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

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

Mycotoxins – Aflatoxin (additional information and EFSA public consultation)

Background

1. As part of the review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding, the Committee in Toxicology (COT) was asked to review the toxicity of chemicals in the diets of infants and young children aged 0-5 years.

2. Following on from a scoping paper presented to the Committee in 2017, summaries on a number of mycotoxins were presented at the meeting in July this year (TOX/2019/30). At the meeting Members asked for information on cancer studies on neonatal/prenatal rats to be provided for aflatoxins, if available, to allow for information regarding the sensitivity differences between infants. Following the information provided by the Secretariat at the September meeting (TOX/2019/54), the Committee agreed that to enable a conclusion on aflatoxin, information on cancer potency in newborns and adults by the same route administration would be required as well as quantitative data on the activation of AFB1 by liver fractions from newborns and adults (rat and human), if available.

3. Since the last Committee meeting in September, EFSA has launched a public consultation on the risks to public health related to the presence of aflatoxins in food. Annex A provides a short overview of additional information provided by the recent assessment and diversions from the previous risk assessment in 2007.

4. The requested information, where available, is provided to the Committee in Annex B. For information, the previously additional information is provided in Annex C, the original paper presented to the Committee in July this year is provided in Annex D.

Questions for the Committee

i) Do the Committee consider the additional information sufficient to conclude on the potential risk from aflatoxin, including the sensitivity differences between infants and adults?

ii) Are there any points the Committee would like to emphasis?

iii) In light of the EFSA consultation, do the Committee still consider it appropriate for aflatoxins to be included in the Addendum to the Overarching Statement?

iv) Do the Members have any other comments?

v) The Committee is asked to send any comments for the EFSA public consultation to the Secretariat by 31/10/2019

Secretariat

September 2019

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

Review of potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years: Mycotoxins – Aflatoxin (additional information and EFSA public consultation)

EFSA public consultation on the risks to public health related to the presence of aflatoxins in food.

1. EFSA launched a public consultation on the risk to public health related to the presence of aflatoxin in food[1]. The following paragraphs provide a short overview of additional information and diversions from the 2007 opinion.

2. Overall, the additional toxicological studies since 2007 add weight to the previous findings. Additional/new information on effects on the gut microbiota and immune system are included, however, EFSA does not consider these effects critical. Liver carcinogenicity is still considered the pivotal effect of aflatoxin exposure.

3. EFSA continues to consider the study by Wogan et al. (1974) the most suitable for the dose response modelling and has derived a $BMDL_{10}$ of 0.4 µg/kg bw per day; the $BDML_{10}$ derived in 2007 was a range from 0.17 – 0.34 µg/kg bw per day. Both assessments applied the same assumptions to the BMD modelling. However, the newest assessment applied model averaging, which was not available in the PROAST software back in 2007. This is most likely the explanation for the difference in the calculated $BMDL_{10}$, although it is not specifically documented in the assessment.

4. EFSA provided a number of studies on children in the recent assessment and concluded that "while child health is an emerging area of interest […] not yet suitable for the use in risk assessment […] and the evidence related to the remaining child health outcomes is sparse, heterogeneous and with methodological limits."

5. Potency estimates for other aflatoxins are based on JECFAs evaluation, as per the previous opinion.

6. The deadline for the submission of comments to **EFSA** is the **15th of November 2019**.

7. The deadline for submission of comments to the Secretariat is the **31st of October 2019**.

[1] https://www.efsa.europa.eu/en/consultations/call/public-consultation-draft-scientific-opinion-risks

8. If Members who wish to comment on the EFSA assessment, could please link their comments to the respective paragraphs.

Annex B to TOX/2019/56

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

Review of potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years: Mycotoxins – Aflatoxin (additional information and EFSA public consultation)

Additional information on cancer potency in newborns and adults by the same route of administration

1. A literature search was performed to retrieve any available information on the cancer potency in or differences of newborns and adults after aflatoxin exposure. The following paragraphs summarize the limited information available from said literature search and the information/conclusions by IARC and EFSA.

In vitro

2. A study by Behroozikha et al. (1992) exposed hepatic microsomal and cytosolic fractions from rats of different ages to AFB1 at 2 mM (microsome mediated DNA binding assay) and 2 nM (extraction of AFB1-GSH conjugate). The authors found that the activity of hepatic microsomal cytochrome P-450 in neonatal rats was approximately half the activity in adults. AFB1 DNA binding was reported at 62, 64, 71, 83, 94% in rats aged 8, 15, 25, 33 and 42 days, respectively. AFB1 DNA binding in adult rats was reported at 100%. Adduct formation in adult microsomes was 1.5 to 2-fold higher compared to newborns (aged 8 days). Cellular hepatic GSH levels develop gradually with age and reach the maximum during middle age. Results reported here indicate the levels hours after birth were 65% that of the adult level. The authors noted that the activity of cytosolic GSH S-transferase activity towards CDNB increased with advancing age, the activity being the highest in the liver of adult rats. The authors suggested that the differences reported here could be due to age dependant differences in key factors in the biological transformation of AFB1, such as changes in the drug metabolising enzymes possibly influencing the detoxification of AFB1. Others have suggested that drug metabolising enzymes are not expressed in newborn rats and that the level of microsomal cytochrome P450 is low. The results in this study suggest that low levels of cytochrome P450 in immature rats can influence the formation of AFB1-hyroxylate metabolites and therefore delay the epoxide formation and aflatoxins residues are deposited in various tissues.

In vivo

Rats

3. A study by Butler and Barnes (1966, summarized in IARC[2] (1993)) exposed six young rats to a diet containing groundnut meal (providing aflatoxins at a concentration of 3000-4000 µg/kg of diet) for three weeks and six adult rats (aged 1 year) to the same diet for 39 weeks. Of the young rats treated, one animal developed a carcinosarcoma of the stomach and one animal a hepatocellular carcinoma. Of the adult rats, anaplastic hepatocellular carcinomas were found in 3/5 animals and adenocarcinomas of the stomach and rectum in 1/5 animals each.

4. A study by Naidu et al. (1991, abstract only) reported extensive cystic lesions of the biliary and hepatic type in young animals only. Multifocal hepatic necrosis, bile ductular proliferation, areas of altered hepatocytes, neoplastic nodules and hepatocellular carcinoma were reported in both adult and newborn animals. The authors suggested that an increased susceptibility to the toxins early in life appears to be responsible for this phenomenon and that this may have a bearing on the genesis of childhood liver disease.

Mice

5. In contrast to humans, mice express a GST isotype that is efficient at AFB1 detoxification and newborn mice are sensitive to hepatocarcinogenesis, while adult mice are resistant. Nevertheless, the following studies in mice have been included here, as they compare newborn mice directly with adult mice, within the same study.

6. A study by Shupe and Sell (1990) found that in mice exposed to AFB1 (2 mg/kg) hepatic AFB1-DNA adduct formation inversely correlates with GST levels in the liver. The latter was reported to increase during the first month of age (from 0.06 to 0.12 mM) to 0.26 mM aged 8 months, while hepatic AFB1-DNA adduct formation decreased from 40.3 pM AFB1/mg DNA at age 4 days to 13.8 pM AFB1/mg DNA at age 30 days and 2 pM/mg DNA at 8 months of age. As the proliferation status of the liver in mice is associated with low GST levels and high AFB1-DNA adduct formation, the authors concluded that the age sensitivity of mice is correlated with the proliferation status of the liver and suggested that the inhibition of hepatic GST during liver proliferation may increase the levels of AFB1 metabolites available for AFB1-DNA adduct formation in humans.

7. A study by Larsson and Tjaelve (1992) found GSH to supress the binding of AFB1 to macromolecules in the liver to a greater degree in adult mice compared to infant mice aged 5 days, after mice were given an s.c. injection of 80 µg 3HAFB1/kg bw and killed 1 hour afterwards. The authors suggested that the low GST activity in young mice may contribute to their sensitivity, however acknowledged that other factors (bioactivity ability, cell replication rate, DNA repair) may also be involved.

8. A study by Chen et al. (2010) exposed (big blue transgenic) neonatal and adult mice to 6 mg/kg and 6 and 60 mg/kg AFB1, respectively. In

[2] https://monographs.iarc.fr/wp-content/uploads/2018/06/mono56-14.pdf

neonates the C*II* liver mutant frequency (MF) was 22-fold higher than in control animals, in adults no significant increase at either dose was detected. G:C → T transversion (major type of AFB1 mutation) was 82-fold increased in neonates compared to controls, 31-fold increase than adults.

Humans

9. IARC[3] (1993) summarize that there is interindividual variation in the rate of activation of aflatoxins, including differences between children and adults and that such differences may be relevant to the pharmacokinetics of aflatoxins, which in humans have not been fully elucidated yet.

10. EFSA (2007) conclude, that the "available data do not indicate that children have a higher dietary exposure to aflatoxins than adults and therefore do not provide a basis for a different risk characterisation. However, the exposure estimates are based on dietary sources not specifically based on children's consumption patterns. Therefore, this conclusion is tentative and better exposure data are required."

11. The recent EFSA assessment (currently out for public consultation, see Annex A) provided a number of studies on children and concluded that "while child health is an emerging area of interest […] not yet suitable for the use in risk assessment […] and the evidence related to the remaining child health outcomes is sparse, heterogeneous and with methodological limits."

Quantitative data on the activation of AFB1 by liver fractions from newborns and adults (rat and human)

12. A study by Robertson and Birnbaum (1982) investigated the ability of liver preparations of rats of different ages (2.5 to 25 months) to metabolise AFB1 to mutagenic products via the Ames test. The authors found a continuous age-related decline of the activation of AFB1, the biggest decline occurring by middle age 13 months).

13. A study by Jayaraj and Richardson (1981) previously had found an age-related decline in AFB activation in rats, however at a slightly higher age (12 to 25 months). The authors found that the S9 fraction or microsomes at age 27 months produced fewer revertants than at 12 months of age. The authors concluded that the metabolic conversion by the liver decreases with increasing age (approximately 40-50% between 12 and 18 months of age) and that this might be related to a measurable decrease in cytochrome P450 content in the liver.

14. A study by Hilali et al. (1993, abstract only) investigated the age-related changes in drug metabolism in the liver of male rats aged 3 weeks to 18 months using liver fractions and the Ames test. The authors found that the activation of AFB1 changes with age and is maximal from 4 to 10 months and concluded that the composition of different cytochrome P450 fractions are

[3] https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100F-23.pdf

modified with age and are thereby altering the ability to convert different promutagens to mutagens.

Annex C to TOX/2019/56

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

Review of potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years: Mycotoxins – Aflatoxin (additional information and EFSA public consultation)

Additional information on neonatal/prenatal exposure to aflatoxins

Secretariat
October 2019

1. The following table and paragraphs provide summaries of the studies assessed by IARC (1993[4]) and EFSA (2007[5]) as well as publications retrieved from a literature search (from 1993, the IARC publication date, to August 2019).

Table 1. Summaries of rodent studies assessing prenatal/neonatal exposure to aflatoxin (B1).

Compound	Concentration and exposure route	Exposure and study duration	Results	Reference
Rats				
Aflatoxin B1	2 mg/kg of diet (0.1 mg/kg bw)[a]	Throughout pregnancy and lactation Male and female weaned offspring Male and female weaned offspring of untreated rats were exposed to same diet from 6-7 weeks of age Treatment until death or until all were killed at 74 weeks	>75% of animals in both treatment groups developed malignant liver neoplasms, which were the main cause of death Hyperplasic hepatic nodules, two types of differently stained areas of hyperplasia in the liver Increase in colonic tumour incidence observed in rats exposed from conception and from rats exposed from 6-7 weeks of age (groups exposed in utero, postnatally and exclusively postnatally were not separated, sex unspecified)	Ward et al., 1975 (IARC)
Aflatoxin	Female rats: 0.5 mg/kg bw i.p. injection	Female rats from GD 17-18 or GD 18-20	Dams: Increased incidence of benign and malignant neoplasms in various organs (liver, GI tract, endocrine organs, mammary gland)	Goerttler et al., 1980 (IARC)

[4] https://monographs.iarc.fr/wp-content/uploads/2018/06/mono56-14.pdf
https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100F-23.pdf
[5] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2007.446

	Offspring: 0 or 0.5 mg/kg bw i.p. injection	Offspring of both sexes on days 2-5 or 14-17 after birth	Offspring exposed in utero (with or without treatment after birth): Significant increase in total number of malignant tumours, except for mammary gland and leukaemia.	
Aflatoxin B1	0.7, 1.4, 3.5 and 7.0 mg/kg bw Subcutaneous injection	GD 8 or 16	Average fetal weight decreased Malformations were not observed	Sharma and Sahai, 1987 (IARC)
Aflatoxin B1	2 mg/kg bw i.p. injection	GD 8-10 or GD 15-17	Significant increase in liver triglyceride content in 1-2 month old offspring of dams exposed at GD 8-10 Decreased motor activity in 1 month old offspring exposed at GD 8-10 or 15-17; behaviour became normal again at the age of 2 or 3 months Persistent neuronal degeneration in the brains.	Chentanez et al., 1986 (IARC)
Aflatoxin B1	10, 20, 50 or 100 µg/kg bw per day Intramuscular injection	GD 12-19	In utero exposure severely compromised postnatal development in female offspring, including reduced birth weight and locomotor activity	Supriya et al., 2016 https://www.ncbi.nlm.nih.gov/pubmed/26956420
Aflatoxin B1	10, 20 or 50 µg/kg bw daily Dosing method not given	GD 12-19	Severely compromised postnatal development of male offspring, causing a delay in testes descent and reduction in steroidogenesis and spermatogenesis Behavioural changes, such as cliff avoidance, negative geotaxis, impairment of exploratory and locomotory activities	Supriya and Reddy, 2015 Abstract only https://www.ncbi.nlm.nih.gov/pubmed/25911313
Aflatoxin B1	0.1, 0.3 or 1.0 ppm (7.1, 21 or 67 µg/kg	GD 6 to day 21 delivery on weaning	Reversal effect on hypocampal neurogenesis targeting typ-3 progenitor cells	Tanaka et al., 2015 https://www.ncbi.nlm.nih.gov/pubmed/26260870

	bw per day (gestation period)[b] Diet			
Aflatoxin B1	0.5, 1, 2, 3 or 4 mg/kg bw i.p. injection Suckling rats: 3 mg/kg bw Direct injection, single dose	GD 8.5	50 to 60% depletion of fetal liver GST towards CDNB Suckling rats: Liver GST significantly induced	Fatami et al., 2006 Abstract only https://www.ncbi.nlm.nih.gov/pubmed/16501953
[3H]Aflatoxin B1	Specific activity 18 mCi/mM) 8 µCi [^{3}H]AFB1 containing 40 pg AFB1/100 g bw i.p. injection	Neonatal and young rats killed 2, 6, 12 and 24 hours after exposure	AFB1 was epoxidized more rapidly by the adult liver and lungs 2 hours after administration, compared to neonatals Differences more pronounced in hepatic than pulmonary tissues	Chelcheleh and Allameh 1995 https://www.ncbi.nlm.nih.gov/pubmed/7596201
Aflatoxin B1	15 µM (4.7 mg) *In vitro*	Cultured rat embryos	Neuronal tube defects	Geissler and Faustman, 1988 (IARC)
Mice				
Aflatoxin B1	16 or 32 mg/kg bw i.p. injection	GD 6-13	Maternal death, decreased bw, increased liver weight Reduced fetal weight, external and skeletal malformations in high dose group	Tanimura et al., 1982 (IARC)
Aflatoxin B1	4 mg/kg bw Oral intubation	GD 8 and 9	Fetal abnormalities after exposure on day 8 No abnormalities after exposure on day 9	Arora et al., 1981 (IARC)
Aflatoxin B1	15, 45 or 90 mg/kg	GD 6-13	i.p.:	Roll et al., 1990 (IARC)

	i.p. injection or oral	Exposure for 2-day periods	Retardation of fetal development at 45 and 90 mg/kg Malformations of the diaphragm at 45 mg/kg Malformations of the diaphragm and kidneys at 90 mg/kg Oral: Diaphragmatic malformations at 45 mg/kg	
Aflatoxin B1	5 or 6 mg/kg (0.1 or 0.12 mg/kg bw)[c] for mutagenesis or mutation analysis, respectively i.p. injection 5 mg/kg (0.1 mg/kg bw)[c] for adduct analysis and mutagenesis Oral gavage	GD 14 Pregnant C57BL/6J females Carrying F1 gestation day 14 embryos of the B6C3F1 genotype	Adducts in GD 14 embryos were 20-fold more potent inducers of mutagenesis than adducts in parallel dosed adults Correlated with Ki67 staining of the liver, reflecting the proliferation potential of the liver tissue	Chawanthayatham et al., 2015 https://www.ncbi.nlm.nih.gov/pubmed/25070670
Aflatoxin B1	6 mg/kg (0.12 mg/kg bw)[c] i.p. injection	Day 4 after birth	10-fold increase in Spi(-)mutant fraction in liver DNA (over control) after 3 weeks After 10 weeks a further increase was observed Using a genetic loci, data show a strong preference for induction of GC to TA mutations after single exposure	Wattanawaraporn et al., 2012 https://www.ncbi.nlm.nih.gov/pubmed/22539618
Aflatoxin B1	6 mg/kg (0.12 mg/kg bw)[c] i.p. injection	Newborn female and male	Similar amounts of DNA damage and mutation that may initiate neoplastic process Mutation frequencies in liver were increased by 20-30 fold	Woo et al., 2011 https://www.ncbi.nlm.nih.gov/pubmed/21507988

			24 hours after dosing, AFB(1)-FAPY adduct was present in liver DNA	
Aflatoxin B1	Neonatal (transgenic): total 6 mg/kg bw, 2 mg/kg bw per treatment i.p. injection Adult: Total 6 and 60 mg/kg bw, 2 and 20 mg/kg bw per treatment i.p. injection	Neonatal exposure at the age of 4, 7, and 10 days Three doses, every third day exposure Adult exposure at 120, 123 and 126 days of age Same exposure regime Animals were sacrificed 6 weeks after treatment	Neonatal: Liver tumours cII liver MF was 22-fold higher than control Frequency of GC to TA transversion was about 82-fold than the control and 31-fold higher than adults treated with 60 mg/kg bw Adult: No tumours No significant increase in liver MF	Chen et al., 2010 https://www.ncbi.nlm.nih.gov/pubmed/19642212

[a] converted using a factor of 0.05 for chronic studies in (adult) rats, given by EFSA[6] (based on the initial assessment by the WHO in 1987)
[b] as given by the authors
[c] converted using an average bw of 0.02 kg for mice, given by JECFA (2016)[7]

Abbreviations: bw (body weight), GD (gestation day), i.p. (intraperitoneal), GI (gastrointestinal), GST (glutathione S-transferase), CDNB (1-chloro-2,4-dinitrobenzene), AFB1 (aflatoxin B1), Spi(-) (sensitive to P2 inhibition), GC (guanine-cytosine), TA (thymine-adenine), AFB(1)-FAPY (), cII gene (encodes a protein that activates transcriptional promoters in λ that are essential for lysogenization), MF (mutant frequency)

[6] http://www.efsa.europa.eu/sites/default/files/consultation/110707a.pdf
[7] https://apps.who.int/iris/bitstream/handle/10665/246173/9789241511155-eng.pdf%3bjsessionid=9E345DBB4E70BA9096BF57CD4165EB8D?sequence=1

2. In humans, aflatoxins are known to cross the placental barrier. There is some evidence suggesting the concentrations in cord blood are higher than maternal blood and that aflatoxins (e.g., B1, G1 and Q1) may accumulate in fetuses exposed *in utero* (Denning *et al*., 1990; Lamplugh *et al*., 1988). The metabolic activation of aflatoxin B1 in human adult and fetal liver to mutagenic metabolites was examined by Kitada *et al*. (1990). Mutation in the *umu* gene in a plasmid containing a strain of salmonella typhimurium was induced in both adult and fetal systems. Antibody inhibition studies indicate the involvement of cytochrome P450 3A4 in the adult system and P450 HFLa in the fetal system.

3. A number of studies have considered polymorphism in aflatoxin metabolism or DNA repair enzymes in relation either to the formation of DNA or protein adducts or in relation to risk of hepatocellular carcinoma (HCC). A paper by Wild et al. (1993) measured serum aflatoxin-albumin (AF-alb) in Gambian children in relation to glutathione S-transferase M1 (GSTM1) genotype and in Gambian adults in relation to GSTM1, glutathione S-transferase theta-1 (GSTT1), glutathione S-transferase Pi 1 (GSTP1) and epoxide hydrolase polymorphism and found no major differences in adduct levels by genotype. Another study in Gambian children (Turner *et al*., 2003) and one in Ghanaian adults (Jiang *et al*. 2005) indicate dietary exposure to AFB1 could result in impairment of cellular immunity that could decrease host resistance.

4. Studies by Gong *et al*. (2002; 2004) reported an increase in AF-alb adduct level with age, up to three years, and was significantly related to weaning status of the 1 to 3 year age group: weaned children had approximately two-fold higher mean aflatoxin–albumin adduct levels than those receiving a mixture of breast milk and solid foods.

5. Infection with hepatitis B (HBV) may increase aflatoxin metabolism. In HBV-infected children there was a higher level of AF-alb adducts than in non-infected children, an observation consistent with altered aflatoxin metabolism (Allen *et al*., 1992; Turner *et al*., 2000). However, similar studies in adults did not show such differences (Groopman *et al*., 1992; Wild *et al*., 2000).

Annex D to TOX/2019/56

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

Review of potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years: Mycotoxins – Aflatoxin (additional information and EFSA public consultation)

TOX/2019/30 Matters Arising – Mycotoxins

Secretariat
October 2019

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

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

Aflatoxins: B1, B2, G1, G2 and M1 (AFB1, AFB2, AFG1, AFG2 and AFM1)

1. Aflatoxins are primarily produced by two species of *Aspergillus* fungus and can be found in foods as a result of fungal contamination both pre- and postharvest, with the rate and degree of contamination dependent on temperature, humidity, soil and storage conditions. Aflatoxins are most commonly associated with groundnuts, tree nuts, dried fruit, spices, figs, crude vegetable oils, cocoa beans, maize, rice, cottonseed and copra.

2. Aflatoxin M1 is a major metabolite of aflatoxin B1 (AFB1) in humans and animals. It may be present in milk from animals fed on AFB1 contaminated feed and also in human breast milk. For the UK, exposure to aflatoxins is generally considered to occur mainly from imported materials. It is currently uncertain whether future changes in climate in the EU would lead to increased aflatoxin contamination.

3. Most of the available toxicological data relate to AFB1. Studies have consistently shown AFB1 to be both genotoxic and carcinogenic in experimental animals. Sufficient experimental evidence is also available for the carcinogenicity of naturally occurring mixtures of aflatoxins, and of AFG1 and AFM1, whereas there is only limited evidence for AFB2 and inadequate evidence for AFG2. The relative potency of aflatoxin congeners is available from bacterial mutagenicity and hepatocarcinogenic effects in the rainbow trout and rats, in the order of AFB1 > (AFG1, AFM1) >> (AFB2, AFG2).

4. The potential carcinogenicity of aflatoxins (either total or AFB1) in humans has been examined in a large number of epidemiology studies, generally carried out in Africa and Asia, where substantial quantities of aflatoxins occur in basic foodstuffs. The International Agency for Research on Cancer (IARC) concluded that naturally occurring aflatoxins are carcinogenic to humans (group 1), with a role in aetiology of liver cancer, notably among subjects who are carriers of hepatitis B virus (HBV) surface antigens.

5. EFSA did not consider it appropriate to establish a health-based guidance value (HBGV) since aflatoxins are both genotoxic and carcinogenic and therefore applied the margin of exposure (MOE) approach in their risk assessment. However, EFSA noted, that the available data would only be sufficient for AFB1, yet AFG1 and AFB2 were also shown to be carcinogenic in rodents, albeit at lower potency than AFB1. Therefore, as a conservative approach EFSA assumed the carcinogenic potency of “total aflatoxin” to be similar to AFB1. EFSA proposed a MOE of 10,000 or higher would be of low health concern, if based on a $BMDL_{10}$ from an animal carcinogenicity study.

To date there have been no conclusions on the magnitude of an MOE based on human data that would be of low concern.

6. Following EFSAs approach, the MOEs for aflatoxins were calculated using UK exposures and a $BMDL_{10}$ of 0.17 µg/kg bw per day, based on liver carcinogenicity in male rats exposed to 1 to 100 µg/kg diet of AFB1 (Wogan et al., 1974). Total aflatoxin was not available as part of the TDS and due to inconsistencies in the reporting across the EU it is not certain whether total exposure could be calculated from the data available.

7. For all children aged 4 to 60 months, the mean and 97.5th percentile MOEs for AFB1 are ≥ 14, the mean and 97.5th percentile MOEs for AFB2, AFG1, AFG2 and AFM1 are ≥19, 15, 8.9 and 24, respectively.

8. The exposures, and respective MOEs, were not based on measured values, but on lower bound (LB) and upper bound (UB) values, all results were below the calculated limit of quantification (LOQs). Therefore, the actual MOEs would be higher than those calculated.

9. Given that aflatoxins are genotoxic and carcinogenic their presence is always undesirable it is not possible to exclude a safety concern.