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

Introduction

1. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risk of toxicity of chemicals in the diets of infants and young children aged 1-5 years, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. 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.

2. A scoping paper (TOX/2015/32) “COT contribution to SACN review of complementary and young child feeding; proposed scope of work for 0 to 5 year old children” was reviewed by the COT in 2015. The members requested exposure assessments should be undertaken for all the mycotoxins measured in the UK Total Diet Study (TDS). A scoping paper on these mycotoxins was presented to the Committee at the July meeting in 2017 and members requested a full review on a number of mycotoxins.

3. Neosolaniol (NeoSol) was included in the full statement on T-2 toxin (T2) and HT-2 toxin (HT2), the statement on OTA was published in 2018. Reviews on 4,15-Diacetoxyscirpenol, Cyclopiazonic acid, Fumonisins, Moniliformin, Patulin, Deoxynivalenol, Fusarenon-x have been previously presented to the COT or will be presented in due course.

4. The summaries in Annex A include mycotoxins for which a further detailed review was not requested (but minor changes may have been). A brief overview of the characteristics of the mycotoxins is provided with a focus mainly on the exposure assessment (where applicable) and the risk characterisation and conclusions, for both infants and young children.

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1 The food safety information sheet for the mycotoxins TDS is at an advanced stage and is being readied for publication. Publication expected late summer/early fall.
2 https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf
3 https://cot.food.gov.uk/sites/default/files/cotstatement-t2ht2andneosolaniol.pdf
Questions to be asked to the Committee

i) Do the Committee, agree with their initial assessment that a full review will not be necessary for these mycotoxins, and that they can be included in the addendum to the overarching statement?

ii) Are there any points regarding individual mycotoxins the Committee would like to emphasise?

iii) Do the members have any other comments?

Secretariat

July 2019
COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

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Mycotoxins

General information

5. Mycotoxins are produced as secondary metabolites by filamentous fungi and are toxic to vertebrates and other animal classes at low concentrations (Bennett and Klich, 2003). There are currently no Government dietary recommendations for infants and young children which relate to mycotoxins.

6. Unless otherwise indicated, the background information provided is based on previous evaluations by the European Food Safety Authority (EFSA) or the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Exposure assessments were carried out using occurrence data from the TDS by the Food and Environment Research Agency (FERA) (Stratton et al., 2015) and consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013) and the National Diet and Nutrition Survey rolling programme (NDNS) (Bates et al., 2014; Bates et al., 2016).

Assessment

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

7. 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.

8. 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.

9. 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).

10. 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.

11. 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 BMDL10 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.

12. Following EFSAs approach, the MOEs for aflatoxins were calculated using UK exposures and a BMDL10 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.

13. 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.

14. 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.

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

Citrinin

16. Citrinin is produced by several species of the genera *Aspergillus*, *Penicillium*, and *Monascus*. and is normally formed under harvest and storage
conditions. It occurs predominantly in grains but also in other plant products such as beans, fruit and herbs and spices. It is also found in red mould rice (RMR), used as a food colourant and preservative in Asian foods. Specific toxicokinetic studies with oral administration are not available. Experimental data indicate the occurrence of citrinin residues in edible tissues and eggs following oral exposure of animals with contaminated feed.

17. The acute lethal toxicity of citrinin ranged from 19 to 134 mg/kg bw depending on species and route of administration. Repeat dosing studies confirmed the nephrotoxicity of citrinin and again highlighted the differences in susceptibility between species. One available subchronic study in rats reported a no observed adverse effect level (NOAEL) of 20 mg/kg bw per day. One available long-term feeding study in rats exposed to high dietary citrinin (initially about 70 mg/kg bw per day) identified the kidney as principal target organ and reported progressive histopathological changes and incidences of adenomas. However, the study was limited to 80 weeks thus no conclusions on potential carcinogenicity can be drawn. Other in vivo studies showed the induction of chromosome abnormalities and hypodiploidy in mice bone marrow. Conventional bacterial and mammalian in vitro assays indicate that citrinin is not mutagenic, mutagenicity was only reported in one study using rat hepatocytes as the activation system in the Ames test. IARC concluded that citrinin is not classifiable as to its carcinogenicity to humans (Group 3).

18. Data from immunotoxicity studies were generally incomplete and did not allow for conclusions to be drawn. Data from in vitro and in vivo studies reported reproductive toxicity and teratogenic and embryotoxic effects of citrinin. However, the in vivo studies also reported maternal toxicity, including nephrotoxicity, indicating that the reproductive, teratogenic and embryotoxic effects may be secondary to maternal toxicity.

19. EFSA concluded that the derivation of a HBGV would not be appropriate, given the available data on genotoxicity and the limitations and uncertainties in the current database. This was not expanded upon by EFSA which furthermore concluded, that due to the lack of human dietary exposure data a MOE approach would not be appropriate. Instead, EFSA decided to characterise the risk of citrinin and determine a level of no concern for nephrotoxicity in humans of 0.2 μg/kg bw per day based on a NOAEL of 20 μg/kg bw per day and application of an uncertainty factor (UF) of 100 for interspecies and interindividual variation. A concern for genotoxicity and carcinogenicity cannot be excluded at the level of no concern for nephrotoxicity.

20. Mean and 97.5th percentile exposures of infants aged 0 to 12 months and young children aged 1 to 5 years are all below the exposure level of 0.2 μg/kg bw per day considered of no concern for nephrotoxicity in humans by EFSA. Therefore, the exposures reported in the TDS are not of toxicological concern for nephrotoxicity. Due to lack and limitations of the available data, a concern for genotoxicity and carcinogenicity cannot be excluded.
21. Occurrence data from all food samples analysed for citrinin were below the LOQ and the exposures calculated are based on the LB and UB values.

Ergot alkaloids (EAs)

22. Ergot alkaloids (EAs) infest plant species including commercially important grains such as rye, wheat, rice, corn, barley, millet and oat. More than 50 different EAs have been identified but the total amounts and patterns vary between fungal strains, geographic regions and host plants.

23. EAs show a broad spectrum of pharmacological effects and have been used in medical applications. EAs or EA-derived products have been applied or tested for prolactin inhibition, treatment of Parkinsonism, cerebrovascular insufficiency, venous insufficiency, thrombosis, emboli, stimulation of cerebral and peripheral metabolism, and are still applied for migraine and uterine stimulation. In addition, lysergic acid diethylamide (LSD), a semi synthetic derivative of the EA-family was legally introduced as a pharmaceutical in the mid-1950s.

24. EAs can act on a number of neurotransmitter receptors particularly adrenergic, dopaminergic and serotonergic receptors, the effects of these receptor interactions may be acute or long-term. Data for the genotoxic potential of EAs other than ergotamine are limited/insufficient. The available \textit{in vitro} data did not indicate bacterial or mammalian mutation, \textit{in vivo} data is inconsistent but there is some evidence of clastogenicity. Tumorigenicity demonstrated in a 2-year carcinogenicity study was exacerbated by a low protein diet, the absence of carcinomas and the regression indicated aetiology related to a non-genotoxic mode of action. Human data are available for the naturally occurring alkaloids used as pharmaceuticals, ergometrine and ergotamine.

25. EFSA derived a group acute reference dose (ARfD) of 1 µg/kg bw for the sum of ergot alkaloids based on a BMDL\textsubscript{10} of 0.33 mg/kg bw per day for incidence of tail muscular atrophy in a 13-week rat feeding study of ergotamine (Spieijers \textit{et al.}, 1993) and application of an overall UF of 300, comprised of the default UF of 100 for intra- and interspecies differences and an UF of 3 for deficiencies in the database.

26. EFSA derived a group tolerable daily intake (TDI) of 0.6 µg/kg bw per day for the sum of ergot alkaloids based on the same BMDL\textsubscript{10} of 0.33 mg/kg bw per day, as for the derivation of the ARfD, and application of an overall UF of 600. EFSA concluded that in addition to the UF of 300 used for the derivation of the ARfD, an additional uncertainty factor of 2 should be applied for the extrapolation from sub-chronic to chronic studies.

27. EFSA noted that the group ARfD is 2-fold below the lowest single dose of 2 µg/kg bw ergometrine used to induce uterine contractions and therefore the margin between this dose in a sensitive subpopulation and the group ARfD is adequate. The lowest prescribed dose of ergotamine used in the treatment of migraine is approximately 10 to 20 times higher than the group
ARfD and 20 to 40 times higher than the group TDI. Furthermore, the group TDI is 13 times lower than the maximum recommended dose for therapeutic use of ergotamine.

28. Twelve EAs were measured in the TDS, and all bread samples contained some or all of these. The main contributing groups for total ergot alkaloid exposures were miscellaneous cereals, breakfast cereals, white sliced bread and wholemeal and granary bread.

29. The mean and 97.5th percentile acute exposures of infants and young children to total EAs are all below the ARfD of 1 µg/kg bw, the mean and 97.5th percentile chronic exposures are all below the TDI of 0.6 µg/kg bw per day. Exposure to EAs are therefore unlikely to be of toxicological concern.

Sterigmatocystin (STC)

30. Sterigmatocystin (STC) is produced by more than a dozen species of Aspergillus and a number of phylogenetically and phenotypically different fungal genera and shares its biosynthetic pathway with aflatoxins. STC is generally produced in storage, rather than in the field, and has been found in grains and grain-based products, green coffee beans, spices, beer, peanuts, crispbread, rye, rice, white bread, muesli, chilli and cheese.

31. STC exhibits genotoxic effects in vitro, in vivo and ex vivo and carcinogenicity has been demonstrated after oral, intraperitoneal (ip), subcutaneous and/or dermal exposure in the animal species tested.

32. EFSA evaluated a number of dose-response effects using data from available carcinogenicity bioassays in mice, rats and monkeys who had been orally administered STC. Most studies were not considered suitable for BMD modelling due to discontinuous dosing, lack of detailed tumour incident reporting, high mortality and too small a number of treatment groups. The incidents of hepatocellular carcinomas (HCC) in the study by Maekawa et al. (1979) was not considered suitable for risk characterisation by EFSA since the study combined tumours from different origins (HCC and haemangiosarcomas). However, EFSA found it appropriate to conduct BMD analysis on haemangiosarcomas as a relevant end point due to zero tumour bearing animals in the control and low dose group and one and three tumour bearing animals in the mid and high dose group, respectively.

33. The lowest BMDL\textsubscript{10} value was 0.16 mg/kg bw per day, with BMD\textsubscript{10} of 0.36 mg/kg bw per day. However, EFSA noted that only 11% of the total number of tumour bearing animals had haemangiosarcomas and that the tumour incidence in the control group was 64%. Therefore, the BMD\textsubscript{10}/BMDL\textsubscript{10} pair is based on a limited tumourigenicity database.

\textsuperscript{5} Ergocornine, ergocorninine, ergocristine, ergocristinine, ergocryptine, ergocryptinine, ergometrine, ergometrinine, ergosine, ergosinine, ergotamine and ergotaminine. Although the -inine forms are described to be biologically inactive on the neuroreceptor sites, an interconversion under alkaline or acidic conditions can take place and thus both forms were considered in the risk assessment.
34. JECFA applied BMD analysis to the same study in their 2017 evaluation and applied a BMDL\textsubscript{10} of 0.16 mg/kg bw per day as the point of departure (POD) for their MOE assessment.

35. EFSA was unable to apply a MOE approach in their evaluation in 2013, due to the lack of European human dietary exposure to STC. However, in general EFSA proposed a MOE of 10,000 or higher would be of low health concern, if based on a BMDL\textsubscript{10} from an animal carcinogenicity study.

36. Mean and 97.5\textsuperscript{th} percentile MOEs for infants and young children based on the exposures calculated from the UK TDS occurrence data are all > 10000. Therefore, the exposures are unlikely to be of toxicological concern to human health.

Zearalenone (ZEN)

37. Zeralenone (ZEN) is produced by several Fusarium species, can grow and invade crops in moist cool field conditions and post-harvest under poor storage conditions, is commonly found in maize and also in wheat, barley, sorghum and rye.

38. IARC has classified ZEN as not classifiable as to carcinogenicity in humans (Group 3) based on the limited evidence in experimental animals. ZEN does not cause gene mutations in bacterial test systems, however it has been reported as clastogenic and aneugenic \textit{in vitro} and clastogenic \textit{in vivo} in the mouse.

39. Based on the limited evidence for carcinogenicity, EFSA (2001) applied the MOE approach using a BMDL\textsubscript{10} of 6.39 mg/kg bw per day based on incidence of pituitary adenomas in male mice exposed to concentrations of 8 and 17 mg/kg bw per day. However, EFSA also noted the wide variability in the sensitivity of species to oestrogenic effects of ZEN and that these effects are observed in pigs at doses approximately 3 orders of magnitude lower than doses reported to cause clastogenicity and increases in adenomas in mice. Therefore, EFSA also established a TDI of 0.25 \(\mu\)g/kg bw per day based on a NOAEL of 10.4 \(\mu\)g/kg bw per day for oestrogenic effects in female pigs and the application of an overall UF of 40, comprising of an UF of 4 for interspecies toxicokinetics and an UF of 10 for interhuman variability; EFSA decided not to use the UF of 2.5 for interspecies toxicodynamics as human females would not be more sensitive to the effects of oestrogen than female pigs. The margin between the BMDL\textsubscript{10} of 6.39 mg/kg bw per day and the TDI of 0.25 \(\mu\)g/kg bw was in the region of 25,000. This exceeds the value of 10,000 of low concern for a genotoxic carcinogen, established by EFSA.

40. EFSA (2011) concluded oestrogenicity to be the critical effect of ZEN, as the reported genotoxicity may be related to oxidative stress mediated mechanisms and ZEN was at most a weak carcinogen.
41. Several modified forms of ZEN have been identified and characterised since the assessment on ZEN in 2011, thus EFSA decided to review the new and relevant data in 2016. There is little information on the absorption, bioavailability and metabolic fate of the metabolites and it was assumed they are as readily bioavailable as ZEN. Acute toxicity of ZEN is low and EFSA did not identify any new studies indicating the need for an ARfD or to revise the current TDI. EFSA however noted, that oestrogenicity is the common mode of action (MoA) for toxicity of ZEN and its metabolites and therefore found it appropriate to establish a group HBGV. To account for the differences in the oestrogenic potencies in vivo, each modified form of ZEN was assigned a potency factor relative to ZEN, the assumption being made that the oestrogenic effects of the various modified forms are additive. EFSA confirmed the TDI of 0.25 µg/kg bw for ZEN as a group TDI for ZEN and its modified forms.

42. However, EFSA did note, that the overall uncertainty associated with its assessment is high and it would probably overestimate the risk of modified ZEN.

43. Mean and 97.5\textsuperscript{th} percentile UK exposures of infants and young children are all below the group TDI of 0.25 µg/kg bw per day and are therefore not of toxicological concern

\textit{Nivalenol}

44. Nivalenol is a type B trichothecene produced by \textit{Fusarium} species under moist and cool conditions and predominantly found in cereal grains and cereal-based products.

45. Generally, trichothecenes are immunotoxic and haematotoxic/myelotoxic. Several \textit{in vivo} studies on nivalenol have reported an increase of IgA or IgM at higher concentrations than those reporting haematotoxic effects such as neutropenia or leukopenia. IARC concluded in 1993 that “there is inadequate evidence in experimental animals for the carcinogenicity of nivalenol” and that nivalenol was not classifiable as to its carcinogenicity to humans (Group 3).

46. As nivalenol is unlikely to be genotoxic, EFSA (2013) considered it appropriate to establish a TDI of 1.2 µg/kg bw based on a BMDL\textsubscript{05} of 0.35 mg/kg bw per day for haematological disturbances in white blood cell (WBC) counts observed in rats and the application of an overall UF of 300, consisting of the default UF of 100 for intra- and interspecies differences and additional UF\textsubscript{s} of 2 and 1.5 for extrapolation from sub-chronic to chronic study duration and limitations in the reproductive and developmental toxicity data, respectively.

47. All mean and 97.5\textsuperscript{th} percentile exposures of infants and young children aged 4 to 60 months are below the TDI of 1.2 µg/kg bw established by EFSA and therefore the exposures to nivalenol are not of toxicological concern.
# Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AFB1</td>
<td>Aflatoxin B1</td>
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<td>Aflatoxin B2</td>
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<td>Aflatoxin M1</td>
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<td>ARID</td>
<td>Acute reference dose</td>
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<td>BMD</td>
<td>Bench mark dose</td>
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<td>bw</td>
<td>body weight</td>
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<td>COT</td>
<td>Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment</td>
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<tr>
<td>DNSIYC</td>
<td>Diet and Nutrition Survey of Infants and Young Children</td>
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<td>EAs</td>
<td>Ergot alkaloids</td>
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<td>EFSA</td>
<td>European Food Safety Authority</td>
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<td>EU</td>
<td>European Union</td>
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<td>HBGV</td>
<td>Health based guidance value</td>
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<td>Hepatocellular carcinomas</td>
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<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<td>ip</td>
<td>intraperitoneal</td>
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<td>JECFA</td>
<td>Joint FAO/WHO Expert Committee on Food Additives</td>
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<td>LB</td>
<td>Lower bound</td>
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<td>LOQ</td>
<td>Limit of quantification</td>
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<td>LSD</td>
<td>Lysergic acid diethylamide</td>
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<td>MoA</td>
<td>Mode of action</td>
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<td>Margin of exposure</td>
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<td>NDNS</td>
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<td>NOAEL</td>
<td>No observed adverse effect level</td>
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<td>Point of departure</td>
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<tr>
<td>RMR</td>
<td>red mould rice</td>
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<td>Scientific Advisory Committee on Nutrition</td>
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<td>STC</td>
<td>Sterigmatocystin</td>
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<td>TDI</td>
<td>Tolerable daily intake</td>
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<td>Total Diet Study</td>
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<td>WBC</td>
<td>White blood cell</td>
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<td>ZEN</td>
<td>Zearalenone</td>
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This is a background paper for discussion. 
It does not reflect the views of the Committee and should not be cited.

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