Two new risk assessments have been published for boric acid that increase the tolerance for soluble boron, boric acid and sodium metaborate based on chronic toxic effects. We currently allow up to 1.2% soluble boron in a product based on testicular toxic concerns. Boron or related compounds are not listed under California’s Proposition 65 regulations.

Toxicity of Boric Acid
A number of studies have been done concerning the acute or chronic toxicity of boron. Studies of either borax or boric acid yield similar results when adjusted for the amount of soluble boron present. Consequently, data from these studies (for boric acid or borax) will be presented in terms of boric acid, adjusting for boron concentration. In rats the lowest lethal dose for boric acid (BA) is 2700 mg/kg (Weir & Fischer, 1972). The NOAEL (no observed adverse effect level) in diet is 1745 ppm in rats (Duke, unpublished) and 4220 ppm in dogs (Weir & Fisher, 1972). In humans Giardini and Cardi (1979) found that the lowest ingested level of BA associated with vomiting was 63.2 mg/kg in infants with no symptoms occurring after ingesting 7.9 mg/kg. No symptoms were seen in children ingesting 130-324 mg BA/kg (Adelhardt & Fogh, 1983) with vomiting seen in a 2 year old ingesting 667 mg BA/kg (Linden et al, 1986). In a larger study, no symptoms occurred in 784 individuals ranging from the age of months to >80 years ingesting up to 55,500 mg/kg BA (mean of 900 mg/kg) while 2 in this study (adults ingesting 1290 and 5121 mg/kg BA) had vomiting. No systemic effects have been seen in rabbits receiving 25-200 mg BA/kg/day for 90 days (Draize & Kelley, 1959).

Infantile Seizures
Seizures have been described in infants given boric acid either acutely in large doses or for weeks in smaller doses. Wong, et al. (1964) described the accidental use of BA in a hospital formula. Eleven infants developed symptoms of BA poisoning. Five infants died, having received 1500-4687 mg/kg (53 mg/kg/d). Several of these severely ill infants had seizures. An additional 6 symptomatic children survived having received 750-1500 mg/kg. One of these infants was found to have brain atrophy at the age of 4 months. This was the one case in the series that was not treated with peritoneal dialysis. No symptoms occurred in infants receiving 184 mg/kg/day for 3-5 days (552-920 mg BA/kg). O’Sullivan and Taylor (1983) found infants given a mixture of borax and honey for a period of 4 to 10 weeks to develop seizures. The dose ranges associated with this phenomenon were 24-30 mg/kg/d. Gordon, et al. (1964) all described seizures in two infants given 28-36 mg/kg/d boric acid for 5-6 weeks.
Testicular Toxicity of Boron in Chronic Oral Dosing Studies (expressed as BA)

Boron and boric acid are testicular toxic in several species as summarized in the following table. The study by Ku et al. has been used for the most recent risk assessment of testicular toxic effects (Moore, et al., 1997) supplanting EPA's older risk assessment done prior to this study that was based on testicular toxicity in dogs (Weir & Fisher, 1972). This latter study currently is felt to be inadequate for risk assessment purposes because of the high frequency of testicular abnormalities in the control group (Moore, et al., 1997).

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>LOAEL (mg/kg/d)</th>
<th>NOAEL (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeiffer, et al '45</td>
<td>Rats</td>
<td></td>
<td>352</td>
</tr>
<tr>
<td>US Borax (unpublished)</td>
<td>Rats</td>
<td></td>
<td>185</td>
</tr>
<tr>
<td>Lee, et al ‘78</td>
<td>Rats</td>
<td>413</td>
<td>210</td>
</tr>
<tr>
<td>Weir &amp; Fisher ’72</td>
<td>Rats</td>
<td>350</td>
<td>117</td>
</tr>
<tr>
<td>Weir, et al ’66</td>
<td>Rats</td>
<td>488</td>
<td>136</td>
</tr>
<tr>
<td>Dixon, Lee &amp; Shearins '76</td>
<td>Rats</td>
<td>286</td>
<td>143</td>
</tr>
<tr>
<td>Ku, et al ‘93</td>
<td>Rats</td>
<td>148</td>
<td>99</td>
</tr>
<tr>
<td>Dixon, Lee &amp; Shearins '76</td>
<td>Rats</td>
<td>360</td>
<td>180</td>
</tr>
<tr>
<td>Fail, et al '91</td>
<td>CD-1 mice</td>
<td>617</td>
<td>154</td>
</tr>
<tr>
<td>Fail, et al '89</td>
<td>Field mice</td>
<td>1235</td>
<td>617</td>
</tr>
</tbody>
</table>

Fetotoxicity of Boric Acid

Price et al. (1996) have recently completed an assessment of developmental toxicity of boric acid in rat. Rats were fed boric acid to a maximum of 0.2% in their diet through gestational day (gd) 20. There were slight reductions of fetal weight at 0.1 and 0.2% BA in the diet with complete recovery in fetal weight by birth (gd 21). There was an increased frequency in short rib 13 and wavy ribs at levels of 0.1% and 0.2%. The no effect level was 0.075% (55 mg/kg/d). By birth effects were only apparent at 0.2% (NOEL 0.1% or 74 mg/kg/d). The results of this study are consistent with an earlier study of Price et al. (1995) who found similar effects in rats with an NOEL of 74 mg/kg. Other studies on fetotoxicity are summarized in the following table.

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>LOaEL (mg/kg/d)</th>
<th>NOaEL (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heindel et al. '92,'94</td>
<td>Mouse</td>
<td></td>
<td>Approx 248</td>
</tr>
<tr>
<td>Heindel et al. '92,'94</td>
<td>Rat</td>
<td></td>
<td>Approx 78</td>
</tr>
<tr>
<td>Heindel et al.,'94</td>
<td>Rabbit</td>
<td>250</td>
<td>125</td>
</tr>
<tr>
<td>Weir &amp; Fisher '72</td>
<td>Rat (3 generation)</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>
Published Risk Assessments for Boric Acid
There have been two recent risk assessments that have looked at either risk of seizures in infants or male reproductive effects in rodents as a risk concern for humans. Health Canada (Craan et al., 1997) has evaluated both neurotoxic and reproductive hazards for use of boron in children’s toys. The most sensitive neurotoxic end points were for the ingestion of boric acid in children. They assigned a 10 fold uncertainty factor to the results of the O’Sullivan and Taylor (1983) study deriving a MTD from this study of 2.4 mg/kg/d for protection against infantile seizures. For testicular effects, they used Weir & Fisher (1972) multigenerational study in rats with an uncertainty factor of 10 to derive a reproductive MTD of 10 mg/kg/d. For fetotoxic effects in rodents, the most sensitive NoaEL was that of Price et al.(1995) study in rats. For this study they assigned an uncertainty factor of 10 deriving a MTD of 7.4 mg/kg/d.

The Institute for Evaluating Health Risks (Moore, et al., 1997) developed a risk assessment for the male reproductive toxicity of boric acid based on the study of Ku et al. (1993). They determined that an uncertainty factor of 10 would be appropriate when using this study for risk assessment purposes. They found that the NOEL in this study was 99 mg/kg/d as BA. The MTD would then be 9.9 mg/kg/d, quite similar to that developed by Health Canada. The also used a benchmark risk assessment approach. The unlikely effect level using this approach was found to be 9.7 mg/kg/d. For reproductive effects they also used the Price et al study. Using a benchmark dose (BMD) approach, they determined a BMD of 62 mg/kg/d. They assigned an uncertainty factor of 30 for a unlikely effect level of 2 mg/kg/d.

Skin Absorption Studies
Both animal and in vitro studies have found little absorption with boric acid application. Boric acid causes systemic toxicity in infants when applied to severely damaged or burnt skin at levels in the range of 333-356 mg/kg/d (Craan et al., 1997). In adult humans, only 0.2% of an applied boric acid dose is absorbed, with or without pre-treatment with an irritating surfactant (Wester, et al, 1998). When used intravaginally at 100%, 6% of an administered dose is absorbed (Van Slyke, et al, 1981). In vitro absorption through human skin ranges from 0.28 to 1.2% for boric acid (Wester et al., 1998). Draize and Kelley (1959) investigated boric acid absorption in rabbits with either normal or abraded skin. 5-100% boric acid was used. Urinary excretion using a poorly absorbed boric acid ointment was 4.6 mg/kg. For intact skin urinary excretion ranged from 0.5-1.4 mg/kg, irrespective of the dose (200-4000 mg/kg). With abraded skin at the same dose, urine excretion ranged from 1.4-7.6 mg/kg, ranging from 0.14–3.8% of the applied dose. Stuttgen, et al. (1982) investigated the application of boric acid to normal or diseased skin. They found that there was no difference in absorption of a water-based 3% boric acid jelly between those with diseased skin vs those with normal skin. Vignec and Ellis (1954) applied 2.8-4.3 g/day of boric acid in the form of a 5% boric acid powder to the diaper area of infants ages 2.5-10 mos old. Applications were spread out over about 10 diaper changes/day. Urine excretion increased from 0.8 mg/L in controls to 1.6 mg/L in treated infants, less than 0.04% of the applied dose. A group of children were evaluated by blood boron levels who developed diaper rashes.
during the study. This group’s average blood boron level was 0.03 mg/dL vs 0.04 mg/dL in the treated group and 0.10 mg/dL in control group.

**Risk Assessment**

Our default weight for children is that of an average 1 year old, 10 kg. For women of child bearing age, we use an average weight of 65.4 kg (USEPA, Exposure Factors Handbook, 1997). The NOaEL for seizures in infants is 920 mg BA/kg and acute adverse effects in older children and adults is an average of 900 mg BA/kg. Health Canada found in infants an MAD of 4 mg/kg based on an NOaEL for vomiting. Health Canada used swallow volume and body weight to determine an MAC of 9.1 mg BA/g of toy, based on vomiting in infants. Using an NOaEL of 900 mg/kg with an uncertainty factor of 10 and a body weight of 10 kg for 1 year olds, the MAD would be \( [900 \text{ mg/kg/10}] \times 10 \text{ kg} = 900 \text{ mg} \). For infants, using an uncertainty factor of 10 on the NOaEL for seizures and assuming mean weight of 3.3 kg (USEPA, Exposure Factors Handbook, 1997), the MAD to prevent seizures would be 304 mg. Jones and Work (1961) found that young children had a mouth volume of 0.33 mL/kg. For an infant, this would be equivalent to 1.1 mL. For a toy of unit density, the MAC would then be 28%, assuming on mouth full of the toy was ingested.

For testicular toxicity, the lowest NOaEL in a chronic, multigenerational study is 117 mg BA/kg/d. Using Health Canada’s uncertainty factor of 10 for this study, an MDI for testicular toxicity would be 12 mg BA/kg/d. Using the average body weight of a 1 year old, an MAD for testicular toxicity would be 120 mg BA/d. EPA assumes that adults ingest incidental dust from 0.4 mg/day for indoor activities to 20 mg/day for outdoor activities (gardening; USEPA Exposure Factors Handbook, 1997). Stopford, et al (2003) recently measured ingestion rates for another art material, polymer clays. Ingested amounts from food contact and incidental mouth contact ranged from 0.3-4.0 mg/day. EPA also finds that older children and ingest 20 mg of dust a day with outdoor activities and 2 mg/day with indoor activities (EPA, Exposure Factors Handbook, 1997). In Europe, the exposure assumption used for developing standards to protect children is that there will be 100 mg of a “toy” which includes children’s art materials, will be ingested each week, that is 14 mg/day. I use the largest incidental ingestion figure (20 mg/day) to estimate exposure from ingestion of toys and art materials. Using this figure, there would be no limit to the amount of boric acid in a toy or art material for an MAC for testicular toxicity.

For reproductive toxicity and fetotoxicity, the lowest NOaEL in a chronic, multigenerational study is 100 mg BA/kg/d. Using Health Canada’s uncertainty factor of 10 for this study, an MDI for testicular toxicity would be 10 mg BA/kg/d. Using the average weight of an adult female (65.4 kg), the MAD for boric acid to prevent reproductive and fetotoxic effects would be 654 mg/day. Assuming incidental ingestion of 20 mg of an art material a day, there would be no MAC for boric acid in art materials to prevent reproductive or fetotoxic effects.

**References**


Price et al. (1995)


