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

First draft 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's dietary recommendations for infants and young children. The SACN is examining the nutritional basis of the advice. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants, most of which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's 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. A scoping paper (TOX/2017/30), highlighting details of the concentration data and toxicology of mycotoxins surveyed in the 2014 Total Diet Survey (TDS) carried out by the Food Standards Agency (FSA) was discussed by the COT in July 2017. Members concluded that the potential risk from certain mycotoxins, including ochratoxin A (OTA), be reviewed in more detail.

3. A discussion paper[1] providing estimated OTA exposures for infants and young children in the UK aged 0 to 12 months and 1 to 5 years, respectively, was presented to the COT in December 2017. At the meeting in the absence of any newer toxicological data considered appropriate, Committee members agreed to use the Tolerable Weekly intake (TWI) value of 120 ng/kg bw that was derived in 2006 and re-confirmed in 2010 by the European Food Safety Authority (EFSA).

4. Members considered the TWI established by EFSA in 2006 was conservative and noted the uncertainties arising from the skewed breastmilk data. They requested updated text to reflect these points and to elucidate infant risk using the available reproductive and developmental studies.

5. The requested amendments and clarifications are shown as tracked changes.

Questions for the Committee

1. Does the Committee agree with the amendments and clarifications made in the text?

[1] https://cot.food.gov.uk/sites/default/files/tox2017-45_0.pdf

This is a draft statement and has not been finalised. Therefore, it should not be cited.

2. Do Members have any further comments on the first draft statement?

Secretariat
January 2018

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Background

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. Details of the concentration data derived from this survey, and the subsequent exposure assessments, were presented to the Committee in a scoping paper (TOX/2017/30) at the July 2017 meeting. To aid the discussions, brief toxicology summaries for each of the mycotoxins surveyed were included, along with available health based guidance values, a risk assessment, where possible, and possible conclusions. The Committee commented on the concentration data and the results of the exposure assessments, and suggested that certain mycotoxins should be reviewed in more detail. A discussion paper presented at the December 2017 meeting[1], provided more toxicological information for ochratoxin A (OTA), an in-depth description of the previously established Health Based Guidance Value (HBGV) by JECFA and EFSA and new *in vivo* toxicological data published since the 2006 EFSA opinion. In addition, the paper provided an exposure assessment for OTA in breast milk using European data from the literature and an updated exposure assessment for OTA in the diet of infants and young children aged 1 to 5 years.

4. OTA is a mycotoxin produced by several fungi species in the *Penicillium* and *Aspergillus* genera, primarily *Penicillum verrucosum*, *Aspergillus ochraceus* and

Aspergilli of the section *Nigri*, especially *A. carbonarius*. OTA has been reported 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[2].

6. In 2010[3] EFSA evaluated 5 research articles providing recent data on the toxicity of OTA and concluded that the data did not alter the evaluation carried out in 2006 (EFSA, 2010).

7. This statement provides a summary of the available toxicity data on OTA. This draws on the EFSA opinion (2006) and the EFSA statement (2010) and a literature review to identify any relevant *in vivo* toxicity studies published since the 2006 EFSA Opinion. The derivation of the health based guidance values (HBGVs) for the above evaluations is described. Exposure assessments have been carried out and risks characterised leading to the conclusions provided.

Toxicokinetics

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

9. OTA is rapidly absorbed following ingestion. Animal studies showed absorptions 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.

10. A two-compartment open model, consisting of a fast distribution and elimination phase followed by a slow elimination phase (plasma clearance) and a long half-life has been described for *in vivo* data. Based on limited data, the longest half-life in humans was described in one individual as 20 hours during the α-phase and 35 days during the β-phase, after ingestion of ^{3}H labelled OTA (Studer-Rohr et al., 2000). Initial testing resulted in 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 found OTA levels to remain constant in some individuals and to vary 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.

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

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

11. In many species, including monkeys and humans, renal elimination is the major route of excretion. In rodents, biliary excretion seems to predominate. The molecular weight of OTA (403.81 D) is above the threshold for biliary excretion in rats (300-400 D) but below the threshold for humans (500-600 D) (EFSA, 2008). Differences in the degree of serum protein binding and its effect on renal clearance, as well as the rate of conjugation and extent of entero-hepatic re-circulation contribute largely to the inter-individual and interspecies variability of kinetic parameters.

Toxicity

Summary from previous evaluations

12. The toxicity of OTA has previously been evaluated by JECFA. JECFA concluded that none of the new data that had become available indicate any reason for the HBGV established by JECFA in 1991 and endorsed in 1995 to be altered. The PTWI of 100 ng/kg bw was therefore retained in the evaluations of 2001 and 2007 (FAO/WHO, 2007). The Scientific Committee for Food (SCF) evaluated OTA 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 TDI's of 1.2 – 14 ng/kg bw/day, preferably below 5 ng/kg bw/day (SCF, 1998).

Studies used in the derivation of the HBGV

13. Both, JECFA and EFSA used two experimental pig studies for the derivation of their HBGVs.

14. In a study by Elling (1979) female pigs were exposed to OTA at 5 mg/kg feed (calculated by the authors to a corresponding exposure of 400 µg/kg bw) for 5 days. Animals exposed to OTA at 1 mg/kg feed (calculated by the authors to correspond to exposure of 24.1 – 50.2 µg/kg bw) for 3 months or 2 years were derived from a previous experiment (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 activity of various enzymes was 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 month, 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).

15. In a study by Krogh et al. (1988) female pigs received a gelatine capsule daily containing OTA at 0.25 mg and 1.17 mg, corresponding to a feed level of 0.2 mg/kg and 1 mg/kg. Renal impairment was observed in both experimental groups after 5 weeks of exposure. Further, the activities of both cytosolic phosphoenolpyruvate carboxykinase (PEPCK) and gamma-glutamyl transpeptidase were decreased after 1 week of exposure and the enzyme activities stayed inhibited 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 an increased renal impairment and decreased enzyme activity, the authors concluded that these enzymes were sensitive indicators of OTA induced porcine nephropathy (Krogh et al. 1988).

HBGV established by JECFA and EFSA

JECFA

16. JECFA first evaluated OTA in 1991, establishing a provisional tolerable weekly intake (PTWI) of 112 ng/kg bw per day based on the deterioration of renal function in pigs as given in the studies by Elling (1979) and Krogh et al. (1988) (Paragraphs 14 and 15). The LOEL 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 2008 evaluation, using carcinogenicity data from the rat bioassay performed by the National Toxicology Program (NTP) in 1989. JECFA considered this to be the most appropriate data for modelling due to the occurrence of combined adenomas and carcinomas in kidneys and male rats being the most sensitive species and sex for kidney carcinogenicity.

19. The lowest $BMDL_{10}$ had a value of 15 µg/kg bw per day and the model having the best fit had a value of 25 µg/kg bw per day. JECFA therefore concluded that for establishing the PTWI, the $BMDL_{10}$ in the rat does not provide a lower point of departure than the previously used LOEL for minimal renal toxicity in the pig.

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

EFSA opinion, 2006

21. In its 2006 opinion, EFSA considered that there was an absence of conclusive evidence that OTA binds to DNA and therefore concluded that the hazard characterisation should be based on nephrotoxicity. The most sensitive and pivotal effects of OTA are its effects on the kidneys in rats and pigs.

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

23. EFSA concluded that 8 µg/kg bw per day was a LOAEL representing an early marker of renal toxicity in experimental animals (i.e. female pigs) and likely to be

close to a NOAEL as the observed changes in biochemical markers indicated transient changes in the kidneys (EFSA, 2006; JECFA 2001).

24. The default factor of 2.5 was used to account for toxicodynamic effects of interspecies differences; the Panel noting that there were significant differences between species, especially with regard to protein binding. A factor of 6 was applied to account for kinetic differences in consideration of the plasma half-life. The common uncertainty factor (UF) of 10 was used to extrapolate from the general population to a potentially sensitive sub-population. In addition, EFSA used a factor of 3 to take into account the extrapolation from a LOAEL to a NOAEL.

25. Using the LOAEL of 8 µg/kg bw/day and applying a total UF of 450 (2.5 x 6 x 10 x 3) EFSA established a tolerable daily intake of approximately 18 ng OTA/kg bw per day.

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

EFSA statement, 2010

27. 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.

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

29. 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 kidney damage. However, in the absence of any additional suitable and more recent data, the Committee agreed the TWI established by EFSA was appropriate to review the potential risk of OTA.

30. It was noted that the use of an UF of 6 for kinetic 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.

In vivo toxicity studies published since the 2006 EFSA opinion

The COT reviewed the new *in vivo* toxicity studies since the EFSA opinion in 2006 in the discussion paper[1] 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 LOEL of 8 µg/kg bw used by EFSA in 2006.

Human breast milk

31. The COT reviewed the available breastmilk data in the discussion paper[1]; in the absence of UK data, studies from all EU member states were included. Most levels were in the range of 1.1 – 182 ng OTA/L. Two Italian studies however reported higher levels of OTA, ranging from < 5 ng/L and 1200/1700 ng/L to maximum levels of 405 ng/L and 6600 ng/L.

32. Based on the available 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) detected agree with a range of other studies, the maximum concentration of 405 ng/mL is 2-fold greater than reported in the other studies and using this value can be considered conservative.

Exposure Assessment

33. Levels of various mycotoxins were measured in the Total Dietary Survey (TDS), including OTA. 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 the following reasons.

34. Since analysis of the TDS samples involved a wide range of matrices (some of which have not been routinely examined previously), existing validated methods 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 & vegetables (e.g. orange, carrot etc.) in addition to grape has led to some analytical difficulties, with poor recoveries and consequently high results. The low recovery meant that the large correction inflated the result and will impact on calculated dietary exposures. Given the low recovery of 32 %, this method is not considered suitable for this food matrix. Also, the reported level 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).

35. Further, a range of matrices was included in a single batch in the analysis of mycotoxins. This has 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 are the same food matrix. In the above example, three very different matrices - dried fruit and 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.

36. A multi-mycotoxin method was used in the analysis for various food groups, which is normally a screening method rather than a sensitive technique. 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.

37. Therefore, occurrence data from the TDS are not suitable for estimating dietary exposures quantitatively. They are not sensitive enough and the methods are not sufficiently standardised and validated for this purpose.

38. Alternative OTA survey data were therefore considered for estimating dietary exposures for infants and young children. 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 0 < 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

39. 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 not been used in the exposure assessment. In general, the available European data for OTA in breastmilk ranging from 1.1 ng/L to 405 ng/L show a highly skewed distribution.

40. Based on the available data, the study by Galvano et al. (2008) has been selected for the exposure assessment. The minimum concentration (< 5 ng/L) detected agrees with a range of other studies; the maximum (405 ng/L) concentration detected is approximately two times the maximum level reported in other studies. The use of 405 ng/L for the exposure assessment can therefore be considered conservative.

41. Based on the levels given by Glavano et al. (2008) OTA exposure levels 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 month olds 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 of 384 and 577 ng/kg bw per week in 0 to < 4 month old infants and 291 and 436 ng/kg bw per week in 4 to < 6 month old infants, respectively.

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

OTA concentration (ng/L)	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	384	291	577	436
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)

42. Based on the levels given by Glavano et al. (2008) OTA exposure levels 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 exposures of up to 261 and 451 ng/kg bw per week in infants and young children, respectively.

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

OTA concentration (ng/L)	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	261	439	189	451	108	328	83	213	72	147
Average 30.43	20	33	14	34	8.1	25	6.3	16	5.4	11

Values rounded to 2 SF

Other dietary sources

43. The FSA recognises the need to monitor foodstuff for the levels of mycotoxins and undertook two FSA retail surveys in 2010 and 2011 (FSA, 2010; FSA, 2011). 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 of foods based on maize, wheat, rye and barley and commercial infant and young children foods.

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

45. Year 2 of the UK retail survey investigated the presence of mycotoxins in food produced for infants and young children. 77 samples of commercial infants and young children foods 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.

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

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

This is a draft statement and has not been finalised. Therefore, it should not be cited.

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	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

This is a draft statement and has not been finalised. Therefore, it should not be cited.

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	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	0.4.1-2.03	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 suitable and more recent data, the TWI by EFSA has been found appropriate.

50. The available breastmilk data from the literature are skewed, with levels 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 breastmilk 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 reason was provided for the high maximum value or it's 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 breastmilk, 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 breastmilk, mean and 97.5th percentile exposures are 2 to 4 times the TWI.

55. The high concentration (405 ng/L) used here is two times any other reported level and might therefore not be representative.

Other dietary sources

56. In infants and young children all mean and 97.5th percentile exposures were below the TWI. These exposures are not of toxicological concern.

Conclusions

57. The TWI established by EFSA in 2006 is conservative. However, in the absence of any additional suitable and more recent data, the TWI by EFSA is considered appropriate to review the potential risk of OTA.

58. 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. Assuming a high concentration, infants exceed the TWI by up to 5 fold.

59. Assuming low or average exposures for infants up to 6 months, fed non-exclusively with breast milk and mean and 97.5th percentile dietary exposures for infants at all age groups are below the TWI. These exposures are of no toxicological concern. Assuming a high concentration, infants exceed the TWI by up to 4 fold.

60. The available breastmilk data suggests generally low exposures, yet the TWI could potentially be exceeded by a few individuals in this population group if exposures were at the highest measured value. Considering the conservativeness of the TWI, the skewed exposure data, the relatively short duration of breastfeeding, the probability that the highest measured value is an outlier and the fact that a (continued) level of 405 ng/L in breastmilk is unlikely, effects on health would not be expected.

61. In addition, levels at which reproductive and developmental effects have been reported were 5 to 344 times higher than the LOEL (8 µg/kg bw) used by EFSA in 2006 to establish the TWI of 120 ng/kg bw.

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
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
IL	Interleukin
NF-kB	Nuclear factor kappa beta
eNOS	Endothelial nitric oxide synthase
iNOS	Inducible nitric oxide synthase
SOD	Superoxide dismutase
FB1	Fumonisin B1
TNF-α	Tumour necrosis factor α
HO-1	Heme oxygenase
ASAT	Aspartate aminotransferase
ALAT	Alanine aminotransferase
MDA	Malondialdehyde
AST	Aminotransferase
ALP	Alkaline phosphatase
TP	Total serum protein
BUN	Blood urea nitrogen
CREA	Creatinine
TG	Triacylglycerol
LDH	Lactate dehydrogenase
GLU	Glucose
ALB	Albumin
PCNA	Proliferating cell nuclear antigen
DSB	Double strand break
HDL	High density lipoprotein

MOA	Mode of action
CLU	Clusterin
OPN	Osteopontin
BdrU+	5-bromo-2-deoxyuridine
TBARS	Thiobarbituric acid-reactive substances
DA	Dopamine
TH	Tyrosine hydroxylase
ED50	Median effective dose
ip	Intraperitoneal
AFB1	Aflatoxin B1
OTB	Ochratoxin B
OTC	Ochratoxin C
GD	Gestation day
PND	Postnatal day

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