Health Based Guidance Values (HBGVs)

In this guide

31. An acute refence dose (ARfD) is the estimated amount of a substance in food or drink that can be ingested in a single meal or day without appreciable health risk to the consumer. The tolerable daily intake (TDI) is the estimated amount of a substance that can be ingested daily over a lifetime without posing a significant health risk.

EFSA’s group acute reference dose (ARfD)

32. In 2017, EFSA established a group ARfD of 0.3 µg/kg bw for T-2, HT-2, and NEO, based on a study examining emesis in mink (Wu et al., 2016). Minks were selected as a suitable model for human vomiting due to their similar response to emetics such as emetine. Wu et al. (2016) monitored emetic

responses in fasted female mink following the administration of varying oral and intraperitoneal doses of T-2 and HT-2. The lowest oral dose causing vomiting was 0.05 mg/kg bw (75 % affected), with a no observed adverse effect level (NOAEL) of 5 µg/kg bw, a lowest observed adverse effect level (LOAEL) of 50 µg/kg bw, and an estimated dose causing an effect in 50 % of the population (ED50) of 20 µg/kg bw.

33. EFSA performed benchmark dose (BMD) analysis using PROAST software and selected a lower 95 % confidence limit on the benchmark dose for a 10 % response (BMDL10) of 2.97 µg/kg bw as their point of departure (POD) for setting an ARfD. Applying an uncertainty factor (UF) of 10 for intraspecies variability (but none for interspecies differences due to similar emetic sensitivity between mink and humans), EFSA derived a group ARfD of 0.3 µg/kg bw. NEO was included based on equipotency data in ducklings. EFSA assumed dose additivity between T-2, HT-2, and their modified forms but noted the possibility of antagonistic or, less likely, synergistic effects of their co-occurrence.

34. The COT agreed with EFSA's ARfD in 2018 but raised concerns about the wide BMD confidence interval, the lack of an interspecies UF for toxicokinetics and the exclusive use of female mink. A later update to the PROAST software generated a higher model-averaged BMDL10 of 12.2 µg/kg bw, but the more conservative EFSA value was retained because of uncertainties around model averaging.

EFSA's group TDI

35. In 2017, EFSA established a group TDI of 0.02 µg/kg bw for the sum of T-2, HT-2, and NEO toxins. This decision was based on structural similarities between these three mycotoxins, their similar toxicological profiles, and the fact that HT-2 is a direct metabolite of T-2. EFSA applied relative potency factors of 1 for T-2 and HT-2, and 0.3 for NEO, using mainly *in vivo* data and a conservative rounding approach.

36. The TDI was derived using data from a 90-day rat study in which male Wistar rats received feed containing 0, 0.5, 0.75 and 1 mg T-2 per kg of diet for up to 12 weeks (Rahman et al., 2014). EFSA calculated that this was equivalent to doses of 0, 45, 68 and 90 µg T-2/kg bw/day, respectively. The study reported dose-dependent reductions in white and red blood cells and platelets, along with clinical signs of toxicity. EFSA selected total leucocyte count as the critical endpoint and derived a BMDL10 of 3.3 µg/kg bw/day, applying a total UF of 200

(10 for interspecies and 10 for intraspecies variability, and 2 for subchronic to chronic extrapolation).

37. EFSA had previously proposed a TDI of 100 ng/kg bw/day in 2011 based on a study in which pigs received a diet containing 0.5 - 15.0 mg/kg of purified T-2 toxin for three weeks (Rafai et al., 1995a,b); however, the 12 week rat study of Rahman et al. (2014) was considered more relevant in 2017 due to its longer duration and clearer haematological effects. EFSA also included phase I metabolites in the group TDI, assuming dose addition, and applied relative potency factors accordingly.

38. EFSA noted a number of uncertainties in their assessment, including the use of a subchronic study to set a chronic TDI, the lack of repeated-dose studies on HT-2 and the unspecified purity of the test material.

39. The COT endorsed EFSA's group TDI in 2018 during its review of infant and young child exposure.

JECFA's group ARfD

40. In April 2022, JECFA agreed that emesis was a common effect of acute exposure to T-2 and HT-2 in both humans and experimental animals and established a group ARfD for T-2, HT-2 and DAS. The POD selected was the BMDL10 of 2.6 µg/kg bw for emesis in mink following acute gavage exposure to T-2 or HT-2. A UF of 8 (2.5 for interspecies variability in toxicodynamics and 3.16 for intra-human variability in toxicodynamics) was considered sufficiently protective.

41. Based on the above, a group ARfD for T-2, HT-2 and DAS of 320 ng/kg bw (rounded down) was established and, considering the highly comparable nature of the methods used in studies concerning the emetic effects of T-2, HT-2 and DAS in mink, a relative potency factor of 0.2 for acute exposure to DAS was recommended.

JECFA's group TDI

42. In April 2022, JECFA established a group TDI of 25 ng/kg bw for T-2, HT-2 and DAS, alone or in combination. JECFA concluded that the most sensitive, reliable and reproducible effects observed following repeated dietary exposure were those reported in by Rafai et al. (1995a,b). This study adequately characterised the test material and background exposure to common mycotoxins detected in feed and examined critical toxicological effects at relatively low doses

(25 µg/kg bw/ day). JECFA also noted that juvenile pigs are sensitive to the emetic and haematotoxic effects of trichothecenes. Dose-response analysis of body weights, daily body weight gain and daily feed intake were conducted, and a BMDL10 of 1.8 µg/kg bw/ day based on reduced daily body weight gain was selected as the most appropriate POD for establishing a group TDI. An overall UF of 72 was applied (8 for the group HBGV, 3 for the extrapolation from subacute to chronic exposure, and 3 for other uncertainties in the database) in recognition that the critical effect (i.e. nausea-induced reductions in feed intake resulting in decreased body weight gain) was likely to be dependent on Cmax and acknowledgement of JECFA's low confidence in the overall toxicological database.

43. Although comparative longer-term data on T-2, HT-2 and DAS were not available, JECFA noted the similar critical effects observed following acute and repeated oral exposures and concluded that the relative potency factor of 0.2 for DAS was applicable for exposure durations longer than acute and should be applied when comparing dietary exposure to DAS with the group TDI.

COT HBGVs

44. In February 2023, the COT reviewed the EFSA and JECFA HBGVs for T-2 and HT-2 mycotoxins, together with the underlying weight of evidence, and was content to continue applying EFSA's HBGVs for future risk assessments. The values of the group HBGVs are almost identical between JECFA and EFSA, and the COT had previously been applying the HBGVs established by EFSA for risk assessments.

45. An overview of the key information underpinning the EFSA and JECFA HBGVs for T-2 and HT-2, on which the COT based its assessment, is provided in Table 1.

Table 1: Summary of the group HBGVs for T-2 and HT-2 established by EFSA (2017) and JECFA (2022).

HBGV	Value of HBGV	Value of critical endpoint	Adverse effect at critical endpoint	Uncertainty factor	Key study

EFSA ARfD (T-2, HT-2, NEO)	0.3 µg/kg bw	BMDL10 of 2.97 µg/kg bw	Emesis in mink.	10 (for intraspecies variability only)[a]	Wu et al. (2016)[b]
EFSA TDI (T-2, HT-2, NEO)	0.02 µg/kg bw	BMDL10 of 3.3 µg/kg bw	Reduced leucocyte count in rats.	200 (10 for interspecies variability, 10 for intraspecies variability, 2 for extrapolation from subchronic to chronic exposure).	Rahman et al. (2014)[c]
JECFA ARfD	320 ng/kg bw (T-2, HT-2 & DAS) (equivalent to 0.32 µg/kg bw)	BMDL10 of 2.6 µg/kg bw	Emesis in mink.	8 (2.5 for interspecies variability in toxicodynamics and 3.16 for intra-human variability in toxicodynamics).	Wu et al. (2016)[b]
JECFA TDI	25 ng/kg bw (T-2, HT-2 & DAS)	BMDL10 of 1.8 µg/kg bw	Reduced body weight gain in pigs.	72 (8 for the group HBGV, 3 for extrapolation from subacute to chronic exposure, 3 for other uncertainties in database[d]).	Rafai et al. (1995a,b)[e]

a) No interspecies uncertainty factor was applied because humans were not considered to be more sensitive than mink to acute emetic effects.

b) In the Wu et al. (2016) study, emetic responses were monitored for six hours post-dosing.

c) The duration of the Rahman et al. (2014) study was 12 weeks; 8 rats were sacrificed at each two-week interval.

d) JECFA noted that these uncertainties include i) many of the studies investigated adverse effects at high doses, ii) the actual intake of the test material and the presence of other related mycotoxins in the basal feed was inadequately described, iii) none of the identified studies that reported the effects of low doses (for example, ≤25 µg/kg bw/ day) followed standard testing guidelines according to GLP standards, and iv) JECFA noted some discordance concerning some of the effects at low doses.

e) The duration of the study conducted by Rafai et al. (1995a,b) was three weeks.