TOX/2021/53

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 1

Background

1. Plant-based drinks have become increasingly popular in the UK both for individuals with an allergy to cow's 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-based 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, therefore the risks and relevant chemical exposures for this paper are 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 classes of compounds, should be added. The list was derived after a literature review and evaluating historical records (back to March 2019) from the FSA incident dashboard. This paper (part 1 of 2) covers the chemicals I to IX, part 2 will cover the remainder.

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 part 2 (a separate paper):

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 Deoxynivalenol (DON)

XIV. Hormones – Oestrogens, Insulin-Like Growth Factor 1 (IGF-1)

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

Veterinary Medicines

9. Veterinary medicines, for example antibiotics, are a crucial element in animal husbandry to alleviate suffering and disease, and UK farmers should follow the Veterinary Medicines Directorate (VMD) recommended guidance of responsible use (VMD, 2014) . These include accurate record keeping, purchasing from authorised sources, correct administration and observing relevant withdrawal periods (the length of time any subsequent animal products must not enter the food chain) after administration.

10. Animal medicines, however, do enter the food chain on occasions when procedures are not followed correctly. Cow's milk is routinely monitored through ongoing surveys with the UK National Reference Laboratory (NRL).

11. 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, chloramphenicol, dapsone, florfenicol, Non-Steroidal Anti-inflammatory drugs (NSAIDS), and other antimicrobials (as a screening method) (VMD, 2015, 2016, 2017, 2018, 2019, 2020). From the analysis over this 6 year period only 0.12% (24) returned a positive result. From these only two residues, penicillin G and triclabendazole both in 2017, resulted in a subsequent risk assessment concluding the milk samples represented a potential food safety risk to the consumer, and this was before taking any dilution effect into account, e.g. from bulk tanks at dairies.

12. Based on the last 6 years UK statutory survey it appears that the risk of veterinary medicine exposure after isolated incidents from drinking cow's milk is negligible.

Pesticides

13. 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.

14. 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.

15. Based on the UK statutory survey results above it is suggested that the risk of pesticide exposure from drinking cow's milk is negligible.

Nitrate and Nitrite

16. 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 consumption. They occur naturally in vegetables but are also used widely as meat preservatives, in agricultural waste streams from e.g. fertiliser use, and as chemical contaminants from industrial processes and materials.

17. Nitrates are widely consumed by animals and humans although nitrite is regulated as an undesirable substance in animal feed (EU 574/ 2011). In animals the largest potential exposure of 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).

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

Exposure Assessment and risk characterisation

19. Only limited occurrence data of nitrate and nitrite in cow's milk could be found from the literature. A literature search was undertaken using the keywords Nitrate OR Nitrite AND Cow AND Milk AND Risk in both PubMed (https://pubmed.ncbi.nlm.nih.gov) and Science Direct (https://www.sciencedirect.com).

20. Three references were found that reported any 'background' contamination of nitrate in cow's milk, with no positives found for nitrite (all 'non detected'). Of the 3 papers, two reported nitrate concentrations in cow's milk outside the EU (Taiwan, USA) where agricultural practices may differ significantly to the UK. Olijhoek *et al*. (2016) reported mean nitrate background concentrations (n = 4) of 0.13 mg/L from a Danish herd (minimum and maximum values were not reported).

21. 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). The data presented in Table 1 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 NHS as a main drink for infants in this age range (NHS, 2018). Table 2 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 1 only (with recipes).

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

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

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

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

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

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

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

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

24. In light of the very low percentages of the recommended ADI for nitrate estimated exposure in cow's milk in young children along with the EFSA (2009) opinion's conclusion above it is suggested that nitrite and nitrate contamination pose a minimal risk in the daily consumption of cow's milk.

Bisphenol A

25. 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. It is known to potentially 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, potential BPA contamination may come from the mechanical milking apparatus and subsequent storage vessels in the dairy chain such as cooling tanks.

26. BPA is an endocrine disrupter in that it potentially interferes with the regulation of hormones in the endocrine system. It is therefore assumed to have toxic effects on metabolism, growth, sexual development, stress response, insulin production, gender behaviour, reproduction, and foetal development (Cirillo *et al.*, 2015). It is also considered a contributing factor in the onset of metabolic disorders, including diabetes and obesity, and immune dysfunction (Bansal, Henao-Mejia and Simmons, 2018).

Risk Characterisation

27. EFSA published an Opinion in 2015 on the risks to public health related to the presence of BPA in foodstuffs in which a reduced temporary Tolerable Daily Intake

(TDI) was proposed, revised from 50 down to 4 µg/kg bw day. This guidance value was determined after a benchmark dose lower confidence limit $(BMDL)_{10}$ of 8,960 µg/kg bw per day was calculated for changes in the mean relative kidney weight in mice, converting this to an oral human equivalent dose (HED) of 609 µg/kg bw per day and then applying a total uncertainty factor of 150 (for inter- and intra-species differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) (EFSA, 2015).

28. EFSA's (2015) comprehensive review of BPA exposure and toxicity concluded that BPA poses no health concern for consumers of any age group (including unborn children, infants and adolescents) at current dietary exposure levels. Although the panel noted some uncertainty regarding BPA exposure from non-dietary sources.

29. 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). For BPA, COT's current position is that they are awaiting EFSA's new updated scientific opinion (currently ongoing) to conclude if a new COT evaluation is required.

Phthalates

30. 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.

31. 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).

32. 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 di-isodecylphthalate (DIDP) and derived TDIs for them (European Food Safety Authority (EFSA), 2005a, 2005b, 2005c, 2005d, 2005e). In 2003 the World Health Organisation derived a TDI for diethyl phthalate (DEP) of 5 mg/kg bw (WHO, 2003).

33. EFSA's risk assessment and revaluation in 2019 of DBP, BBP, DEHP, DINP and DIDP for use in food contact materials re-confirmed the same critical effects and individual TDIs (mg/kg bw per day) derived in 2005, i.e. reproductive effects for DBP (0.01), BBP (0.5), DEHP (0.05), and liver effects for DINP and DIDP (0.15 each). Based on a plausible common mode of action (i.e. reduction in fetal testosterone) underlying the reproductive effects of DEHP, DBP and BBP, the Panel considered it

appropriate to establish a group-TDI for these phthalates, taking DEHP as an index compound as a basis for introducing relative potency factors.

34. The EFSA 2019 panel on Food Contact Materials, Enzymes and Processing Aids (CEP) (EFSA, 2019) noted that DINP also affected fetal testosterone levels at doses around three-fold higher than liver effects and therefore considered it prudent to include it within the group-TDI. To account for the different potencies towards the hepatic and reproductive endpoints an additional factor of 3.3 was used in the relative potency factor for DINP to ensure that it would not exceed the TDI derived from hepatic effects.

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

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

Risk Characterisation

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

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

39. In the recent COT review with SACN on the risk of toxicity of chemicals in the diets of infants and young children the COT were content that for DBP, BBP, DEHP, DINP the exposures estimated by EFSA did not indicate a health concern using the group TDI. However, COT noted that the uncertainty assessment in the draft opinion did not adequately reflect on the conclusions on DINP. Since this assessment would have included exposure from cow's milk, these compounds have not been considered further.

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

40. 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 Panel on Contaminants in the Food Chain (CONTAM), 2018).

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

42. The COT evaluated dioxins and dioxin-like PCBs in 2001 (COT, 2001). The COT agreed with the evaluation of the EU Scientific Committee on Food (SCF, 2000) that in 2000 recommended a temporary tolerable weekly intake (t-TWI) of 7 pg WHO-TEQ/kg bw. SCF (2001) re-evaluated this t-TWI based on rat studies which investigated reproductive effects only on male offspring. Applying an overall uncertainty factor of 10 to the Lowest Observed Adverse Effect Dose (LOAEL) derived from estimated human daily intakes (EHDI) the SCF concluded that 14 pg/kg bw per week should be considered as a tolerable intake for 2,3,7,8-TCDD. COT in 2001 recommended that a tolerable daily intake of 2 pg WHO-TEQ/kg bw per day is established based upon effects on the developing male reproductive system mediated via the maternal body burden. It was also considered that this TDI is adequate to protect against other possible effects, such as cancer and cardiovascular effects.

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

44. The COT has recently produced a position paper (COT, 2021b) on dioxins and DL-PCBs, addressing the seven-fold reduction in the TWI proposed by EFSA. The Committee concluded that EFSA's estimation was based upon weak data sets and provided little justification for such a reduction in the Health Based Guidance Values (HBGV), the current value of 14 pg TEQ/kg bw /week having previously been shown to afford protection to the developing foetus. The European Commission (EC) has not yet adopted EFSA's new TWI due to ongoing work at the international level

to review the basis and values of the WHO toxic equivalent factors (TEFs). The review of the TEFs and a finalised assessment by the EC are not expected until 2022, at the earliest.

Exposure Assessment and risk characterisation

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

46. To obtain published concentrations for dioxins and DL-PCBs in cow's milk a literature search was undertaken using the keywords Dioxin AND Cow AND Milk AND Risk in both PubMed and Science Direct. Results returned were for a limited number of papers with low sample numbers, except the survey published by EFSA in 2018. Results are summarised in Table 4 for this survey which included cow's milk samples from 23 EU countries, including the UK. When converting results from the survey that have been presented on a 'per fat' basis, a value of 3.5% fat has been used as a general worst case scenario for fat content of the range of milk types, as the minimum legal requirement for fat content of whole milk in the UK (Dairy UK, 2018). This is a worst case scenario as the chemical contaminants will reside in the fat portion of the milk, i.e. the higher the fat content the greater potential of contamination. The NHS recommend that children should only consume cow's milk as a drink from the age of 1 year. Whole cow's milk should be used until the age of 2 after which, semi skimmed can be introduced - but lower fat milks can be used in cooking from the age of 1. Therefore, although the youngest children would potentially be more exposed to any dioxin contamination, this will reduce as lower fat milks replace whole milk in the diet.

Table 4. Summary of Dioxins plus DL-PCBs concentrations in cow's milk (whole sample basis) from EFSA Panel on Contaminants in the Food Chain (CONTAM) (2018).

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

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

Table 5. Dioxin plus DL-PCBs exposure assessment from cow's milk consumption using the upper bound mean concentration from EFSA Panel on Contaminants in the Food Chain (CONTAM) (2018)

Age (months	Estimated Exposure mean) (pg WHO TEQ / kg bw day)	Estimated Exposure (97.5th percentile) (pg WHO TEQ / kg bw day))	% TDI (mean consumption)	% TDI (97.5th percentile consumption)
6 – <12	0.416	1.54	20.8	76.8
12 – <18	1.024	2.40	51.2	120.0
18 – <24	0.928	2.53	46.4	126.4
24 – <48	0.736	1.89	36.8	94.4
48 – <60	0.544	1.47	27.2	73.6

Table 6. Dioxin plus DL-PCBs exposure assessment from cow's milk consumption using the upper bound 95th percentile concentration from EFSA Panel on Contaminants in the Food Chain (CONTAM) (2018)

Age (months	Estimated Exposure (mean) (pg WHO TEQ / kg bw day)	Estimated Exposure (97.5th percentile) (pg WHO TEQ / kg bw day))	% TDI (mean consumption)	% TDI (97.5th percentile consumption)
6 – <12	0.91	3.36	45.5	168.0
12 – <18	2.24	5.25	112.0	262.5
18 – <24	2.03	5.53	101.5	276.5
24 – <48	1.61	4.13	80.5	206.5
48 – <60	1.19	3.22	59.5	161.0

48. Based on the 97.5th percentile consumption data two age ranges exceed the % TDI of 2 pg WHO-TEQ/kg bw per day when using the upper bound mean concentration from the EFSA occurrence data (Table 5). All age ranges using the 97.5th percentile consumption data exceed this % TDI when using the 95th percentile concentration from the EFSA occurrence data (Table 6). Two age ranges using the mean consumption data and the 95th percentile concentration from the EFSA occurrence data exceeded the % TDI (Table 6). However, given the added safety margin of using the upper bound occurrence concentrations along with the worst case scenario of all the milk from the EFSA survey containing 3.5% fat, it is suggested that, in practice, dioxins plus DL-PCBs in cow's milk represent a lower safety risk than suggested in the above assessment.

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

Non-dioxin-like (NDL) PCBs

50. Some PCBs do not share the same toxic endpoints 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 are present in the environment and food.

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

52. EFSA published a scientific opinion on non-dioxin-like PCBs in feed and food in 2005 concluding that “no health-based guidance value for humans can be established for NDL-PCB because simultaneous exposure to NDL-PCB and dioxin-like compounds hampers the interpretation of the results of the toxicological and epidemiological studies, and the database on effects of individual NDL-PCB congeners is rather limited. There are however indications that subtle developmental effects, being caused by NDL-PCB, DL-PCB, or polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans alone, or in combination, may occur at maternal body burdens that are only slightly higher than those expected from the average daily intake in European countries. Because some individuals and some European (sub)-populations may be exposed to considerably higher average intakes, a continued effort to lower the levels of NDL-PCB in food is warranted.” (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2005).

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

54. In the 2005 opinion EFSA stated ‘the absence of mutagenicity indicates that a threshold approach is appropriate for the hazard characterisation, the toxicological

database however, was considered to be too limited to allow the establishment of a health based guidance value for NDL-PCB. The Panel therefore decided to perform its health risk characterisation on the basis of a margin of exposure approach'. This was using a NOAEL for liver and thyroid toxicity in a 90 day rat study and applying an estimated 'body burden' margin of exposure approach (MoBB, calculated by dividing the estimated rat body burden NOAEL of 400, 800, and 1,200 µg/kg b.w. for PCB 28, 128, and 153, respectively with the estimated median human body burden). For all NDL-PCBs EFSA estimated an overall body burden NOAEL of 500 µg/kg.

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

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

Risk characterisation

57. From the EFSA (2005) opinion , it was concluded that the overall NOAEL for all NDL-PCBs MoBB was approximately 10. Although this margin appears low it is conservative due to the potential influence of dioxins and DL-PCBs contamination of the assessment, as these have the same toxicological endpoints. No overall conclusion was drawn from this opinion apart from 'A continuing effort to lower the levels of NDL-PCB in food is warranted.'

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

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

Polycyclic Aromatic Hydrocarbons (PAHs)

60. 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 and are widely distributed in the environment as the result of vehicle exhaust and industrial processes and in the diet in cooked food and cooking by-products such as 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.

61. EFSA in 2008 (European Food Safety Authority (EFSA), 2008b) addressed PAHs in food. Considering the large number of possible members in the group, they concluded that although benzo[a]pyrene (BaP) alone has been used as a marker for PAHs, the presence of a mixture of BaP, benz[a]anthracene (BaA), benzo[b]fluoranthene (BbF) and chrysene (ChR), designated PAH4, gave a better measure for risk assessment purposes.

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

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

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

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

66. EU regulatory limits, (EU) 835/ 2011 have been set for milk intended for infants of 1 µg/kg for BaP and 1 µg/kg for the sum of the PAH4.

Exposure assessment and risk characterisation

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

68. Due to this limited occurrence data in the literature the UK TDS results for PAHs in 44 UK milk samples from 2012 were used for an exposure assessment (Fernandes *et al.*, 2012). Only averages are provided in the report for lower and upper bound concentrations, not maximum or upper percentile values. Data are summarised in Table 6.

Table 6. Summary of PAHs in cow's milk (whole sample basis) from UK TDS(Fernandes *et al.*, 2012)

	µg/kg
Number of samples	44
Mean concentration BaP, Lower Bound	< 0.04
Mean concentration BaP, Upper Bound	0.04
Mean concentration PAH4, Lower Bound	< 0.01
Mean concentration PAH4, Upper Bound	0.1

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

70. A MOE assessment has been undertaken using the upper bound average concentrations from the TDS 2012 data (Table 6) and consumption rates in Table 1 against the $BMDL_{10}$ values from EFSA (2008b). This assessment is presented in Tables 7 and 8 for benzo[a]pyrene and PAH4 respectively.

Table 7. Benzo[a]pyrene exposure assessment from cow's milk consumption

Age (months	Estimated Exposure (mean) (µg/kg bw day)	Estimated Exposure (97.5th percentile) (µg/kg bw day	Margin of Exposure to $BMDL_{10}$ (EFSA 2008b) (mean consumption)	Margin of Exposure to $BMDL_{10}$ (EFSA 2008b) (97.5th percentile consumption)
6 – <12	0.00052	0.00192	134,615	36,458
12 – <18	0.00128	0.0030	54,688	23,333
18 – <24	0.00116	0.00316	60,345	22,152
24 – <48	0.00092	0.00236	76,087	29,661
48 – <60	0.00068	0.00184	102,941	38,043

Table 8. PAH4 exposure assessment from cow's milk consumption

Age (months	Estimated Exposure (mean) (µg/kg bw day)	Estimated Exposure (97.5th percentile) (µg/kg bw day	Margin of Exposure to $BMDL_{10}$ (EFSA 2008b) (mean consumption)	Margin of Exposure to $BMDL_{10}$ (EFSA 2008b) (97.5th percentile consumption)
6 – <12	0.0013	0.0048	261,538	70,833
12 – <18	0.0032	0.0075	106,250	45,333
18 – <24	0.0029	0.0079	117,241	43,038
24 – <48	0.0023	0.0059	147,826	57,627
48 – <60	0.0017	0.0046	200,000	73,913

71. The MOE's presented are all above 10,000 for both average and high-level consumers across all age ranges of young children, based on the UK TDS from 2012. These high MOE's indicate there is a very low safety risk of the PAH4 from drinking cow's milk.

72. 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 the intakes of PAHs (BaP and PAH4) from human breast milk and food are of low concern for health in children aged 12 to 60 months.

Isoflavones

73. 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.

74. 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).

75. 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 greatest oestrogenic activity (McCarver *et al.*, 2011).

76. 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 conflicting. 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.

77. 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.

78. The 2003 COT report concludes that it is not possible to propose HBGVs for infants. 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 possibility of bias and chance effects in the available human studies. In a more recent 2013 COT report (COT, 2013) , assessing literature since 2003, the same conclusions were drawn , in that it is not possible to propose HBGVs due to limitations in the available data.

79. 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 for inter species differences and intraspecies variation.

80. 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 or contaminated red clover for example will have greatly increased concentrations of isoflavones (Höjer *et al*., 2012).

Risk characterisation

81. To obtain published 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 were returned from European countries. The UK data only are summarised in Table 9 from Nørskov *et al.*, (2019).

Table 9. Summary of mean isoflavone concentrations (all µg/kg) GEN, EQU, FOR and DAI from differing cow's milk types in the UK and a comparison with mean soya milk concentrations (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
Low fat soya*	1	875	-	-	567	1,442

*From 2019 COT report (COT, 2019), isoflavone content of soya-based foods and beverages is highly variable and these figures are a guide only

82. As noted above, COT have not established a HBGV for isoflavones for young children and the significance of the exposures summarised in Table 9 is uncertain. However, exposures from cow's milk are considerably lower than those from soya alternatives, suggesting that any associated risk will also be lower.

Summary

83. To aid in assessment of the chemicals described, two summary tables are provided (Table 10 and Table 11), providing a summary of conclusions and where appropriate to this paper, the HBGV for each substance and the highest age range estimated exposure via the diet, based on the mean consumption data.

Table 10 Summary of risk assessment conclusions for cow's milk based on previous authority opinions

Compound (s)	**HBGV , kg bw/day (endpoint)**	**Effect**	**Authority**	**Suggested conclusion**
Nitrite	n/a	Methemoglobinemia	EFSA	No health concern
Bisphenol A	4 µg (Increase in mouse kidney weight	Endocrine disrupter affecting metabolism, growth, sexual development, stress response, insulin production, gender behaviour, reproduction, and foetal development	EFSA	No health concern
DBP, BBP, DEHP, DINP (Summed as DEHP equivalents)	0.05 mg (reproductive effects in rats)	Reproductive effects, hepatic effects	EFSA / COT	No health concern
DEP	5 mg (increased liver and prostate weights, decreased epididymal sperm concentration of the F1 generation in mice)	Organ weight changes	WHO / COT	No health concern
NDL-PCBs	n/a	Neurological, endocrine, immunological and carcinogenic effects	JECFA	No health concern
Isoflavones GEN, EQU, FOR, DAI	0.07 mg (GEN only)	Endocrine disrupter (oestrogenic effects) effecting thyroid and immune function and sexual development	Nordic Council	No health concern

Table 11 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 , kg bw/day (endpoint)**	**Authority**	**Highest Exposure (mean consumption) , kg bw/day**	**% HBGV or MOE**	**Highest exposure age range (months)**	**Effect**	**Suggested conclusion**
Nitrate	3.7 mg (growth retardation in dogs and rats)	EFSA	0.00416 mg	0.112	12 – <18	Methemoglobinemia	No health concern
Dioxins plus DL-PCBs	2 pg WHO-TEQ, (reproductive effects in rats)	EFSA	1.024 pg	51.2	12 – <18	Range of toxic effects including chloracne and reproductive effects	No health concern
Benzo[a]pyrene (BaP)	None, $BMDL_{10}$ of 70 µg (total tumour-bearing animals)	EFSA	0.00128 µg	54,688 (MOE)	12 – <18	Carcinogenic	No health concern
Sum of BaP, BbF,ChR and BaA (PAH4)	None, $BMDL_{10}$ of 340 µg (total tumour-bearing animals)	EFSA	0.0032 µg	106,250 (MOE)	12 – <18	Carcinogenic	No health concern

Discussion

84. This is the first 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 nitrate, nitrite, BPA, phthalates, dioxins, DL-PCBs, NDL-PCBs and PAHs. The risk characterisations are taken from the most recent opinions from regulatory authorities such as EFSA and JECFA, or derived from a new exposure assessment using the most up to date UK consumption data for cow's milk in children of different age ranges. All risks are suggested to be low with no health concerns.

85. Veterinary medicine and pesticide exposure risk were assessed using comprehensive milk survey data from 2015 to 2020 with very low incident levels.

86. In the absence of a HBGV, isoflavones in cow's milk were compared to the isoflavone levels in soya plant-based drinks, with a much lower concentration potentially occurring in cow's milk.

Questions for the Committee

87. 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 forthcoming part 2 which the Committee would like to see included?
d) Does the Committee have any other comments on this paper?

Secretariat

October 2021

Abbreviations

ADI	Acceptable Daily Intake
AFB_1	Aflatoxin B1
AFM_1	Aflatoxin M1
BaA	Benz[a]anthracene
BaP	Benzo[a]pyrene
BbF	Benzo[b]fluoranthene
BBP	Butyl-benzyl-phthalate
BMDL	Benchmark Dose Lower Confidence Limit
BIO	Biochanin A
BPA	Bisphenol A
CEP	EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
ChR	Chrysene
CONTAM	EFSA Panel on Contaminants in the Food Chain
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
COC	Committee on Carcinogenicity
DAI	Daidzein
DBP	Di-butylphthalate
DEHP	Bis(2- ethylhexyl)phthalate
DHSC	Department of Health and Social Care
DIDP	Di-isodecylphthalate
DINP	Di-isononylphthalate
DL-PCBs	Dioxin-Like Polychlorinated Biphenyls
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
DON	Deoxynivalenol
EC	European Commission
EFSA	European Food Safety Authority
EHDI	Estimated Human Daily Intakes
EQU	Equol
ERs	Oestrogen Receptors
FAO	Food and Agriculture Organisation
FOR	Formononetin
GEN	Genistein
HED	Human Equivalent Dose
ICES- 6	Indicator PCBS: 28, 52, 101, 138, 153 and 180
IGF	Insulin-Like Growth Factor
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MoBB	Margin of Body Burdens
MOE	Margin Of Exposure
MRL	Maximum Residue Limit
NDL-PCBs	Non-Dioxin-Like Polychlorinated Biphenyls
NDNS	National Diet and Nutrition Survey
NOAELs	No-Observed-Adverse-Effect Levels
NRL	National Reference Laboratory
NSAIDS	Non-Steroidal Anti-inflammatory drugs
PAHs	Polycyclic Aromatic Hydrocarbons

PCBs	Polychlorinated Biphenyls
PCDDs	Polychlorinated Dibenzodioxins
PCDFs	Polychlorinated Dibenzofurans
PHE	Public Health England
RASFF	Rapid Alert System for Food and Feed
SACN	Scientific Advisory Committee on Nutrition
SCF	Scientific Committee on Food
TCDD	2,3,7,8-Tetrachlorodibenzyl Dioxin
TDI	Tolerable Daily Intake
TDS	UK Total Diet Study
TEFs	Toxic Equivalency Factors
TEQ	Toxic Equivalent Value
TWI	Tolerable Weekly Intake
US-EPA	United States Environmental Protection Agency
VMD	Veterinary Medicines Directorate
WHO	World Health Organisation

References

Bansal, A., Henao-Mejia, J. and Simmons, R.A. (2018) 'Immune System: An Emerging Player in Mediating Effects of Endocrine Disruptors on Metabolic Health', Endocrinology, 159(1), pp. 32–45. doi:10.1210/en.2017-00882.

Bates, B., Lennox, A., Prentice, A., Bates, C., Page, P., Nicholson, S. and Swan, G. (2014). Available at: 'National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012)'

Bláhová, L., Kohoutek, J., Procházková, T., Prudíková, M. and Bláha, L. (2016) 'Phytoestrogens in milk: Overestimations caused by contamination of the hydrolytic enzyme used during sample extraction', *Journal of Dairy Science*, 99(9), pp. 6973–6982. doi:10.3168/jds.2016-10926.

Byrne, M.P., Tobin, J.T., Forrestal, P.J., Danaher, M., Nkwonta, C.G., Richards, K., Cummins, E., Hogan, S.A. and O'Callaghan, T.F. (2020) 'Urease and Nitrification Inhibitors—As Mitigation Tools for Greenhouse Gas Emissions in Sustainable Dairy Systems: A Review', Sustainability, 12(15), p. 6018. doi:10.3390/su12156018.

Cirillo, T., Latini, G., Castaldi, M.A., Dipaola, L., Fasano, E., Esposito, F., Scognamiglio, G., Francesco, F.D. and Cobellis, L. (2015) Abstract of 'Exposure to Di-2-Ethylhexyl Phthalate, Di-N-Butyl Phthalate and Bisphenol A through Infant Formulas', *Journal of Agricultural and Food Chemistry*, 63(12), pp. 3303–3310. doi:10.1021/jf505563k.

Cockburn, A., Brambilla, G., Fernández, M.-L., Arcella, D., Bordajandi, L.R., Cottrill, B., van Peteghem, C. and Dorne, J.-L. (2013) 'Nitrite in feed: From Animal health to human health', *Toxicology and Applied Pharmacology*, 270(3), pp. 209–217. doi:10.1016/j.taap.2010.11.008.

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (1997). Available at: 'Statement by the committee on toxicity of chemicals in food, consumer products and the environment on the health hazards of polychlorinated biphenyls'

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2001). Available at: 'Statement on the tolerable daily intake for dioxins and dioxin-like polychlorinated biphenyls'

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2003). Available at: 'Phytoestrogens and Health'

Committee on toxicity of chemicals in food, consumer products and the environment (COT). (2011). Available at: 'Statement on dietary exposure to phthalates – data from the total diet study'

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2013). Available at: 'Statement on the potential risks from high levels of soyaphytoestrogensin the infant diet'

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2019a). Available at: 'Discussion paper on soya drink consumption in children aged 6 months to 5 years of age'

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2019b). Available at: 'Overarching statement on the potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 year'

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2020). Available at: 'Addendum to the Overarching Statement on the potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years'

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2021a). Available at: 'Overarching statement on consumption of plant-based drinks in children aged 6 months to 5 years of age'

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2021b). Available at: Position paper on dioxins

Culp, S.J., Gaylor, D.W., Sheldon, W.G., Goldstein, L.S. and Beland, F.A. (1998) 'A comparison of the tumors induced by coal tar and benzo[a]pyrene in a 2-year bioassay', *Carcinogenesis*, 19(1), pp. 117–124. doi:10.1093/carcin/19.1.117.

Dairy UK (2018). Available at: Milk: Nutrition information for all the family

Department of Health (2011). Available at: 'Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011'

Diggs, D.L., Huderson, A.C., Harris, K.L., Myers, J.N., Banks, L.D., Rekhadevi, P.V., Niaz, M.S. and Ramesh, A. (2011) 'Polycyclic aromatic hydrocarbons and digestive tract cancers: a perspective', *Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews*, 29(4), pp. 324–357. doi:10.1080/10590501.2011.629974.

EFSA Panel on Contaminants in the Food Chain (CONTAM) (2005) 'Opinion of the Scientific Panel on contaminants in the food chain [CONTAM] related to the presence of non dioxin-like polychlorinated biphenyls (PCB) in feed and food', *EFSA Journal* [Preprint], (EFSA Journal). doi:10.2903/j.efsa.2005.284.

EFSA Panel on Contaminants in the Food Chain (CONTAM) (2018) 'Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food', *EFSA Journal*, 16(11). doi:10.2903/j.efsa.2018.5333.

EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) (2019) 'Update of the risk assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP) for use in food contact materials', *EFSA Journal*, 17(12). doi:10.2903/j.efsa.2019.5838.

European Food Safety Authority (EFSA) (2005a) 'Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Bis(2-ethylhexyl)phthalate (DEHP) for use in food contact materials', *EFSA Journal* [Preprint], (EFSA Journal). doi:10.2903/j.efsa.2005.243.

European Food Safety Authority (EFSA) (2005b) 'Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Butylbenzylphthalate (BBP) for use in food contact materials', *EFSA Journal* [Preprint], (EFSA Journal). doi:10.2903/j.efsa.2005.241.

European Food Safety Authority (EFSA) (2005c) 'Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to di-Butylphthalate (DBP) for use in food contact materials', *EFSA Journal* [Preprint], (EFSA Journal). doi:10.2903/j.efsa.2005.242.

European Food Safety Authority (EFSA) (2005d) 'Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Di-isodecylphthalate (DIDP) for use in food contact materials', *EFSA Journal* [Preprint], (EFSA Journal). doi:10.2903/j.efsa.2005.245.

European Food Safety Authority (EFSA) (2005e) 'Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Di-isononylphthalate (DINP) for use in food contact materials', *EFSA Journal* [Preprint], (EFSA Journal). doi:10.2903/j.efsa.2005.244.

European Food Safety Authority (EFSA) (2008a) 'Nitrate in vegetables - Scientific Opinion of the Panel on Contaminants in the Food chain', *EFSA Journal*, 689(EFSA Journal), pp. 1–79. doi:10.2903/j.efsa.2008.689.

European Food Safety Authority (EFSA) (2008b) 'Polycyclic Aromatic Hydrocarbons in Food - Scientific Opinion of the Panel on Contaminants in the Food Chain', *EFSA Journal* [Preprint], (EFSA Journal). doi:10.2903/j.efsa.2008.724.

European Food Safety Authority (EFSA) (2009) 'Nitrite as undesirable substances in animal feed - Scientific Opinion of the Panel on Contaminants in the Food Chain', *EFSA Journal*, 7(4). doi:10.2903/j.efsa.2009.1017.

European Food Safety Authority (EFSA) (2010) 'Results of the monitoring of non dioxin-like PCBs in food and feed', *EFSA Journal* [Preprint], (2010; 8(7):1701). doi:10.2903/j.efsa.2010.1701.

European Food Safety Authority (EFSA) (2015) 'Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs', *EFSA Journal*, 13(1), p. 3978. doi:10.2903/j.efsa.2015.3978.

European Union (EU) (2011a). Available at: 'Commision Regulation (EU) No 574/2011 of 16 June 2011 amending Annex I to Directive 2002/32/EC of the European Parliament and of the Council as regards maximum levels for nitrite, melamine, Ambrosia spp. and carry-over of certain coccidiostats and histomonostats and consolidating Annexes I and II thereto'

European Union (EU) (2011b). Available at: 'Commision Regulation (EU) No 835/2011 of of 19 August 2011 amending Regulation (EC) No 1881/2006 as regards maximum levels for polycyclic aromatic hydrocarbons in foodstuffs'

European Union (EU) (2011c). Available at: 'Commision Regulation (EU) No 1259/2011 of 2 December 2011 amending Regulation (EC) No 1881/2006 as regards maximum levels for dioxins, dioxin-like PCBs and non dioxin-like PCBs in foodstuffs'

Fernandes, A., Rose, M., Smith, F. and Holland, M. (2012). Available at: 'Organic Environmental Contaminants in the 2012 Total Diet Study Samples'

Food Safety Authority of Ireland (2009). Available at: 'Dioxins and PCBs in Food'

Heudorf, U., Mersch-Sundermann, V. and Angerer, J. (2007) 'Phthalates: toxicology and exposure', *International Journal of Hygiene and Environmental Health*, 210(5), pp. 623–634. doi:10.1016/j.ijheh.2007.07.011.

Höjer, A., Adler, S., Purup, S., Hansen-Møller, J., Martinsson, K., Steinshamn, H. and Gustavsson, A.-M. (2012) 'Effects of feeding dairy cows different legume-grass silages on milk phytoestrogen concentration', *Journal of Dairy Science*, 95(8), pp. 4526–4540. doi:10.3168/jds.2011-5226.

Joint FAO/WHO Expert Committee on Food Additives (JECFA) (2016). Available at: 'Safety evaluation of certain food additives and contaminants: Supplement 1, Non-dioxin-like polychlorinated biphenyls'

Kim, K.-H., Jahan, S.A., Kabir, E. and Brown, R.J.C. (2013) 'A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects', *Environment International*, 60, pp. 71–80. doi:10.1016/j.envint.2013.07.019.

Li, R., Zhao, F., Diao, H., Xiao, S. and Ye, X. (2014) 'Postweaning dietary genistein exposure advances puberty without significantly affecting early pregnancy in C57BL/6J female mice', *Reproductive Toxicology (Elmsford, N.Y.)*, 44, pp. 85–92. doi:10.1016/j.reprotox.2013.12.003.

McCarver, G., Bhatia, J., Chambers, C., Clarke, R., Etzel, R., Foster, W., Hoyer, P., Leeder, J.S., Peters, J.M., Rissman, E., Rybak, M., Sherman, C., Toppari, J. and Turner, K. (2011) Abstract of 'NTP-CERHR expert panel report on the developmental toxicity of soy infant formula', *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, 92(5), pp. 421–468. doi:10.1002/bdrb.20314.

Mínguez-Alarcón, L., Sergeyev, O., Burns, J.S., Williams, P.L., Lee, M.M., Korrick, S.A., Smigulina, L., Revich, B. and Hauser, R. (2017) 'A Longitudinal Study of Peripubertal Serum Organochlorine Concentrations and Semen Parameters in Young Men: The Russian Children's Study', *Environmental Health Perspectives*, 125(3), pp. 460–466. doi:10.1289/EHP25.

Montgomery, H., Haughey, S.A. and Elliott, C.T. (2020) 'Recent food safety and fraud issues within the dairy supply chain (2015–2019)', *Global Food Security*, 26, p. 100447. doi:10.1016/j.gfs.2020.100447.

Moorthy, B., Chu, C. and Carlin, D.J. (2015) 'Polycyclic aromatic hydrocarbons: from metabolism to lung cancer', *Toxicological Sciences: An Official Journal of the Society of Toxicology*, 145(1), pp. 5–15. doi:10.1093/toxsci/kfv040.

National Health Service (NHS) (2018). Available at: 'Drinks and cups for babies and young children'

Nordic Council of Ministers (2020). Available at: 'Soy intake and possible adverse health effects in Nordic children and pregnant women'

Nørskov, N.P., Givens, I., Purup, S. and Stergiadis, S. (2019) 'Concentrations of phytoestrogens in conventional, organic and free-range retail milk in England', *Food Chemistry*, 295, pp. 1–9. doi:10.1016/j.foodchem.2019.05.081.

Olijhoek, D.W., Hellwing, A.L.F., Brask, M., Weisbjerg, M.R., Højberg, O., Larsen, M.K., Dijkstra, J., Erlandsen, E.J. and Lund, P. (2016) 'Effect of dietary nitrate level on enteric methane production, hydrogen emission, rumen fermentation, and nutrient digestibility in dairy cows', *Journal of Dairy Science*, 99(8), pp. 6191–6205. doi:10.3168/jds.2015-10691.

Pesticide Residues in Food (PRiF) (2015). Available at: 'The expert committee on Pesticide Residues in Food (PRiF) Annual Report 2015'

Pesticide Residues in Food (PRiF) (2016). Available at: 'The expert committee on Pesticide Residues in Food (PRiF) Annual Report 2016'

Pesticide Residues in Food (PRiF) (2017). Available at: 'The expert committee on Pesticide Residues in Food (PRiF) Annual Report 2017'

Pesticide Residues in Food (PRiF) (2018). Available at: 'The expert committee on Pesticide Residues in Food (PRiF) Annual Report 2018'

Pesticide Residues in Food (PRiF) (2019). Available at: 'The expert committee on Pesticide Residues in Food (PRiF) Annual Report 2019'

Pesticide Residues in Food (PRiF) (2020). Available at: 'The expert committee on Pesticide Residues in Food (PRiF) Annual Report 2020'

Roberts, C., Steer, T., Maplethorpe, N., Cox, L., Meadows, S., Page, P., Nicholson, S. and Swan, G. (2018). Available at: 'National Diet and Nutrition Survey Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 – 2015/2016'

Roshandel, G., Semnani, S., Malekzadeh, R. and Dawsey, S.M. (2012) 'Polycyclic Aromatic Hydrocarbons and Esophageal Squamous Cell Carcinoma-A Review', *Archives of Iranian medicine*, 15(11), pp. 713–722.

Rychen, G., Jurjanz, S., Toussaint, H. and Feidt, C. (2008) 'Dairy ruminant exposure to persistent organic pollutants and excretion to milk.', *Animal : an international journal of animal bioscience* [Preprint]. doi:10.1017/S1751731107001139.

Science Committee on Food (SCF) (2000). Available at: 'Opinion of the SCF on the Risk Assessment of Dioxins and Dioxin-Like PCBs in Food'

Science Committee on Food (SCF) (2001). Available at: 'Risk Assessment of Dioxins and Dioxin-Like PCBs in Food: Update based on new scientific information available since the adoption of the SCF opinion of 22nd November 2000'

Socas-Rodríguez, B., Hernández-Borges, J., Salazar, P., Martín, M. and Rodríguez-Delgado, M.Á. (2015) 'Core-shell polydopamine magnetic nanoparticles as sorbent in micro-dispersive solid-phase extraction for the determination of estrogenic compounds in water samples prior to high-performance liquid chromatography-mass spectrometry analysis', *Journal of chromatography A*, 1397, pp. 1–10. doi:10.1016/j.chroma.2015.04.010.

Sun, Y., Yan, K., Wu, S. and Gong, G. (2020) 'Occurrence, spatial distribution and impact factors of 16 polycyclic aromatic hydrocarbons in milks from nine countries', *Food Control*, 113, p. 107197. doi:10.1016/j.foodcont.2020.107197.

The World Health Organisation (WHO) (2003). Available at: 'Diethyl Phthalate. Concise International Chemical Assessment, Document 52'

Van den Berg, M., Birnbaum, L.S., Denison, M., De Vito, M., Farland, W., Feeley, M., Fiedler, H., Hakansson, H., Hanberg, A., Haws, L., Rose, M., Safe, S., Schrenk, D., Tohyama, C., Tritscher, A., Tuomisto, J., Tysklind, M., Walker, N. and Peterson, R.E. (2006) 'The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds', *Toxicological Sciences: An Official Journal of the Society of Toxicology*, 93(2), pp. 223–241. doi:10.1093/toxsci/kfl055.

Veterinary Medicines Directorate (VMD) (2014). Available at: 'Code of Practice on the responsible use of animal medicines on the farm'

Veterinary Medicines Directorate (VMD) (2015) Available at: 'National statutory surveillance scheme for veterinary residues in animals and animal products: 2015'

Veterinary Medicines Directorate (VMD) (2016). Available at: 'National statutory surveillance scheme for veterinary residues in animals and animal products: 2016'

Veterinary Medicines Directorate (VMD) (2017). Available at: 'National statutory surveillance scheme for veterinary residues in animals and animal products: 2017'

Veterinary Medicines Directorate (VMD) (2018). Available at: 'National statutory surveillance scheme for veterinary residues in animals and animal products: 2018'

Veterinary Medicines Directorate (VMD) (2019) Available at: 'National statutory surveillance scheme for veterinary residues in animals and animal products: 2019'

Veterinary Medicines Directorate (VMD) (2020). Available at: 'National statutory surveillance scheme for veterinary residues in animals and animal products: 2019'

Xiao, C.W. (2008) 'Health Effects of Soy Protein and Isoflavones in Humans', *The Journal of Nutrition*, 138(6), pp. 1244S-1249S. doi:10.1093/jn/138.6.1244S.