TOX/2019/68

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

Additional information on DON and its acetylated/modified forms

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. Since EFSA had recently (2017) published its scientific opinion on Don and its acetylated and modified forms in food and feed, Members asked for an update on the EFSA opinion, especially regarding the derivation of the health-based guidance values (HBGVs). Furthermore, Members requested the sum of DON and its three forms detected in the TDS to be included in the exposure assessment.

4. Annex 1 provides a brief overview of JECFAs and EFSAs derivation of the HBGVs and an update on the exposure assessment, including an updated risk characterisation.

5. Since last reviewed by the Committee, the actual values of the HBGVs have not changed. The inclusion of the additional information on HBGVs and exposures has not changed the overall conclusions of the risk characterisation much. Therefore, the Secretariat, in the interest of time, has already included draft text in the Addendum which will be discussed later today. Any discussions of DON and any points the Committee would like to emphasise will be added to the final version, should the Members still be content with DON being included in the Addendum.

Questions for the Committee

i) Do the Committee have any comments on the derivation of EFSAs HBGVs, specifically the use of epidemiological data for the derivation of the ARfD?

ii) Do the Committee agree that a full review of DON will not be necessary and it can be included in the Addendum?

iii) If so, do Members have any points, regarding the derivation of the HBGVs or otherwise, they would like to emphasis?

iv) Do the Committee have any other comments?

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Additional information on DON and its acetylated/modified forms

1. DON is produced by *Fusarium* species growing on cereal crops, preferably at temperate climates. 3- and 15-Ac-DON are fungal metabolites of DON, DON-3-glycoside is a plant metabolite of DON. Consequently, these four chemicals have been measured in cereal crops and in cereal-based foods such as bread, pasta and biscuits.

2. In 1999, the SCF established a temporary TDI (t-TDI) of 1 µg/kg bw per day for DON based on the NOAEL of 0.1 mg/kg bw per day from a 2-year mouse study (Iverson *et al.* 1995) and the application of an UF of 100. In 2002, the SCF assessed the group-combined effect of common trichothecenes including T-2 and HT-2 toxins, DON and nivalenol, and concluded that the available data were insufficient to establish a group TDI for either the combined effects or the relative potencies of the trichothecenes. Based on its assessment, the SCF decided to turn the t-TDI of 1 µg/kg bw per day for DON to a full TDI.

3. JECFA considered emesis the critical end point for acute effects as this effect has consistently been observed after DON intoxication in both experimental animals and humans.

4. In 2011, JECFA combined data from 2 studies on emesis in pigs and piglets following exposure to DON via the diet, for BMD modelling. The $BMDL_{10}$ ranged from 0.21 - 0.74 mg/kg bw per day, the lowest of which was used as the POD for establishing the ARfD. JECFA applied an UF of 25 based on the consideration that “DON-induced emesis is a systemic effect and more dependent on Cmax than on area under the plasma concentration–time curve (AUC)” and previous use by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) for acute Cmax-dependent effects, and derived a group ARfD of 8 µg/kg bw for DON, 3- and 15-Ac-DON.

5. Limited data from human case reports indicate that dietary exposures up to 50 µg/kg bw per day are not likely to induce emesis.

6. In 2001, JECFA established a PMTDI for DON of 1 µg/kg bw on the basis of a NOEL[1] of 100 µg/kg bw per day based on decreased body weight

[1] At its sixty-eighth meeting (2007), the Committee decided to differentiate between NOAEL and NOEL. This NOEL would now be considered a NOAEL.

in a 2-year feeding study in mice and the application of an UF of 100. Repeat dose short-term studies considered in the 2011 evaluation indicated that this NO(A)EL of 100 µg/kg bw per day remains appropriate and JECFA reconfirmed its PMTDI. JECFA furthermore decided to convert the PMTDI for DON to a group PTMDI for DON and its acetylated derivatives (3-Ac-DON and 15-Ac-DON) as 3-Ac-DON is converted to DON and therefore contributes to the total DON-induced toxicity; the toxicity of the acetylated derivatives are considered equal to that of DON.

7. However, JECFA concluded there was insufficient information to include DON-3-glucoside in the group PMTDI or ARfD.

8. In 2017, EFSA derived a group ARfD of 8 µg/kg bw per eating occasion and a group TDI of 1 µg/ kg bw per day.

9. While the mode of action and the toxicity data for 3-Ac-DON and 15-Ac-DON indicated a similar toxicity as that of DON, toxicity data for DON-3-glucoside were limited and in vivo data on chronic toxicity were missing with the consequence that EFSA could not make a firm conclusion on the hazard of DON-3-glucoside and could also not compare it with that of DON and the two acetylated forms. Therefore, EFSA applied a conservative approach assuming that (1) 3-Ac-DON, 15-Ac-DON and DON-3-glucoside are all metabolised to DON and absorbed at the same extent as DON, (2) the acetylated forms of DON induce the same acute and chronic adverse health effects as DON and (3) similar health effects of DON-3-gluciside as DON cannot be excluded. EFSA therefore decided to characterise the three forms and DON together, both for chronic and acute health effects.

10. EFSA identified vomiting as the critical acute effect in humans. Since EFSA did not consider studies based on experimental and farm animals appropriate, epidemiological studies were used as the basis for the derivation of the HBGV. EFSA calculated a NOAEL of 26 µg DON/kg bw for one single eating occasion from a human outbreak in China and applied an UF of 3.16 for toxicodynamic differences in intra-human population variability to derive an ARfD of 8 µg/kg bw per eating occasion. The dose-range calculated from human urinary biomarker data supported the reference dose. The highest urinary biomarker was reported for a healthy pregnant woman from which an exposure of 74 µg DON/kg bw was back-calculated. The next highest exposure based on urinary biomarkers was 36 µg DON/kg bw per day. EFSA concluded that the range of 36 - 74 µg DON/kg bw per day would represent a range of NOAELs at which adverse effects (vomiting) would not be expected to occur in humans. However, EFSA did note a number of uncertainties such as the inconsistency between urinary DON biomarker levels using different methods, neglecting the variation of DON excretion and urine volume amongst individuals and inconsistent reporting. EFSA noted however, that the calculated NOAEL of 26 µg DON/kg bw per eating occasion is not in disagreement with the calculations based on human data by JECFA.

11. In the absence of chronic epidemiological data, EFSA identified reduced bodyweight gain in experimental animals as the critical chronic effect.

EFSA calculated a $BMDL_{05}$ of 0.11 mg/kg bw per day based on a study in mice, the only chronic/carcinogenicity study identified (Iverson et al., 1995), and applied an UF of 100 for inter- and intra-species variability. Since the $BMDL_{05}$ is larger than the BMDLs calculated for reproductive and developmental toxicity, EFSA considered it sufficiently protective.

12. Acute and chronic exposures were calculated using data from the TDS (2014). 3-Ac-DON and 15-Ac-DON were not detected in any samples above the limit of detection (LOD). A total concentration for 15-Ac-DON, 3-Ac-DON and DON was not provided to the FSA as part of the TDS, thus the sum used in the exposure assessment was estimated by summing the individual concentrations of all three forms.

Table 1 Estimated acute exposures (LB-UB) in infants aged 4 to 12 months (µg/kg bw per day)

	4 to <6 month-olds (n=116)		6 to <9 month-olds (n=606)		9 to <12 month-olds (n=686)	
	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile
DON	0.042-0.047	0.23-0.24	0.20-0.21	0.86-0.87	0.35-0.36	0.96-0.97
3-Ac-DON	0.000-0.008	0.001-0.037	0.000-0.022	0.002-0.079	0.001-0.032	0.003-0.081
15-Ac-DON	0.000-0.038	0.000-0.16	0.000-0.12	0.000-0.39	0.000-0.18	0.000-0.46
Total	0.042-0.091	0.23-0.38	0.20-0.34	0.86-1.3	0.34-0.55	0.96-1.3

Table 2 Estimated acute exposures (LB-UB) in young children aged 12 to 18 months (µg/kg bw per day)

	12 to <15 month-olds (n=670)		15 to 18 month-olds (n=605)	
	Mean	97.5th percentile	Mean	97.5th percentile
DON	0.48-0.51	1.2-1.2	0.56-0.59	1.4-1.4
3-Ac-DON	0.001-0.042	0.003-0.096	0.001-0.046	0.003-0.10
15-Ac-DON	0.000-0.23	0.000-0.500	0.000-0.26	0.000-0.58
Total	0.48-0.75	1.2-1.6	0.56-0.86	1.4-1.9

Table 3 Estimated acute exposures (LB-UB) in young children aged 18 to 60 months (µg/kg bw per day)

	18 to 24 month-olds (n=118)		24 to 60 month-olds (n=688)	
	Mean	97.5th percentile	Mean	97.5th percentile
DON	0.55-0.58	1.1-1.2	0.56-0.59	1.3-1.3
3-Ac-DON	0.001-0.050	0.003-0.099	0.001-0.041	0.003-0.082
15-Ac-DON	0.000-0.270	0.000-0.58	0.000-0.24	0.000-0.50
Total	0.55-0.88	1.1-1.7	0.55-0.83	1.3-1.7

Table 4 Estimated chronic exposures (LB-UB) in infants aged 4 to 12 months (µg/kg bw per day)

	4 to <6 month-olds (n=116)		6 to <9 month-olds (n=606)		9 to <12 month-olds (n=686)	
	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile
DON	0.022-0.025	0.13-0.16	0.10-0.11	0.42-0.44	0.21-0.22	0.55-0.59
3-Ac-DON	0.000-0.004	0.000-0.018	0.000-0.012	0.001-0.043	0.000-0.020	0.001-0.054
15-Ac-DON	0.000-0.019	0.000-0.083	0.000-0.067	0.000-0.25	0.000-0.11	0.000-0.29
Total	0.022-0.048	0.13-0.27	0.10-0.19	0.42-0.69	0.20-0.35	0.55-0.91

Table 5 Estimated chronic exposures (LB-UB) in young children aged 12 to 18 months (µg/kg bw per day)

	12 to <15 month-olds (n=670)		15 to 18 month-olds (n=605)	
	Mean	97.5th percentile	Mean	97.5th percentile
DON	0.30-0.32	0.71-0.73	0.35-0.37	0.80-0.86
3-Ac-DON	0.000-0.027	0.002-0.061	0.000-0.030	0.002-0.064
15-Ac-DON	0.000-0.15	0.000-0.33	0.000-0.17	0.000-0.39
Total	0.29-0.50	0.71-1.1	0.34-0.58	0.78-1.3

Table 6 Estimated chronic exposures (LB-UB) in young children aged 18 to 60 months (µg/kg bw per day)

	18 to 24 month-olds (n=118)		24 to 60 month-olds (n=688)	
	Mean	97.5th percentile	Mean	97.5th percentile
DON	0.35-0.38	0.68-0.70	0.36-0.39	0.75-0.77
3-Ac-DON	0.001-0.034	0.002-0.062	0.000-0.029	0.002-0.058
15-Ac-DON	0.000-0.18	0.000-0.34	0.000-0.16	0.000-0.31
Total	0.34-0.59	0.68-1.1	0.35-0.58	0.68-1.1

13. Mean and 97.5th percentile acute exposures to 15-Ac-DON, 3-Ac-DON and DON and the sum of all three forms were below the group ARfD of 8.0 µg/kg bw per day, for all age groups and are therefore not of toxicological concern.

14. Mean and 97.5th percentile chronic exposures to 15-Ac-DON, 3-Ac-DON and DON were below the TDI of 1.0 µg/kg bw per day, for all age groups

and are therefore not of toxicological concern. All mean and 97.5th percentile chronic exposure to the sum of all three forms were below the TDI, except the 97.5th percentile UB exposure in children > 12 months of age, which are at or up to 1.3-fold the TDI. This is unlikely to be of toxicological concern. However, the sum of all forms is not based on measured values but on summing the individual concentrations provided. Therefore, the estimated exposures could be an over- or underestimation of the actual values.

Secretariat

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