences in conclusions of risk assessment bodies on the genotoxicity of 17β-oestradiol and the role of its genotoxicity in its carcinogenicity.

94. From the collated studies in Snoj and Majdič, (2018) there were mixed evidence on the effects of oestrogens on experimental animals with many focussing on the effects of cows' milk. In human studies in Mongolian children significant elevations in the growth factor IGF-1, IGF-1/IGFBP-3 ratio and GH levels were found compared to children who did not consume milk. In this same study no significant variations were seen in Bostonian girls (Rich-Edwards *et al.*, 2007). Within men there has been evidence of acute effects upon full-fat dairy product consumption including lowered motility of sperm, and raised FSH blood levels (Afeiche et al., 2013). In another study progesterone and E1 levels were observed to rise 30-60 minutes after consumption of a litre of cow's milk and serum levels of testosterone, follicle stimulating hormone (FSH), and luteinising hormone (LH) were seen to decrease suggesting milk may have activated a negative feedback loop suppressing gonadotropin secretion (Maruyama, Oshima and Ohyama, 2010). This study also demonstrated E1, E2, oestriol and pregnanediol increases in prepubertal children on milk consumption. These studies suggest the HPG axis may be affected by the intake of milk however an association between this and endogenous oestrogens is uncertain and should be ascertained with research focussing on effects on prepubertal children.

95. The carcinogenicity of milk was also reviewed in Snoj and Majdič (2018). There is varied epidemiological evidence on the impact of cow's milk on breast cancer studying the effects of cows' milk and dairy intake (SA Missmer et al., 2002; Moorman and Terry, 2004; Ganmaa and Sato, 2005; Snoj and Majdič, 2018). In Sprague-Dawley rats there has been conflicting evidence on oestrone sulphate's ability to play a role in mammary cancer incidence (Qin et al., 2004; Nielsen *et al.*, 2011).

96. There are epidemiological correlations between dairy consumption and prostate and testicular cancer in some populations; however, there is overall no conclusive link between milk or dairy sex steroid hormones and prostate cancer (Andersson et al., 1995; Aune *et al.*, 2014; Downer et al., 2017; Tat *et al.*, 2018). A study in rats found high consumption of milk (representing 10% of body mass) and co-treatment with amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine led to increased incidence of neoplastic lesions; however, this is not representative of human consumption (Qin et al., 2006).

97. Regarding testicular cancer, epidemiological data suggests a correlation between dairy consumption and testicular cancer rates with Davies et al. identifying adolescent exposure and Garner et al. adult cheese consumption as correlating to testicular cancer incidence. Snoj and Majdič (2018) suggests a higher incidence of prostate cancer in Garner *et al*. may have influenced rates of testicular cancer (Davies et al., 1996; Garner et al., 2003).

98. No conclusive link to non-hormone related cancers were identified in Snoj and Majdič, (2018). Milk was stated as exhibiting both carcinogenic and anti-carcinogenic properties based on current data.

99. In the Snoj and Majdič. review and in additional information found during the literature search, it was often reported that the contribution of milk oestrogens in comparison to circulating levels of oestrogens was expected to be minimal (Pape-Zambito, Magliaro and Kensinger, 2008; Macrina *et al*., 2012; Parodi, 2012; Snoj and Majdič, 2018).

100. Hormones for use as growth-promotors in beef cattle were evaluated by JECFA in (2000). For 17β-oestradiol it was concluded that hormonal effects occur at doses lower than other toxicological responses and are a more appropriate basis for evaluating its safety. 17β-oestradiol was considered to have genotoxic potential but it's carcinogenic effects were considered most likely due to hormone receptor interaction. JECFA established an ADI of 0.05 µg/kg bw/day based on a NOEL for multiple hormone dependent parameters in postmenopausal women. A total uncertainty factor of 100 was applied, which included a factor of 10 to allow for

interindividual variation and a further factor of 10 to protect sensitive population subgroups. Exposure to the sum of all oestrogens found in the occurrence data will be compared to this ADI.

101. Other scientific committees have reviewed the safety of oestrogens and 17β-oestradiol for use as growth promoting hormones inn beef cattle. The Veterinary Products Committee (VPC) considered as an intermediate conclusion that 17β-oestradiol should be considered a 'complete' carcinogen (having both tumour initiating and tumour promoting properties) until further evidence was available on its mode of action (VPC, 2006). The European Scientific Committee on Veterinary measures relating to Public Health (SCVPH) concluded in 2002 that there were convincing data demonstrating the pro-genotoxicity of 17β-oestradiol through metabolic activation to reactive quinones. 17β-oestradiol had been found to induce mutations in various cell cultures whilst the metabolite oestradiol-3,4-quinone was found to cause DNA-adducts in mouse skin in vivo. Catechol-oestrogen-quinones were found to form DNA adducts in vitro and in vivo in mouse skin (SCVPH, 2002). IARC, in its assessments in 2008 of oestrogen-only menopausal therapy and combined oestrogen-progestogen menopausal therapy, concluded that receptor-mediated responses are a plausible and probably necessary mechanism for oestrogen carcinogenesis. In addition, there is support for a genotoxic effect of oestrogenic hormones or their by-products such as reactive oxygen species. Current knowledge does not allow a conclusion as to whether either of these mechanisms is the major determinant of oestrogen-induced cancer. It is entirely possible that both mechanisms contribute to and are necessary for oestrogen carcinogenesis (IARC, 2012). The main oestrogens used were conjugated oestrogens, 17β-oestradiol and its semi-synthetic esters.

Exposure Assessment and Risk Characterisation

102. Two papers reporting EU occurrence data were found for naturally occurring oestrogens in milk. The highest occurrence was for the sum of oestrone, 17α-oestradiol, 17β-oestradiol and oestriol collected in Malekinejad, Scherpenisse and Bergwerff (2006). This consisted of 4 samples of processed milk collected from local

grocery stores and a sample of organic milk. Below in table 8 the mean concentrations of each oestrogen are presented after the milk had been enzymatically treated. Due to a lack of detections for some oestriol samples, where no oestriol was detected for the LB scenario the concentration was assumed to be 0 whilst in the UB scenario it was assumed that concentrations were at the limit of detection 10 ng/L. Where the signal was obscured by interference the concentration was assumed to be the limit of detection in both scenarios.

Table 8: Occurrence data for oestrone, α-oestradiol, β-oestradiol and oestriol in milk from Malekinejad, Scherpenisse and Bergwerff (2006)

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

103. Two exposure assessments have been performed using the JECFA ADI of 0.05 µg/kg bw/day for 17β-Oestradiol and the mean concentration the sum of oestrogens found within milk (267.4 – 273.4 ng/L) (LB-UB) from Malekinejad, Scherpenisse and Bergwerff, (2006) in addition to the consumption rates from Table 2. It will be assumed that a litre of milk is equivalent to a kilogram. This assessment is presented in Table 9 and 10.

Table 9: Lower Bound exposure assessment using the mean occurrence value for liquid milk from Malekinejad, Scherpenisse and Bergwerff (2006) and consumption data from the NDNS and the JECFA ADI.

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

Table 10: Upper Bound exposure assessment using the mean occurrence value for liquid milk from Malekinejad, Scherpenisse and Bergwerff, (2006) and consumption data from the NDNS and the JECFA ADI.

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

104. From occurrence data sourced from Malekinejad, Scherpenisse and Bergwerff, (2006) and NDNS consumption data no exceedances of the ADI

established by JECFA in 2000 can be seen. It should be noted however that there is uncertainty regarding the role of genotoxicity in the carcinogenicity of 17β-oestradiol.

105. The literature, focussing on the review by Snoj and Majdič (2018), regarding the potential health impacts of oestrogens in cows' milk suggest potential links between both positive and negative human health outcomes and milk consumption, however no definitive conclusions have yet been drawn however from this information there is likely a low risk of oestrogens in cows' milk significantly affecting health in humans due to the low concentration in milk compared to already present endogenous oestrogens in the body. Further research is required however on the effects of cow's milk containing oestrogens for all population ranges. Regarding 17β-oestradiol, uncertainty exists, with international risk assessment groups presenting varied opinions on its genotoxicity. The now disbanded SCVPH considered the compound to be genotoxic whilst the VPC advised to consider it as a complete carcinogen until further information became available. JECFA concluded that it had genotoxic potential. The exposure assessment performed in this paper displayed no exceedances of the JECFA (2000) ADI in any population group; however, due to uncertainty of 17β-oestradiol's genotoxicity a risk to health cannot be excluded for infants and children aged 6 months to 5 years.

**Mycotoxins**

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

Aflatoxins

107. Aflatoxins can enter milk through feed contaminated with fungi such as Aspergillus flavus and *A*spergillus parasiticus. The aflatoxin $AFB_1$ is a common

aflatoxin in feed. This is converted within the bovine liver via cytochrome P450 hydroxylation to form the major metabolite AFM1. AFM1 is the most commonly reported and researched mycotoxin within milk however AFB1 has also been detected in milk (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 have been detected in milk however far less information is available on these mycotoxins in milk (EFSA, 2020a).

108. Chronic aflatoxin exposure can lead to immunotoxic effects due to impaired DNA duplication in bone marrow resulting in low leukocyte levels and immunodeficiency, as well as carcinogenic and mutagenic effects. Non-specific cell multiplication inhibition can also affect other cell types with effects prominent within the gastrointestinal tract. The liver is the primary target for aflatoxin exposure. This results in bile duct proliferation, hepatic lesions, centrilobular necrosis and fatty acid infiltration. This often results in liver cancer (Ráduly et al., 2020).

109. Aflatoxins have been reviewed by the SCF in 1996, and EFSA in 1996, 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 endpoint (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). This value was also used in the COT (2021) statement on plant based drinks (see below).

110. The COT's (2021) 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 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

111. EFSA calculated the contributions of individual food categories in the collected surveys using the LB mean 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. For the 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 (≥ 36 months to < 10 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.

112. 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 the risk of harm from $AFB_1$ exposure from milk is low.

113. 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.

114. In 2020 EFSA utilised both an animal derived $BMDL_{10}$ and human epidemiological data to perform 2 risk characterisations.

115. 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 at a rate of 0.1 of that of $AFB_1$. This produced a value of 4.0 µg/kg bw/day for the assessment of $AFM_1$ using a MOE approach (EFSA, 2020a). For mean 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 95$^{th}$ percentile of 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 only occur for a short period in a child's life. For AFT +$AFM_1$ all age groups and exposure levels exhibited MOEs below 10,000 suggesting there is a health concern. MOEs for $AFM_1$ exposure are presented below in table 11, 12, 13 and 14. MOEs for AFT + $AFM_1$ are presented below in tables 15, 16, 17 and 18

Table 11: MOEs at the lower bound of the minimum, median and maximum at mean exposure levels 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 12:MOEs at the upper bound of the minimum, median and maximum at mean exposure levels to AFM1 from EFSA (2020a).

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

Table 13:MOEs at the lower bound of the minimum, median and maximum at 95th percentile exposure levels to AFM1 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 14: MOEs at the upper bound of the minimum, median and maximum at 95th percentile exposure levels to AFM1 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 15: MOEs at the lower bound of the minimum, median and maximum at 95th percentile exposure levels to AFT + $AFM_1$ 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 16: MOEs at the upper bound of the minimum, median and maximum at 95th percentile exposure levels to AFT + $AFM_1$ 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 17: MOEs at the lower bound of the minimum, median and maximum at 95$^{th}$ percentile exposure levels to AFT + $AFM_1$ from EFSA (2020a).

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

Table 18: MOEs at the upper bound of the minimum, median and maximum at 95$^{th}$ percentile exposure levels to AFT + $AFM_1$ from EFSA (2020a).

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

116. Human epidemiological data was utilised to perform a separate risk characterisation using cancer potency estimates reported by JECFA (FAO/WHO, 2018). The CONTAM panel also incorporated hepatitis B virus (HBV) and hepatitis C virus (HCV) prevalence as an additional risk factor when modelling the data (EFSA, 2020a). The World Health Organisation (WHO) drinking water guidelines were used to provide context for the cancer potency estimates which states that an excess lifetime cancer risk of $10^{-5}$ is of low concern, exceeding this threshold would lead to concern. With a 70 year life expectancy this was translated to a yearly excess cancer risk of 0.014 added cancer cases per 100,000 subjects. Excess cancer risk is not used in the UK and Europe to express risk, the MoE approach being preferred.

117. Regarding sole exposure to $AFM_1$ at mean exposures and 0.2% HBV/HVC prevalence, for toddlers the 0.014 threshold was met at the median UB value and

exceeded in higher exposures. For toddlers the threshold was exceeded above median UB exposures and for other children the threshold was met at the maximum LB and exceeded at the maximum UB. For the 95$^{th}$ percentile exposure infants exceeded the threshold at and above the minimum UB whilst other children exceeded the threshold at all levels at and above the median LB. At 7.6% HBV/HCV prevalence and mean exposures infants exceeded the threshold at all values excluding the minimum LB and the median LB. Toddlers and other children exceeded the threshold for all values. At the 95$^{th}$ percentile of exposure infants, toddlers and other children exceeded the threshold for all values (EFSA, 2020a)

118. Regarding AFT + $AFM_1$ at mean exposures and 0.2% HBV/HVC prevalence the 0.0014 threshold was exceeded in infants (< 12 months old) and toddlers (≥ 12 months to < 36 months old) for all values at and above the minimum UB whilst for other children (≥ 36 months to < 10 years old) all values exceeded the threshold. For the 95$^{th}$ percentile of exposure all values for toddlers and other children exceeded the threshold whilst 'infants' exceeded the threshold for all but the minimum LB value. At 7.6% HBV/HCV prevalence all cancer risk estimate values exceeded the threshold in both the mean and 95$^{th}$ percentile of exposure scenarios (EFSA, 2020a).

119. EFSA concluded that the findings from this risk characterisation were concurrent with the conclusion found from their MOE approach using an animal data derived point of departure (EFSA, 2020a).

120. In light of EFSA's latest risk assessment it is unlikely that $AFB_1$ in liquid milk provides a risk to human health. Cow's milk was however found to be a significant contributor (up to 89%) to 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 a mean exposure level, a risk to human health cannot be excluded for infants and children aged 6 months to 5 years.

121. In the overarching statement on plant based drinks it was noted that the margins of exposure for estimated exposure to aflatoxins from almond drink or from the general diet in children 6 months to < 10 years were in general below 10,000, the indicative value for low concern from exposure to a genotoxic

carcinogen. However, the exposure estimates were very uncertain, and while exposure would have been overestimated, it was not possible to determine by how much.

Other Mycotoxins

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

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

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

**Per- and polyfluoroalkyl substances (PFAS)**

125. 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. 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.'

126. The 2 main classes of PFAS are perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAs). In 2020 EFSA undertook a risk assessment related to human health related to the presence of perfluoroalkyl substances in food focussing on 4 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, 2020).

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

128. Based on the high concentrations of PFAS observed in the blood of individuals exposed to contaminated water and by what is known for PFSO and PFOA, it may be assumed that the gastrointestinal (GI) absorption of most of the PFASs occurs to a significant extent in humans. PFAS are widely distributed with the

highest concentrations found in blood, liver and kidney. PFAS in blood bind to albumin. PFSA and PFCA metabolism has never been observed, however, precursor compounds such as fluorotelomer alcohols (FTOHs) and polyfluorinated phosphate esters (PAPs) can be biotransformed in humans to PFCAs and other metabolites. PFASs are eliminated in urine and faeces, and breast milk is also a substantial route of excretion. Shorter chain PFCAs are preferentially excreted in urine, whereas longer chain PFASs are preferentially eliminated through the bile and faeces. Extensive uptake from enterohepatic circulation and reabsorption by organic anion transporters (OATs) in the kidneys are believed to be more active processes in humans compared to rodents, slowing down the excretion of these substances. Short chain PFASs were found to have half-lives ranging from a few days to approximately one month, whereas PFHxS, PFOS, PFOA and PFNA estimated half-lives can exceed 3 years.

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

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

131. EFSA (2020c) concluded that effects on the immune system, as decreased antibody responses, recorded at the lowest serum PFAS concentrations in both human and animal studies were critical for the risk assessment and evaluation. This was considered a robust conclusion as a reduced immune response was seen consistently for PFOS and PFOA in humans and rats. A TWI of the sum of PFHxS, PFOS, PFOA and PFNA of 4.4 µg/kg bw/day was derived from a $BMDL_{10}$ of 17.5

ng/ml, based on reduced antibody levels against diphtheria vaccine in 1-year old children (Abraham et al., 2020).

Risk Characterisation

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

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

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

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 et al., (2021) it is suggested that PFAS exposures via cow's milk are unlikely to be of current 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 are 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 retardant 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 varies depending on product application.

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

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

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

Risk characterisation

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

144. From this dietary exposure assessment EFSA (2021b) presented data that showed the largest contributing food groups for HBCDDs exposure were fish, poultry, livestock meat and eggs. From the 198 milk analyses undertaken as part of this assessment, the mean LB concentration was 0.01 µg/kg representing <5% of the contributing dietary exposure to HBCDDs.

145. EFSA (2021b) subsequently calculated MOE's for different population groups, comparing the 2.35 µg/kg bw day chronic intake concentration with results from the dietary exposure assessment. MOE's ranged from 650 to 34,000 and EFSA concluded that HBCDD concentrations in food do not raise a health concern.

146. Fernandes et al., (2016) looked at BFRs in UK food and feed. From 3 cow's milk samples they did not find any occurrence of HBCDDs ( < 0.01 µg/kg).

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

148. In light of the EFSA (2021b) and COT (2015) conclusions and evidence from the literature that cow's milk does not contain levels of concern, it is suggested that HBCDDs in cow's milk does not pose a health risk to infants and children aged 6 months to 5 years.

**Polybrominated biphenyls (PBB)s**

149. (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, television, textiles and plastic foams, and were able to leave 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.

150. Individual PBB congeners vary in their pattern of toxicity. PBBs have been categorised on a similar structural basis as the PCBs, with category I comprising congeners lacking ortho substituents (coplanar PBBs). Coplanar PCBs are dioxin-like with regards to their toxicity and are included in the toxicity equivalency factor (TEF) concept. A number of PBB effects are dioxin-like and consistent with the Aryl hydrocarbon receptor (AhR)-mediated mechanism of action, including altered vitamin A homeostasis, thymic atrophy, dermal and ocular effects (e.g. chloracne and inflammation of eyelids), and body weight changes (wasting syndrome). This is determined by the magnitude of the response that is initiated by binding with the AhR. The binding affinity, in turn, is determined by the substitution pattern of the congener, many of the most toxic congeners resemble the structural configuration of 2,3,7,8-TCDD. The dioxin-like coplanar PBB-169 (3,3’,4,4’,5,5’-hexaBB) has been found to be the most toxic congener in several test systems (COT, 2006).

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

152. For planar PBBs, as previously concluded by the COT (2006, 2015b), the World Health Organization (WHO) toxicity equivalency factors (2005 WHO-TEFs) assigned to PCBs could be applied to the corresponding PBB congeners, to determine toxicity equivalences (TEQs). This would be a conservative approach since the corresponding chlorinated congeners are expected to be more toxic than

their brominated counterparts due to their higher relative potencies and lower clearance. The toxicity equivalences (TEQs) for planar PBBs could then be added to those for other relevant compounds to give a measure of the total intake of chemicals with dioxin-like properties, which could be compared with the TDI of 2 pg WHO-TEQ/kg bw/day.

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

Risk characterisation

154. In EFSA's dietary exposure assessment minimal concentrations of PBBs were found. Results were obtained from the analysis of 16 PBB congeners on 794 food samples, with a focus on samples from animal origin. The most contributing food group to exposure, fatty fish, contained concentrations that would relate to approximately 6 times lower than the NOEL of 0.15 mg/kg bw. For liquid milk (n = 51) samples only BB-52 and BB-101 were detected and this was only in 37% of samples. Concentrations ranged from 0.55 to 6.83 ng/kg fat (LB and UB) and 0.64 to 6.92 pg/g fat (LB and UB) for BB-52 and BB-101 respectively. EFSA concluded that 'the risk to the European population from exposure to PBBs through the diet is of no concern.

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

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

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

158. In light of the EFSA (2010b) conclusion and evidence from the literature that cow's milk does not contain levels of concern , it is suggested that PBBs in cow's milk does not pose a health risk to infants and children aged 6 months to 5 years.

**PBDEs**

159. 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.

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

161. EFSA (2011b) published an opinion on PBDEs in food. Within this they described the main toxicological end points as the reproductive system, immune system, thyroid hormone homeostasis and liver function. They also indicated a

potential DNA damaging effect via the induction of reactive oxygen species. Neurodevelopmental effects were classified as the critical endpoint and $BMDL_{10}$ concentrations were derived for PBDE congeners as summarised in Table 19.

162. The COT previously assessed the risks associated with exposure to PBDEs in the infant diet in 2015, using the $BMDL_{10}$ values and corresponding reference points for behavioural changes observed in adult mice given PBDE congeners by gavage neonatally (COT, 2015c). These are also summarised in Table 19.

Table 19: $BMDL_{10}$ concentrations of 4 PBDEs for neurodevelopmental effects from EFSA (2011) and COT (2015c)

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

Risk characterisation

163. EFSA (2011b) decided that due to uncertainty regarding the data from the studies used to calculate the $BMDL_{10}$s in Table 19, they could not be used to set HBGVs. Instead, they used a MOE approach after undertaking a dietary exposure assessment using PBDE occurrence data from 3,971 food samples originating from 11 EU countries.

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

the $BMDL_{10}$, would have resulted in an overestimation of the risk.' For liquid milk, 149 samples were included for the assessment. The milk food category represented a low % of total dietary exposure. For example, the BDE – 99 mean occurrence concentration was over 10 times higher for eggs than milk.

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

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

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

168. In light of the EFSA (2011b) and COT (2015) conclusions and evidence from the literature that cow's milk does not contain levels of concern, it is suggested that PBDEs in cow's milk does not pose a health risk to infants and children aged 6 months to 5 years.

**Tribromobisphenol A (TBBPA)**

169. 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.

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

Risk characterisation

171. EFSA (2011c) decided that due to uncertainty regarding the data from the studies used to calculate the $BMDL_{10}$ health based guidance values could not be derived. Instead, they used a MOE approach after undertaking a dietary exposure assessment using TBBPA occurrence data from 652 food samples from 4 EU countries (Ireland, Norway, Spain and UK). The majority of these food samples (465) were either fish or other seafood as the most likely source of contamination.

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

173. COT in 2019 in the ‘Review of potential risks from tetrabromobisphenol A (TBBPA) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years’ undertook a chronic dietary TBBPA exposure. These were calculated using

occurrence data from the UK 2004 Total Diet Study (TDS) (Driffield et al. 2008) and consumption data from DNSIYC and NDNS (COT,2019).

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

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

176. In light of the EFSA (2011c) and COT (2019) conclusions and evidence from the literature that cow's milk does not contain levels of concern, it is suggested that TBBPA in cow's milk does not pose a health risk to infants and children aged 6 months to 5 years.

**Microplastics**

177. 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.

178. Currently there is no internationally agreed definition of a microplastic, however, publications by Verschoor and de Valk, (2016) and Hartmann et al*., (2019)* have proposed criteria and considerations to be included in the definition of microplastics. In Europe, the European Chemicals Agency (ECHA) has proposed a regulatory definition for a microplastic under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation.

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

180. The chemical composition of microplastics can vary (Rochman *et al.*, 2019). Some can be made from single monomer repeats (i.e. polymers) such as polyethylene (PE) and polypropylene (PP), which are common in food packaging applications, and some are made from two monomers (i.e. co-polymers), for example styrene-butadiene.

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

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

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

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

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

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

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

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

185. For occurrence data of microplastics in cow's milk, a literature search was undertaken using the keywords Microplastic AND Cow AND Milk AND UK in both PubMed and Science Direct (https://www.sciencedirect.com). This returned very few results.

186. Microplastics have been occasionally reported in cow's milk in other continents such as in Mexico (Kutralam-Muniasamy et al., 2020; Shruti et al., 2021), where the authors stated 'that thermoplastic sulfone polymers (polyethersulfone and polysulfone) were common types of microplastics in milk samples, which are highly used membrane materials in dairy processes.' They found the presence of microplastics at low levels (1 – 14 particles / Litre) in all 23 cow's milk samples analysed.

Risk characterisation

187. In 2019, the European Chemical Agency (ECHA) published a restriction report in response to the European Commission's request (ECHA, 2019). In this, ECHA identified four concerns stemming from the potential environmental and human health risks posed by the presence of microplastics in the environment. These were; 'their size, small (typically microscopic) making them readily available for ingestion and potentially liable to transfer within food chains, very resistant to environmental

(bio)degradation, (bio)degrade in the environment progressively via fragmentation, and are practically impossible to remove from the environment after release."

188. COT (2021c) 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 microplastics in different food types and the difficulty of performing an accurate exposure assessment.

**Summary**

189. To aid in assessment of the chemicals described, three summary tables are provided (Table 20, Table 21 and Table 22 ), providing a summary of conclusions and where appropriate to this paper, the HBGV for each substance and highest age range estimated exposure via the diet, based on the mean consumption data.

Table 20: Summary of risk assessment conclusions based on previous authority opinions.

| **Compound (s)** | **HBGV, (endpoint)** | **Effect (s)** | **Authority** | **Suggested conclusion** |
|---|---|---|---|---|
| Lead | None, $BMDL_{01}$ of 0.5 µg/kg bw/day ( (development of intellectual function) | Multiple toxic effects | EFSA/COT | No health concern |
| Inorganic Arsenic | None. $BMDL_{0.5}$ of 3 µg/kg bw/day JECFA / COT (lung cancer) | Multiple toxic effects including carcinogenicity | EFSA/COT | No health concern |
| Inorganic Mercury | TWI – 4 µg/kg bw/week (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 bw/week (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 |
| AFM1 | None. Guidance value of 4 µg/kg bw/day derived from a $BMDL_{10}$ based on tumour incidence for AFB1 in rats with a 0.1 potency factor applied | Multiple effects such as immunotoxicity, carcinogenicity and mutagenicity | EFSA / COT | Low - moderate concern |

| | | | | |
|---|---|---|---|---|
| AFB1 | None. $BMDL_{10}$ of 0.4 µg/kg bw/day based on tumour incidence in rats after AFB1 exposure. | Multiple effects such as immunotoxicity, carcinogenicity and mutagenicity | EFSA / COT | No health concern |
| Total aflatoxins | None. $BMDL_{10}$ of 0.4 µg/kg bw/day based on tumour incidence in rats after AFB1 exposure. | Multiple effects such as immunotoxicity, carcinogenicity and mutagenicity | EFSA / COT | Low concern as contributions driven by AFM1 milk occurrence. |
| PFAS (PFHxS, PFOS, PFOA and PFNA) | TWI of 4.4 µg/kg bw/day (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. From a LOAEL (neurodevelopmental effects in mice) maximum chronic intake of 2.35 µg/kg bw per day | Neurodevelopmental, immune system effects, reproductive system effects, liver effects and thyroid hormone homeostasis | EFSA | No health concern |

| | | | | |
|---|---|---|---|---|
| PBBs | None. NOEL of 0.15 mg/kg bw (hepatic carcinogenicity) | Multiple effects (dioxin like) such as altered vitamin A homeostasis, chloracne and body weight changes | EFSA | No health concern |
| PBDEs | None. Range of $BMDL_{10}$s between 12 and 1,700 µg/kg bw (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 (thyroid hormone homeostasis) | Thyroid hormone regulation | EFSA | No health concern |

Table 21: Comparison of highest estimated mean exposures (occurrence and consumption) to potential chemical contaminants of cow's milk with their health-based guidance values.

| **Compound (s)** | **HBGV, (endpoint)** | **Authority** | **Highest Exposure (mean consumption), kg bw/day** | **% HBGV or MOE** | **Highest exposure age range (months)** | **Effect** | **Suggested Conclusion** |
|---|---|---|---|---|---|---|---|
| Iodine | Guidance level of 15 µg/kg bw/day (Alterations in serum thyroid hormone levels from human studies) | COT | 15.2 µg | 102 | 12 – <18 | Varied effects dependent on previous exposures to iodine. | Low health concern |
| Perchlorate | TDI of 0.3 µg/kg bw/day (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/day | EFSA | 0.544 µg | 18.1% | 12 – <18 | Inhibition of iodine uptake, depletion | No health concern |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | (Carried over from perchlorate with a 0.1 potency factor, inhibition of radiolabelled iodine uptake by the thyroid) | | | | | of thyroid hormones | |
| Endogenous Oestrogens | ADI – 0.05 µg/kg bw/day for 17β-oestradiol (NOEL based off of 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, 17β-oestradiol is a carcinogen with uncertainty regarding its status as a | Low compared to endogenous hormones |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | genotoxic carcinogen. | |

Table 22: A summary of information for compounds where a satisfactory risk assessment could not be performed.

| **Compound (s)** | **Literature evaluation** | **Effect** | **Conclusion** |
|---|---|---|---|
| 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 | Effects including immunotoxicity, carcinogenicity and mutagenicity | No health concern |

| | | | |
|---|---|---|---|
| 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 | Various, depending on type | n/a |

## Discussion

190. This is the second of two papers assessing the potential effects of chemicals that may be present in milk to allow a comparison with plant-based drinks. It presents the risk characterisation for a range of potential chemical contaminants in cow's milk. These are lead (Pb), mercury (Hg), arsenic (As), cadmium (Cd), iodine, perchlorate, chlorate, IGF-1, endogenous oestrogens, aflatoxins and other mycotoxins, per- and polyfluoroalkyl substances (PFAS), brominated flame retardants (BFRs) and microplastics.

## Questions for the Committee

191. The Committee are asked to consider:

a) Whether there are any risks to health from the consumption of cow's milk containing the chemicals discussed in this paper?
b) Are there any substances for which the Committee would like to see further details?
c) Are there any chemicals not covered in this paper or the previously presented part 1 which the Committee would like to see included?
d) Does the Committee have any other comments on this paper?

**Secretariat**

**December 2021**

**Abbreviations**

| | |
|---|---|
| µg | microgram |
| 15-Ac-DON | 15-Acetyldeoxynivalenol |
| 3-Ac-DON | 3-Acetyldeoxynivalenol |
| ADME | Absorption, Distribution, Metabolism and Excretion |
| AFB1 | Aflatoxin $B_1$ |
| AFB2 | Aflatoxin B2 |
| AFG1 | Aflatoxin G1 |
| AFM1 | Aflatoxin $M_1$ |
| AFM2 | Aflatoxin M2 |
| AFT | Sum of AFB1, AFB2, AFG1 and AFG2 |
| AhR | Aryl Hydrocarbon Receptor |
| As | Arsenic |
| BFRs | Brominated Flame Retardants |
| BIO | Biochanin A |
| BMDL | Benchmark Dose Level |
| BPA | Bisphenol A |
| Br | Bromine |
| BST | Bovine Somatotropin |
| bw | Body Weight |
| CAR | Constitutive androstane receptor |
| Cd | Cadmium |
| CF2 | Perfluorinated Methylene Group |
| CF3 | Perfluorinated Methyl Group |

| | |
|---|---|
| Cl | Chlorine |
| COC | The Committee on Carcinogenicity Food, Consumer Products and the Environment |
| CONTAM | The Panel on Contaminants in the Food Chain |
| COT | The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment |
| DAI | Daidzein |
| DecaBDE | Decabromodiphenyl ether |
| DEFRA | Department for Environment, Food and Rural Affairs |
| DHSC | Department of Health and Social Care |
| DL-PCBs | Dioxins and Dioxin-Like Polychlorinated |
| DNYISC | Diet and Nutrition Survey of Infants and Young Children |
| DON | Deoxynivalenol |
| DON-3-glucoside | Deoxynivalenol-3-Glucoside |
| E1 | Oestrone |
| E2 | 17β-Oestradiol |
| ECHA | European Chemical Agency |
| EFSA | European Food Safety Authority |
| EQU | Equol (metabolite of DAI) |
| EU | European Union |
| EVM | Expert Group on Vitamins and Minerals |
| FDA | Food and Drug Administration |
| FTOHs | Fluorotelomer alcohols |
| FOR | Formononetin |
| FSA | Food Standards Agency |

| | |
|---|---|
| FSH | Follicle Stimulating Hormone |
| GEN | Genistein |
| GH | Growth Hormone |
| GI | Gastrointestinal |
| H | Hydrogen |
| HBCD | Hexabromocyclodecane |
| HBGV | Health Based Guidance Value |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| 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 |
| IGF-1 | Insulin-like Growth Factor 1 |
| IGFBP-3 | Insulin Growth Promoting Factor Binding Protein 3 |
| IQ | Intelligence quotient |
| JECFA | Joint FAO/WHO Committee on Food Additives |
| LB | Lower Bound |
| LH | Luteinising Hormone |
| LOD | Limit of Detection |

| | |
|---|---|
| mg | Milligram |
| mm | Millimetre |
| MOE | Margin of Exposure |
| MT | Metallothionein |
| NDL-PCBs | Non-Dioxin-Like Polychlorinated Biphenyls |
| NDNS | National Diet and Nutrition Survey |
| ng | Nanogram |
| NHS | National Health Service |
| NIS | $Na^+/I^-$ symporter |
| nm | Nanometre |
| NOEL | No Observed Effect Level |
| 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 |
| 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 |
| 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 | European Scientific Committee on Food |
| SCVPH | Scientific Committee on Veterinary measures relating to Public Health |
| SD | Standard Deviation |
| SUL | Safe Upper Level |
| TBBPA | Tribeomobisphenol A |
| TDI | Tolerable Daily Intake |
| TEF | Toxicity Equivalency Factor |
| TSH | Thyroid-Stimulating Hormone |

| | |
|---|---|
| TUL | Tolerable Upper Level |
| TWI | Tolerable Weekly Intake |
| UB | Upper Bound |
| U-Cd | Urinary Cadmium |
| UK | United Kingdom |
| US | United States |
| VPC | Veterinary Products Committee |
| WHO | World Health Organisation |
| β2M | β-2-microglobulin |

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