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

Addendum to the 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 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 infant aged 0 to 12 months and children aged 1 to 5 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. The subsequent statement on OTA was published in 2019.

3. In 2020, EFSA updated their 2006 assessment on ochratoxin A (OTA) in food and concluded that due to the uncertainties surrounding the genotoxic/carcinogenic mode of action, it would not be appropriate to establish a health-based guidance value (HBGV) and applied a margin of exposure (MOE) approach instead.

4. Following the update by EFSA, the imminent publication of the SACN report and the ongoing work on plant-based drinks, which includes OTA, this paper provides an update/addendum to the 2019 OTA statement. The MOE approach has been applied to the 2019 exposure assessment, utilising the $BMDL_{10}$ for non-neoplastic and neoplastic effects calculated by EFSA.

Questions to the Committee

i. Does the Committee agree with the revised risk characterisation and conclusions?

ii. Does the Committee agree this addendum will be sufficient and that it is not necessary to re-open the assessment of OTA ?

iii. Do Members have any other comments?

Secretariat

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Background

5. In 2020, EFSA published an updated assessment on ochratoxin A (OTA) in food revising their 2006 opinion used in the 2019 COT evaluation.

6. OTA is a potent renal toxin in all tested animal species, with the pig being the most sensitive. The extent of renal injury is associated with the duration of exposure, as OTA accumulates in renal tissue. Kidney tumours having been observed in mice and rats, in both sexes. *In vitro*, OTA induced gene mutation, single and double strand breaks, and chromosome damage in mammalian cells, often associated with pathological findings in the rat kidney.

7. The genetic damage induced by OTA is seemingly independent of metabolic activation, some effects may be secondary to oxidative stress. Overall, EFSA concluded that the mechanisms of genotoxicity are unclear, with direct and indirect genotoxic and non-genotoxic mode of actions each possibly contributing to the reported tumour formation.

8. EFSA did not identify studies in humans which provided reliable biomarkers of OTA-specific effects, in particular on kidney function. Epidemiological studies using cross-sectional designs were unable to establish a causal link between exposure and adverse effects (kidney disease, bladder or hepatocellular cancer) in humans.

9. Given the uncertainties regarding the mode of action for kidney carcinogenicity, EFSA considered it inappropriate to establish a health-based guidance value (HBGV) and instead applied a margin of exposure approach to their assessment in 2020. Increased incidences of microscopic kidney lesions in female pigs were identified as the critical non-neoplastic effect, with a $BMDL_{10}$ of 4.73 µg/kg body weight per day. Kidney tumours in rats were identified as the critical neoplastic effect, with a $BMDL_{10}$ of 14.5 µg/kg body weight.

10. For the characterisation of non-neoplastic effects EFSA considered an MOE of ≥ 200 of low health concern; a default uncertainty factor (UF) of 100 for intra- and interspecies differences and an additional UF of 2 for the extrapolation from a 3-month study to chronic exposure was applied. Following the EFSA guidance an MOE of ≥ 10,000 was considered of low health concern for neoplastic effects. EFSA

considered that the MOE of 10,000 for substances that are genotoxic and carcinogenic could be particularly conservative in this case because the evidence for a direct interaction of OTA with the DNA is inconclusive.

11. OTA was last assessed by the COT within the scope of the infant feeding review in 2019 (COT, 2019). In light of EFSAs new assessment and application of the MOE approach, as well as the current COTs work on plant-based drinks, the COT considered the previous exposure levels and conclusions against the MOE approach.

Exposure assessment

12. Please note that the following information and estimated exposures have been taken from the 2019 COT statement.

13. In brief, in the absence of UK data of OTA in breastmilk, studies from other EU member states were considered and 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 agreed 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.

14. Based on the concentrations reported, OTA exposures were estimated for exclusively breastfed infants consuming average (800 mL) and high-level (1200 mL) volumes of breast milk (Table 1).

Table 1 Estimated chronic OTA exposures (ng/kg bw per week) in exclusively breastfed infants.

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	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)

15. Based on the concentrations reported in Galvano et al. (2008) OTA exposures were also calculated for non-exclusive breastfed infants using consumption data from DNSIYC (Table 2).

Table 2 Estimated chronic OTA exposure (ng/kg bw per week) in non-exclusively breastfed infants.

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	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

16. While the data obtained from the Total Diet Study (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. Data from the 2010/2011 FSA retail survey were used for the exposure assessment instead (for details see COT, 2019; Tables 3-5).

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

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

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

Margin of exposure (MOE) approach

17. The following MOEs (Table 6-15) were calculated applying EFSAs $BMDL_{10}$ of 4.73 and 14.5 µg/kg body weight per day for critical non-neoplastic and neoplastic effects, respectively, and the estimated OTA exposures from the 2019 COT assessment provided in Tables 1-5 above.

Table 6 MOEs for non-neoplastic effects of OTA in exclusively breastfed infants.

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	< 7000	< 9100	< 4700	< 6100
Maximum 405	86	110	57	75
Average 30.43	1100	1500	770	1000

Table 7 MOEs for neoplastic effects of OTA in exclusively breastfed infants.

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	< 22000	< 2800	< 14000	< 19000
Maximum 405	260	350	180	230
Average 30.43	3500	4600	2400	3100

Table 8 MOEs for non-neoplastic effects of OTA in non-exclusively breastfed infants.

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	<10000	<6100	<14000	<5900	<25000	<8000	<33000	<13000	<37000	<18000
Maximum 405	130	75	170	74	300	100	400	160	460	220
Average 30.43	1700	1000	2400	970	4100	1300	5300	2100	6100	3000

Table 9 MOEs for neoplastic effects of OTA in non-exclusively breastfed infants.

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	<32000	<19000	<44000	<18000	<78000	<25000	<100000	<39000	<110000	<56000
Maximum 405	390	230	530	230	920	310	1200	490	1400	680
Average 30.43	5100	3100	7300	3000	13000	4100	16000	6300	19000	9200

Table 10 MOEs for non-neoplastic effects of OTA in children aged 4 to 12 months.

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	39000-8000	9700-2100	578	34000-6600	8900-1800	618	34000-6900	9200-1800
Maize (corn) products (75 samples)	15	1200000-110000	190000-19000	150	1800000-180000	430000-43000	250	1300000-130000	110000-34000
Wheat products (75 samples)	21	36000-25000	10000-7200	383	13000-9500	3400-2500	607	9200-6500	3000-3200
Rye and barley products (35 samples)	7	300000-240000	110000-89000	32	130000-100000	25000-21000	65	79000-62000	22000-17000
TOTAL of 4 groups above	**100**	**9000-7500**	**8900-1800**	**599**	**13000-4700**	**3900-1700**	**685**	**8100-3600**	**3000-1500**

Table 11 MOEs for neoplastic effects of OTA in children aged 4 to 12 months.

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	120000-25000	30000-6300	578	100000-20000	27000-5600	618	100000-21000	28000-5600

Maize (corn) products (75 samples)	15	3600000-350000	600000-60000	150	5600000-560000	1300000-130000	250	4000000-400000	350000-100000
Wheat products (75 samples)	21	110000-78000	31000-22000	383	41000-29000	10000-7800	607	28000-20000	9200-6800
Rye and barley products (35 samples)	7	920000-720000	350000-270000	32	400000-320000	78000-63000	65	240000-190000	68000-51000
TOTAL of 4 groups above	**100**	**28000-23000**	**27000-5600**	**599**	**39000-15000**	**12000-5000**	**685**	**25000-11000**	**9200-4600**

Table 12 MOEs for non-neoplastic effects of OTA in children aged 12 to 18 months.

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	47000-97000	11000-2400	338	72000-14000	18000-3600
Maize (corn) products (75 samples)	302	1000000-100000	300000-30000	296	970000-95000	250000-25000
Wheat products (75 samples)	649	6900-4900	2500-1700	597	6200-4300	2800-1900
Rye and barley products (35 samples)	47	30000-24000	6600-5300	25	32000-25000	7700-6000
TOTAL of 4 groups above	**667**	**6400-3600**	**2400-1500**	**602**	**6000-3600**	**2500-1700**

Table 13 MOEs for neoplastic effects of OTA in children aged 12 to 18 months.

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	150000-300000	35000-7300	338	220000-44000	56000-11000
Maize (corn) products (75 samples)	302	3200000-320000	920000-92000	296	3000000290000	780000-78000
Wheat products (75 samples)	649	21000-15000	7800-5300	597	19000-13000	8500-6000
Rye and barley products (35 samples)	47	92000-73000	20000-16000	25	97000-78000	24000-18000
TOTAL of 4 groups above	**667**	**20000-11000**	**7300-4600**	**602**	**18000-11000**	**7800-5100**

Table 14 MOEs for non-neoplastic effects of OTA in children aged 18 to 60 months.

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	80000-16000	22000-4700	78	170000-34000	25000-5000
Maize (corn) products (75 samples)	56	800000-81000	180000-18000	301	850000-85000	250000-25000
Wheat products (75 samples)	118	5800-4300	2000-1500	678	6700-4900	3000-2200
Rye and barley products (35 samples)	6	59000-47000	25000-19000	27	59000-47000	24000-18000
TOTAL of 4 groups above	**118**	**5600-3600**	**21000-1400**	**685**	**6900-4800**	**30000-2100**

Table 15 MOEs for neoplastic effects of OTA in children aged 18 to 60 months.

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	250000-50000	68000-15000	78	500000-100000	78000-15000
Maize (corn) products (75 samples)	56	2500000-250000	560000-56000	301	2600000-260000	780000-78000
Wheat products (75 samples)	118	18000-13000	6300-4600	678	21000-15000	9200-6800
Rye and barley products (35 samples)	6	180000-150000	78000-60000	27	180000-150000	730000-560000
TOTAL of 4 groups above	**118**	**17000-11000**	**63000-4200**	**685**	**21000-15000**	**92000-6300**

Risk characterisation

18. EFSA considered it was not appropriate to establish a HBGV in their 2020 assessment of OTA but applied an MOE approach instead.

19. MOEs of ≥ 200 and ≥ 10,000 were considered of low health concern for non-neoplastic and neoplastic effects, respectively. EFSA emphasised that for neoplastic effects it was not possible to clearly distinguish between direct and indirect mechanisms of genotoxicity. If the mechanism of genotoxicity were direct, then the MOE of 10,000 would be sufficiently cautious but for an indirect mechanism it would be overcautious. However, it is likely to be particularly conservative, as the evidence for a direct interaction of OTA with the DNA is inconclusive and other threshold mechanism make play a role in kidney tumour formation.

20. The MOEs for non-neoplastic effects in exclusively and non-exclusively breastfed infants are > 200, with the exception of a number of MOEs based on the maximum OTA concentration reported in breastmilk.

21. However, 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. 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.

22. Hence, estimating exposure from the highest value within this range leads to considerable uncertainty in the extent of overestimation of the risk and the respective MOEs (< 200) are likely to be of low concern.

23. All MOEs for neoplastic effects at the reported minimum concentration of OTA in exclusively and non-exclusively breastfed infants are > 10,000 and therefore of low concern. All MOEs for neoplastic effects at the maximum and several MOEs at the reported average concentration of OTA however are < 10,000. Considering all MOEs are > 5000, the uncertainties in the breastmilk data and the conservativeness in EFSAs MOE of 10,000 for OTA, the MOEs here are unlikely to be of health concern.

24. All MOEs for non-neoplastic effects following dietary OTA exposure are > 200 and therefore of low health concern.

25. The majority of MOEs for neoplastic effects following dietary exposure to OTA are > 10,000, with the exceptions of MOEs at the 97.5th percentile for wheat products and the sum of all 4 food groups. Considering all MOEs are > 4000, the exposures being conservative and EFSAs consideration that an MOE of 10,000 may be conservative, given the uncertainties surrounding the mechanism of action for

carcinogenicity, while undesirable, these exposures to OTA are likely to be of low health concern.

Conclusions

26. The MOEs < 200 for exclusively and non-exclusively breastfed infants are of low concern due to the considerable uncertainties in the data. Hence, all MOEs for non-neoplastic effects are of low concern.

27. While a number of MOEs at the 97.5th percentile are < 10,000 for neoplastic effects in dietary exposures to OTA, the uncertainties and conservativeness in the MOE of 10,000 means that while undesirable, these exposures are likely to be of low concern overall.

28. Given that the uncertainties in the MOE approach are high, the assessment is more likely to over- than underestimate the risk.

29. Applying the MOE approach to the estimated exposures from the COTs 2019 assessment did not alter the previous conclusions on OTA. While exposures to OTA are undesirable, given it is a potential genotoxic carcinogen and no safe levels can be applied, overall, the exposures are of low health concern to infants aged 0 to 12 months and children 1 to 5 years.