HBGVs

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EFSA’s group acute reference dose (ARfD)

28. In 2017, EFSA established a group ARfD of 0.3 µg/kg body weight for T-2, HT-2, and neosolaniol (NEO), based on a study by Wu et al. (2016) examining emesis in mink. Minks were selected as a suitable model for human vomiting due to their similar response to emetics like emetine. In the study, fasted female mink were administered varying oral and intraperitoneal doses of T-2 and HT-2, and emetic responses were monitored. The lowest oral dose causing vomiting was 0.05 mg/kg bw (75 % affected), with a NOAEL of 5 µg/kg bw, LOAEL of 50 µg/kg bw, and ED50 of 20 µg/kg bw.

29. EFSA performed a benchmark dose (BMD) analysis using PROAST software and selected a BMDL10 of 2.97 µg/kg bw. Applying an uncertainty factor 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.

30. The COT agreed with EFSA's ARfD in 2018 but raised concerns about the wide BMD confidence interval, lack of interspecies factor 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 due to uncertainties around model averaging, the more conservative EFSA value was retained.

EFSA's group TDI

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

32. The TDI was derived using data from a 90-day rat study by Rahman et al. (2014), in which male Wistar rats were fed T-2 at doses of 0, 45, 68, or 90 µg/kg bw/day. 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 uncertainty factor of 200 (10 for interspecies and 10 for intraspecies variability, and 2 for subchronic to chronic extrapolation).

33. EFSA had previously proposed a TDI of 100 ng/kg bw/day in 2011 based on a pig study by Rafai et al. (1995), but the Rahman study was considered more relevant due to its longer duration and clearer haematological effects. EFSA also included phase I metabolites in the group TDI, assuming dose addition, and applied RPFs accordingly.

34. EFSA however noted a number of uncertainties 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.

35. The COT endorsed EFSA’s group TDI in 2018 during their review of infant and young child exposure.

JECFA’s group ARfD

36. In April 2022, JECFA agreed that emesis is a common effect of acute trichothecene exposure in both humans and experimental animals. On this basis, the Committee established a group ARfD for T-2, HT-2 and DAS. JECFA applied the lower 95 % confidence limit on the benchmark dose for a 10 % response (BMDL10) of 2.6 µg/kg bw for emesis in mink following acute gavage exposure to T2 or HT2 as the point of departure (POD). Based on the available evidence, the Committee decided that an uncertainty factor of 8 (2.5 for interspecies variability in toxicodynamics and 3.16 for intra-human variability in toxicodynamics) was sufficiently protective.

37. Based on the above, JECFA established a group ARfD for T2, HT2 and DAS of 320 ng/kg bw (rounded down). Considering the highly comparable nature of the methods used in studies concerning the emetic effects of T2, HT2 and DAS in mink, the Committee recommended a relative potency factor of 0.2 for acute exposure to DAS.

JECFA’s group TDI

38. In April 2022, JECFA established a group TDI of 25 ng/kg bw for T2, HT2 and DAS, alone or in combination. JECFA concluded that the most sensitive, reliable and reproducible effects observed following repeated dietary exposure were reported in a 3-week toxicity study in juvenile pigs (Rafai et al., 1995). 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 per day). JECFA also noted that juvenile pigs have been identified previously as a species 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 per day based on reduced daily body weight gain was selected as the most appropriate POD for establishing a group TDI. Considering that the critical effect (i.e. nausea-induced reductions in feed intake resulting in decreased body weight gain) is likely to be dependent on Cmax (the maximum concentration in plasma), and given JECFA’s low confidence in the overall toxicological database, a composite uncertainty factor of 72 was considered appropriate (8-fold

for the group HBGV, 3-fold for extrapolation from subacute to chronic exposure, and 3-fold for other uncertainties in the database).

39. Although comparative longer-term data on T2, HT2 and DAS are not available, JECFA concluded that the relative potency factor of 0.2 for DAS was applicable for exposure durations longer than acute, (due to the similar critical effects observed following acute and repeated oral exposures), and hence should be applied in comparing dietary exposure to DAS with the group TDI.

COT HBGVs

40. In February 2023, in reviewing the existing HBGVs for T-2 and HT-2 mycotoxins set by EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the COT was content to continue applying EFSA’s HBGVs for future risk assessments.