**TOX/2019/02**

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

## Review of potential risks from fumonisins in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

## Background

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, 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 the concentrations of 36 mycotoxins in relevant foods in the 2014 Total Diet Study (TDS) – mycotoxins analysis (FSA, to be published). 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]. This discussion paper for the risk characterisation of fumonisins is a review of the Joint Food and Agriculture Organisation of the United Nations/World Health Organisation Expert Committee on Food Additives (JECFA) technical report (2017)[3] and the recently published European Food Standards Agency Panel on Contaminants in the Food Chain (EFSA CONTAM) Scientific Opinion (2018)[4].

4. JECFA first evaluated fumonisins in 2001, following the increased attention being given to food contaminants by the Codex Committee on Food

[1] COT scoping paper (TOX/2015/32) available at: https://cot.food.gov.uk/sites/default/files/TOX2015-32%20Feeding%20Review%20Scoping%20Paper.pdf
[2] COT mycotoxins scoping paper available at: https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf
[3] JECFA technical report available at: http://www.who.int/foodsafety/publications/technical-report-series-1002/en/
[4] EFSA CONTAM SO report available at: https://www.efsa.europa.eu/en/efsajournal/pub/5172

Additives and Contaminants. Additionally, increasing concern about the potential risks associated with their intake among consumers was highlighted. Subsequent evaluations were performed in 2011 and 2016. In 2001, JECFA concluded that nephrotoxicity was the most sensitive toxic effect of pure fumonisin B1 (FB1) exposure. A health-based guidance value (HBGV) was calculated from available data. The 2011 evaluation highlighted that some regions within some countries would exceed the HBGV, where maize is a major dietary staple food and where high levels of contamination can occur. The JECFA Committee also concluded that the risk from fumonisin exposure from animal feed products is not of human health concern, because fumonisins do not carry over from feed to animal products in significant amounts. Review of published studies since the 2011 evaluation was completed by JECFA in 2016. No new data would change the previous overall toxicological risk assessment, so the established HBGV was retained. The adverse effects of mycotoxin co-exposure were evaluated, however, the JECFA Committee concluded that there were few data available to support co-exposure as a contributing factor to human disease.

5. Following a request from the European Commission, the EFSA CONTAM Panel assessed whether it is appropriate and feasible to set a HBGV for FB1 and fumonisin B2 (FB2) and their modified forms related to their presence in food and feed, and to consider, whether it would be appropriate to use the parent compound as a marker for toxicity.

6. This discussion paper has considered exposures based on occurrence data from the 2014 UK TDS – mycotoxins analysis[5] and consumption data from the DNSIYC (Lennox *et al*., 2011) and the NDNS (Bates *et al*., 2011) (Bates *et al*., 2014) (Bates *et al*., 2016) (Roberts *et al*., 2018).

*7.* Fumonisins are produced by *Fusarium verticillioides*, *F. proliferatum* and *F. fujikuroi*, as well as some less common Fusarium species, for example *F. anthophilum*, *F. dlamini*, *F. napiforme* and *F. thapsinum*. There are 4 main fumonisins: FB1, FB2, FB3 and FB4 which are the major forms found in food as contaminants. FB1, FB2 and FB4 are also produced by *Aspergillus niger*. Fumonisins are common contaminants of maize and have also been found in rice, grapes, green coffee beans, onions, mango, corn and other cereals, peanuts and dried fruits (FAO/WHO, 2017; FAO/WHO, 2012).

*Toxicokinetics*

8. Comparison of limited available human data with other animal mammalian toxicokinetic data on fumonisins suggests that findings are comparable. Fumonisins are poorly absorbed from the gastrointestinal tract after oral exposure (<4%). Once in the circulatory system, they have a half-life of ~4 hours. Following absorption, small amounts of fumonisins are distributed to virtually all organs, particularly the kidney and liver. Ester metabolites are hydrolysed into two tricarballylic acid moieties, and the amino group is

[5] UK Total Diet Study. (2014) Available at: https://www.food.gov.uk/sites/default/files/media/document/fs102081-tds-hallmark-report.pdf

acetalized. The metabolites are rapidly excreted mainly in the bile (>=90% of the parent metabolite), which results in low plasma, tissue and urinary concentrations (EFSA CONTAM, 2018).

*Mode of Action*

9. Fumonisins are structural analogues of sphingolipids and exhibit their toxicity by competitive inhibition of ceramide synthase (CerS), an enzyme that modulates the acylation of sphinganine (SA) and recycling of sphingoisine. CerS inhibition causes disruption of sphingolipid metabolism; an increased cellular concentration of SA may lead to cytotoxic effects.

## Toxicity

10. Fumonisins can have significant health effects in livestock and other animals, although evidence for adverse health effects in humans is currently inconclusive. Concerns over the exposure to fumonisins and its contribution to outcomes such as birth defects and stunting growth in children have been identified, however, the potential to act as a carcinogen is the main concern.

*Acute Toxicity*

11. Previous evaluations by the JECFA Committee concluded that FB1 is not acutely toxic (FAO/WHO, 2017).

12. The EFSA CONTAM Panel has also concluded that FB1 is not acutely toxic in humans since no lethality was observed in available *in vivo* animal data, therefore no acute reference dose was calculated (EFSA CONTAM, 2018).

*Genotoxicity*

13. The JECFA Committee reviewed published data since 2011, there was lack of evidence for fumonisin-induced DNA damage, either as a cause of direct interaction to DNA macromolecules or as a result of metabolism to a DNA-reactive metabolite. The disruption of the mitochondrion's cellular membrane integrity was suggested as a source of reactive oxygen species. The JECFA Committee concluded that an increase in oxidative stress may play a role in the DNA damage observed in *in vivo* studies (FAO/WHO 2017).

14. The EFSA CONTAM Panel stated that FB1 was not mutagenic in bacterial assays, however, in some cellular *in vitro* assays, FB1 was found to cause chromosomal and DNA strand breaks. Parallel to this finding, increased concentrations of malondialdehyde and catalase were also noted, supporting the hypothesis that the genotoxicity of FB1 is mediated via oxidative stress (EFSA CONTAM, 2018).

*Carcinogenicity*

15. Several chronic studies observed tumours in the liver of female mice and rats. The kidney also seemed to be a target organ of toxicity, with reports of kidney tumours in male rats (EFSA CONTAM, 2018).

16. In 2002, the International Agency for Research on Cancer (IARC), evaluated the carcinogenic potential of FB1. Their analysis concluded that FB1 is possibly carcinogenic to humans (Group 2B), as there is sufficient evidence in experimental animals, and inadequate evidence in humans (IARC, 2002).

*Reproductive and developmental toxicity*

17. In several animal models (mice, rats and rabbits), embryotoxicity was only made evident in doses that caused maternal toxicity. However, data from one study in Syrian hamsters that was exposed to high doses of FB1 embryotoxicity was observed in the absence of maternal toxicity. There is evidence that FB1 causes neural tube defects in sensitive mice strains, which was seen to be a high dose toxic effect but overall, the evidence is inconclusive (EFSA CONTAM, 2018).

18. Human observations for reproductive and developmental toxicity have not been causally related to fumonisin exposure (EFSA CONTAM, 2018).

# Previous evaluations

19. JECFA have previously evaluated fumonisins in 2001 (FAO/WHO, 2001), 2012 (FAO/WHO, 2012) and 2017 (FAO/WHO, 2017). The same provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg bw for FB1, FB2 and FB3, alone or in combination, was established and retained by the Committee.

20. The EFSA CONTAM Panel have also published their scientific opinion in February 2018 (EFSA CONTAM, 2018). They established a lower tolerable daily intake (TDI) of 1 µg/kg bw for FB1. Due to the limited data available on toxicity and mode of action for other fumonisin sub-types, the EFSA CONTAM Panel has considered it appropriate to include FB's 2-4 in a group TDI with FB1 based on assessment for structural similarity.

### Health-based guidance values (HBGVs)

*JEFCA*

21. In 2011, data from a short-term dose response study (preliminary report) of liver toxicity in male transgenic mice fed diets containing purified FB1 was used to derive an HBGV. A lower benchmark dose level $(BMDL)_{10}$ of 0.165 mg/kg bw/day was calculated for megalocytic hepatocytes and after application

of an uncertainty factor of 100 for intraspecies and interspecies variation, a group PMTDI of 2 µg/kg bw was derived for FB1, FB2 and FB3, alone or in combination. As this was the same as the PMTDI derived at the 2001 meeting, the group PMTDI was retained (FAO/WHO, 2017; FAO/WHO, 2012).

22. The most recent evaluation (2017), used the final report of the same study employed in the evaluation in 2012. The final report contained a number of changes including slight differences in the incidence of lesions and pathology scores for megalocytic hepatocytes and for apoptosis due to the addition of four mice in the study, but the JECFA Committee concluded that this would not change the overall toxicological assessment performed by the Committee of 2011 (FAO/WHO, 2017).

23. In light of this updated report, the committee reviewed the previous dose-response analysis and confirmed it.

*EFSA*

24. The EFSA CONTAM Panel, calculated a TDI for FB1 by using the $BMDL_{10}$ of 0.1 mg/kg bw per day derived for induction of megalocytic hepatocytes in mice, from the updated study reviewed by JECFA. An uncertainty factor of 100 for intra and interspecies variability was applied, resulting in a TDI of 1 µg FB1/kg bw per day. The PANEL decided that FB2, FB3 and FB4 should be included in a group TDI with FB1 due to structural similarities, however, modified forms of FB1-FB4 cannot be included in the TDI since their relative toxicity could not be quantified (EFSA CONTAM, 2018).

*Prior consideration of other sources of exposure*

25. A literature search on exposure to fumonisins via breast milk was performed. One paper by Magoha *et al*., (2014) was identified to be relevant; detection of high levels of FB1 were reported in breast milk from Tanzanian women. The exposure levels seen in this study are unlikely to be reflective of a typical European diet *i.e.* less maize/cereal based, however, the Committee members considered that ethnic influence(s) in diet was an issue to be aware of.

26. Fumonisin contamination on infant formula was also considered as a potential source of exposure. A diet observation study was carried out by Zimmer *et al*., (2008) on the exposure to fumonisins in German consumers during December 1998 - July 2001. Twenty-five out of sixty-two dietetic foods (including infant and follow-on formulae and therapeutic foods) for infants and young children tested positive for fumonisin contamination. The following fumonisin levels were reported (µg/kg): mean; 42.6, median; 2.5, and $90^{th}$ percentile; 159.0. Daily fumonisin intake by infants and young children were calculated on the basis of the data submitted by the manufacturer (one portion of 150-200 mL, converts to 45-50 grams of dry powder), it was assumed that 97% of babies aged 4-7 months old would have a body weight of 8-10.8 kg. Calculated fumonisin intake was 1.12-1.51 µg/kg bw/day. The data presented

is reflective of the average fumonisin levels of the period examined. Contamination levels in these products have strongly decreased, however, continued exposure to high contamination levels of fumonisins may lead to regular excess of the TDI for infants and young children.

27. Analytical results from a 4-year surveillance study for mycotoxins carried out by the FSA, reported no detectable levels of fumonisins in infant formula or ready to drink milk products. The limit of detection (LOD) was 5 µg/kg (per fumonisin sub-type), and the limit of quantification was 10 µg/kg. The total sample size was 19 milk products; 2 formulas (soya & lactose free), 10 infant milks (4/10 were ready to feed/use), 7 follow-on/toddler milk (4/7 were ready to feed/use) and 1 wheat product with milk (FSA, 2011).

28. Co-exposure of fumonisins with other mycotoxins have been identified within the literature. The JECFA (2017) report has considered the adverse toxicological effects of the co-occurrence of fumonisins with aflatoxins (e.g. childhood stunting), primarily in infant cereal-based food commodities. The JECFA Committee concluded that co-exposure is possible in the diet of infants from infant foods, however, two prospective epidemiological studies do not support the hypothesis of an interaction between aflatoxins and fumonisins to cause an adverse effect on growth. Furthermore, few data are available to support that co-exposure is a contributing factor to human disease. Even so, possible interaction between these inherently hazardous chemicals (aflatoxin; genotoxicity and fumonisins; potential to induce regenerative cell proliferation), remains a concern for the JECFA Committee.

## Exposure Assessment

29. Exposures were calculated using occurrence data from the TDS and consumption data from DNSIYC and NDNS. Fumonisin B1, B2 and B3 were measured in the TDS. The total exposure was determined from a distribution of exposures of any combination of B1, B2 and B3 rather than by summation of the respective individual mean/97.5$^{th}$ percentile exposure value for each of the three fumonisins. The results from almost all of the food sample groups that were analysed for fumonisins were below the LOD[6]. These exposures provided in Table 1 are lower bound (LB) and upper bound (UB) mean dietary exposure limits. FB1 was detected in the sample of “herbs and spices” at a level of 5.53 µg/kg, below the limit of quantification of 7.15 µg/kg.

30. Fumonisin exposures, for all age groups, the mean values were all below 0.089 µg/kg bw/day and the 97.5$^{th}$ percentile exposures were all below 0.188 µg/kg bw/day, whilst the total fumonisin mean values were under 0.25 µg/kg bw/day and under 0.52 µg/kg bw/day for the 97.5$^{th}$ percentile (Table 1a – 1b).

[6] LODs for FB1 ranged from 3.87 µg/kg, for beers and cider to 7.95 µg/kg for flour, and chocolate biscuits which had a much higher LOD of 37.1 µg/kg. For FB2 LODs were in the range 3.4 to 8.9 µg/kg apart from chocolate biscuits where it was 36.8 µg/kg. For FB3 LODs were in the range 3.1 to 6.5 µg/kg, with an LOD in chocolate biscuits of 31.5 µg/kg.

31. Exposure estimates for 0 to 6-month olds were calculated for exclusive feeding on infant formulae using the default consumption values of 800 and 1,200 mL (Table 2). Consumption data from the DNSIYC were used to estimate exposures for 4 to 18-month olds (Tables. 3-4) (DH, 2013). It appears that the infant formulae analysed were dry powder therefore consumption data has been based on the dry powder content of made-up formula where consumption has been recorded as made-up. Exposures have been estimated for a range between the median and the maximum levels of fumonisins reported by Zimmer *et al*., (2008); 2.5 µg/kg and 403 µg/kg respectively.

**Table 1a**. Estimated fumonisin chronic exposures from the TDS in infants and young children aged 4 to 15 months (µg/kg bw/day).

| Fumonisin | 4 to <6 month-olds (n=116) | | 6 to <9 month-olds (n=606) | | 9 to <12 month-olds (n=686) | | 12 to 15 month-olds | |
|---|---|---|---|---|---|---|---|---|
| | Mean | 97.5th percentile | Mean | 97.5th percentile | Mean | 97.5th percentile | Mean | 97.5th percentile |
| B1 | 0.000-0.0079 | 0.000-0.032 | 0.000-0.030 | 0.0011-0.11 | 0.000-0.052 | 0.00089-0.13 | 0.000-0.071 | 0.0014-0.16 |
| B2 | 0.000-0.0068 | 0.000-0.026 | 0.000-0.027 | 0.000-0.10 | 0.000-0.048 | 0.000-0.13 | 0.000-0.067 | 0.000-0.15 |
| B3 | 0.000-0.0063 | 0.000-0.025 | 0.000-0.024 | 0.000-0.088 | 0.000-0.042 | 0.000-0.11 | 0.000-0.058 | 0.000-0.13 |
| **Total** | **0.000-0.021** | **0.000-0.083** | **0.000-0.082** | **0.0011-0.30** | **0.000-0.14** | **0.00089-0.37** | **0.000-0.20** | **0.0014-0.44** |

Values rounded to 2 significant figures (SF)

**Table 1b**. Estimated fumonisin chronic exposures from the TDS in infants and young children aged 15 to 60 months (µg/kg bw/day).

| Fumonisin | 15 to 18 month-olds | | 18 to 24 month-olds | | 24 to 60 month-olds | |
|---|---|---|---|---|---|---|
| | Mean | 97.5th percentile | Mean | 97.5th percentile | Mean | 97.5th percentile |
| B1 | 0.000-0.083 | 0.0015-0.19 | 0.000-0.089 | 0.0020-0.15 | 0.000-0.080 | 0.0014-0.15 |
| B2 | 0.000-0.078 | 0.000-0.17 | 0.000-0.085 | 0.000-0.150 | 0.000-0.077 | 0.000-0.14 |
| B3 | 0.000-0.068 | 0.000-0.16 | 0.000-0.073 | 0.000-0.13 | 0.000-0.066 | 0.000-0.13 |
| **Total** | **0.000-0.23** | **0.0015-0.52** | **0.000-0.25** | **0.0020-0.43** | **0.000-0.22** | **0.0014-0.42** |

Values rounded to 2 SF

**Table. 2** - Estimated average and high-level exposures to fumonisins from exclusive feeding on infant formulae for 0 to 6-month olds.

| **Food** | Fumonisins Exposure (µg/kg bw/day) | | Fumonisins Exposure (µg/kg bw/day) | |
|---|---|---|---|---|
| | 0 to <4 months | | 4 to <6 months | |
| | **Average consumer (800 mL/day)** | **High level consumer (1200 mL/day)** | **Average consumer (800 mL/day)** | **High level consumer (1200 mL/day)** |
| Infant Formula [a, b] (median level) | 0-0.051 | 0-0.076 | 0-0.038 | 0-0.058 |
| Infant Formula [c, b] (maximum level) | 0-8.2 | 0-12 | 0-6.2 | 0-9.3 |

Values rounded to 2 SF
[a] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 2.5 (upper-bound) µg/kg
[b] Average bodyweights: 0 to <4 m-olds = 5.9 kg (DH,1994) & 4 to <6-m-olds = 7.8 kg (DH, 2013)
[c] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 403 (upper-bound) µg/kg

**Table. 3** - Estimated exposures to fumonisins from infant formulae for 4 to 12-month olds from using consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013).

| **Food** | **Fumonisins Exposure (µg/kg bw/day)** | | **Fumonisins Exposure (µg/kg bw/day)** | | **Fumonisins Exposure (µg/kg bw/day)** | |
|---|---|---|---|---|---|---|
| | **4 to <6 Months (n=116)** | | **6 to <9 Months (n=606)** | | **9 to <12 Months (n=686)** | |
| | **Mean** | **97.5th** | **Mean** | **97.5th** | **Mean** | **97.5th** |
| Infant formula [a] (median level) | 0-0.030 | 0-0.053 | 0-0.023 | 0-0.042 | 0-0.018 | 0-0.035 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Infant Formula [b] (maximum level) | 0-4.9 | 0-8.5 | 0-3.7 | 0-6.8 | 0-2.9 | 0-5.6 |

[a] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 2.5 (upper-bound) µg/kg
[b] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 403 (upper-bound) µg/kg

**Table. 4** - Estimated exposures to fumonisins from infant formulae in children aged 12 to 18 months from using consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013).

| **Food** | Fumonisins Exposure (µg/kg bw/day) | | Fumonisins Exposure (µg/kg bw/day) | |
|---|---|---|---|---|
| | 12 to <15 Months (n=670) | | 15 to <18 Months (n=605) | |
| | **Mean** | **97.5th** | **Mean** | **97.5th** |
| Infant formula [a] (median level) | 0-0.013 | 0-0.029 | 0-0.012 | 0-0.023 |
| Infant formula [b] (maximum level) | 0-2.2 | 0-4.7 | 0-1.9 | 0-3.7 |

[a] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 2.5 (upper-bound) µg/kg
[b] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 403 (upper-bound) µg/k

# Risk characterisation

32. Total fumonisin results were not provided to the FSA as part of the TDS and due to the inconsistent reporting of the total fumonisins across the European Union it is not certain whether total exposures could be calculated from the data available. The total fumonisin rows provided in Tables. 1a-b were collected from Crème and the data was corrected to two significant figures. Therefore, in this paper comparison to the PMTDI of 2 µg/kg bw or TDI of 1 µg/kg bw has been used for individual fumonisins.

33. All calculated mean and 97.5$^{th}$ percentile exposures of FB1, FB2 and FB3 for all age groups are below both HBGVs from previous evaluations; PMTDI of 2 µg/kg bw by JECFA and TDI of 1 µg/kg bw by the EFSA CONTAM Panel (Tables. 1a-b).

34. Since both HBGVs can be utilised alone or in combination of fumonisin sub-types, and it is assumed that exposure from other sources discussed in paragraphs 25-28 are considered for the median level exposure rates according to the reported detection values of Zimmer *et al*., (2008), summing of the fumonisin exposures is not expected to change the risk characterisation across all age groups.

35. However, both HBGVs are exceeded for maximum level exposure rates according to the reported detection values of Zimmer *et al*., (2008), across all age groups. It must be noted, that the fumonisin level range was calculated across a variety of food commodities for dietetic foods for infants and young children, and not exclusively for infant and follow-up formulae. As such, the data presented by Zimmer *et al*., (2008) should be considered a worst-case exposure and therefore would be overly precautionary.

*RISK21*

The RISK21 integrated evaluation strategy webtool[7], is a problem formulation-based exposure-driven risk assessment roadmap, that takes advantage of existing data to graphically represent the relationship of exposure and toxicity.

In order to assess the risk from fumonisins, available exposure data from Table. 1 for the 15-18 months old age group and the TDI from EFSA is shown in Fig.1.

The graph indicates that there is a moderate risk of toxicity for the chronic exposure of total fumonisins (FB1-3) in the 15-18 months old age group (worst-case; utilising the 97.5$^{th}$ percentile) when utilising the EFSA HBGV value of 1 µg/kg bw/day, since the bar lies between the yellow-green to yellow coloured area.

The same exposure value was then plotted against the PMTDI value as set by JECFA at 2 µg/kg bw/day for comparison (Fig.2). This graph illustrates the same risk as that of Fig.1, however, there is a greater proportion of the estimate of toxicity lying towards the green coloured area.

[7] RISK21 Webtool Version 2.0. Available at: http://risk21.org/the-risk21-webtool-v-2-0/

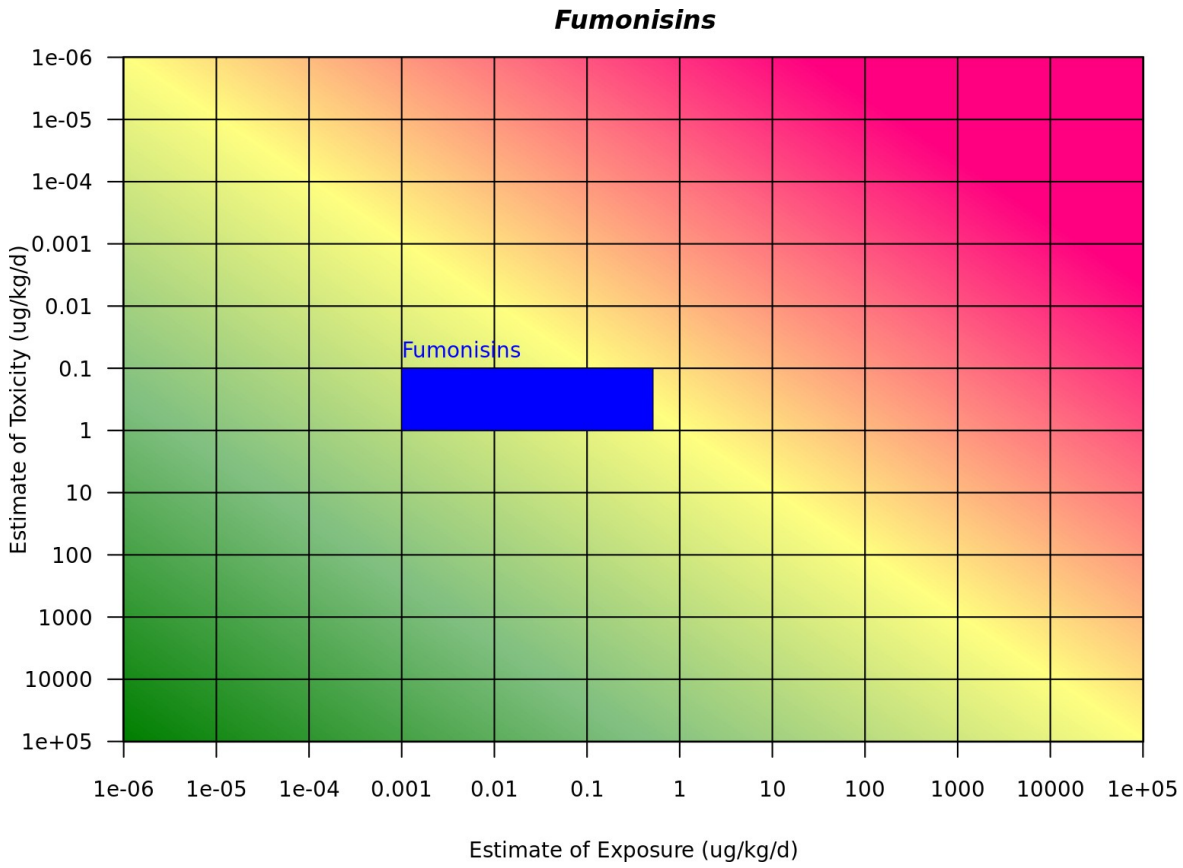


Figure 1 shows a visual comparison of potential chronic exposure and toxicity information (EFSA TDI of 1 µg/kg bw/day) using the mean and 97.5$^{th}$ percentile exposure for total FBs in the diet of infants aged 15 to 18 months.

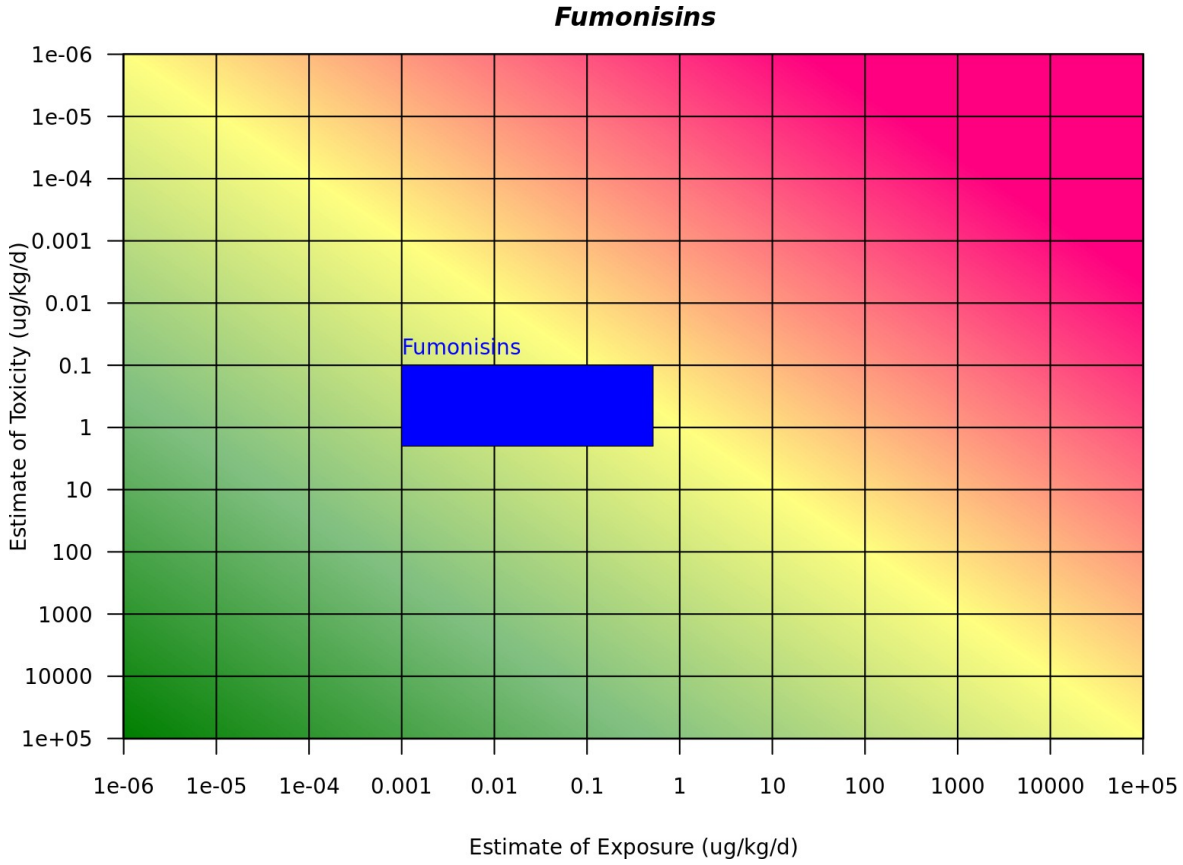


Figure 2 shows a visual comparison of potential chronic exposure and toxicity information (JECFA TDI of 2 µg/kg bw/day) using the mean and 97.5$^{th}$ percentile exposure for total FBs in the diet of infants aged 15 to 18 months.

# Conclusions

36. Fumonisins are a type B trichothecene mycotoxin produced by several *Fusarium* species, some fumonisin sub-types can also be produced by *Aspergillus niger*. They are found as contaminants in several food commodities such as; maize, rice, corn and other cereals, peanuts, fruits (grapes and mangoes), dried fruits, green coffee beans and onions.

37. Following oral exposure, fumonisins are poorly absorbed in the GI tract and have a short half-life of ~4 hours. The compound is metabolised via hydrolysis and acetylation reactions, the metabolites are then rapidly excreted in the bile.

38. Fumonisins cause toxicity by disruption of sphingolipid metabolism via CerS enzyme inhibition; an increased cellular concentration of SA may lead to cytotoxic effects.

39. Exposure to fumonisins have been shown to have significant health effects in livestock and other animals, however, evidence of adverse health effects in humans is inconclusive.

40. Fumonisins are not considered to be acutely toxic as evaluated by both JECFA and the EFSA CONTAM Panel.

41. It is thought that the genotoxic effects of fumonisins is caused because of indirect interaction to DNA macromolecules by reactive oxygen species. The IARC has concluded that fumonisins (FB1) is possibly carcinogenic to humans (Group 2B).

42. Reprodevelopmental effects has been reported in several animal models *e.g.* neural tube defects in sensitive mice strains, but the overall evidence remains inconclusive. Human observations have not been causally related to fumonisin exposure.

43. HBGVs have been set by the EFSA CONTAM Panel and JECFA working groups at 1 µg/kg bw (TDI) and 2 µg/kg bw (PMTDI), respectively. These values can be used alone or in combination with the other fumonisin sub-types (FB's 2-6).

44. Breast milk and infant formula mixtures were identified to be additional potential sources of fumonisin exposure. High detection rates of fumonisin levels were reported in the breast milk of Tanzanian women, however, the appropriateness of the methodology of quantification; HPLC was deemed inappropriate for the matrix by JECFA. Fumonisins were also detected in infant formula present in the German market ranging from <5-403 µg/kg, it was concluded that the continued consumption and therefore exposure to high levels of fumonisins may lead to regular excess of the (PM)TDI for infants and young children.

45. The co-exposure of fumonisins with other mycotoxins *e.g.* aflatoxins were evaluated by the JECFA Committee and concluded that co-exposure is possible in the diet of infants from infant foods, however, prospective epidemiological studies do not support the hypothesis of an adverse effect in growth resulting from the interaction of both mycotoxins.

46. Fumonisin exposures, for all age groups, the mean values were all below 0.089 µg/kg bw/day and the 97.5$^{th}$ percentile exposures were all below 0.188 µg/kg bw/day, whilst the total fumonisin mean values were under 0.247 µg/kg bw/day and under 0.517 µg/kg bw/day for the 97.5$^{th}$ percentile.

47. In this current risk assessment, the calculated mean and 97.5$^{th}$ percentile fumonisin exposures, alone or in combination, for all age groups were below the PMTDI of 2 µg/kg bw by JECFA and TDI of 1 µg/kg bw by the EFSA CONTAM Panel, and it is unlikely that there would be a toxicological concern.

48. <u>Questions to be asked of the Committee</u>

i). Do the Committee have any thoughts on the estimated exposure data utilising fumonisin detection levels reported by Zimmer *et al*., (2008)?

ii). Do the Committee consider that both exposures from breast milk and infant formula are negligible, and would not affect the overall risk assessment?

iii). Do the Committee wish to utilise the EFSA or JECFA HBGV?

iv). Do the Committee have any other comments on this discussion paper?

v). Do the Committee want a separate statement for fumonisins or can it be included in the addendum of the overarching statement?

**Secretariat**

**January 2019**

# Abbreviations

| | |
|---|---|
| BMDL | Benchmark Dose Level |
| bw | Body Weight |
| CerS | Ceramide Synthase |
| COT | Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment |
| DNSIYC | Diet and Nutrition Survey of Infants and Young Children |
| EFSA | European Food Standards Agency Panel on Contaminants in the Food Chain |
| FB1 | Fumonisin B1 |
| FB2 | Fumonisin B2 |
| FSA | Food Standards Agency |
| HBGV | Health-Based Guidance Value |
| HPLC | High Performance Liquid Chromatography |
| JECFA | Joint Food and Agriculture Organisation of the United Nations/World Health Organisation Expert Committee on Food Additives |
| kg | Kilogram |
| LB | Lower Bound |
| LOD | Limit of Detection |
| µg | Milligram |
| NDNS | National Diet and Nutrition Survey |
| PMTDI | Provisional Maximum Tolerable Daily Intake |
| SA | Sphinganine |
| SACN | Scientific Advisory Committee on Nutrition |
| SF | Significant Figures |
| TDI | Tolerable Daily Intake |
| TDS | Total Diet Study |
| UB | Upper Bound |

# References

Bates, B., Lennox, A., Prentice, A., Bates, C., Swan. G. (2012) National Diet and Nutrition Survey: Headline Results from Years 1, 2 and 3 (combined) of the Rolling Programme 2008/09 – 2010/11. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/207708/NDNS-Y3-report_All-TEXT-docs-combined.pdf

Bates, B., Lennox, A., Prentice, A., Bates, C., Page, P., Nicholson, S., Swan. G. (2014) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/594361/NDNS_Y1_to_4_UK_report_full_text_revised_February_2017.pdf

Bates, B., Cox, L., Nicholson, S., Page, P., Prentice, A., Steer, T., Swan, G. (2016) National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/551352/NDNS_Y5_6_UK_Main_Text.pdf

DH. (2013) Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011. Available at: http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

EFSA CONTAM (2018): Appropriateness to set a group health-based guidance value for fumonisins and their modified forms. Available at: https://www.efsa.europa.eu/en/efsajournal/pub/5172

FAO/WHO (2001). WHO Food Additives Series 47. Safety evaluation of certain mycotoxins in food. Prepared by the Fifty-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Available at: http://www.inchem.org/documents/jecfa/jecmono/v47je01.htm

FAO/WHO (2012). WHO Food Additives Series 65. Safety evaluation of certain food additives and contaminants. Prepared by the Seventy-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Available at: http://apps.who.int/iris/bitstream/10665/44813/1/9789241660655_eng.pdf

FAO/WHO (2017). WHO Technical Report Series. Eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain contaminants in food. Available at: http://www.who.int/foodsafety/publications/technical-report-series-1002/en/

FSA. (2015) Food Survey Information Sheet: 02/11. Surveillance programme for Mycotoxins in foods. Year 2: Mycotoxins in foods for infants and young, children, patulin in apple juice and ergot alkaloids in cereal products. Available at: https://admin.food.gov.uk/sites/default/files/multimedia/pdfs/fsis0211.pdf

IARC. (2002) IARC Monographs on the evaluation of carcinogenic risks to humans Volume 82: Some traditional herbal medicines, some mycotoxins, naphthalene and

styrene. Available at: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono82.pdf

Lennox, A., Sommerville, Ong, K., Henderson, H., Allen, R. (2011) Diet and Nutrition Survey of Infants and Young Children, 2011. Available at: https://webarchive.nationalarchives.gov.uk/20130402174302/http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

Mahoga, H., De Meulenaer, B., Kimanya, M., Hipolite, D., Lachat, C., Kolsteren, P. (2014) Fumonisin B1 contamination in breast milk and its exposure in infants under 6 months of age in Rombo, Northern Tanzania. Food and Chemical Toxicology 74, pp. 112-116.

Roberts, C., Steer, T., Maplethorpe, N., Cox, L., Meadows, S., Nicholson, S., Page, P., Swan, G. (2018) National Diet and Nutrition Survey Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 to 2015/2016). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/699241/NDNS_results_years_7_and_8.pdf