Health-based guidance values

In this guide

40. EFSA (2012) considered the vasoconstrictive effect as the critical effect for EAs and derived a benchmark dose lower bound for a 10 % response (BMDL10) of 0.33 mg/kg bw per day, based on the finding of tail muscular atrophy in rats fed for 13 weeks with ergotamine. EFSA applied an overall uncertainty

factor (UF) of 300, the default UF of 100 for intra- and interspecies differences and an additional UF of 3 to account for deficiencies in the database, to establish an acute reference dose (ARfD) of 1 µg/kg bw (rounded to one significant figure). In line with EFSA's recommendations, an additional UF of 2 was applied to the establishment of the tolerable daily intake (TDI) for the extrapolation from a sub-chronic to a chronic study. Therefore, an overall UF of 600 was applied to the same BMDL10 of 0.33 mg/kg bw per day to establish a TDI of 0.6 µg/kg bw per day. EFSA concluded that the available data were not sufficient to determine the relative potencies of individual EAs, but the limited data available for some EAs showed no apparent differences in potencies.

41. In 2021, JEFCA, identified uterine contractions in humans during late pregnancy and postpartum, based on the pharmacological effect of ergotamine maleate, as the critical effect for the evaluation of EAs in the diet (JEFCA, 2021). JECFA established an ARfD based on the lowest oral therapeutic dose of 0.2 mg ergometrine maleate (equivalent to 2.5 µg/kg bw, expressed as ergometrine). An UF of 2 was applied for extrapolating a pharmacological lowest observed effect level (LOEL) to a no-observed effect level (NOEL) and an UF of 3.16 to account for possible interindividual toxicodynamic differences. Applying an overall UF of 6.3 an ARfD of 0.4 µg /kg bw ergometrine was established. JECFA also considered two 4-week studies on ergotamine tartrate and α-ergocryptine in rats and derived a reference point (BMDL10) of 1.3 mg/kg bw, based on muscular degeneration in the tail. However, JECFA considered the human pharmacological effect level of 2.5 µg/kg bw and resulting NOEL to provide a much more sensitive and relevant reference point than a downstream toxic effect in animals. A TDI of 1 µg/kg bw per day was initially established by selecting the lowest BMDL10 value of 0.6 mg/kg bw per day. However, JECFA concluded that a TDI should not be higher than the ARfD and hence decided to establish a group TDI for the sum of total EAs in the diet at the same value as the group ARfD of 0.4 µg/kg bw per day.

42. The COT considered that the JECFA evaluation provided the more conservative health based guidance value (HBGV), and, in addition, this was based on human endpoints and was more recent than the 2012 EFSA evaluation. The COT concluded they would align with JECFA and agreed on an ARfD of 0.4 µg/kg.