Toxicological Summary for: Boron

CAS: 7440-42-8

The 2008 MDH SONAR directs the Health Risk Assessment unit (HRA) to develop guidance values that are protective of all humans, including sensitive populations such as infants, children, and pregnant women. In the case of boron, HRA calculated an initial value of 2000 µg/L that was protective of pregnant women, in utero exposures, children, and adults. This was further adjusted downward to 500 µg/L by use of a database uncertainty factor to address the unknown toxicity and exposures of bottle-fed infants. Therefore, 2000 µg/L is protective to all persons except bottle-fed infants, for which 500 µg/L is protective.

Acute Non-Cancer Risk Assessment Advice \( (nRAA_{\text{Acute}}) = \text{Not Derived (Insufficient Data)} \)

Short-term Non-Cancer Risk Assessment Advice \( (nRAA_{\text{Short-term}}) = 500 \mu g/L \)

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]

\[
(\text{Short-term Intake Rate, L/kg-d})
\]

\[
= (0.047\text{ mg/kg-d}) \times (0.5)^* \times (1000\text{ µg/mg})
\]

\[
(0.043\text{ L/kg-d})^**
\]

= 547 rounded to 500 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1 and US EPA 2011. MDH applied an RSC of 0.5, by using the subtraction method, instead of the default 0.2 for pregnant women. Food is the only other major source of boron exposure; comprising approximately half of the RfD, leaving the other half for water ingestion exposures (Rainey, 2002).

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Table 3-3. The RfD is based on decreased fetal body weight that occurred in utero; therefore, the intake rate for a pregnant woman is used rather than the default infant intake rate as described in the 2008 SONAR (p. 46). No related postnatal effects were reported in available studies.

Reference Dose/Concentration: HED/Total UF = 2.81/60 = 0.047 mg/kg-d***

(Sprague-Dawley rats)

Source of toxicity value: Determined by MDH in 2017

Point of Departure (POD): 9.37 mg/kg-d (administered dose BMDL05, Heindel 1992/Price 1996b)

Dose Adjustment Factor (DAF): 0.30; MDH-derived Chemical-Specific Toxicokinetic Adjustment, applicable only for pregnant rats and humans: \( (\text{CL}_{H} X F_{R} X \text{BW}_{H}) / (\text{CL}_{R} X F_{H} X \text{BW}_{H}) = 0.30; \)

where \( \text{CL}_{H} = \) human renal clearance; \( \text{CL}_{R} = \text{rat renal clearance}; \)

\( F_{H} = \) human oral bioavailability; \( F_{R} = \text{rat \ldots} \)

Human Equivalent Dose (HED):
POD x DAF = 9.37 mg/kg-d x 0.30 = 2.81 mg/kg-d

Total uncertainty factor (UF): 60

Uncertainty factor allocation:
3 for interspecies differences (for toxicodynamics), 3 for human intraspecies variability in toxicodynamics, 2 for human intraspecies variability in toxicokinetics****, and 3 for database uncertainty (lack of adequate multigenerational reproductive and immunotoxicity studies, and uncertainty regarding sensitivity for the neonatal period)

Critical effect(s): Decreased fetal weight
Co-critical effect(s): Fetal skeletal malformations
Additivity endpoint(s): Developmental

*** MDH added a data base uncertainty factor due to the ambiguity surrounding neonatal exposure to boron and uncertainty regarding the sensitivity of the neonatal period. This resulted in a water concentration of 500 µg/L. MDH considers the short-term RAA to be protective of infants.

****The uncertainty factor (UF) for human intraspecies variability in toxicokinetics is based on chemical-specific data showing dependence of boron kinetics on kidney glomerular filtration rate (GFR). As GFR increases during pregnancy, the UF was based on data characterizing glomerular filtration rates among pregnant women (Dourson 1998, EPA 2014).

Subchronic Non-Cancer Risk Assessment Advice (nRAA_subchronic) = 500 µg/L

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]
\[
(\text{Subchronic Intake Rate, L/kg-d})
\]
\[
= (0.047 \text{ mg/kg-d})^\# \times (0.5)^* \times (1000 \text{ µg/mg})
\]
\[
(0.043 \text{ L/kg-d})^{**}
\]
\[
= 547 \text{ rounded to } 500 \text{ µg/L}
\]

^The calculated Subchronic RfD (0.21 mg/kg-d) is higher than the Short-term RfD (0.047 mg/kg-d), which is based on developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Subchronic RfD.


**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Table 3-3. See (**) footnote in short-duration.

Chronic Non-Cancer Risk Assessment Advice (nRAA_chronic) = 500 µg/L

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]
\[
(\text{Chronic Intake Rate, L/kg-d})
\]
\[
= (0.047^\# \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ µg/mg})
\]
\[
(0.043 \text{ L/kg-d})^{**}
\]
\[
= 547 \text{ rounded to } 500 \text{ µg/L}
\]

^The calculated Chronic RfD (0.17 mg/kg-d) is higher than the Short-term RfD (0.047 mg/kg-d), which is based on developmental effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure.

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result of chronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Chronic RfD.


** Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Table 3-3. See (**) footnote in short-duration.

**Cancer Risk Assessment Advice (cRAA) = Not Applicable**

Cancer classification: Data are inadequate for assessment (US EPA 2014)
Slope factor (SF): Not Applicable
Source of cancer slope factor (SF): Not Applicable
Tumor site(s): Not Applicable

**Volatile:** No

**Summary of Guidance Value History:** A non-cancer HRL of 600 µg/L (based on effects of the male reproductive system) was derived for boron, by MDH, in 1993/1994. In 2008, updated Risk Assessment Advice (RAA) was provided by MDH (1,000 µg/L) based on the EPA RfD of 0.20 mg/kg-d for developmental effects, and the 2001 National Academy of Science’s estimate of boron ingestion that is safe for adults. In 2017, MDH derived an RAA of 500 µg/L for boron. The guidance value changed as a result of: 1) using MDH’s most recent risk assessment methodology; 2) incorporation of a boron-specific DAF for pregnant women (the sensitive population) in the short-term duration; 3) an uncertainty factor of 2 instead of the default of 3 for toxicokinetic variability of the glomerular filtration rate of pregnant women in the short-term duration; and 4) application of a database uncertainty factor. MDH’s guidance is categorized as RAA due to the ambiguity surrounding infant neonatal exposure to boron and uncertainty regarding the sensitivity of the neonatal period.

**Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):**

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

<table>
<thead>
<tr>
<th>Tested for specific effect?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects observed?</td>
<td>Yes¹</td>
<td>Yes²</td>
<td>Yes³</td>
<td>Yes⁴</td>
<td>Yes⁵</td>
</tr>
</tbody>
</table>

**Comments on extent of testing or effects:**

¹ Changes in hormone levels in rats exposed to boron have been observed. Boron exposures 150-300 times higher than the short-term reference dose resulted in increased follicular stimulating hormone (FSH) and luteinizing hormone (LH) levels, as well as decreased basal testosterone levels. However, at extremely high boron exposure (approximately 2,000 times higher), there was no change in serum levels of LH, FSH, thyroid stimulating hormone, or prolactin. In rats dosed with boron at levels 400 times higher than the short-term reference dose, weight changes in the adrenal gland occurred. At boron levels 250 times higher than the short-term reference dose, structural changes in the adrenal glands occurred in beagles. Histological and weight changes in the thyroid began occurring at levels 350 times higher than the short-term reference dose in beagles and rats. In humans, one study reported that nutritional supplementation with boron tablets was reported to affect 17β-estradiol and testosterone concentrations.
There are currently very few immune studies in animals. At boron levels 250 times higher than the short-term reference dose, there was a reduced T-cell response in mice. At levels 150 times higher than the short-term reference dose, mice experienced lymphoid depletion and increased blood cell production in the spleen.

The short-term reference dose is based on developmental effects in rats (reduced fetal weight). Doses 90-fold higher than the short-term reference dose resulted in fetal skeletal variations, whereas doses 600-fold higher resulted in pregnancy resorptions. These effects were also observed in mice and rabbits, beginning at levels 200-fold and 400-fold, respectively, higher than the short-term reference dose. One human epidemiology study associated high boron exposure during the 3rd trimester of pregnancy with shorter and lighter newborns at birth.

Aside from resorptions in the pregnant female mouse, rat, and rabbit occurring at boron levels between 200 to 600 times higher than the short-term reference dose, reproductive effects occurred primarily in the male. These effects in mice and rats include reduced organ weights (testes, prostate, and epididymis), organ atrophy (testes and seminiferous tubules), enzymatic changes in the testes; shrunken scrotum, and reduced fertility and pregnancy rates beginning at levels 150 times higher than the short-term reference dose. At boron levels 300 times higher than the short-term reference dose, sperm defects appeared. At levels 500 times higher than the short-term reference dose, the process of producing sperm ceased. To date, there are no epidemiological studies that confirm fertility loss in humans exposed to high amounts of boron.

Brain chemistry changes occurred in rats dosed with boron at levels 100 times higher than the short-term reference dose. In rats dosed with boron at levels 200 times higher than the short-term reference dose, structural changes in the brain occurred. Additional neurotoxicity studies have not been reported for boron.

Resources Consulted During Review:


