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

Review of potential presence of fumonisins in infant formula in the United Kingdom (UK), and differences between the metabolism of fumonisins in infants and adults (Matters arising)

1. A paper was presented to the COT in the July 2019 meeting under matters arising[1], which provided exposure estimates from a possible source of exposure to fumonisins via consumption of infant formula, based on detected levels published by Zimmer et al., (2018). Further information was obtained from one of the co-authors; Usleber (personal communication, 2019). The first discussion paper had been presented in February 2019[2].

2. Following the July 2019 meeting, the Committee wished to further review available UK data for the presence of fumonisins in infant formula, since the provided exposure estimates were based on German data. Additionally, the Secretariat was requested to review the literature for the differences between the metabolism of fumonisins in infants and adults. The latter information was requested following discussions on the immunotoxic potential of fumonisins since exposure occurs at a critical time period i.e. for vaccination in infants aged from 6 months.

Presence of fumonisins in infant formula in the UK

3. In an unpublished Food Standards Agency (FSA) mycotoxin surveillance report (Patel et al., 2011) there were no positive sample results for the presence of any of the three subtypes of fumonisins (FB1, FB2 and FB3) in infant milk formulations (n=20). For these samples, of which 12 were powder and 8 were ready to drink, with expiry dates ranging from 2011-2013, the limit of detection (LOD) was 5 µg/kg and the limit of quantification (LOQ) was 10 µg/kg).

4. No further data could be obtained from the literature for the presence of fumonisins in infant formula in the UK.

Differences between the metabolism of fumonisins in infants and adults

5. Fumonisins are poorly absorbed from the gastrointestinal tract (<4 % of an oral dose), those that are absorbed are rapidly excreted mainly in the bile based on experimental animals. The rapid excretion results in low plasma, tissue and urinary concentrations (EFSA, 2018).

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[1] https://cot.food.gov.uk/sites/default/files/tox2019-28.pdf
[2] https://cot.food.gov.uk/sites/default/files/tox2019-02_0.pdf

6. Data regarding the bioavailability of fumonisins in infants could not be identified within the literature, however, it is believed that toxicants that are carried in food will be delivered at 2-3 times higher rates in children than in adults (WHO, 2008).

7. With reference to xenobiotic drugs, the majority of these agents are more slowly eliminated in neonates and infants that in adults. This may be associated with an increased volume of distribution of water-soluble drugs and their metabolites. At birth the glomerular function is more developed that tubular function, which persists for 6 months. This leads to decreased and prolonged half-lives in neonates and infants for any chemical that is eliminated by the kidney (Miller et al., 2002). Fumonisins are excreted mainly in the bile and so differences in renal function between infants and adults are not expected to greatly affect the toxicity observed.

8. Studies have reported that fumonisins modulate the expression of cytochrome P450 (Cyp) 1b1 enzymes in HepG2 cells by repressing Mir-27b, which poses as an additional mode of hepatic neoplastic transformation (Chuturgoon et al., 2014). It has been generally agreed that the total hepatic microsomal P450 content tends to increase during development (Hakkola et al., 1998). Additionally, during infancy and juvenile stages, P450 activities are generally lower than expression (Sadler et al., 2016).

9. FB_1 is a potent and specific inhibitor for ceramide synthases. No comparative values for levels of ceramide synthase present in children or adults could be identified within the literature, however, currently, there is no evidence that FB_1-induced ceramide synthase inhibition is involved in any diseases. Additionally, there is no evidence that FB_1-induced ceramide synthase inhibition is in itself an adverse effect. Although, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) noted that the disruption of lipid metabolism consequent to inhibition of ceramide synthases, seem to play an important and early role in fumonisin toxicity and carcinogenicity in animal models (JECFA, 2017).

10. The role of dietary constituents (i.e. proteins, plant extracts (providing antioxidants), and dietary iron) and their different recommended intake levels at different age groups should also be taken into consideration, as it will determine the outcome of the observed adverse effect seen at the specific target organ (Gelderblom & Marasas, 2012). Sphingolipid profiles in liver and kidneys were indicative of tissue-dependent differences in the uptake and metabolism of free sphingoid bases, which accounted for target organ sensitivity and specificity of fumonisins in mice (Bondy et al., 2012).

11. The weight of evidence linking fumonisin exposure to stunting of growth in children, with an emphasis in world regions where young children consume maize-based weaning foods, has been increasing. Chen et al., (2018) have inferred that the disruption of lipid metabolism induced by fumonisin could lead to physiological changes that might increase the risk of growth impairments in humans.

12. Gong et al., (2015) evaluated fumonisin exposure in children and adults in a family study in rural Tanzania. Maize intake was obtained using a seven-day food frequency questionnaire and a duplicate diet method. Urine samples were analysed

using liquid chromatography–mass spectrometry methods. Urinary FB_1 geometric means were 0.62, 1.25, and 1.38 ng/mL in children (n=50; females: 24, males: 26), mothers (n=50), and fathers (n=41), respectively. The observed lower levels of FB_1 in children when compared to adults became non-significant when corrected for creatinine concentration. FB_1 urinary excretion between children and adults was calculated at 1:1.105.

Conclusion

13. The presence of fumonisins in UK infant formula has not been reported within the literature nor has it been detected in the FSA's mycotoxin surveillance programme (LOD; 5 µg/kg, LOQ; 10 µg/kg).

14. Direct comparisons of the differences between fumonisin metabolism in children and adults were not explicit within the JECFA, EFSA reviews nor within the literature.

15. Although Cyp activities in foetal liver are lower than in adults, urine excretion data suggest that there is no significant difference in the metabolism of fumonisins between these age groups.

Questions to ask the Committee

16. Members are invited to consider the following questions:

a) Do the Committee find the additional data provided sufficient to clear and include fumonisins within the 0-5 addendum by Chair's action?

b) Do the Committee have any other comments on this item?

c) As a further note on mycotoxins, do the Committee wish the Secretariat to prepare a scoping paper presenting the information currently available on the potential cumulative risks of mycotoxins (for all age groups)? And if required a full review in the future, including how we are able to assess the risks.

Secretariat
August 2019

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