COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Statement on potential risks from ochratoxin A (OTA) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government dietary recommendations for infants and young children. The SACN is examining the nutritional basis for the advice. The COT was asked to review the risk of toxicity of chemicals in the diets of infants and young children. The reviews will identify new evidence that has emerged since the Government recommendations were formulated and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. The Food Standards Agency (FSA) has completed a survey of 36 mycotoxins in the 2014 Total Diet Survey (TDS) – Mycotoxins Analysis (FSA, to be published). The results of the survey provide information on the concentrations of aflatoxins (B1, B2, G1, G2 and M1), ochratoxin A, zearalenone, fumonisins (B1, B2 and B3), 3-acetyldeoxynivalenol, 15-acetyldeoxynivalenol, deoxynivalenol, diacetoxyscirpenol, fusarenon-X, HT2 toxin, neosolaniol, nivalenol, T2 toxin, sterigmatocystin, citrinin, cyclopiazonic acid, moniliformin, patulin and ergot alkaloids (ergocornine, ergocorninine, ergocristine, ergocristinine, ergocryptine, ergocryptinine, ergometrine, ergometrinine, ergosine, ergosinine, ergotamine, ergotaminine) in relevant foods. Estimates of dietary exposures were calculated for each mycotoxin for UK infants and young children aged 4 to 60 months using food consumption data taken from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) and the National Diet and Nutrition Survey (NDNS).

3. This statement gives an overview of the potential risks from ochratoxin A (OTA) in the diets of infants and young children in the UK aged 0 to 12 months and 1 to 5 years, respectively. It draws on the EFSA opinion (2006) and statement (2010) and any relevant *in vivo* toxicity studies published since the 2006 EFSA Opinion. None of the Government's current dietary recommendations for infants and young children relate to OTA.

Background

4. OTA is a mycotoxin produced by several fungal species in the *Penicillium* and *Aspergillus* genera, primarily *Penicillum verrucosum*, *Aspergillus ochraceus* and *Aspergilli* of the section *Nigri*, especially *A. carbonarius*. OTA has been found in a variety of plant products such as cereals and cereal products, coffee beans, beans, pulses, cocoa products, nuts and spices and dried fruit all over the world. It has also been detected in products such as coffee, wine, beer and grape juice and occurs in kidney, liver and blood from farm animals by transfer from animal feed (EFSA, 2006; EFSA, 2010).

5. OTA has been assessed previously by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2001 and the European Food Safety Authority (EFSA) in 2006[1].

6. In 2010[2] EFSA evaluated 5 research articles providing recent data on the toxicity of OTA and concluded that the new information did not alter the conclusions of the evaluation carried out in 2006 (EFSA, 2010).

Toxicokinetics

7. The toxicokinetics of OTA have been previously reviewed by EFSA (2006).

8. OTA is rapidly absorbed following oral ingestion. Animal studies showed absorption between 40% (chickens) and 66% (pigs). OTA reaches the systemic circulation, where it is primarily bound to plasma proteins. The unbound fraction of OTA is as low as 0.02% in humans.

9. A two-compartment pharmacokinetic open model, consisting of a fast distribution and elimination phase followed by a slow elimination phase (plasma clearance) with a long half-life best describe the concentration-time profile of radiolabelled OTA *in vivo*. Based on limited data, in a single individual, the half-life was 20 hours during the α-phase and 35 days during the β-phase (Studer-Rohr *et al*., 2000). Initial testing showed stabilization of OTA after addition of bovine serum albumin (BSA); no significant increase in tritiated water could be detected by the authors between day 1 (1.6%) and day 21 (2.0%). The authors therefor assumed that human plasma proteins would stabilize the labelled OTA in a comparable fashion. A concurrent study by the same authors with eight individuals investigated the intraindividual fluctuation of OTA; no labelled or unlabelled OTA was specifically administered to these subjects. During the first week, blood samples were taken every second day, thereafter at weekly intervals. OTA concentrations remained constant in some individuals and varied considerably in others; dietary habits of the individuals were not recorded in the study. The half-life in other species ranged from 5 days in Wistar rats, 6 days in pigs and 9-21 days in non-human primates.

10. In many species, including non-human primates and humans, renal excretion is the major route of elimination of OTA. In rodents, biliary excretion seems to

[1] EFSA opinion available at: https://www.efsa.europa.eu/en/efsajournal/pub/365

[2] EFSA statement available at: https://www.efsa.europa.eu/en/efsajournal/pub/1626

predominate. The molecular weight of OTA (403.81 D) is such that biliary excretion will predominate in rats (300-400 D) but not in humans (500-600 D) (EFSA, 2008). Differences in the degree of plasma protein binding and its effect on renal clearance, as well as the rate of conjugation and extent of entero-hepatic re-circulation largely determine the inter-individual and interspecies variability of pharmacokinetic parameters.

Toxicity

Summary from previous evaluations by the Scientific Committee for Food (SCF)

11. The toxicity of OTA was evaluated by the Scientific Committee for Food (SCF) in 1996 and 1998 (EC, 1996; EC, 1998). In 1998, based on concerns about potential genotoxicity of OTA, the SCF recommended that exposures should be reduced as much as possible and kept to the lower end of a range of tolerable daily intakes (TDI's) of 1.2 – 14 ng/kg bw, preferably below 5 ng/kg bw (SCF, 1998).

Studies used in the derivation of the JECFA and EFSA HBGVs

12. Both, JECFA and EFSA used two experimental pig studies by Elling and Krogh *et al.* for the derivation of their HBGVs. Whilst OTA is carcinogenic to the kidney, JECFA (2007) concluded that the evidence pointed to a non-genotoxic mode(s) of action and that nephrotoxicity in the pig is the most appropriate endpoint on which to base the HBGV. EFSA (2006) concluded that in the absence of conclusive evidence that OTA binds to DNA, the HBGV should be based on nephrotoxicity, and that the pig was the most sensitive species.

13. In a study by Elling (1979), female pigs were given crystalline OTA orally by capsule at a dose of 400 µg/kg bw per day, corresponding to 5 mg/kg feed, for 5 days. Female pigs in a previous study had been exposed orally to OTA in capsules at doses related to bodyweight, corresponding to a concentration of about 1 mg/kg of the feed, for 3 months or 2 years. This resulted in a mean daily dose of OTA of 24.1 – 50.2 µg/kg bw per day (mean 37.7 µg/kg bw ± 0.98) (Krogh *et al.*, 1979). In the higher dose group, desquamation and focal necrosis of epithelial cells were detected in the proximal tubule of some nephrons. The activities of a number of enzymes (including NADH-tetrazolium reductase and succinate dehydrogenase) were reduced in the area of the proximal tubules that showed morphological changes. In the lower dose group, the histopathological changes observed were focal degeneration and necrosis of the proximal tubular cells. The lesions after 2 years were the same as after 3 months, except the tubular atrophy and the interstitial fibrosis were more widely distributed in the renal cortex. The authors concluded that OTA induced a reduction in enzyme activity, thus appearing to cause the impairment of proximal tubular function and morphological changes observed in porcine nephropathy (Elling, 1979).

14. In a study by Krogh *et al.* (1988) female pigs received daily a gelatine capsule containing OTA at 0.25 mg, corresponding to a feed level of 0. 2 mg/kg feed, or 1.17 mg, corresponding to a feed level of 1 mg/kg feed, for 5 weeks. Renal impairment was observed in both experimental groups after 5 weeks of exposure. Further, the activities, in renal biopsies, of both cytosolic phosphoenolpyruvate carboxykinase

(PEPCK) and gamma-glutamyl transpeptidase were decreased after 1 week of exposure and the enzyme activities remained reduced for the duration of the experiment. No light-microscopic changes could be detected in kidneys of any of the animals. Due to the correlation of increased renal impairment with decreased enzyme activity, the authors concluded that these enzymes were sensitive indicators of OTA induced porcine nephropathy (Krogh *et al*., 1988).

15. The administered doses are reported in the original studies as corresponding to 1 mg/kg feed and 5 mg/kg feed (Elling *et al*., 1979) and 0.2 mg/kg feed and 1 mg/kg feed (Krogh *et al*., 1988), respectively. The corresponding OTA doses on a body weight basis are reported in the 2001 JECFA evaluation as 0.008, 0.04 and 0.2 mg/kg bw per day, respectively. EFSA used the values given by JECFA.

HBGVs established by JECFA and EFSA

JECFA

16. JECFA first evaluated OTA in 1991, establishing a PTWI of 112 ng/kg bw based on the deterioration of renal function in pigs as reported in the studies by Elling (1979) and Krogh *et al*. (1988) (Paragraphs 13 and 14). The LOAEL was 8 µg/kg bw per day to which the Committee applied an uncertainty factor of 500.

17. Since then JECFA has re-evaluated OTA in 1995, 2001, 2006 and 2007 due to new toxicological data becoming available. JECFA confirmed the PTWI in each evaluation, rounding it to 100 ng/kg bw per day in 1995. For the 2006 evaluation JECFA also considered the EFSA opinion from earlier that year.

18. To provide additional information for the risk assessment, JECFA performed BMD modelling in their 2007 evaluation, using carcinogenicity data from the rat bioassay performed by the National Toxicology Program (NTP) in 1989. JECFA considered the occurrence of combined adenomas and carcinomas in kidneys of male rats, as the most sensitive species and sex for OTA renal carcinogenicity, were the most appropriate carcinogenicity data for modelling.

19. The lowest $BMDL_{10}$ was 15 µg/kg bw per day and with the model providing the best fit it was 25 µg/kg bw per day. JECFA therefore concluded that for the $BMDL_{10}$ in the rat did not provide a lower point of departure than the previously used LOAEL[3] for minimal renal toxicity in the pig and hence confirmed the use of the latter for establishing the PTWI.

20. JECFA concluded that the new data on nephrotoxicity, developmental toxicity, neurotoxicity and immunotoxicity did not indicate any reason to modify the previously taken approach and retained the previous PTWI of 100 ng/kg bw.

EFSA opinion, 2006

[3] In earlier JECFA evaluations, such as in 2001, PODs were referred to as NOELs/LOELs, whereas others would consider them as NOAELs/LOAELs. This was a difference in nomenclature rather than in scientific judgement.

21. The selected (female) pig studies used by EFSA were based on those used in the 2001 JECFA evaluation. The LOAEL for progressive nephropathy was 40 µg OTA/kg bw per day, whereas the NOAEL for this effect was 8 µg/kg bw per day in the diet for 2 years. However, in a 90-day feeding study in female pigs 8 µg OTA/kg bw per day was reported to produce effects on renal enzymes and renal function tests (Elling, 1979; Krogh *et al*., 1988).

22. EFSA concluded that 8 µg/kg bw per day was a LOAEL, reflecting early changes in renal function in experimental animals (i.e. female pigs) and likely to be close to a NOAEL, as the observed biochemical changes were transient (EFSA, 2006; JECFA, 2001).

23. A default uncertainty factor (UF) of 2.5 was used to account for interspecies differences in toxicodynamic effects. A UF of 6 was applied to account for toxicokinetic differences in consideration of the plasma half-life; only limited data were available on inter-individual variability in humans. The Panel noted that there were significant differences in the toxicokinetics of OTA between species, particularly with regard to protein binding. The default UF of 10 was used to extrapolate from the general population to a potentially sensitive sub-population. EFSA used an additional UF of 3 to take into account the use of a LOAEL rather than a NOAEL.

24. Using the LOAEL of 8 µg/kg bw per day, representing changes in early markers of renal toxicity, and applying a composite UF of 450 (2.5 x 6 x 10 x 3), EFSA derived a tolerable daily intake of approximately 18 ng OTA/kg bw per day.

25. However, given the relatively long half-life of OTA, approximately 20 days in non-human primates, 5 days in Wistar rats, 6 days in pigs and 35 days in humans (one individual), EFSA considered that expressing the HBGV as a tolerable weekly intake (TWI) of up to 120 ng/kg bw was more appropriate.

EFSA statement, 2010

26. In 2010, EFSA was asked to assess five publications with recent scientific information on the toxicity of OTA. EFSA noted that four of these publications addressed the possible co-exposure of OTA and aristolochic acid of populations in areas previously associated with higher prevalence of Balkan Endemic Nephropathy.

27. The Panel concluded that the information provided was not relevant to its overall risk assessment of OTA and neither contradicted nor changed the conclusions reached in the 2006 opinion. The TWI of 120 ng/kg bw was retained.

Choice of HBGV for current risk characterisation

28. Taking both EFSA publications into account, the COT considered the HBGV established by EFSA in 2006 to be conservative as it was based on sensitive early markers of kidney damage rather than overt renal toxicity and the relationship between changes in these early markers and renal toxicity has not yet been established.

29. It was noted that the use of an UF of 6 for toxicokinetic differences in consideration of the plasma half-life leading to the application of a total UF of 450 increased the overall conservativeness of the TWI.

30. The COT reviewed the new *in vivo* toxicity studies published since the EFSA opinion in 2006 in the discussion paper[4] and concluded that the findings of these studies were in line with the 2006 EFSA opinion. None of the studies proposed new/different HBGVs and all NAOELs/LOAELS provided were higher than the LOAEL of 8 µg/kg bw used by EFSA in 2006.

31. Hence, in the absence of more suitable information, the Committee agreed that, despite its conservative nature, the TWI of 120 ng/kg bw established by EFSA should be used in the Committee's assessment of the potential risks of OTA.

Occurrence data

Human breast milk

32. The COT reviewed the available breast milk data in the discussion paper[4]; in the absence of UK data, studies from other EU member states were considered, some of which provided raw data. Most concentrations were in the range of 1.1 – 182 ng OTA/L. Two Italian studies however reported higher concentrations of OTA; Galvano *et al*. (2008) reported concentrations ranging from < 5 ng/L to 405 ng/L, Micco *et al*. (1991) reported concentrations ranging from 1200 ng/L to 6600 ng/L.

33. Due to improved detection methodologies in recent years and the high LOD of 200 ng/L in the study by Micco *et al*. (1991), this study was considered of limited relevance and has therefore been excluded from the exposure assessment.

34. After consideration of the available studies, despite not including raw data, the study by Galvano *et al*. (2008) was selected for the exposure assessment. The minimum and average concentration (< 5 ng/L and 30.43 ng/L, respectively) detected agree with those found in a number of other studies; the maximum concentration of 405 ng/L is 2-fold greater than that reported in the other studies.

Total Diet Study (TDS)

35. Levels of a number of mycotoxins, including OTA, were measured in the TDS. Only five food categories contained measurable residues of OTA, the rest were all below the LOQ. OTA was found in the fruit and vegetable juices, dried fruit, herbs and spices and bread (granary, brown) food categories. While the data obtained from the TDS could be used as a qualitative indicator of mycotoxins present in various food categories, it was not possible to use it for a quantitative estimation of dietary exposures for a number of reasons.

36. Since analysis of the TDS samples involved a wide range of matrices (some of which had not been routinely examined previously), existing validated methods

[4] Discussion paper on OTA: https://cot.food.gov.uk/sites/default/files/tox2017-45_0.pdf

were adapted/extended to some of the new matrices. For example, the method used for grape juice or wine was used to analyse the composite sample of fruit and vegetable juices. However, the presence of other fruit and vegetables (e.g. orange, carrot) in addition to grape led to some analytical difficulties, with poor recoveries and consequently high results. The low recovery of 32% meant that the large correction inflated the result and will impact on calculated dietary exposures. Given the low recovery, this method is not considered suitable for this food matrix. Also, the reported concentration of 5.62 µg/kg OTA in the fruit and vegetable juice category was much higher than the average based on EFSA survey data (0.55 µg/kg).

37. Further, a range of matrices was included in a single batch in the analysis of mycotoxins. This had an impact on recoveries, since usually in a given batch, similar matrices are included and a batch average recovery is applied and the spiked samples use the same food matrix. In the above example, three very different matrices - dried fruit, herbs and spices were included in the batch with fruit and vegetable juices (each individually spiked). If a batch recovery average which is not specific to the fruit juice matrix and grape juice method is applied, it would give an average recovery of 72% when applied to this sample. This would give a lower result but is also not a reliable approach given the differences in sensitivities of the methods and food matrices used in the TDS.

38. A multi-mycotoxin method was used in the analysis for various food groups, which is normally used as a screening method rather than for quantification of low concentrations. This is reflected in generally poor recoveries, higher Limits of Quantification/Detection (LOQ/LOD) and when these were corrected for recovery, led to artificially inflated occurrence levels in some cases. This also indicates the unsuitability of using the TDS data for quantitative exposure estimates.

39. Therefore, occurrence data from the TDS are not suitable for estimating dietary exposures quantitatively. The methods lack suitable sensitivity and are not sufficiently standardised and validated for this purpose.

OTA survey data

40. The FSA undertook two FSA retail surveys in 2010 and 2011 (FSA, 2010; FSA, 2011). Samples of a total of 225 products, were collected on behalf of FSA; samples were purchased from major and independent supermarkets, independent and specialist retailers and online. The products tested comprised foods based on maize, wheat, rye and barley and commercial infant and young children foods.

41. Year 1 of the UK retail survey investigated the presence of mycotoxins in a range of cereals and cereal based products. In 75 samples of maize (corn) products analysed for OTA, 92% (69 samples) were below the LOQ (0.1 µg/kg). In 75 samples of wheat products analysed for OTA, 47% (35 samples) were below the LOQ (0.1 µg/kg). In 35 samples of rye and barley products analysed for OTA, 66% (23 samples) were below the LOQ (0.1 µg/kg).

42. Year 2 of the UK retail survey investigated the presence of mycotoxins in food produced for infants and young children. 77 samples of commercial foods for infants and young children were analysed for OTA. 83% (64 samples) were below the LOQ

(0.05 µg/kg); 2.6% (2 samples) were above the LOD (0.02 µg/kg) but below the LOQ and 14% (11 samples) were at or above the LOQ. These analytical data were used for calculating the exposures provided in Tables 3, 4 and 5 as lower bound (LB) and upper bound (UB) estimates.

Exposure Assessment

43. Exposures were calculated using data from foods analysed in years 1 and 2 of the four-year retail survey (FSA, 2010; FSA 2011) and consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) and the National Diet and Nutrition Survey rolling programme (NDNS) years 1 – 6 (Bates *et al.*, 2014; Bates *et al*., 2016). Exposures were assessed for infants aged 0 - < 4, 4 - < 6, 6 - < 9 and 9 - < 12 months, and for young children aged 12 - < 15, 15 - < 18, 18 - < 24 and 24 - < 60 months. Consumption data from DNSIYC was used for children aged 4 – 18 months and from NDNS for children aged 10 – 60 months.

Human breast milk

44. Based on the concentrations reported in Galvano *et al.* (2008), OTA exposures were estimated for exclusively breastfed infants consuming average (800 mL) and high-level (1200 mL) volumes of breast milk (Table 1). Using the average OTA concentration of 30.43 ng/L, exposures in the 0 to < 4 months old were 29 and 43 ng/kg bw per week for average and high consumers, respectively; for 4 to < 6 months old exposures were 22 and 33 ng/kg bw per week for average and high consumers, respectively. The maximum concentration of OTA (405 ng/L) resulted in mean and high-level exposure estimates of 380 and 580 ng/kg bw per week in 0 to < 4 months old infants and 290 and 440 ng/kg bw per week in 4 to < 6 months old infants, respectively.

Table 1 OTA exposure estimates (ng/kg bw per week) from exclusive breastfeeding for average and high-level consumption of breast milk.

OTA concentration (ng/L)	Estimated exposure (ng/kg bw/week)			
	Average consumer (800 mL/day)		High consumer (1200 mL/day)	
	0 to < 4 months	4 to < 6 months	0 to < 4 months	4 to < 6 months
Minimum < 5	< 4.7	< 3.6	< 7.1	< 5.4
Maximum 405	380	290	580	440
Average 30.43	29	22	43	33

Infant exposure is based on consumption of 800 mL or 1200 mL per day, and expressed on a bodyweight (5.9 kg for infants aged 0-4 months and 7.8 kg for infants aged 4 to < 6 months) basis. Values rounded to 2 significant figures (SF)

45. Based on the concentrations reported in Glavano *et al.* (2008) OTA exposures were also calculated for non-exclusive breastfed infants using consumption data from DNSIYC. An OTA average concentration in breast milk of 30.43 ng/L could lead to mean OTA exposures of 5.4 to 20 ng/kg bw per week and 97.5th percentile exposures of 11 to 34 ng/kg bw per week (Table 2) in infants aged 4 to 18 months. The maximum OTA concentration (405 ng/L) resulted in mean and 97.5th percentile

exposure estimates of up to 260 and 450 ng/kg bw per week in infants and young children, respectively.

Table 2 OTA exposure estimates (ng/kg bw per week) from non-exclusive breastfeeding.

OTA concentration (ng/L)	Estimated exposure (ng/kg bw/week)									
	4 to < 6 months		6 to < 9 months		9 to < 12 months		12 to < 15 months		15 to < 18 months	
	Mean	97.5th	Mean	97.5th	Mean	97.5th	Mean	97.5th	Mean	97.5th
Minimum < 5	<3.2	<5.4	<2.3	<5.6	<1.3	<4.1	<1.01	<2.6	<0.89	<1.8
Maximum 405	260	440	190	450	110	330	83	210	72	150
Average 30.43	20	33	14	34	8.1	25	6.3	16	5.4	11

Values rounded to 2 SF

OTA survey data

46. For children aged 4 to 18 months (Table 3 and 4) mean total UB exposure estimates ranged from 4.4 – 9.1 ng/kg bw per week; the 97.5th percentile total UB exposure estimates ranged from 18 – 22 ng/kg bw per week (UB).

47. For children aged 18 to 60 months (Table 5) the total mean UB exposure estimates ranged from 6.9 – 9.1 ng/kg bw per week (UB). The corresponding 97.5th percentile UB total exposure estimates ranged from 16 – 24 ng/kg bw per week.

48. Wheat products made the main contribution to total exposure in all age groups.

Table 3 Estimated OTA chronic exposure to children aged 4 to 12 months using data from foods analysed in years 1 and 2 of the four - year surveillance programme (retail survey).

Food Groups	Estimated exposure LB-UB (ng/kg bw/week)								
	4 to < 6 m-olds (n=116)			6 to < 9 m-olds (n=606)			9 to < 12 m-olds (n=686)		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Commercial Infant & young children Foods (77 samples)	100	0.84-4.1	3.43-16	578	0.98-5.04	3.7-18	618	0.98-4.8	3.6-18
Maize (corn) products (75 samples)	15	0.028-0.29	0.17-1.7	150	0.018-0.18	0.077-0.77	250	0.025-0.25	0.29-0.98
Wheat products (75 samples)	21	0.91-1.3	3.3-4.6	383	2.5-3.5	9.8-13	607	3.6-5.1	11-15
Rye and barley products (35 samples)	7	0.11-0.14	0.29-0.37	32	0.25-0.32	1.3-1.6	65	0.42-0.53	1.5-2.0
TOTAL of 4 groups above	**100**	**3.6-4.4**	**3.7-18***	**599**	**2.6-7.0**	**8.4-20***	**685**	**4.1-9.1**	**11-22***

* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories.

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution.

Table 4 Estimated OTA chronic exposures to children aged 12 to 18 months using data from foods analysed in years 1 and 2 of the four - year surveillance programme (retail survey)

Food Groups	Estimated exposure LB-UB (ng/kg bw/week)					
	12 to < 15 m-olds (n=670)			15 to < 18 m-olds (n=605)		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Commercial Infant & young children Foods (77 samples)	471	0.7-0.3.4	2.9-14	338	0.46-2.3	1.8-9.1
Maize (corn) products (75 samples)	302	0.032-0.32	0.11-1.1	296	0.034-0.35	0.13-1.3
Wheat products (75 samples)	649	4.8-6.7	13-19	597	5.3-7.7	12-17
Rye and barley products (35 samples)	47	1.1-1.4	5.0-6.3	25	1.05-1.3	4.3-5.5
TOTAL of 4 groups above	**667**	**5.2-9.1**	**14-22***	**602**	**5.5-9.1**	**13-20***

* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories.

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution.

Table 5 Estimated OTA chronic exposure to children aged 18 to 60 months using data from foods analysed in years 1 and 2 of the four - year surveillance programme (retail survey)

Food Groups	Estimated exposure LB-UB (ng/kg bw/week)					
	18 to 24 m-olds (n=118)			24 to 60 m-olds (n=688)		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Commercial Infant & young children Foods (77 samples)	43	0.41-2.03	1.5-7.0	78	0.20-0.98	1.3-6.6
Maize (corn) products (75 samples)	56	0.041-0.41	0.18-1.8	301	0.039-0.39	0.13-1.3
Wheat products (75 samples)	118	5.7-7.7	16-22	678	4.8-6.7	11-15
Rye and barley products (35 samples)	6	0.56-0.7	1.3-1.7	27	0.56-0.7	1.4-1.8
TOTAL of 4 groups above	**118**	**5.9-9.1**	**1.6-24***	**685**	**4.8-6.9**	**1.1-16***

* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories.

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution.

Risk characterisation

Uncertainties in the risk characterisation

49. The COT considered the TWI established by EFSA in 2006 conservative. However, in the absence of any additional, more suitable and recent data, the TWI by EFSA was considered acceptable for use in the current risk characterisation.

50. The available breast milk data from the literature are skewed to the left, with concentrations ranging from 1.1 ng/L to 405 ng/L. The maximum value used for the exposure assessment (405 ng/L) is 2-fold greater than the maximum value reported in other studies. Due to the highly skewed distribution, estimating exposure from the highest value within this range leads to considerable uncertainty in the extent of overestimation of the risk.

51. The study used to perform the exposure assessment (Galvano *et al*., 2008) reported concentrations of OTA in breast milk ranging from < 5 to 405 ng/L, with an average of 30.43 ng/L. No information on LODs or LOQs were given in the study and while the higher concentrations in breast milk were linked to high consumption of bread and cereal based foods as well as alcoholic beverages in a few cases, no clear explanation was provided for the high maximum value or its possible link to consumption.

Human breast milk

52. Assuming a low or average concentration of OTA, all estimated exposures for infants under the age of 6 month, fed exclusively on breast milk are below the TWI. These exposures are not of toxicological concern.

53. Assuming a low or average concentration of OTA, all mean and 97.5th percentile exposures for infants under the age of 18 months, fed non-exclusively on breast milk are below the TWI. These exposures are not of toxicological concern.

54. Assuming a high OTA concentration (405 ng/L) in infants fed exclusively on breast milk, exposures for low consumption (800 mL) are 2.5 – 3 times the TWI and for high consumption (1200 mL) 3.5 – 5 times the TWI. Assuming the same concentration of OTA for infants fed non-exclusively on breast milk, mean and 97.5th percentile exposures are 2 to 4 times the TWI.

55. The high concentration (405 ng/L) used here is twice any other reported concentration and given the highly skewed distribution of the data might therefore not be representative of OTA concentrations in breast milk.

OTA survey data

56. In infants and young children all mean (< 10 ng/kg bw per week) and 97.5th percentile (< 25 ng/kg bw per week) exposures were well below the TWI. These exposures are not of toxicological concern.

Conclusions

57. The TWI of 120 ng/kg bw per week established by EFSA in 2006 is conservative. However, in the absence of any additional, more suitable and recent data, the Committee agreed that this TWI should be used in its assessment of the potential risk of OTA.

58. At low or average concentrations of OTA in breast milk, all estimated exposures for infants under the age of 6 months, exclusively breastfed are below the TWI. These exposures are therefore not of toxicological concern. Assuming a high concentration of OTA in breast milk, infants could exceed the TWI by up to 5-fold.

59. At low or average concentrations of OTA in breast milk, mean and 97.5th percentile dietary exposures for all age groups, fed non-exclusively with breast milk, are below the TWI. These exposures are therefore not of toxicological concern. Assuming a high concentration of OTA in breast milk, infants fed non-exclusively on breast milk could exceed the TWI by up to 4-fold.

60. The available breast milk data suggest generally low exposures, but the TWI could potentially be exceeded by a few individuals in this population group if concentrations were at or above the highest measured value. Considering the conservativeness of the TWI, the skewness in the exposure data, the relatively short duration of breastfeeding, the probability that the highest measured value is an outlier and the fact that continued exposure to a concentration of 405 ng/L OTA in breast milk is very unlikely, adverse effects on health would not be expected.

61. In addition, concentrations at which reproductive and developmental effects have been reported were 5 to 344 times higher than the LOAEL (8 µg/kg bw) used by EFSA in 2006 to establish the TWI of 120 ng/kg bw. There was therefore no concern for these endpoints in any of the sub-groups, in view of the respective margins of exposure.

62. In infants and young children (4 months to 5 years), consuming commercial foods for these age groups, exposures were well below the TWI and hence there is no toxicological concern for OTA exposure in these groups.

Abbreviations

DNSIYC	Diet and Nutrition Survey of Infants and Young Children
FSA	Food Standards Agency
NDNS	National Diet and Nutrition Survey
TDS	Total Diet Survey
OTA	Ochratoxin A
EFSA	European Food Safety Authority
JECFA	Joint FAO/WHO Expert Committee on Food Additives
FAO	Food and Agriculture Organization of the United Nations
WHO	World Health Organisation
HBGV	Health based guidance value
PTWI	Provisional tolerable weekly intake
SCF	Scientific Committee for Food Standards Agency
EC	European Community
TDI	Tolerable daily intake
PEPCK	Phosphoenolpyruvate carboxykinase
NADH	Nicotinamide adenine dinucleotide
NTP	National Toxicology Program
BMD	Benchmark dose modelling
BMDL	Benchmark dose lower confidence limit
bw	Body weight
LOEL	Lowest observed effect level
LOAEL	Lowest observed adverse effect level
NOAEL	No observed adverse effect level
UF	Uncertainty factor
TWI	Tolerable weekly intake
LOQ	Limit of quantification
LOD	Limit of detection
UB	Upper bound
LB	Lower bound
GD	Gestation day
PND	Postnatal day

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