Evaluations by other authoritative bodies

In this guide

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60. The evaluations conducted by various authoritative bodies are summarised below in order of publication.

World Health Organisation (WHO, 1993)

61. In 1993, WHO derived a tolerable daily intake for boron of 0.088 mg/kg bw/day.

62. For this evaluation, the WHO considered the critical effect of boron to be testicular atrophy in a 2 year dog study (assumed to be Weir and Fisher 1972), with a NOAEL of 8.8 mg B/kg bw/day. A total uncertainty factor of 100 for interspecies and intraspecies variability was applied (WHO, 1993).

European Centre for Ecotoxicology and Toxicology of Chemical (ECETOC, 1995)

63. ECETOC considered that acute and long-term exposure studies of boron indicated that testis was a target organ. Borates were not considered to be genotoxic or carcinogenic. A risk assessment was carried out based on reproductive and developmental effects as this was considered the most sensitive endpoint.

64. The NOAEL was based on boron intake from the diet noted in the Weir and Fisher 1972, Lee et al., 1978 and Ku et al., 1993a studies in rats and the Fail et al., 1971 study in mice. The 2-year study in dogs by Weir and Fisher in 1972 was not considered for this due to several inadequacies. Based on these studies, the LOAEL for reproductive toxicity was determined to be 17.5 mg B/kg bw. The NOAEL and LOAEL for testicular changes in rodents was noted to be 17 mg B/kg bw and 26 mg B/kg bw, respectively. Developmental toxicity studies in rats (Heindel et al., 1992; Price et al.,1994), mice (Heindel et al.,1992) and rabbits (NTP, 1991) noted that rats were the most sensitive species with a NOAEL of 9.6 mg B/kg bw. Different NOAELs were determined for 3 different endpoints. Considering interspecies and intraspecies differences, the possible TDIs were calculated to be 35 mg B/day (0.583 mg/kg bw/day) for fertility, 34 mg B/day (0.567 mg/kg bw/day) for testicular effects and 19.2 mg B/day (0.32 mg/kg bw/day) for developmental effects. The TDI of 19.2 mg B/day (0.32 mg/kg bw/day) was agreed and considered adequate to protect human health.

Expert Group on Vitamins and Minerals (EVM, 2003)

65. The NOAEL of 9.6 mg/kg bw/day from the Price et al., 1996 study was used to establish a Safe Upper Level (SUL). Reproductive toxicity was identified as the most sensitive endpoint and an uncertainty factor of 10 for inter-species variation and 6 for intra-species variation (based on a factor of 1.8 to account for variation in glomerular filtration in women and a factor of 3.2 to account for variability in toxicodynamics) as proposed by Dourson et al (1998) was used to derive a Safe Upper Level (SUL) of 0.16 mg boron/kg bw/day.

World Health Organization (WHO, 2009)

66. In 2009, WHO derived a further tolerable daily intake (TDI) for boron of 0.2 mg/kg bw/day (WHO, 2009).

67. The WHO considered the critical effect of boron to be decreased fetal body weight in rats, for which the NOAEL was 9.6 mg B/kg bw/day (Price et al., 1996). Multiple developmental end point data from the Heindel et al. (1992) and Price et al. (1996) studies were pooled and subjected to multiple benchmark dose analyses (Allen et al. 1996). The 95% lower confidence limit on the benchmark dose associated with a 5% reduction in mean fetal body weight (BMDL05) was calculated to be 10.3 mg B/kg bw/day. This BMDL05 is close to the Price et al. (1996) NOAEL of 9.6 mg B/kg bw/day. A total uncertainty factor of 60 was applied to the BMDL − 10 for interspecies variation and 6 for intraspecies variation based on a factor of 1.8 to account for variation in glomerular filtration in women and a factor of 3.2 to account for variability in toxicodynamics, as proposed by Dourson et al (1998). This was used to establish a TDI of 0.17 mg/kg bw/day, rounded to 0.2 mg/kg bw/day.

Agency for Toxic Substances and Disease Registry (ATSDR, 2010)

68. The ATSDR has derived an intermediate-duration oral Minimal Risk Level (MRL) for boron of 0.2 mg/kg bw/day. An MRL is an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure; the intermediate duration used in this instance covers exposures between 15 and 365

days.

69. ATSDR noted that the available intermediate-duration oral database clearly identifies the developing fetus as the most sensitive target of toxicity. Two studies in rats (Heindel et al. 1992; Price et al. 1996) identified LOAELs of 13–13.6 mg B/kg bw/day for decreases in fetal body weight and skeletal malformations (only identified in the Price et al. 1996 study). These LOAELs are lower than the NOAEL of 30 mg B/kg bw/day identified for reproductive toxicity in a 3-generation study (Weir and Fisher 1972) and NOAELs of 35 or 45 mg B/kg bw/day for haematological and dermal effects (Weir and Fisher 1972) (ATSDR, 2010).

70. The BMDL05 of 10.3 mg boron/kg/day based on decreased fetal body weight in rats derived by Allen et al. 1996 (described above) was divided by a chemical-specific uncertainty factor of 66 (3.3 for toxicokinetic extrapolation from animals to humans, 3.16 for toxicodynamic extrapolation from animals to humans, 2.0 for variability in human toxicokinetics, and 3.16 for variability in human toxicodynamics) resulting in an intermediate-duration oral MRL of 0.2 mg B/kg bw/day (rounded value).

European Food Safety Authority (EFSA, 2013)

71. In 2013, the EFSA also considered that the male reproductive system in animals is a target for boron toxicity. From a developmental study in rats (Price et al., 1996a), a NOAEL of 9.6 mg B/kg bw/day for developmental toxicity (decreased fetal weight) was identified. Application of a total uncertainty factor of 60 (6 for intraspecies variation based on a factor of 1.8 to account for variation in glomerular filtration in women and a factor of 3.2 to account for variability in toxicodynamics and 10 for interspecies variation) produced a TDI of 0.16 mg/kg bw/day (EFSA 2013).

Health Canada

72. A BMDL05 of 2.90 mg/kg bw/day (using the US EPA BMD Software (v2.7)) was estimated for the testicular effects (decreased testicular weight) in dogs in the study by Weir and Fisher 1972. A total uncertainty factor of 300 (10 for interspecies variability, 10 for intraspecies variability and 3 for database uncertainties, including that histological changes may occur at lower doses than those associated with testicular weight) was applied which produced a TDI of 0.01 mg/kg bw/day (Health Canada, 2023).

73. Health Canada noted that if an alternative NOAEL were used from the study in rats by Price et al., 1996, then an alternative TDI of 0.18 mg/kg bw/day could be estimated. By using the data from Price et al., (1996) study based on decreased fetal body weight, Health Canada derived a BMDL05 of 10.6 mg B/kg bw/day using the US EPA BMD Software (v2.7). It was acknowledged that this value was consistent with the BMDL05 established by Allen et al. (1996) using the same dataset. A total uncertainty factor of 60 (6 for intraspecies variability, 10 for interspecies variability) was applied to this BMDL05, which produced a TDI of 0.18 mg/kg bw/day (Health Canada, 2023).