Chemicals assessed

In this guide

In this guide

Veterinary medicines

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

13. Veterinary medicines can be present below the maximum residue limits (MRLs) following use according to good veterinary practice and this does not constitute a risk to health. However, they can on occasion be present in animal derived products above these MRLs when procedures are not followed

correctly. Cow's milk is routinely monitored through ongoing surveys with the UK National Reference Laboratory (NRL).

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

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

Pesticides

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

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

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

Nitrate and nitrite

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

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

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

22. In light of the very low percentages of the recommended ADI for nitrate that would occur through consumption of cow's milk in young children, along with the conclusion in EFSA's (2009) opinion on nitrite, the COT concluded that nitrate and nitrite contamination of cow's milk do not pose a health risk for children aged 6 months to 5 years of age.

Bisphenol A

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

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

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

26. EFSA's 2023 opinion on BPA, discussed in Annex A, advised a reduced TDI based on an effect on TH17 immune cells. Applying the new TDI to their 2015 exposure assessment, EFSA concluded that mean and 95th percentile dietary exposures exceeded the new TDI by two to three orders of magnitude for all populations (EFSA, 2023).

27. In 2019, COT was asked to review the risk of toxicity of chemicals in the diets of infants and young children aged 0-5 years, in support of a review by SACN of Government recommendations on complementary and young child feeding (COT, 2019b, 2020) and BPA was considered as part of that review. In light of the recent opinion from EFSA, the COT has reconsidered BPA. The Committee has a number of reservations about EFSA's evaluation and has agreed to conduct its own assessment. The Committee is in the process of producing an interim position paper capturing the COT's views and proposed next steps following EFSA's updated scientific opinion (EFSA, 2023). Whilst the COT considered it possible that the TDI for BPA may need to be revised to account for new evidence and ensure it was sufficiently protective, on balance the weight of evidence did not support the conclusions drawn by EFSA, or a TDI as low as that established by EFSA in 2023. The Committee previously agreed with EFSA's assessment of the safety of BPA in 2007, 2008c and 2015. Based on the 2015 opinion, the COT do not currently consider that levels of BPA within cow's milk present a risk to health for children aged 6 months to 5 years of age.

Phthalates

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

29. Phthalates do not form covalent bonds with the material into which they are incorporated, therefore can readily migrate into food from packaging materials. The extensive and historic use of phthalates has led to their being widely distributed in the environment and the food chain. The general population is exposed to phthalates via food (including migration from food contact materials) and drinking water, but also through inhalation and dermal exposure (Heudorf, Mersch-Sundermann and Angerer, 2007).

30. In 2005, EFSA performed risk assessments on a small range of the most widely used phthalates, namely, di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2- ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and diisodecylphthalate (DIDP) and established TDIs for them (EFSA, 2005b, 2005c, 2005d, 2005e, 2005f).

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

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

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

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

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

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

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

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

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

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

40. The current view of the COT from the exposure assessments conducted in annex A is that dioxins within cow’s milk do not present a risk to health for children aged 6 months to 5 years of age.

Non-dioxin-like PCBs

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

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

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

Polycyclic Aromatic Hydrocarbons (PAHs)

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

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

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

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

Isoflavones

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

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

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

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

52. *In vitro* experiments reviewed in the 2003 COT report (COT, 2003) showed that phytoestrogens could modulate the levels of sex hormone binding globulin (SHBG), inhibit enzymes involved in oestrogen biosynthesis and metabolism to modulate concentrations of endogenous oestrogens, and inhibit thyroid peroxidase activity to reduce the concentrations of thyroid hormones.

GEN was found to interact with topoisomerase II and protein kinases (enzymes involved in cellular proliferation and differentiation) and to inhibit human T-cell proliferation and interleukin-2 production.

53. The 2003 COT report concludes that it is not possible to propose HBGVs for infants (COT, 2003). Reasons for this include the difficulty in extrapolation from animals to humans because of differences in toxicokinetics, uncertainty about differences between adults and infants (particularly those arising from development of the gut microflora), and the lack of dose-response data and the possibility of bias and chance effects in the available human studies. In a more recent 2013 COT report (COT, 2013a) assessing literature since 2003, the same conclusions were reached, in that it was not possible to propose HBGVs due to limitations in the available data.

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

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

Risk Characterisation

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

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

Milk Type	Number of samples	GEN	EQU	FOR	DAI	Sum
Conventional	48	0.83	63.6	0.08	0.95	67.7
Organic	48	2.32	411	1.10	2.69	417
Free range	24	0.85	66.4	0.09	0.96	70.4

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

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

Lead

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

60. EFSA's 2012 opinion on lead and the COT's 2013 and 2016 statements on lead exposure in the diets of infants and children have been considered (Annex A). Whilst exceedances of the benchmark dose lower confidence limit (BMDL01) of 0.5 µg/kg bw per day were observed in EFSA's total dietary exposure estimate for infants aged 1 year (0.83 and 0.91 µg/kg bw per day in two surveys), toddlers aged 1-3 years (1.32 µg/kg bw per day) and other children aged 3-10 years (1.03 µg/kg bw per day), at most this was 3-fold and as the contribution of cow's milk to total middle bound lead exposure did not exceed 2% for infants, 5% for toddlers and 4% for other children, lead within cow's milk never exceeds a 20th of total exposure and is therefore not a concern (EFSA, 2012b). The COT's statement found diet contributed little to lead exposure compared to other sources of exposure (COT, 2013b, 2016a).

61. Based on the information provided in EFSA (2012b) and the evaluation by the COT in 2013 and 2016, the COT concludes that it is unlikely that lead would pose a risk to the health of infants and children from the ages of 6 months

to 5 years from consumption of cow’s milk.

Arsenic

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

63. The COT’s 2016 statement and EFSA’s 2021 evaluation have been considered in Annex A. The COT’s 2016 risk assessment suggested that at mean levels of consumption, for infants aged 4 months to 5 years the MOE’s for the overall diet were below 10, therefore a risk to health may exist from dietary exposure. However, in EFSA’s recent 2021 evaluation cow’s milk was shown to contain minimal amounts of iAs (EFSA, 2021a).

64. The COT concluded from the above information that levels of inorganic arsenic in cow’s milk do not present a risk to health to children aged 6 months to 5 years of age.

Mercury

65. Mercury is a metal released from both anthropogenic and natural sources. It is found as elemental mercury (Hg0), inorganic mercury (mercurous and mercuric cations (Hg+ and Hg2+ respectively)) and organic mercury. Methylmercury is the most abundant organic mercury compound in the food chain (COT, 2018c).

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

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

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

Cadmium

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

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

71. In the EFSA exposure assessment (EFSA, 2012a), collected surveys were merged and the results from the different age groups weighted according to the number of years included out of an average life span of 77 years, producing mean average upper bound lifetime exposures. For infants aged 1 year this was 3.50 µg/kg bw per week, for toddlers aged 1- 3 years this was 5.9 µg/kg bw per week and for other children aged 3-10 years this was 4.69 µg/kg bw per week. These all exceed the EFSA (2011c) TWI of 2.5 µg/kg bw per week. For infants, liquid milk contributed 1.59% to total dietary cadmium exposures whilst for toddlers it contributed 1.78%, and for other children 2.28%.

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

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

Iodine

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

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

76. In 1989 the Joint Expert Committee on Food Additives (JECFA) established a provisional Maximum Tolerable Daily Intake (PMTDI) for iodine of 17 µg/kg bw from all sources (FAO/WHO, 1989). No safety factors were used as these studies encompassed a relatively large number of subjects (FAO/WHO, 1989).The JECFA PMTDI was utilised to perform a risk assessment in the COT's 2000 statement on iodine in cow's milk (COT, 2000). Based on the same human studies as used by JECFA, the European Scientific Committee on Food (SCF) in 2002 established a TUL of 600 µg/day for adults, scaled according to body weight for children, recorded in EFSA, (2006).

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

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

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

80. In 2002, the SCF published an opinion on the tolerable upper intake levels of vitamins and minerals, recorded in EFSA, (2006). For iodine, they established a tolerable upper level (TUL) of 600 µg/day for adults, reduced on a body surface area (body weight0.75) basis for children to 200 µg/day for ages 1-3 years and 250 µg/day for ages 4-6 years. This TUL was based on dose-response studies of short duration in humans, which showed changes in serum thyroid hormone levels at dose levels of 1800 µg/day and was supported by longer term studies with approximately similar doses that did not show any adverse effects but lacked detailed iodine intake data. An uncertainty factor of 3 was used to account for these uncertainties. These values were endorsed by EFSA (2006).

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

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

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

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

Exposure Assessment and Risk Characterisation

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

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

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

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

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

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

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

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

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

89. Comparing exposure to the JECFA PMTDI as in Table 5, there were no exceedances at mean levels of consumption in any of the selected populations. For the 97.5th percentile of consumption there were exceedances, of up to 2.2-fold, in all populations.

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

risk characterisation was undertaken which is presented in Table 6.

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

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

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

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

Table 7: Risk characterisation for cow's milk consumption using annual mean iodine occurrence in O'Kane et al. (2018), consumption data from the NDNS (Table 1) and TUL's derived from EFSA's 2006 values (EFSA, 2006; Department of Health, 2013; Bates et al., 2014, 2016, 2020; Roberts et al., 2018).

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

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

94. In the COT's 2000 paper, a survey of UK cow's milk from 1998-9 was discussed and it was reported that the overall mean iodine concentration in cow's milk was 311 µg/kg, with a lower mean concentration in summer (200 µg/kg). These values were used to estimate exposure and safety was assessed against guidance values calculated from the JECFA PMTDI of 0.017 mg/kg bw per day (17 µg/kg bw per day) which was available at the time. At mean levels of consumption of the total diet, exceedance of the guidance values was observed for the age group 1½ - 2½ years at 221 µg/day. For the age groups 2½ - 3½, and 3½ - 4 years iodine exposure approached the guidance level at 215 and 204 µg/day respectively. For high level consumers, exceedances for the 3 age groups 1 ½ - 2 ½, 2 ½ - 3 ½, and 3 ½ - 4 ½ years were observed, with exposures of 362, 379 and 330 µg/day respectively. For milk consumption alone, exceedances of the guidance values calculated from the previously adopted PMTDI were present in high level consumers (97.5th percentile) for the groups aged 1 ½ - 2 ½ and 2 ½ - 3 ½ years. The COT concluded that iodine in cow's milk was unlikely to pose a risk to health even in children who are high level consumers (COT, 2000). In part, this was based on the reassurance provided by a study in which 1-11 year old

children received doses of iodide up to 1000 µg /day for four months without signs of toxicity. This corresponds to 59-94 µg /kg bw per day in children aged 1 ½ - 4 ½ years, which is more the three times the JECFA PMTDI.

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

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

96. In the COT paper of 2000 on iodine in cow's milk, exceedances were identified for 97.5th percentile consumers. This was mirrored in the exposure assessments produced in this paper with high level consumers of milk exceeding the EVM guidance level, TULs derived from EFSA and the JECFA PMTDI. For mean level consumers however, iodine exposure approached the 2003 EVM guidance level of 15 µg/kg bw per day for the group 12- 18 months. COT's 2000 and 2017 statements stated that iodine levels in cow's milk were considered to pose no toxicological concern as exceedances of the HBGV occurred only at the 97.5 %ile estimates, these were at most 2.5-fold, and for the additional reasons discussed above. With similar results from the current exposure assessment, the COT concluded that the risk to health to children aged 6 months to 5 years of age from iodine from consumption of cow's milk is likely to be low.

Perchlorate

97. Perchlorate (ClO4-) has both natural and anthropogenic sources. Previous biomonitoring studies have suggested it is most likely to be a ubiquitous environmental contaminant. It is present in the environment due to use of sodium nitrate (also known as Chilean nitrate) fertilisers and industrial emissions such as from the use of ammonium perchlorate in solid rocket fuel propellants, explosives, fireworks, flares, air-bag inflators, and in other industrial processes,

and formation during the degradation of chlorine-based cleaning products. Within the EU, likely sources include use of nitrate (fertiliser) leading to accumulation in plants. Plant protection products and water disinfection could slightly increase exposure (EFSA, 2014).

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

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

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

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

Chlorate

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

within the EU however plant derived foods can be washed.

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

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

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

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

107. From this information the COT concluded that the levels of chlorate in cow's milk do not pose a risk to health of infants and children aged 6 months – 5 years.

Insulin-like Growth Factor (IGF-1)

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

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

110. The COC's 2018 'Statement on possible carcinogenic hazard to consumers from insulin-like growth factor-1 (IGF-1) in the diet' (COC, 2018) is discussed in annex A. Naturally occurring levels in milk are considered, with the COC stating

that the levels in milk consumed by humans are unlikely to exceed 100 ng/ml. The COC concluded there was ‘insufficient evidence to draw any firm conclusions as to whether exposure to dietary IGF-1 is associated with an increased risk of cancer in consumers. However, the data indicate that the levels of IGF-1 consumed are likely to be low and that IGF-1 is likely to be broken down in the gut and not absorbed to any significant extent. Thus, the risk, if any, is likely low.’.

111. From the information above and that presented in annex A the COT concluded that the levels of IGF-1 in cow’s milk pose no concern for the health of children aged 6 months to 5 years of age.

Naturally occurring oestrogens in cow’s milk

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

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

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

115. In addition, an exposure assessment has been performed and is presented within Annex A, which compares exposures to the JECFA (2000) ADI of

0.05 µg/kg bw, based on hormonal effects for 17β-oestradiol. No exceedance of the ADI was seen in any population group.

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

Mycotoxins

117. Mycotoxins are a group of fungal-derived compounds, some of which are highly toxic. Cow's milk can be contaminated with multiple mycotoxins. A wealth of information exists regarding occurrence of aflatoxin M1, a major metabolite of aflatoxin B1, in milk. Regarding other mycotoxins, contamination studies have shown variation in the extent to which fumonisins, zearalenone, ochratoxin and trichothecenes and their metabolites transfer from feed to dairy cows and then subsequently into milk. The scientific literature contains far less information on these other mycotoxins and their occurrence in milk.

118. Discussion of mycotoxins other than aflatoxins can be found in Annex A, with the literature currently suggesting that ochratoxin (OTA), zearalenone and it metabolites, trichothecenes including deoxynivalenol (DON) and T2 and HT-2 are unlikely to transfer into cow's milk from feed and do not present a risk to health for children aged 6 months to 5 years of age. However, no specific information could be found regarding the transfer of 3-Ac-DON, 15-Ac-DON and DON-3-glucoside to cow's milk, therefore risk cannot be excluded, although transfer of these seems unlikely, particularly of DON-3-glucoside, given their hydrophilicity.

Aflatoxins

119. Aflatoxins can enter cow's milk through feed contaminated with fungi such as Aspergillus flavus and Aspergillus parasiticus. Aflatoxin AFB1 is the most common aflatoxin found in feed. This is converted within the bovine liver via P450 mediated hydroxylation to form the major metabolite AFM1. AFM1 is the most commonly reported and researched mycotoxin within milk, however, AFB1 has also been detected albeit in non-European countries after cattle were exposed to very high levels of AFB1, a scenario which is highly unlikely in UK and EU dairy cattle (Scaglioni et al., 2014; Becker-Algeri et al., 2016). Other aflatoxins include aflatoxins B2, G1, G2 and M2 (AFB2, AFG1, AFG2 and AFM2) and these have also been detected in milk, however, far less information is available on these

compounds (EFSA, 2020a).

120. Chronic aflatoxin exposure can lead to immunotoxic effects due to impaired DNA duplication in bone marrow resulting in low leukocyte counts and immunodeficiency, as well as carcinogenic and mutagenic effects. Non-specific inhibition of cell division can also affect other cell types with effects particularly apparent within the gastrointestinal tract. The liver is the primary target of aflatoxin toxicity. This results in bile duct proliferation, hepatic lesions, centrilobular necrosis and fatty acid infiltration. This often progresses to liver cancer (Ráduly et al., 2020). AFB1 and some other aflatoxins are also directly mutagenic, which contributes to their carcinogenic effects.

121. Aflatoxins were reviewed by the SCF in 1996, and EFSA in 2007 and 2020. They have also been evaluated by JECFA in 1998, 2001 and AFM1 was also reviewed in 2018. EFSA's most recent risk assessment produced by the CONTAM panel concluded that the chronic endpoint of liver carcinogenicity in rats was the most relevant effect (EFSA, 2020a). They considered the Wogan et al, study of 1974 to be the most satisfactory for dose response modelling (Wogan, Paglialunga and Newberne, 1974). The resulting BMD value was also used in the COT's 2021 statement on plant-based drinks (see below).

122. The COT's (2021a) overarching statement on consumption of plant-based drinks in children aged 6 months to 5 years of age describes the Wogan, et al. (1974) study as follows: "Groups of male Fisher (sic) rats were administered diets containing 0, 1, 5, 15, 50, or 100 µg/kg diet of AFB1 (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 AFB1 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 AFB1 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 BMDL10 for AFB1 was 0.4 µg/kg bw per day".