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

Review of potential risks from moniliformin 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. The Food Standards Agency (FSA) has completed a survey of 36 mycotoxins in the 2014 Total Diet Study (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, T-2 toxin (T2), HT-2 toxin (HT2), neosolaniol (NEO), nivalenol, 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 have been 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. A scoping paper (TOX/2015/32)[1] "COT contribution to SACN review of complementary and young child feeding; proposed scope of work for 1-5 year old children" was reviewed by the COT in 2015. A further scoping paper for mycotoxins was presented to the COT in 2017[2]. It was decided that a risk characterisation should be completed for moniliformin (MON) once EFSA had published a scientific opinion.

[1] https://cot.food.gov.uk/sites/default/files/TOX2015-32%20Feeding%20Review%20Scoping%20Paper.pdf

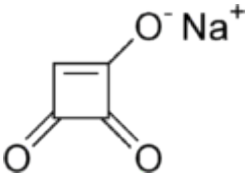
[2] https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf

4. This risk characterisation for MON makes use of the recently published scientific opinion from EFSA (EFSA, 2018). Following a request of the European Commission, the EFSA Panel on Contaminants in the Food Chain (CONTAM) assessed the risk of MON to human and animal health related to its presence in food and feed.

5. No previous scientific risk assessments on MON in food and/or feed by national agencies, national and international independent expert advisory committees were identified by the Panel. In the European Union (EU) and worldwide, no legal maximum levels or guidance levels have been set for MON in foods and feeds.

Background

6. MON is a mycotoxin with low molecular weight produced by several Fusarium species and Penicillium melanoconidium. It occurs predominantly in cereal grains and subsequently cereal products. Its IUPAC name is 3-hydroxy-3-cyclobutene-1,2-dione and the chemical structure is displayed below:



7. Co-occurrence of MON with other mycotoxins such as type A and B trichothecenes has been reported (reviewed in Grenier & Oswald 2011, Streit et al. 2012). However, the Panel concluded that the available database describing possible effects of combined exposure to MON and other mycotoxins was weak and insufficient for establishing the nature of combined effects.

8. No relevant human epidemiological data on MON were identified by ESFA. Although it has been hypothesised in published literature that dietary exposure to MON was involved in past incidence and prevalence of Keshan disease (KD) (a cardiomyopathy) in some regions in China (Liu 1996), the Panel noted that the evidence for a causal relation between dietary exposure to MON and the incidence of KD was too weak and insufficient for human hazard characterisation.

9. The data on the toxicokinetics of MON in experimental animals were limited. Only two in vivo studies on the toxicokinetics of MON were identified, both in S-D rats. In rats, a large portion of MON was absorbed and rapidly excreted in urine after administration. The authors noted that fate of at least half of the amount ingested remained unknown in the study. Tissue concentrations were not measured. The authors speculated that MON might be biotransformed and then excreted in urine to some unknown form (Jonsson et al. 2013, 2015).

10. Acute toxicity of MON was identified in rats, with oral LD_{50} values ranging from 19 to 25 mg MON/kg b.w. in experiments using 99% pure MON. Acute oral toxicity in mice was lower with LD_{50} values of about 50 mg MON/kg b.w. Adverse effects included ultrastructural myocardial lesions, decreased myocardial contractile force, ventricular arrhythmia and congestive heart failure. The Panel identified one subacute study in rats, where indications of cardiotoxicity were observed at 9 mg MON/kg b.w. per day, and a no observed adverse effect level (NOAEL) of 6 mg MON/kg b.w. per day. One subchronic study with a limited number of rats was identified in which cardiotoxicity and mortality were induced at 32.5 mg MON/kg b.w. per day, and a NOAEL of 16.6 mg MON/kg b.w. per day was identified for mortality for male rats. Data on haematotoxicity and immunotoxicity were too scarce to conclude on the hazard of MON in experimental animals. For developmental and reproductive toxicity, one study in mink was identified. Exposure to 1.94 mg MON/kg b.w. per day resulted in significant neonatal mortality and reduced offspring body weights, and a NOAEL of 0.92 mg MON/kg b.w. per day was identified.

11. Studies show MON does not induce bacterial reverse mutation. MON has been shown to be clastogenic in vitro, inducing chromosomal aberrations and micronuclei, however no data were identified to conclude on whether this is caused by a direct or indirect mechanism. No in vivo genotoxicity data or carcinogenicity data were identified in the published literature.

Margin of Exposure

12. Due to the limitations in the available toxicity data in animals, neither acute nor chronic health-based guidance values (HBGV) could be established by the Panel. Therefore, a margin of exposure (MOE) approach was used to assess the level of risk.

13. For acute and subacute exposure to MON, the Panel identified cardiotoxicity as a critical adverse health effect. Heart failure was observed at 15 mg/kg b.w. per day and indications of cardiotoxicity were seen at 9 mg MON/kg b.w. per day from a subacute study in S-D rats (Jonsson et al. 2015). EFSA used the NOAEL of 6 mg MON/kg b.w., identified from this study, as the reference point to calculate the MOE for acute human exposures to MON.

14. For chronic exposure to MON, the Panel identified haematotoxicity as the most sensitive endpoint measured in barrow pigs for human hazard characterisation (suitable dose-response data in other experimental animals were absent). The Panel identified a benchmark dose (lower confidence limit) ($BMDL_{05}$; where change in response is likely to be < 5%) of 0.20 mg MON/kg b.w. from the dose-response data on the decrease of haematocrit and haemoglobin levels from a 28-day study in pigs (Harvey et al. 2001). This value was used as the point of departure to calculate MOE for chronic human exposures to MON.

Exposure assessment

15. Exposure assessment in this discussion paper uses data from the FSA-funded 2014 Total Diet Study (TDS) carried out by the Food and Environment Research Agency (FERA), which provides concentrations of mycotoxins detected in food.

16. The analysis of MON in the TDS was not straightforward, especially due to the number of food matrices analysed for the TDS. Recovery results were low, as the mean recovery for cereal spiked at 25 µg/kg was 8 %. However "the sensitivity of the LC-MS/MS method and the fact that every sample was overspiked at 25 µg/kg meant that even with very low recovery reasonable LOQs could be determined, and if moniliformin had been present in the samples it would have been detected" (Stratton et al. 2015 unpublished).

17. In all food group samples analysed, MON was detected at levels below the LOQ, and in one food group below the LOD (dried fruit). The LOQ ranged from 1.31 to 39.50 µg/ kg. Corresponding acute and chronic human exposures are provided in Tables 1a and 1b, respectively, and are expressed as a range of lower bound (LB) and upper bound (UB). The LB is obtained by assigning a value of zero (minimum possible value) to all samples reported as < LOD or < LOQ. The UB is obtained by assigning the numerical value of LOD to values reported as < LOD, and LOQ to values reported as < LOQ (maximum possible value), as recommended by WHO (2009). Thus, the use of LB and UB estimates are likely to underestimate and overestimate human exposures, respectively.

18. MON exposures from dietary consumption were calculated using occurrence data from the TDS - mycotoxin analysis (Stratton et al., 2015) and consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH 2013, Lennox et al. 2013) and the National Diet and Nutrition Survey rolling programme (NDNS) (Bates et al. 2014 & 2016, Roberts et al. 2018).

Acute exposures

19. For acute exposures, mean and 97.5th percentile MON exposures for infants aged 4 to 12 months ranged from 0 - 0.12 and 0 - 0.29 µg/kg b.w./day, respectively. For young children aged 12 to 18 months the mean and 97.5th percentile exposures ranged from 0 - 0.20 and 0 - 0.44 µg/kg b.w./day, respectively. Calculated mean and 97.5th percentile dietary exposures for young children aged 18 to 60 months ranged from 0 - 0.22 and 0 - 0.45 µg/kg b.w./day, respectively.

Chronic exposures

20. For chronic exposures, mean and 97.5th percentile MON exposures for infants aged 4 to 12 months ranged from 0 - 0.072 and 0 - 0.18 µg/kg b.w./day, respectively.

For young children aged 12 to 18 months the mean and 97.5th percentile exposures ranged from 0 - 0.13 and 0 - 0.31 µg/kg b.w./day, respectively. Calculated mean and 97.5th percentile dietary exposures for young children aged 18 to 60 months ranged from 0 - 0.15 and 0 - 0.29 µg/kg b.w./day, respectively.

Table 1a. Estimated acute MON exposures from the TDS infants and young children aged 4 to 60 months (µg/kg b.w./day)

Age (months)	**Mean (LB, UB)**	**97.5th percentile (LB, UB)**
4 to <6 (n = 116)	0.000-0.018	0.000- 0.11
6 to <9 (n = 606)	0.000-0.037	0.000-0.14
9 to <12 (n = 686)	0.000-0.12	0.000-0.29
12 to <15 (n = 670)	0.000-0.17	0.000-0.42
15 to <18 (n = 605)	0.000-0.20	0.000-0.44
18 to 24 (n = 118)	0.000-0.21	0.000-0.45
24 to 60 (n = 688)	0.000-0.22	0.000-0.44

Values rounded to 2 significant figures (SF)

Table 1b. Estimated chronic MON exposures from the TDS infants and young children aged 4 to 60 months (µg/kg b.w./day)

Age (months)	**Mean (LB, UB)**	**97.5th percentile (LB, UB)**
4 to <6 (n = 116)	0.000- 0.010	0.000- 0.047
6 to <9 (n = 606)	0.000- 0.037	0.000- 0.14
9 to <12 (n = 686)	0.000- 0.072	0.000- 0.18
12 to <15 (n = 670)	0.000- 0.11	0.000- 0.24
15 to <18 (n = 605)	0.000- 0.13	0.000- 0.31
18 to 24 (n = 118)	0.000- 0.15	0.000- 0.29
24 to 60 (n = 688)	0.000- 0.15	0.000- 0.29

Values rounded to 2 significant figures (SF)

Risk characterisation

21. MOEs for MON were calculated by dividing the point of departure by the estimated UK acute and chronic exposures in Tables 1a and 1b.

Acute MOEs

22. The point of departure used for calculating MOEs for acute exposures (Table 2a) was the NOAEL of 6.0 mg/ kg b.w. derived from the subacute study in rats (Jonsson et al. 2015). For infants aged 4 to 12 months, the smallest MOE was 21000 which occurred at the 97.5th percentile for 9 to <12 month-olds. For children aged 12 to 18 months, the smallest MOE was 14000, which occurred at the 97.5th percentile for 15 to <18 month-olds. For young children aged 18 to 60 months, the smallest MOE was 13000, which occurred at the 97.5th percentile for 18 to 24 month-olds.

Chronic MOEs

23. The point of departure used for calculating MOEs for chronic exposures (Table 2a) was the $BMDL_{05}$ of 0.20 mg MON/kg b.w. per day derived from a 28-day study in pigs (Harvey et al. 2001). For infants aged 4 to 12 months, the smallest MOE was 1100 which occurred at the 97.5th percentile for 9 to <12 month-olds. For children aged 12 to 18 months, the smallest MOE was 650, which occurred at the 97.5th percentile for 15 to <18 month-olds. For young children aged 18 to 60 months, the smallest MOE was 700, which occurred at the 97.5th percentile for 18 to 24 month-olds.

The RISK21 Matrix

24. The RISK21 matrix been developed under a program of the Health and Environmental Sciences Institute as a highly visual method of assessing risk using exposure and hazard information and uses the acceptable MOE to derive the visualisation onto which the risk calculation is plotted. Figure 1 shows minimum (LB) and maximum (UB) potential chronic exposure for MON in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. MON is situated in the lower left region of the matrix indicating a low risk of adverse health effects.

Figure 1. Risk 21 matrix

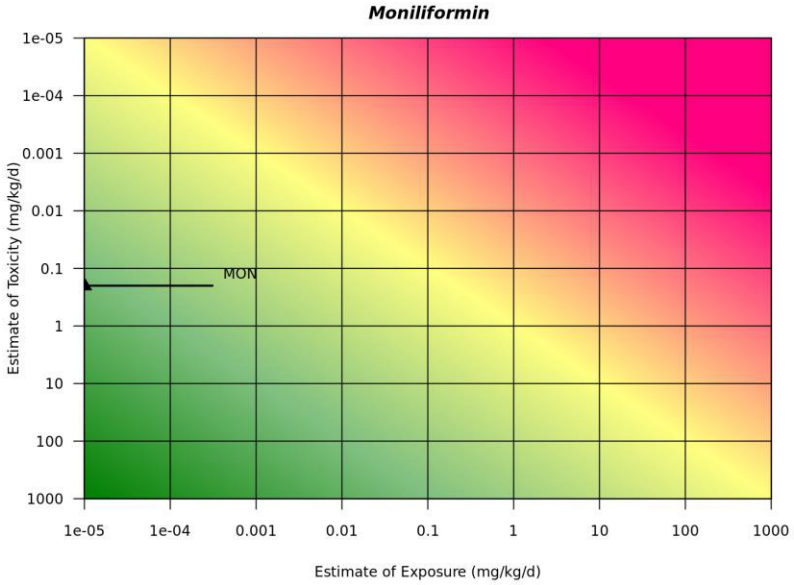


Table 2a. MOEs from estimated acute exposure to MON from the TDS infants and young children aged 4 to 60 months

Age (months)	**Mean (LB, UB)**	**97.5th percentile (LB, UB)**
4 to <6 (n = 116)	≥330000	≥55000
6 to <9 (n = 606)	≥330000	≥55000
9 to <12 (n = 686)	≥50000	≥21000
12 to <15 (n = 670)	≥35000	≥14000
15 to <18 (n = 605)	≥30000	≥14000
18 to 24 (n = 118)	≥29000	≥13000
24 to 60 (n = 688)	≥27000	≥14000

Values rounded to 2 significant figures (SF)

Table 2b. MOEs from estimated chronic exposure to MON from the TDS infants and young children aged 4 to 60 months

Age (months)	**Mean (LB, UB)**	**97.5th percentile (LB, UB)**
4 to <6 (n = 116)	≥20000	≥4300
6 to <9 (n = 606)	≥5400	≥1500
9 to <12 (n = 686)	≥2800	≥1100
12 to <15 (n = 670)	≥1800	≥840
15 to <18 (n = 605)	≥1500	≥650
18 to 24 (n = 118)	≥1400	≥700
24 to 60 (n = 688)	≥1300	≥710

Values rounded to 2 significant figures (SF)

Margins of Exposure calculated by EFSA

25. To get an indication of the risk from acute MON exposure, the Panel calculated MOEs between the NOAEL of 6.0 mg/kg b.w. and estimates of acute UB dietary human exposure across consumption studies for each age group. For 'infants' (< 12 months), toddlers (≥ 12 months to < 36 months), and 'other children' (≥ 36 months to < 10 years), the MOEs ranged from:

- 11000 to 50000 (UB) at the mean exposure, and
- 4000 to 12000 (UB) at the 95th percentile dietary exposures.

26. To get an indication of the risk from chronic MON exposure, the Panel calculated MOEs between the $BMDL_{05}$ of 0.20 mg MON/kg b.w./day and estimates of chronic dietary human exposure across consumption studies for each age group. For 'infants' (< 12 months), toddlers (≥ 12 months to < 36 months), and 'other children' (≥ 36 months to < 10 years), the MOEs ranged from:

- 3900 to 5000000 (LB) and 880 to 18000 (UB) at the mean exposure, and
- 1500 to 590000 (LB) and from 380 to 2500 (UB) at the 95th percentile exposure estimates.

27. The Panel concluded that the MOE values for both acute and chronic exposures (calculated across consumption studies for each age group) were sufficiently large to indicate a low health concern for humans, however they were associated with uncertainty. The Panel therefore recommended the acquisition of additional scientific data to address several sources of uncertainty: lack of general toxicity data in animals, limited data on mode of action, lack of data on in vivo genotoxicity and carcinogenicity, and limited toxicokinetic data.

Conclusions

28. All estimates of the MOE for MON (based on UK consumption data) exceed the lowest MOE value calculated by EFSA for both acute and chronic exposures. The UK MOE values appear to be adequately protective, and indicate minimal risk from estimated acute and chronic dietary exposures.

Questions on which the views of the Committee are sought

29. Members are invited to consider the following questions:

i). Do Members agree with the MOE approach taken for MON for assessing human health risk?

ii). Do Members consider the calculated MOEs for UK acute & chronic human exposure to MON to be adequately protective for public health?

iii). Do Members think it is possible to derive an MOE value below which there would be a concern for human health?

Secretariat

January 2019

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