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Safety assessment of boron by application of new uncertainty factors and their subdivision

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ABSTRACT

The available toxicity information for boron was reevaluated and four appropriate toxicity studies were selected in order to derive a tolerable daily intake (TDI) using newly proposed uncertainty factors (UFs) presented in Hasegawa et al. (2010). No observed adverse effect levels (NOAELs) of 17.5 and 8.8 mg B/kg/day for the critical effect of testicular toxicity were found in 2-year rat and dog feeding studies. Also, the 95% lower confidence limit of the benchmark doses for 5% reduction of fetal body weight ($BMDL_{05}$) was calculated as 44.9 and 10.3 mg B/kg/day in mouse and rat developmental toxicity studies, respectively. Measured values available for differences in boron clearance between rats and humans and variability in the glomerular filtration rate (GFR) in pregnant women were used to derive chemical specific UFs. For the remaining uncertainty, newly proposed default UFs, which were derived from the latest applicable information with a probabilistic approach, and their subdivided factors for toxicokinetic and toxicodynamic variability were applied. Finally, overall UFs were calculated as 68 for rat testicular toxicity, 40 for dog testicular toxicity, 247 for mouse developmental toxicity and 78 for rat developmental toxicity. It is concluded that 0.13 mg B/kg/day is the most appropriate TDI for boron, based on rat developmental toxicity.

1. Introduction

To ensure drinking water safety, a variety of toxicity information on environmental pollutant chemicals is collected and evaluated in order to derive a tolerable daily intake (TDI). A TDI is derived by dividing the no observed adverse effect level (NOAEL) for the selected critical effect (identified from key toxicity studies such as repeated dose toxicity, reproductive and developmental toxicity, and carcinogenicity) by an appropriate composite uncertainty factor (UF). A default composite UF of 100, consisting of 10 for interspecies differences (UF_a) and 10 for human variability (UF_h), has been commonly used in the derivation of TDIs in Japan and some international organizations. WHO (2005) took the approach further by determining that each component UF can be subdivided into toxicokinetics (TK), disposition of substance (generally measured as species differences in blood concentration at the same dose), and toxicodynamics (TD), toxic intensity of substances (generally measured as species differences in toxicity level at the same blood concentration). Appropriate measured or estimated TK and/or TD values can be incorporated into the safety assessment process by replacing the default component UFs.

To date, this subdivision approach has been applied in several situations in Health Canada (Meek et al., 1994) and the United States (US EPA, 2004), but the approach is limited internationally. The WHO drinking water quality guidelines used the approach for boron, where measured data on the human glomerular filtration rate (GFR) was used to determine the chemical specific UF used in the TDI calculation (WHO, 2009). However, an even newer approach for UF selection has been derived from the latest data related to interspecies differences and human variability with a probabilistic approach to the TK and TD subdivisions (Hasegawa et al., 2010). Therefore, in this article, we apply the new UF probabilistic subdivisions during the UF selection process in order to derive a TDI for boron.

2. Concept of current uncertainty factor

An UF of 100 (Lehman and Fitzhugh, 1954) was proposed for boron without substantial reasons, as was common practice, and has been widely used around the world until recently. Dourson and Stara (1983) justified using an UF of 100 (UF_a = 10, UF_h = 10) in risk calculations by gathering and organizing supporting

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information. Analysis of interspecies differences (Freireich et al., 1966) demonstrated a good relationship between the body surface area and the maximum tolerated dose of 18 anti-cancer drugs after repeated administration in humans and various experimental animals. The body surface area can be presented as:

$$BW^{2/3} \times K \times 10^{-4}\ m^2$$

the body surface area per body weight becomes:

$$BW^{2/3} \times K \times 10^{-4} \times BW^{-1} = K \times 10^{-4} \times BW^{-1/3}$$

where BW is the body weight (g) and K is an adjustment factor.

As K ranges from 9 to 11 in various experimental animals as well as humans, the body surface ratio of animal/human is:

$$K_a \times 10^{-4} \times BW_a^{-1/3} / K_h \times 10^{-4} \times BW_h^{-1/3} = BW_h^{1/3} / BW_a^{1/3} = (BW_h/BW_a)^{1/3}.$$

The body surface correction factor becomes 5.6 for rats and 11.4 for mice when the body weight is 60 kg for humans, 350 g for rats and 40 g for mice. Based on these data, a default UF_a of 10 is considered to be an appropriate numerical value, since it lies between these two values. When logarithmic dose/probit slopes were calculated for acute rat toxicity data on 490 chemicals, 92% of the slopes were 3 or greater, suggesting that a 10-fold decrease in dose would yield a 3 probit reduction in risk. This supports the use of an UF_h of 10 for within species variability.

Renwick (1993) proposed that the UF_a and UF_h can each be subdivided into a TK and TD component. Renwick analyzed toxicokinetic parameter data, such as clearance rate and area under the concentration time curve (AUC) in plasma or tissue for TK and *in vitro* dose–response or *in vivo* toxicodynamic data were analyzed for TD to support the UF division. IPCS and WHO (IPCS, 1994; WHO, 2005) determined that the distribution of the TK:TD ratio is 60:40 for UF_a and 50:50 for UF_h:

$$UF_a = (TK) \times (TD) = 10^{0.6} \times 10^{0.4} = 4\ (TK) \times 2.5\ (TD)$$

$$UF_h = (TK) \times (TD) = 10^{0.5} \times 10^{0.5} = 3.2\ (TK) \times 3.2\ (TD).$$

The default value of 4 for UF_a (TK) is consistent with the differences in fundamental physiological parameters, for example, the heart output volume of rats is approximately 4-fold higher than in humans. The equal subdivision of UF_h is supported by the analysis of kinetic parameters for 60 chemicals and toxicity dose–response data for 49 chemicals.

3. Toxicity-related information on boron

Boron has almost complete absorption via the gastrointestinal tract and is excreted via the urine in both humans and experimental animals. The average clearance rate for boron is 163 mL/h/kg (2.72 mL/min/kg) in rats and 41 mL/h/kg (0.68 mL/min/kg) in humans, the rat clearance value is approximately 4-fold higher than the human value (Dourson et al., 1998). Boron clearance in pregnant women averages at 1.02 mL/min/kg (66.1 mL/min/person) (Pahl et al., 2001) and the rate in pregnant rats is 3.3 mL/min/kg (1.0 mL/min/rat) (Vaziri et al., 2001), indicating that boron clearance rates increase during pregnancy by 50% in humans and 21% in rats.

Evidence of human male reproductive toxicity was not observed in the epidemiological studies of men exposed to high levels of boron (Sayli, 2001, 2003; Whorton et al., 1994; Yazbeck et al., 2005; Robbins et al., 2010; Duydu et al., 2011). However, testicular and developmental toxicity were observed in multiple experimental animal toxicity studies. Boron was neither genotoxic nor carcinogenic in cancer bioassays (NTP, 1987).

Nine repeat dose toxicity studies and five reproductive/developmental toxicity studies for boric acid were evaluated in order to derive a TDI for boron. Brief study details and NOAELs for selected target organs or endpoints are shown in Table 1. NOAELs are expressed as mg B (boron)/kg (body weight)/day, which are converted to mg of boron by multiplying by the ratio of the molecular weight of boron to the molecular weight of boric acid (10.81/61.84 = 0.1748).

4. Derivation of boron TDI in WHO and US

4.1. Drinking water quality guideline in WHO (2009)

The critical endpoint of interest for boron was determined to be fetal body weight changes and skeleton malformations (high incidence of short rib XIII and wavy ribs) observed in two rat developmental toxicity studies (Heindel et al., 1992; Price et al., 1996b). The 95% lower confidence limit of the benchmark dose for 5% reduction of fetal body weight ($BMDL_{05}$ = 10.3 mg B/kg/day) (Allen et al., 1996) was adopted as the point of departure (POD) for this evaluation.

The available boron data was not sufficient to derive a chemical specific interspecies UF, thus the default UF of 10 was used. The UF for human variability was subdivided into TK and TD components according to the WHO methodology (IPCS, 1994; WHO, 2005). TK data from pregnant women were analyzed as a sensitive subpopulation to determine the TK portion of the UF_h. Given that boron is essentially not metabolized and is mostly excreted via the urine, the GFR in pregnant women is used in place of the default TK UF_h. Dourson et al. (1998) combined data from multiple studies obtaining a GFR of 144 ± 32 mL/min for healthy pregnant women in their last trimester. In order to account for 95% of the population, the average GFR_A (144 mL/min) was divided by the GFR_{2SD} at two standard deviations below the average ($GFR_A - GFR_{2SD}$ = 144 − 2 × 32 = 80 mL/min), resulting in a human TK variability UF_h of 1.8 (144/80 = 1.8) (Dourson et al., 1998). There were no data on TD variation in pregnant women, therefore the default TD UF_h of 3.2 was used. The resulting human variability UF is approximately 6; derived by multiplying the TK and TD values together (1.8 × 3.2 = 5.7).

Finally, a TDI of 0.20 mg B/kg/day was derived by applying the composite UF of 60 ($UF_a \times UF_h = 10 \times 6$) to the $BMDL_{05}$ of 10.3 mg B/kg/day for rat developmental toxicity.

$$\frac{10.3\ \text{mg B/kg/day}}{60} = 0.2\ \text{mg B/kg/day}$$

4.2. Toxicological review by US EPA (2004)

As with WHO, combined data on fetal body weight changes, rib XIII effects and variations of the first lumbar rib from two rat developmental toxicity studies (Heindel et al., 1992; Price et al., 1996b) were selected as the critical endpoints, and the $BMDL_{05}$ of 10.3 mg B/kg/day calculated for reduction of fetal body weight by Allen et al. (1996) was selected as the POD.

In a slightly different approach US EPA subdivided the default UF of 10 for UF_a and UF_h into 3.16 for TK variability and 3.16 for TD variability in animals and humans. As there was no TD data for interspecies differences and human variability, only TK data were analyzed. TK analysis was conducted for differences between pregnant rats and women (species difference) and for variations in pregnant women (human variability). Boron is easily absorbed after oral administration in both humans and animals, but is not metabolized in the body. More than 90% of the absorbed boron was excreted in a short period via the urine. In humans, 92–94%