TOX/2017/47

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

First draft statement of T2-toxin (T2) and HT2-toxin (HT-2) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government dietary recommendations for infants and young children. The SACN is examining the nutritional basis for the advice. The COT was asked to review the risk of toxicity of chemicals in the diets of infants and young children. The reviews will identify new evidence that has emerged since the Government 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 36 mycotoxins in the 2014 Total Diet Study (TDS) – mycotoxins analysis (FSA, to be published). The results of the survey provide information on the concentrations of aflatoxins (B1, B2, G1, G2 and M1), ochratoxin A, zearalenone, fumonisins (B1, B2 and B3), 3-acetyldeoxynivalenol, 15-acetyldeoxynivalenol, deoxynivalenol, diacetoxyscirpenol, fusarenon-X, HT2 toxin, neosolaniol, nivalenol, T2 toxin, sterigmatocystin, citrinin, cyclopiazonic acid, moniliformin, patulin and ergot alkaloids (ergocornine, ergocorninine, ergocristine, ergocristinine, ergocryptine, ergocryptinine, ergometrine, ergometrinine, ergosine, ergosinine, ergotamine, ergotaminine) in relevant foods. Estimates of dietary exposures have been calculated for each element 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. Details of the concentration data derived from this survey, and the subsequent exposure assessments, were presented to the Committee in a scoping paper (TOX/2017/30) at the July meetings. To aid the discussions, brief toxicology summaries for each of the mycotoxins surveyed were included, along with available health based guidance values (HBGVs), a risk assessment, where possible and conclusions. The Committee commented on the concentration data and the results of the exposure assessments, and suggested that certain mycotoxins be reviewed in more detail. A discussion paper (TOX-2017-41) provided more toxicological information for T2, HT2 and neosolaniol, a metabolite of T2 and an in-depth exposure assessment. The Committee requested that additional benchmark dose modelling be undertaken for the acute reference dose to calculate the model average. This was undertaken by the Secretariat using the PROAST software. Unfortunately, it was not possible to use model averaging in this instance as the software is still under development.

4. At the September meeting Members had agreed that the TDS data should not be used to calculate T2 and HT2 exposures. The data were all left censored and whilst it could be used qualitatively it was not suitable for quantitative estimate of exposures. Therefore, alternative retail surveys where T2 and HT2 were included were considered. In a retail survey of mycotoxins in foods for infants and young children (FSA, 2011), T2 and HT2 were not detected in all 77 of the samples examined. Similarly, in a survey of ethnic foods (FSA, 2013), T2 and HT2 were not detected in any of the samples tested. Another retail survey of oat-based products following initial high results in oat grain in the 2014 harvest showed low levels of T2 and HT2 in various products. Since oats and oat-based products are reported to have higher levels of T2 and HT2 toxin (EFSA, 2017a), and since all the other data did not show any detectable levels of these mycotoxins, data from this survey, in which actual levels of the mycotoxins were measured in oat-based foods, will be used for estimating exposures to T2 and HT2.

5. Samples were analysed for neosolaniol in two retail surveys. 210 retail samples of wheat, maize, oat and rye-based products were tested (FSA, 2010) and neosolaniol was not detected in any sample (LOQ of 10 µg/kg). In another survey of food for infants and young children (FSA, 2011), neosolaniol was not detected in any of the 77 samples analysed (LOD of 5µg/kg and LOQ of 10µg/kg). As there are no UK occurrence data with detectable levels of neosolaniol, it will not be considered further.

6. This draft statement provides a summary of the toxicokinetics and toxicity of T2 and HT2. The derivation of the health based guidance values (HBGVs) for each of the above evaluations is summarised and the most recent HBGVs established by EFSA (2017b) are detailed. Exposure assessments have been carried out and risk characterisations and conclusions/discussion provided.

7. Questions to be asked of the Committee

Members are invited to comment on this first draft statement and consider the following questions:

i). Do the Committee endorse the ARfD established by EFSA in 2017?

ii). Do the Committee have any other comments on this draft statement?

References

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

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Background

1. T2 and HT2 are type A trichothecenes and are produced by a variety of *Fusarium* species (*F. sporotrichoides, F. poae. F. equiseti, F. acumninatum*). They may also be produced by species of *Myrothecium, Cephalosporum, Verticimonosporum, Trichoderma, Trichothecium* and *Stachybotrys*).The *Fusarium* species grow and invade crops and produce the T2 and HT2 toxins under cool, moist conditions prior to harvest. T2 and HT2 toxins are predominantly found in cereal grains (particularly oats) and their products. (EFSA, 2017a).

2. T2 and HT2 toxins have been assessed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2001, the Scientific Committee on Food (SCF) in 2002 and the European Food Safety Authority (EFSA) in 2011 and 2017.

Toxicokinetics

3. The toxicokinetics of T2 and HT2 have been reviewed previously by JECFA (2001) and EFSA (2011).

4. There is very little information on the *in vivo* absorption of T2 and HT2 in animals after oral administration. However 40 to 57 % of radioactive T2 has been measured in bile and blood in studies using tritiated T2. Low amounts of T2 were observed in these studies suggesting an extensive hydrolysis to HT2 and other metabolites during the rapid intestinal absorption of T2. The rapid absorption has been confirmed by the excretion of total radioactivity in rats within 48 hours after oral gavage. T2 radioactivity was rapidly distributed to the liver, kidney and other organs without accumulation in any organ in orally dosed rats and mice. (EFSA, 2017a). The metabolism of T2 and HT2 in human and animals is complex and was reviewed by EFSA (2011). Phase I metabolites arise from either hydrolysis of ester groups; hydroxylation; or de-epoxidation. These reactions may also occur in combination. Glucuronides are the most prevalent mammalian phase II metabolites of T2 and HT2. (EFSA, 2017a).

Toxicity

Summary from previous evaluations

5. The toxicity of T2 and HT2 has been reviewed previously by EFSA, JECFA and the SCF. The EFSA 2011 evaluation, concluded that T2 induces haemato- and myelotoxicity and that these effects occurred at lower doses than other toxic effects such as dermal toxicity, developmental and reproductive toxicity, and neurotoxicity. Some clastogenicity tests produced a positive result. However this was mainly at concentrations which also inhibited protein and DNA synthesis and caused cytotoxicity. EFSA concluded that T2 inhibited protein-, DNA-, and RNA synthesis and that there were studies indicating that T2 causes apoptosis, necrosis and lipid peroxidation. The pig was identified as one of the most sensitive species. (EFSA, 2011).

In vivo toxicity studies published since the 2011 EFSA Opinion and reviewed by EFSA (2017a)

Acute toxicity studies

8. In a study by Wu *et al.* (2015) groups of female B6C3F1 mice (n = 6) were fasted for 8 hours prior to dosing. Animals were administered T2 or HT2 toxin at 0, 0.01, 0.1, 0.5 and 1 mg/kg bw by intraperitoneal (i.p.) injection or oral gavage. The mice were then immediately provided with a pre-weighed feed pellet and feed intakes measured at 0.5, 1, 2, 3, 6, 16, 24 and 48 hours after oral exposure and at 72 and 96 hours in addition for i.p. exposure. Oral and i.p. administration produced marked reduction in feed intake for 0.1, 0.5 and 1 mg/kg bw from 0.5 – 48 hours and 0.5 – 96 hours, respectively for both T2 and HT2 toxins. No effects were observed at 0.01 mg/kg bw T2 and HT2 toxins. The authors identified a lowest observed adverse effect level (LOAEL) of 0.1 mg/kg bw and a no observed adverse effect level (NOAEL) of 0.01 mg/kg bw for both T2 and HT2 toxins via i.p. and oral administration. (Wu *et al.*, 2015).

9. In a study by Wu *et al.* (2016) groups of fasted female mink (n = 4) were given 50 g of feed 30 minutes prior to either, i.p. administration of 0, 0.001, 0.01, 0.05 or 0.25 mg/kg bw of T2 or HT2 toxin or 0, 0.5, 1, 2.5 or 5 mg/kg bw emetine, or administration by oral gavage of 0, 0.005, 0.05, 0.25 or 0.5 mg/kg bw T2 or HT2 or 0, 0.5, 1, 2.5 or 5 mg/kg bw emetine. The animals were then monitored for emetic events[1] for 6 hours. In a 2nd study, 3 groups of fasted female mink (n = 4) were given 50 g of feed 30 minutes prior to 0.5 mg/kg bw T2 or HT2 or 5 mg/kg bw emetine by oral gavage. Emetic events were recorded for up to 2 hours and levels of plasma anorectic peptide pancreatic peptide YY3-36 (PYY_{3-36}) and 5-hydroxytryptamine (5-HT) (hormones known to be implicated in emesis) measured. The lowest dose at which emetic events were observed after i.p. administration was 0.05 mg/kg

[1] An emetic event was classed as either vomiting or retching. According to Wu *et al.* (2016) vomiting is rhythmic abdominal contraction with oral expulsion of either solid or liquid material. Retching is a response which mimics vomiting but without the expulsion of any material.

bw for T2 and HT2 and 25 % of animals were affected for each. After oral exposure the lowest dose at which emetic events occurred were 0.05 mg/kg bw and 75 % of animals were affected for both T2 and HT2. At 0.25 mg/kg bw 4 animals (100 %) were affected for both T2 and HT2 via i.p. and oral administration. The lowest doses at which emetic events occurred in animals dosed with emetine was 2.5 (50 %) and 1 mg/kg bw (50 %) for i.p. and oral administration routes, respectively. The latency of emetic events decreased while duration and frequency of emetic events increased with dose. Oral administration of T2 and HT2 caused increases in plasma concentrations of PYY_{3-36} and 5-HT. The authors concluded that via the oral route NOAELs were 5 µg/kg bw, LOAELs were 50 µg/kg bw and ED_{50}s were 20 µg/kg bw for both T2 and HT2.

Subacute toxicity studies

10. In a study by Chandratre *et al.* (2014) Male Wistar rats (n = 12) were divided into 2 groups of 6 rats. The groups were fed either a control diet or normal feed mixed with T2 toxin at 20 mg/kg (ppm) (equivalent to 2.4 mg/kg bw/day) *ad libitum* for 14 days. Rats fed the T2 toxin exhibited symptoms of anorexia, diarrhoea, decreased body weight gain, lethargy and hunched posture etc. after 7 days. No mortality was observed. Absolute organ weights of spleen, thymus, liver, kidney, testes and epididymis were significantly decreased in dosed animals compared to control animals, but not absolute brain weight. Relative organ weights of brain, kidneys, testes and epididymis were significantly increased, but those of spleen and thymus were significantly decreased with no significant change for liver. Haematological parameters were decreased in T2 toxin fed rats. Total lymphocyte counts and circulating lymphocyte counts in T2 fed rats were 2.6 x and 1.3 x 10^3/µl compared to control values of 17 and 14 x 10^3/µl, respectively. Aspartate amino transferase (AST) and alanine amino transferase (ALT) activity levels were significantly increased and blood glucose significantly decreased in T2 fed rats compared to control rats. Malondialdehyde (MDA) (a marker for lipid peroxidation) levels were significantly increased in serum and liver of T2 toxin fed rats compared to controls. Levels of catalase and superoxide dismutase (SOD) were decreased in serum and liver from T2 fed rats compared to control animals.

11. In a study by Obremski *et al.* (2013) 30 Polish Large White female pigs were divided into 2 groups (n = 15) and became a control group or were fed 200 µg/kg feed/day of T2 toxin (equivalent to 10 µg/kg bw/day as calculated by EFSA (2017)). At 14, 28 and 42 days 5 randomly selected pigs were euthanized and the ileum sampled. The percentage of cluster of differentiation $(CD)8^+$ T lymphocytes significantly increased in animals administered T2 compared to controls at days 14 and 42, but significantly decreased at day 28. $CD21^+$ B cells percentage in treated animals decreased over time compared with controls, with significant decreases at days 28 and 42. The percentages of $CD4^+/CD8^+$ double positive T lymphocytes in treated animals were lower than controls on days 14 and 28 and statistically significant at day 28. There was a significant decrease in the messenger (m)RNA level of interleukin (IL)-10 in ileal Peyer's patches after 42 days of treatment with T2. Throughout the

experiment there was a non-significant gradual decrease in the amount of IL-4 and interferon (IFN)-gamma cytokine transcripts.

12. In a study by Rafai *et al*. (2013) 30 Dutch Landrace x Hungarian Large White F1 pigs were divided into 3 groups (n = 10) and administered 0, 300 and 500 µg/kg T2 toxin/day (equivalent to 0, 11.5 and 18.6 µg/kg bw/day (Rafai *et al.*, 2013)) for 21 days. The average dietary feed intake and weight of pigs administered T2, at either concentration, was consistently and significantly lower than that of control animals. Both T2 doses also significantly suppressed weight gain of the pigs. The T2 treatments did not cause significant changes in the metabolic (glucose and free fatty acids, AST, albumin, total protein and urea), Immunological (anti-horse globulin antibody titres, in vitro lymphocyte proliferation tests and phagocytic activity) and other (calcium, inorganic phosphorous, magnesium, sodium, potassium, copper, zinc and iron) blood parameters tested. The authors considered that the lower intake of T2 due to feed refusal in this study might explain why the immunotoxicity was not observed, unlike in Rafai *et al.* (1995).

Subchronic toxicity studies

13. In a study by Raut *et al.* (2013) 40 male Wistar rats were assigned to 4 groups of 0, 0.25, 0.50 and 0.75 mg T2 toxin /kg (ppm) (equivalent to 0, 23, 45 and 68 µg T2 toxin/kg bw/day (as calculated by EFSA (2017a))) and dosed for 90 days. All T2 toxin dosed rats displayed signs of mild anorexia, weakness and rough hair coat. By 90 days the mean bodyweights and body weight gains of animals administered 0.50 and 0.75 mg/kg bw/day were significantly lower than control animals. The mean total thrombocyte counts (TTC) decreased with increasing T2 dose, significant at the highest dose. Total erythrocyte counts (TEC) and total leucocyte counts (TLC) were reduced, although not statistically significantly. The authors attributed the non-statistically significant decrease in total leucocyte counts to lymphocytopaenia as (not statistically significant) decreases in the proportion of lymphocytes of the total leucocyte counts were observed. Total protein was statistically significantly reduced in all dose groups compared to the controls. Albumin and globulin levels decreased as did the albumin:globulin ratio. Levels of AST, ALT and creatinine increased whereas levels of alkaline phosphatase (ALP) decreased. At the highest dose livers were comparatively pale and slightly enlarged. The relative weights of the liver, kidney and brain increased and those of the testes, thymus and spleen decreased. Lipid peroxidase increased whereas SOD and catalase activities decreased. (Raut *et al.*, 2013). EFSA did not identify a NOAEL in this study but considered the lowest dose tested (23 µg/kg bw/day) a LOAEL. EFSA decided not to use this study for hazard characterisation because, although the decrease in total thrombocyte counts was in line with other studies, the absence of significant effects on total leucocyte and erythrocyte count was not. (EFSA, 2017a).

14. In a study by Rahman *et al.* (2014) 192 male Wistar rats were assigned to 4 groups (n = 48) and dosed with 0, 0.5, 0.75 or 1.0 mg T2/kg (ppm) (equivalent to 0, 45, 68 and 90 µg T2/kg bw/day, respectively) daily via the diet for 12 weeks. Eight animals each were sacrificed at 2, 4, 6, 8, 10 and 12

weeks. Rats dosed with T2 toxin showed varying degrees of clinical signs, including dullness, weakness, lethargy, growth retardation, reduced feed intake, reluctance to move and rough hair coat, which worsened over time in groups 68 or 90 µg/kg bw/day. After the 8th and 10th week, respectively animals treated with 90 µg/kg bw/day showed gangrenous dermatitis of the tail (15/24) and facial and podal dermatitis. A statistically significant dose-dependent decrease in bodyweights was seen after 90 days of dosing. Mean body weights were 264, 219, 184 and 160 g for rats dosed with 0, 45, 68 and 90 µg/kg bw/day. Significant decreases in haemoglobin (Hb), packed cell volume (PCV), TEC, TTC, TLC, mean corpuscular volume (MCV), mean corpuscular Hb (MCHb), and percentages of lymphocytes was observed but the percentage of neutrophils increased. Generally, all of these observations became more pronounced with study length. After 90 days of feeding mean TECs were 8.97, 5.85, 5.77 and 4.65 x10^{6}/µl in rats fed 0, 45, 68 and 90 µg/kg bw/day, respectively; mean TLCs were 14.83, 8.95, 6.92 and 5.20 x10^{3}/µl in animals dosed with 0, 45, 68 and 90 µg/kg bw/day, respectively; mean TTCs were 122.5, 77.7, 56.5 and 38.0 x10^{3}/µl in animals fed 0, 45, 68 and 90 µg/kg bw/day. (Rahman *et al.*, 2014). The authors concluded that T2 induces microcytic hypochromic anaemia, leukocytopaenia (due to lymphocytopaenia) and thrombocytopaenia in rats which increased with dose and duration of exposure. When EFSA reviewed this study they did not identify a NOAEL and considered the lowest dose tested (45 µg/kg bw/day) a LOAEL. (Rahman *et al.*, 2014). EFSA noted that the thrombocyte counts were unusually low in this study compared with other studies. (EFSA, 2017a).

Developmental toxicity studies

15. In a study by Tanaka *et al.* (2016) 52 pregnant mice were randomly assigned to 4 groups (n = 13) and dosed with 0, 1, 3 or 9 mg T2/kg in the diet (equivalent to 0, 0.14, 0.40 and 1.18 mg T2/kg bw/day) from gestation day (GD) 6 to 21, and to 0, 0.49, 1.39 and to 3.79 mg T2/kg bw/day during lactation. Offspring were maintained through day 77 without T2 exposure. At postnatal day (PND) 21, changes in the hippocampus paralleled with increased apoptosis were seen in male offspring of dams of the 2 highest dose groups and reduced relative brain weight was seen in male offspring of dams treated with the highest dose. Neurogenesis-related changes disappeared on PND 77, suggesting that T2 reversibly affects neurogenesis by inducing apoptosis. The authors identified a NOAEL of 140 – 490 µg/kg bw/day for effects of T2 on offspring neurogenesis. (Tanaka *et al.*, 2016)

Summary

16. A number of acute and subacute toxicity studies had been published since the EFSA 2011 evaluation. These consisted of studies on the anorectic effects (feed refusal, reduced body weight gain, vomiting and retching) of T2 and HT2 at low doses and predominantly in 3 species (mink, pig and mouse). There have been reports of nausea and emesis in humans consuming mouldy grain contaminated with T2 producing strains of *Fusarium poae* and *Fusarium*

sporotrichioides (EFSA, 2011). Due to these reports and studies EFSA decided that it was necessary to establish an ARfD (EFSA, 2017a).

17. Subchronic toxicity studies published since 2011 had investigated similar endpoints to those used by EFSA in its 2011 evaluation for derivation of an HBGV. They tended to be of longer duration than the pig studies used but confirmed the immunotoxicity and haematotoxicity of T2 and HT2.

18. The COT have assessed the *in vivo* studies published since 2011 and reviewed by EFSA (2017a) and agreed with the studies used by EFSA for determination of an acute reference dose (ARfD) and updating the TDI.

Studies used in the derivation of an HBGV

Rafai et al., 1995a

19. In a study by Rafai *et al.* (1995a) 4 groups (n = 10) of conventional Dutch Landrace x Hungarian Large White F1 pigs were fed diets for 21 days containing 0, 0.5, 1.0, 2.0 and 3.0 mg T2/kg feed. The average daily intake of toxin was 0.38, 0.81, 1.24 and 1.42 mg. T2 toxin exposures of 0, 29, 62, 105 and 129 µg/kg bw/day were calculated (Rafai *et al.*, 1995b). Differences in weight gains between control and experimental groups were only statistically significant for a decrease in the 130 µg/kg bw/day group. Feed intakes were, on average, 12.6, 5.4, 19.3 and 41 % of the controls for pigs dosed with 29, 62, 105 and 129 µg/kg bw/day. T2 toxin doses greater than 29 µg/kg bw/day depressed the glucose content of the plasma significantly. Lower concentrations of free fatty acids in the plasma indicated that T2 toxin had a negative effect on energy metabolism, however this was only significant for animals dosed with 105 µg/kg bw/day. AST activity was significantly increased at doses of 29 and 62 µg T2/kg bw/day. In animals administered 62, 105 and 129 µg/kg bw/day there were significant increase in inorganic phosphorous and magnesium concentrations. (Rafai *et al.*, 1995a)

Rafai *et al*., 1995b

20. The methods for this study were as described for Rafai *et al.* (1995a). In addition, on the 1st and 4th days control and dosed pigs were immunised intramuscularly with 5 ml of purified horse globulin adsorbed in aluminium hydroxide gel. Blood samples were withdrawn from the vena cava cranialis before the 1st immunisation and then after 7, 14 and 21 days. Significant decreases in red blood cell (RBC) count and the haematocrit caused in pigs with diets containing 105 and 129 µg T2/kg bw/day. Leucocyte numbers and Hb decreased as the T2 toxin concentration increased. In general, the humoral immune response of pigs dosed with T2 toxin was significantly reduced compared to control animals. Lymphocyte stimulation by homologous antigen, phytohaemagglutinin A (PHA) and concanavalin A (Con A) decreased by varying degrees by the diets containing T2 toxin. Histological changes were observed in the thymus, spleen and lymph nodes. (Rafai *et al.*, 1995b).

Wu *et al*., 2016

21. See paragraph 7.

Rahman *et al*., 2014

22. See paragraph 12.

HBGV's established by EFSA, JECFA and the SCF

JECFA 2001 provisional maximum tolerable daily intake (PMTDI)

23. The JECFA Committee concluded that immunotoxicity and haematotoxicity are the critical effects of T2 after short-term intake. JECFA used the lowest observed effect level (LOEL) of 29 µg/kg bw/day for changes in red and white blood cell counts identified in the Rafai (1995 a,b) studies. An uncertainty factor of 500 was applied to derive a provisional maximum tolerable daily intake (PMTDI) for T2 of 60 ng/kg bw/day. HT2 was included in the PMTDI which resulted in a group PMTDI of 60 ng/kg bw/day for T2 and HT2, alone or in combination.

SCF 2001 temporary TDI (tTDI)

24. The SCF considered the general toxicity, haematotoxicity and immunotoxicity of T2 to be the critical effects. They used the haematotoxicity and immunotoxicity of T2 toxin in pigs in a short term study (Rafai *et al.* 1995b) as the basis for the risk assessment. The SCF noted that slight effects were seen on immune parameters and approximately a 10% reduction in feed intake at the lowest dose. An uncertainty factor of 500 was applied and a temporary TDI (tTDI) of 0.06 µg/kg bw (60 ng/kg bw) was established. It was also concluded that because the toxicity of T2 *in vivo* may be partly attributed to HT2, it was appropriate to set a combined tTDI for the sum of T2 and HT2.

EFSA 2011 (TDI) (EFSA, 2011a)

25. EFSA performed a benchmark dose (BMD) analysis on the specific antibody response, anti-horse globulin response from Rafai *et al.* (1995a,b). EFSA carried out a BMD analysis and used the PROAST software (version 26.0 under R 2.10.2), following EFSA advice (2011b). EFSA used the BMD_{L05} of 10 µg/kg bw/day for T2 toxin as a reference point to derive a TDI. Due to the rapid metabolism of T2 to HT2 and the fact that T2 toxicity may in part be due to HT2 EFSA decided to establish a group TDI for the sum of T2 and HT2 toxins. The default uncertainty factor of 100 was applied to the $BMDL_{05}$ of 10 µg/kg bw/day to derive a TDI of 100 ng/kg bw/day for the sum of T2 and HT2 toxins.

EFSA 2017 ARfD and TDI

ARfD

26. Recent studies have reported anorectic effects at low doses in mice mink and pig. Acute effects were seen at the lowest dose in mink in a study by Wu *et al.* (2016). Emetine (an *ipecacuanha* alkaloid) was used as a positive control in this study and the ED_{50} obtained was 1030 µg/kg bw via the oral route. Emetine has been used to induce vomiting in humans and the effective dose is in the same range as that given to mink. The mink, *in lieu* of the ferret (which is more expensive and difficult to raise), has been suggested as the model species for emesis in drug testing (Gordon, 1985; Zhang *et al.*, 2006; Percie du Sert *et al.*, 2012). EFSA (2017a) therefore concluded that the mink was an appropriate animal model to investigate vomiting in humans (EFSA, 2017a).

27. This study was used by EFSA for the BMD analysis as the basis for an ARfD. Following oral gavage in two independent tests, one with T2 and one with HT2, each with four animals/dose group, identical results at identical doses were seen.

28. The BMD analysis was performed using the EFSA guidance on the use of the BMD (EFSA, 2017b). The data used in the BMD analysis are shown in Table 1. “For quantal response data observed in experimental animals, BMR values of 1 %, 5 % and 10 % (extra or additional risk) were initially proposed. Various studies estimated that the median of the upper bounds of extra risk at the NOAEL was close to 10 %, suggesting that a $BMDL_{10}$ may be an appropriate default. Also a BMR of 10 % appears preferable for quantal data because the BMDL can become substantially dependent on the choice of dose-response models at lower BMRs” (EFSA, 2017a). EFSA (2011a) selected a benchmark response of 10 % and used PROAST software version 38.9. One additional assumption was noted, in that the results from 2 independent experiments on T2 and HT2 were combined and the experiments considered as covariate. The results from the BMD analysis are shown in Table 2.

Table 1. Data used in the BMD analysis to establish an ARfD

Substance	Dose (µg/kg bw)	Animals showing emesis	Number of animals (N)	Sex
T2	0	0	4	F
	5	0	4	F
	50	3	4	F
	250	4	4	F
	500	4	4	F
HT2	0	0	4	F
	5	0	4	F
	50	3	4	F
	250	4	4	F

	500	4	4	F

bw: bodyweight

Table 2. Results of the BMD analysis to establish an ARfD

Models	Number of parameters	Log likelihood	AIC[(a)]	$BMDL_{10}$ (µg/kg bw)[(b)]	BMD_{10} (µg/kg bw)[(b)]	$BMDU_{10}$ (µg/kg bw)[(b)]
Full	8	-4.50[(e)]	25.00	-	-	-
Null	2	-27.73	59.05	-	-	-
Gamma	3	-4.50	15.00	2.97	28.3	44.3
Logistic	2	-4.50	13.00	12.30	42.7	49.8
LogLogistic	3	-4.50	15.00	4.29	37.1	47.1
LogProbit	3	-4.50	15.00	4.02	26.8	49.7
Two-stage[(c)]	3	-4.61	15.22[(b)]	NR[(d)]	NR[(d)]	NR[(d)]
Probit[(e)]	2	-4.50	13.00	11.0	36.1	NR[(d)]
Weibull	3	-4.50	15.00	3.02	29.9	47.9

(a): AIC: Akaike's information criterion
(b): BMD: benchmark dose calculated at 10 % extra risk. $BMDL_{10}$: 95th lower confidence limit (one-sided) of BMD;$BMDU_{10}$: 95th upper confidence limit (one-sided) of BMD.
(c): Model not fulfilling the criterion (AIC $\leq AIC_{min}$ +2)
(d): NR: Not reported
(e): Calculated using BMDSv2.6086, pooling data from the 2 experiments.

29. It was not possible to perform model averaging in this instance using the PROAST software. The overall BMDL-BMDU range is 2.97 – 49.8 µg/kg bw (when considering all models with AIC ≤ AIC_{min} +2). Following the EFSA guidance (EFSA, 2017b), EFSA selected a $BMDL_{10}$ of 2.97 µg/kg bw for further consideration as this was the lowest valid $BMDL_{10}$.

30. An uncertainty factor of 10 for intraspecies variability was applied to the BMDL10 of 2.97 µg/kg bw derived for emetic response in mink. However, no interspecies variability factor was applied because humans were not considered more sensitive than mink to the acute emetic effect of T2 or HT2. An ARfD of 0.3 µg T2 or HT2/kg bw was established.

TDI for T2, HT2 and their modified forms

31. Since 2011, several subacute and subchronic toxicity studies have been published. In the 90-day study in rats by Rahman *et al.* (2014), dose-dependent decreases in total erythrocyte, leucocyte and thrombocyte counts as well as a decrease in the percentage of lymphocytes were observed. This effect progressed during the whole study period with no signs of reaching a plateau at the end. The exposure duration to T2 is longer (90 days) in absolute terms, but also relative to species life time than for pigs in the Rafai et al. (1995) study.

32. EFSA (2017a) noted that, in essence, the effects observed (i.e. anorectic effects and effects on immune system and blood parameters) in the new (longer term) rat study were essentially similar to those seen in the pig study confirming the immune system and the blood cell production as target organs of T2 through species.

33. Therefore, EFSA (2017a) decided, considering the longer exposure duration of the study from Rahman *et al.* (2014) and its biological relevance, to use the total leucocytes count reported from this study (Table 5) for calculating a new BMD for T2. EFSA used the EFSA guidance (EFSA, 2017b) to calculate a BMD. EFSA used a BMR of 10%, considering such a response in leucocyte counts to be within the individual physiological variation and negligible, and further noted that the selected BMR is slightly below the control standard deviation of the controls in the Rahman *et al.* study (14%). A series of other potentially relevant effects seen in repeat dose experiments with T2 have been used for alternative calculations of a chronic BMD. EFSA (2017a) concluded that the BMD derived as described below was the most appropriate and has therefore been used for risk characterisation. The calculations of alternative endpoints are shown in Annex B. The data from the Rahman *et al.* (2014) study used to derive the BMD are presented in Table 5 and the results of the BMD analysis are shown in Table 4.

Table 3. Data used in the BMD analysis to establish a TDI

Dose (µg/kg bw/day)	Mean total leucocyte count (x 10^3/µl)	SE[(a)]	Number of animals (N)	Sex
0	14.83	0.73	8	M
45	8.95	0.36	8	M
68	6.92	0.83	8	M
90	5.2	0.73	8	M

(a): SE: standard error

Table 4. Results of the BMD analysis to establish a TDI

	Model	Number of parameters	Log Likelihood	AIC	$BMDL_{10}$	BMD_{10}	$BMDU_{10}$
	Null	1	-21.99	45.98			
Exponential	3[(a)]	3	-1.14	8.28	3.30	11.52	23.75
	5	4	-1.14	10.28			
Hill	3[(a)]	3	-1.15	8.30	5.95	15.70	27.60
	5	4	-1.15	10.30			
	Full	4	-1.14	10.28			

34. The overall BMDL-BMDU range is 3.30-27.60 µg/kg bw (when considering all models with AIC ≤ AIC_{min} +2). A 95% lower confidence limit for

the benchmark dose response ($BMDL_{10}$) of 3.3 µg T2/kg bw was derived. EFSA used this value as a reference point for establishing a chronic TDI for T2 and HT2 as it was the lowest valid $BMDL_{10}$.

35. To this value an uncertainty factor of 200 was applied. A factor of 10 for interspecies variability, 10 for intraspecies variability and 2 for extrapolation from subchronic to chronic exposure duration and for the progression of the toxic effect through the duration of the study with no signs of reaching a plateau at the end. EFSA established a TDI of 0.02 µg T2/kg bw.

36. Haematotoxicity with reduced production of erythrocytes, leucocytes and platelets, is the critical chronic effect of T2. The underlying mode of action is inhibition of protein synthesis, induction of ribotoxic stress and apoptosis. Based on similar toxic profile and potency, structural similarity and the fact that HT2 is an immediate metabolite of T2 in agreement with the EFSA assessment of 2011, it was concluded that T2 and HT2 can be included in a group TDI with the same potency.

Uncertainties

37. EFSA (2017a) identified a series of uncertainties in their evaluation.

38. The test compound in the study used to determine the TDI was purified from fungal culture material and its purity was not specified. It therefore cannot be excluded that minor amounts of other mycotoxins, including modified forms, were present.

39. There is uncertainty associated with using a subchronic study to establish a chronic HBGV. Additionally there were no repeated dose studies available for HT2 which has been included in the group TDI with T2, based on similar toxic profile and potency, structural similarity and because HT2 is an immediate metabolite of T2.

40. EFSA established an ARfD for T2 and HT2 based on a $BMDL_{10}$ derived from observations of emesis in 2 similar acute studies with T2 and HT2. EFSA noted that there is considerable uncertainty associated with the BMDL calculation due to the large dose spacing at the lower doses and the small number of animals used.

41. Dose additivity of T2 and HT2 and their modified forms was assumed, although EFSA noted that, antagonistic or less likely, synergistic, effects of their co-occurrence cannot be excluded in principle.

Exposure Assessment

42. T2 and HT2 toxins were measured in the 2014 TDS – mycotoxins analysis (FSA, to be published).

43. Although occurrence data for T-2 and HT-2 toxin were measured for various food groups in the mycotoxins TDS, all were left censored. All values were below the limit of quantification (LOQ) and several below the limit of detection (LOD). While this data could be used as a qualitative indicator of mycotoxins present in various food categories, it is not possible to use it for a quantitative estimation of dietary exposures for the following reasons:

44. Because of the way the TDS is done it can lead to high LOQs which significantly influence the UB values, and consequently the exposure assessment. A multi-mycotoxin method and approach was used in the analysis for the various food groups, which is normally a screening technique rather than a sensitive quantitative analytical method. This is reflected in generally poor recoveries for T-2 and HT-2 toxin. Also, the analysis of the TDS samples involved a wide range of food matrices (some of which have not been routinely examined previously) and so existing validated methods were adapted/extended to some of the new matrices and this may have also impacted on recovery for T-2 and HT-2 toxins. Recoveries ranged from 13 - 140 % for T-2 toxin and 19 - 100% for HT-2 toxin. For T-2 toxin the limit of detection (LOD) ranged from 0.10 – 0.78 µg/kg. The Limit of Quantification (LOQ) ranged 3.58 – 38.94 µg/kg. The LOD for HT-2 toxin ranged from 1.00 – 5.39 µg//kg and the LOQ 4.98 – 26.94 µg/kg. Poor recoveries and higher Limits of Quantification/Detection (LOQ/LOD) when these are corrected for recovery, led to artificially inflated occurrence levels in some cases.

45. Upper bound exposure estimates resulted in a considerable overestimation of potential exposure. This is not an unfamiliar situation and is routinely encountered in cases where a majority of the occurrence data are left-censored. Recently EFSA have published their updated exposure assessment for T-2 and HT-2 toxin. The very same problem has been documented in their analysis and they have reported that UB estimations were on average fourfold higher than lower bound (LB) estimations.

46. For these reasons, it is not possible to use the T-2 and HT-2 toxin occurrence data from the TDS for a quantitative estimation of dietary exposure. An exposure assessment cannot be based solely on the calculated UB levels from the sum of LOQs and therefore alternative survey data were considered for calculating dietary exposures for infants and young children.

47. In a retail survey of mycotoxins in foods for infants and young children (FSA, 2011), T2 and HT2 were not detected in all 77 of the samples examined. Similarly, in a survey of ethnic foods (FSA, 2013), T2 and HT2 were not detected in any of the samples tested. In another retail survey of oat-based products (FSA, 2015), low levels of T2 and HT2 were detected in various products. Since oats and oat-based products are reported to have higher levels of T2 and HT2 toxin (EFSA, 2017c), and since all the other data did not show any detectable levels of these mycotoxins, data from this survey, in which actual levels of the mycotoxins were measured in oat-based foods, were used for estimating exposures to T2 and HT2.

48. Acute and chronic exposure assessments for T2 and HT2 were carried out using occurrence data from a retail survey commissioned by the FSA in 2015 (FSA, 2015). The FSA survey was commissioned following initial results from the 2014 harvest that showed high levels of T2/HT2 in oat grains. So, the retail survey was commissioned to estimate exposures in a worst-case scenario. The samples collected as part of the survey were oat based as follows: porridge oats (n=56), oat-based breakfast cereals (n=56), oat biscuit products (n=67), black pudding & oatmeal bread (n=6), and oatmeal (n=15). The samples were obtained from major retailers and some convenience type stores.

49. The consumption data used for the exposure assessments, were from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013) and the National Diet and Nutrition Survey rolling programme (NDNS) years 1 – 6 (Bates *et al.*, 2014; Bates *et al.*, 2016). Exposures were assessed for infants aged 4 - <6, 6 - <9 and 9 - <12 months, and for young children aged 12 - <15, 15 – <18, 18 – <24 and 24 – <60 months. Consumption data from DNSIYC was used for children aged 4 – 18 months and from NDNS for children aged 18 – 60 months. The detailed exposure assessments can be found in Annex B.

50. T-2 and HT-2 were detected in 200 samples of oat products from the retail survey that were categorised as follows: biscuits and oatcakes; black pudding; drinking oats; flapjacks and oaty snack bars; muesli oat breakfast cereals and granola; oat bread; oatbran and porridge oats. 78% (155 samples) had concentrations of T-2 and HT-2 above the LOQ (1 µg/kg). Exposure to the sum of T2 and HT2 has been estimated from the results of the retail survey.

Acute

51. Table 5 shows the calculated acute total mean and 97.5th percentile exposures to the sum of T2 and HT2 for infants and young children as lower-bound (LB) and upper-bound (UB) estimates. Total mean and 97.5th percentile exposures ranged from 0.022 (lowest LB) – 0.032 (highest UB) and 0.056 (lowest LB) – 0.11(highest UB) µg/kg bw, respectively. EFSA (2017) reported acute exposure levels of the sum of T2 and HT2 for the consumption of diverse single commodities, therefore UK data could not be compared to the total exposures in table 5.

Chronic

52. Table 6 shows the calculated chronic total mean and 97.5th percentile exposures to the sum of T2 and HT2 for infants and young children. Total mean and 97.5th percentile exposures ranged from 0.0099 (lowest LB) – 0.014 (highest UB) and 0.029 (lowest LB) – 0.063 (highest UB) µg/kg bw/day, respectively. This is comparable to the range of chronic exposures from oat

containing commodities reported by EFSA (2017) for UK infants: mean of 0.016 - 0.039 and 95th percentile of 0.045 - 0.090 µg/kg bw/day. For UK toddlers, EFSA (2017) reported mean and 95th percentile exposures ranging from; 0.021 - 0.057 and 0.047 - 0.11 µg/kg bw/day respectively. The data reported by EFSA is for seven food categories, namely: 'Grains and grain-based products' (unspecified), 'Grains for human consumption', 'Breakfast cereals', 'Grain milling products', 'Fine bakery wares', 'Pasta (raw)' and 'Bread and rolls'.

Table 5. Estimated sum of T2 and HT2 acute exposures from the 2015 retail survey in infants and young children aged 4 to 60 months (µg/kg bw)

	4 to <6 month-olds (n = 20)		6 to <9 month-olds (n = 273)		9 to <12 month-olds (n = 386)		12 to <15 month-olds (n = 404)		15 to <18 month-olds (n = 371)		18 to 24 month-olds (n = 63)		24 to 60 month-olds (n = 390)	
	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile
Sum of T2 and HT2	0.022 – 0.023	0.056 – 0.057	0.029 – 0.030	0.097 – 0.099	0.029 – 0.030	0.091 – 0.093	0.029	0.096 – 0.098	0.029 – 0.030	0.10 – 0.11	0.031 – 0.032	0.075 – 0.076	0.022 – 0.023	0.068 – 0.069

Table 6. Estimated sum of T2 and HT2 chronic exposures from the 2015 retail survey in infants and young children aged 4 to 60 months (µg/kg bw/day)

	4 to <6 month-olds (n = 20)		6 to <9 month-olds (n = 273)		9 to <12 month-olds (n = 390)		12 to <15 month-olds (n = 404)		15 to <18 month-olds (n = 371)		18 to 24 month-olds (n = 63)		24 to 60 month-olds (n = 390)	
	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile	Mean	97.5th percentile
Sum of T2 and HT2	0.011	0.029 – 0.030	0.014	0.051 – 0.052	0.014	0.059 – 0.060	0.014	0.050 – 0.051	0.013	0.062 – 0.063	0.012 – 0.013	0.042 – 0.043	0.0099 – 0.010	0.032 – 0.033

Risk characterisation

Acute

53. The sum of T2 and HT2 acute mean and 97.5th percentile exposures are below the EFSA ARfD of 0.3 µg/kg bw and are therefore not a health concern

Chronic

54. All chronic mean exposures are below the EFSA TDI of 0.02 µg/kg bw and are not a health concern.

55. The chronic 97.5th percentile exposures range from 145 – 315 % of the EFSA TDI. However the survey data were taken following a harvest year when levels of T2 and HT2 were higher than in previous years and designed to be a worst case scenario. Therefore it is likely that these exposures are conservative.

56. Whilst an effect on health cannot be entirely excluded it is doubtful that children would be exposed to these levels in a normal harvest year. It is certainly unlikely that these exposure levels would be achieved over their entire lifetime and therefore unlikely that there will be chronic effects.

Conclusions/Discussion

57. There is very little information on the *in vivo* absorption of T2 and HT2 in animals after oral administration. T2 is rapidly absorbed in the intestine and extensively hydrolysed to HT2 and other metabolites. It is rapidly distributed to the liver, kidney and other organs without accumulation. Excretion is also rapid. The metabolism of T2 and HT2 in human and animals is complex and Phase I and II metabolites can be produced.

58. A number of acute and subacute toxicity studies had been published since the EFSA 2011 evaluation and predominantly focussed on the anorectic effects of T2 and HT2 at low doses (mink, pig and mouse. Subchronic toxicity studies published since 2011 had investigated similar endpoints to those used by EFSA in its 2011 evaluation for derivation of an HBGV. They tended to be of longer duration than the pig studies used but confirmed the immunotoxicity and haematotoxicity of T2 and HT2.

59. Prior to 2017 HBGVs had been established for T2 and HT2 by JECFA, SCF and EFSA. In their 2017 Opinion EFSA established a group ARfD of 0.3 µg/kg bw and a group TDI of 0.02 µg/kg bw for T2 and HT2.

60. Acute and chronic exposures were calculated for a sum of T2 and HT2 using occurrence data from a retail survey commissioned by the FSA in 2015 and consumption data from NDNS and DNSIYC. Mean and 97.5th percentile acute exposures ranged from 0.022 – 0.032 and 0.056 – 0.11 µg/kg bw,

respectively. These were all below the ARfD of 0.3 µg/kg bw and are therefore of no toxicological concern.

61. Mean and 97.5th percentile chronic exposures were calculated and ranged from 0.0099 – 0.014 and 0.029 – 0.063 µg/kg bw/day, respectively. All the mean exposures were below the TDI of 0.02 µg/kg bw and are therefore of no toxicological concern. The chronic 97.5th percentile exposures range from 145 – 315 % of the EFSA TDI. Whilst an effect on health cannot be entirely excluded it is doubtful that children would be exposed to these levels over their entire lifetime and therefore unlikely that they will be of toxicological concern.

Secretariat

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Abbreviations

5-HT	5-hydroxytryptamine
ALP	alkaline phophatase
ALT	alanine amino transferase
ARfD	acute reference dose
AST	aspartate amino transferase
BMD	benchmark dose
BMDL	95 % lower confidence limit for benchmark dose
BMR	benchmark response
bw	bodyweight
CD	cluster of differentiation
Con A	conconavalin A
CYP	cytochrome P450
DH	Department of Health
DNA	deoxyribonucleic acid
DNSIYC	Diet and Nutrition Survey in Infants and Young Children
ED_{50}	dose causing emesis in 50 % of animals tested
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
GD	gestation day
Hb	Haemoglobin
HBGV	health based guidance value
HT2	HT2 toxin
IFN	interferon
Ig	immunoglobulin
IL	interleukin
i.p.	intraperitoneal
i.v.	intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
LB	lower bound
LD_{50}	lethal dose at which 50 % of the test population is dead
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
LOD	limit of detection
LOQ	limit of quantification
µg	microgram
MCHb	mean corpuscular haemoglobin
MCV	mean corpuscular volume
MDA	malondialdehyde
mg	milligram
mRNA	messenger RNA
NDNS	National Diet and Nutrition Survey
NEO	neosolaniol
NOAEL	no-observed adverse effect level
NOEL	no-observed effect level
OVA	ovalbumin
PCV	packed cell volume
PHA	phytohaemagglutinin

PMTDI	provisional maximum tolerable daily intake
PND	postnatal day
ppm	parts per million
PYY_{3-36}	anorectic peptide pancreatic peptide YY_{3-36}
RBC	red blood cell
RNA	ribonucleic acid
RPF	relative potency factor
SCF	Scientific Committee on Food
SOD	superoxide dismutase
T2	T2 toxin
TDS	total diet study
TEC	total erythrocyte counts
TLC	total leucocyte counts
TTC	total thrombocyte counts
tTDI	temporary tolerable daily intake
UB	upper bound
UBMD	95 % upper confidence limit for benchmark dose
UGT	uridine 5’-diphospho-glucuronosyl transferase
WHO	World Health Organization

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

Review of potential risks from T2, HT2 in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Possible T2 toxin and HT2 toxin exposure from dietary sources in young children aged 4 to 60 months

1. T2 and HT2 exposure was estimated using results from a retail survey commissioned by the FSA in 2015. During the planning stage of the retail survey, the FSA's Standard Recipes Database (SRD) was used to prioritise food groups and product types based on oat content and consumption pattern.

2. Samples were categorised as follows:

- Biscuits and oatcakes
- Black Pudding
- Drinking Oats
- Flapjacks and oaty snack bars
- Muesli oat breakfast cereals and granola
- Oat Bread
- Oatbran
- Porridge oats

3. The "Sum T-2 and HT-2" was used for estimating exposure assessments upon advice which is consistent with what has been done previously for other contaminants. Results annotated as follows are treated as detects:

- Results which do not meet the acceptance criteria for identification in the LC-MS SOP are annotated "i".
- Results which do not meet the acceptance criteria for quantification in the LC-MS SOP are annotated "q".

For oat porridges recorded "as eaten" (i.e. prepared with milk, water etc.) the SRD was used to determine the amount of dry porridge and only that portion of the meal was considered in estimating exposure to "Sum T-2 and HT-2"

since it was the dry product that was analysed in the retail survey. Consumption of the other oat based retail food products surveyed are reported in the dietary surveys as purchased. Tables A1 to A6 below provides exposure assessments for all the products combined for infants and young children.

4. The upper bound 97.5th percentile chronic exposures (for consumers) range from 0.029 to 0.063 µg/kg bw/day. The upper bound 97.5th percentile acute exposures (for consumers) range from 0.056 to 0.11 µg/kg bw/day.

Table A1. Estimated Sum T2 and HT2 chronic exposure from oat-based foods commonly eaten by children aged 4 to 12 months using data from the 2015 retail survey

Type of oat product	Exposure LB-UB (µg/kg bw/day)								
	4 to <6			6 to <9			9 to <12		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Biscuits and oatcakes	3	0.0045 - 0.0046	0.0067 - 0.0069	27	0.003 – 0.0031	0.0097 – 0.010	86	0.0030 – 0.0031	0.0094 – 0.0097
Black Pudding	0	n/a	n/a	1	0.0013 – 0.0014	0.0013 – 0.0014	0	n/a	n/a
Drinking Oats	0	n/a	n/a	2	0.026 – 0.037	0.028 – 0.039	0	n/a	n/a
Flapjacks and oaty snack bars	0	n/a	n/a	4	0.0071 – 0.0076	0.012 – 0.013	16	0.0056 – 0.0060	0.013 – 0.014
Muesli oat breakfast cereals and granola	0	n/a	n/a	67	0.0086 – 0.0088	0.036 – 0.037	116	0.0085 – 0.0087	0.037 – 0.038
Oat Bread	0	n/a	n/a	3	0.0043 – 0.0059	0.0067 – 0.0091	8	0.0021 – 0.0028	0.0046 – 0.0062
Oatbran	0	n/a	n/a	0	n/a	n/a	0	n/a	n/a
Porridge oats	17	0.012	0.030	199	0.015 – 0.016	0.054 – 0.055	250	0.016	0.058 – 0.059
Total	**20**	**0.011**	**0.029 – 0.030**	**273**	**0.014**	**0.051 – 0.052**	**390**	**0.014**	**0.059 – 0.060**

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution

Table A2. Estimated Sum T2 and HT2 chronic exposure from oat-based foods commonly eaten by children aged 12 to 18 months using data from the 2015 retail survey

Type of oat product	Exposure LB-UB (µg/kg bw/day)					
	12 to <15			15 to <18		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Biscuits and oatcakes	130	0.0045 – 0.0047	0.014 – 0.015	133	0.0052 – 0.0054	0.018
Black Pudding	1	0.0016 – 0.0017	0.0016 – 0.0017	0	n/a	n/a
Drinking Oats	2	0.0020 – 0.0028	0.0034 – 0.0047	0	n/a	n/a
Flapjacks and oaty snack bars	61	0.0060 – 0.0064	0.015 – 0.016	71	0.0071 – 0.0076	n/a
Muesli oat breakfast cereals and granola	142	0.0063 – 0.0065	0.030	135	0.0055 – 0.0057	0.017 – 0.018
Oat Bread	10	0.0027 – 0.0037	0.0067 – 0.0090	10	0.0032 – 0.0043	0.022
Oatbran	0	n/a	n/a	1	0.0020	0.0064 – 0.0087
Porridge oats	224	0.017	0.055 – 0.056	173	0.017	0.020
Total	**404**	**0.014**	**0.050 – 0.051**	**371**	**0.013**	**0.062 – 0.063**

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution

Table A3. Estimated Sum T2 and HT2 acute exposure from oat-based foods commonly eaten by children aged 4 to 12 months using data from the 2015 retail survey

Type of oat product	Exposure LB-UB (µg/kg bw/day)								
	4 to <6			6 to <9			9 to <12		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Biscuits and oatcakes	3	0.012	0.014	27	0.0084 – 0.0087	0.022	86	0.0088 – 0.0091	0.026
Black Pudding	0	n/a	n/a	1	0.0053 – 0.0056	0.0053 – 0.0056	0	n/a	n/a
Drinking Oats	0	n/a	n/a	2	0.032 – 0.044	0.037 – 0.051	0	n/a	n/a
Flapjacks and oaty snack bars	0	n/a	n/a	4	0.022 – 0.024	0.028 – 0.030	16	0.017 – 0.018	0.033 – 0.035
Muesli oat breakfast cereals and granola	0	n/a	n/a	67	0.021	0.082 – 0.084	116	0.019 – 0.020	0.069 – 0.071
Oat Bread	0	n/a	n/a	3	0.015 – 0.021	0.026 – 0.036	8	0.0059 – 0.0079	0.012 – 0.017
Oatbran	0	n/a	n/a	0	n/a	n/a	0	n/a	n/a
Porridge oats	17	0.024 – 0.025	0.058 – 0.059	199	0.033	0.097 – 0.098	254	0.033 – 0.034	0.087 – 0.088
Total	**20**	**0.022 – 0.023**	**0.056 – 0.057**	**273**	**0.029 – 0.030**	**0.097 – 0.099**	**386**	**0.029 – 0.030**	**0.091 – 0.093**

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution

Table A4. Estimated Sum T2 and HT2 acute exposure from oat-based foods commonly eaten by children aged 12 to 18 months using data from the 2015 retail survey

Type of oat product	Exposure LB-UB (µg/kg bw/day)					
	12 to <15			15 to <18		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Biscuits and oatcakes	130	0.013 – 0.014	0.037 – 0.039	133	0.014	0.038 – 0.040
Black Pudding	1	0.0064 – 0.0067	0.0064 – 0.0067	0	n/a	n/a
Drinking Oats	2	0.0047 – 0.0065	0.0070 – 0.0097	0	n/a	n/a
Flapjacks and oaty snack bars	61	0.015 – 0.017	0.025 – 0.027	71	0.020 – 0.021	0.051 – 0.055
Muesli oat breakfast cereals and granola	142	0.015	0.047 – 0.049	135	0.014	0.049 – 0.050
Oat Bread	10	0.0077 – 0.010	0.018 – 0.025	10	0.011 – 0.015	0.021 – 0.028
Oatbran	0	n/a	n/a	1	0.0040	0.0040
Porridge oats	224	0.035	0.098 – 0.099	173	0.038 – 0.039	0.110
Total	**404**	**0.029**	**0.096 – 0.098**	**371**	**0.029 – 0.030**	**0.100 – 0.110**

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution

Table A5. Estimated Sum T2 and HT2 chronic exposure from oat-based foods eaten by children aged 18 to 60 months using data from the 2015 retail survey

Type of oat product	Exposure LB-UB (µg/kg bw/day)					
	18 to <24			24 to <60		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Biscuits and oatcakes	25	0.0061 – 0.0062	0.024 – 0.025	144	0.0052 – 0.0053	0.016 – 0.016
Black Pudding	0	n/a	n/a	4	0.0040 – 0.0042	0.0051 – 0.0053
Drinking Oats	0	n/a	n/a	1	0.0081 – 0.011	0.0081 – 0.011
Flapjacks and oaty snack bars	14	0.0075 – 0.0080	0.015 – 0.016	67	0.0059 – 0.0063	0.017 – 0.018
Muesli oat breakfast cereals and granola	26	0.0047 – 0.0048	0.017 – 0.017	181	0.0055 – 0.0056	0.016
Oat Bread	0	n/a	n/a	9	0.0023 – 0.0032	0.0048 – 0.0066
Oatbran	0	n/a	n/a	1	0.00036	0.00036
Porridge oats	28	0.014	0.053 – 0.054	141	0.012 – 0.013	0.046 – 0.047
Total	**63**	**0.012 – 0.013**	**0.042 – 0.043**	**390**	**0.0099 – 0.010**	**0.032 – 0.033**

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution

Table A6. Estimated Sum T2 and HT2 acute exposure from oat-based foods eaten by children aged 18 to 60 months using data from the 2015 retail survey

Type of oat product	Exposure LB-UB (µg/kg bw/day)					
	18 to <24			24 to <60		
	Number of consumers	Mean	97.5th Percentile	Number of consumers	Mean	97.5th Percentile
Biscuits and oatcakes	25	0.017 – 0.018	0.058 – 0.059	144	0.016	0.047 – 0.048
Black Pudding	0	n/a	n/a	4	0.016 – 0.017	0.020 – 0.021
Drinking Oats	0	n/a	n/a	1	0.019 – 0.026	0.019 – 0.026
Flapjacks and oaty snack bars	14	0.016 – 0.018	0.021 – 0.023	67	0.015 – 0.016	0.033 – 0.036
Muesli oat breakfast cereals and granola	26	0.012 – 0.013	0.031 – 0.032	181	0.013	0.032 – 0.033
Oat Bread	0	n/a	n/a	9	0.0078 – 0.011	0.010 – 0.013
Oatbran	0	n/a	n/a	1	0.0014	0.0014
Porridge oats	28	0.040 – 0.041	0.150	141	0.029	0.087 – 0.088
Total	**63**	**0.031 – 0.032**	**0.075 – 0.076**	**390**	**0.022 – 0.023**	**0.068 – 0.069**

NOTE: Please note that consumption or exposure estimates made with a small number of consumers may not be statistically reliable. As a guide, estimates based on less than 60 consumers should be treated with extreme caution

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