



Rio Tinto Borax
26877 Tourney Road
Valencia, CA 91355
United States
(661) 287-5400

Hazard Assessment of Boric Acid, Boric Oxide, Disodium Tetraborate (Anhydrous, Pentahydrate and Decahydrate) and Disodium Octaborate Decahydrate

DR. SUE HUBBARD

Introduction

A number of detailed hazard assessments and reviews of the toxicology of borates have been published (Culver et al, 1994a; ECETOC, 1995; European Commission, 1996; Murray, 1995; Culver and Hubbard, 1996; Hubbard and Sullivan, 1996, Hubbard, 1998; IPCS, 1998; WHO, 1998; Moore et al., 1998; U.S. Food and Nutrition Board, 2001; US EPA, 2004; UK EVM, 2003; EFSA, 2004).

Most of the simple inorganic borates exist predominantly as un-dissociated boric acid in dilute aqueous solution at physiological pH, leading to the conclusion that the main species in the plasma of mammals is un-dissociated boric acid. Since other borates dissociate to form boric acid in aqueous solutions, they too can be considered to exist as un-dissociated boric acid under physiological conditions. For example disodium octaborate tetrahydrate is a solid solution of boric acid and disodium tetraborate decahydrate

For this reason, the majority of toxicological studies of borates have involved either boric acid (H_3BO_3) or disodium tetraborate decahydrate (i.e., borax, or $Na_2B_4O_7 \cdot 10H_2O$). Both acute and longer-term studies have been carried out on these two substances. For boric oxide and other sodium borates such as disodium tetraborate pentahydrate, disodium tetraborate anhydrous and disodium octaborate tetrahydrate, only acute toxicity studies have been carried out.

For comparative purposes, dose levels of borates have been expressed in terms of boron (B) equivalents based on the fraction of boron on a molecular weight basis. Conversion factors are given in Table 1 below. These conversion factors are important as some studies express dose in terms of B, whereas other studies express the dose in units of boric acid or disodium tetraborate decahydrate. The B equivalents used are a generic designation rather than a designation of the element boron.

Table 1: Conversion factors to Boron Equivalents

		Conversion factor for Equivalent dose of B
Boric acid	H_3BO_3	0.175
Boric oxide	B_2O_3	0.311
Disodium tetraborate decahydrate (Borax)	$Na_2B_4O_7 \cdot 10H_2O$	0.113
Disodium tetraborate pentahydrate	$Na_2B_4O_7 \cdot 5H_2O$	0.148
Disodium tetraborate anhydrous	$Na_2B_4O_7$	0.215
Disodium octaborate tetrahydrate	$Na_2B_8O_{13} \cdot 4H_2O$	0.210

Essentiality and Nutritional Importance

Since the 1920s, boron has been known as an essential micronutrient plants (Woods, 1994). Therefore plant-derived foods such as fruits, vegetables, and nuts contain significant amounts of boron. The human diet is the largest source of human boron exposure (Coughlin, 1998; Meacham and Hunt, 1998; Rainey and Nyquist, 1998) with healthy diets contributing the largest amount of B, with high fat diets contributing relatively low levels of B. The foods with the highest concentrations of boron include avocado, peanut butter, peanuts, prune juice, grape juice, chocolate powder, wine, pecans, granola raisin

cereal, and raisin bran cereal (Meacham and Hunt, 1998). In the US the greatest sources of boron are coffee, milk, apples, dried beans, and potatoes, which together account for 27% of the dietary boron consumption (Rainey et al., 1999). Coffee and milk contribute the greatest because they are consumed in large quantities, not because they are high in B content

Essentiality in animals

Boron has been found to be critical for normal reproduction and embryonic development in several animal species. Low boron culture conditions have resulted in abnormal development and increased malformations in frog (*Xenopus laevis*) embryos (Fort et al., 1998, 1999) and mechanisms for this essentiality are beginning to be revealed (Fort 2002). Survival of rainbow trout and zebrafish was impaired in low-B conditions (Eckert, 1998, Rowe and Eckert, 1999). Like many essential elements, it is likely that boric acid exhibits a "U-shaped" dose response curve in animals, as demonstrated by Rowe et al. (1998). Growth of vitamin D3-deficient chicks was stimulated by supplementation of boron (3 mg-B/kg-diet) in a low-B basal diet (Hunt and Nielsen 1981). Boron supplementation in pig diets (5 mg-b/kg-diet) decreased the inflammatory response to an intradermal injection of phytohemagglutinin in pigs, altered plasma lipid metabolites, and tended to increase the production of cytokines following a stress (Armstrong et al., 2001, Armstrong et al., 2000, Armstrong and Spears 2003). In rats, maternal exposure to a low boron diet was associated with a reduction in embryo implantation sites (Lanoue et al, 1998a). In vitro exposures of mouse embryos to low B growth medium showed reduced blastocyst formation and increased embryo degeneration (Lanoue et al.1998b)

Nutritional Importance in Humans

There is also wide database of references relating to the nutritional importance of boron. Several authors have proposed a role for boron in the metabolism of vitamin D and estrogen (Nielsen, 1998; Nielsen and Penland, 1999; Samman et al., 1998). In addition, dietary boron deprivation studies in both rats and humans have consistently found an effect of boron intake on brain electrophysiology and, in humans, on performance of tasks measuring eye-hand coordination, attention, and short-term memory (Penland, 1998). Although to date insufficient data is available to conform the essentiality in humans, the U.S. Food and Nutrition Board in 2001, published a Tolerable Upper Intake Level (UL) for boron of 20 mg/day, which confirms the nutritional importance for humans. Also, the UK Expert Group on Vitamins and Minerals (UK EVM, 2002) also regarded boron as nutritionally important and determined an acceptable daily intake for boron (0.16 mg /kg/day).

Significant advances in the search for essentiality of boron have been made recently in the discovery of a "Quorum sensing" cell-cell communication autoinducer molecule containing a borate-sugar diester (Chen et al., 2002); the B transporter membrane protein, BOR1, identified in plant roots of *Arabidopsis thaliana* (Takano et al., 2002); the incidence of esophageal cancer has been reported to be significantly higher in a low boron region, compared to an area with boron exposure. (Kibblewhite et al, 1984). a case-control study that found no significantly elevated risk of prostate cancer in an occupational cohort with boron exposure (Rooney C, 1993; Zhang et al., 2001) and the identification of a role for boron in the inhibition of human prostate cancer cell proliferation (Barranco and Eckert, 2004)

Toxicokinetics (Fate and Behaviour)

The toxicokinetics of boric acid are similar in rats and humans with respect to absorption, distribution, and metabolism (Dourson et al., 1998; Murray, 1998).

Absorption

Boric acid and sodium borates given orally are readily and completely absorbed in humans and animals. Animals investigated include rats (Ku et al., 1991), rabbits (Draize & Kelly, 1959), sheep (Brown et al., 1989) and cattle (Owen, 1944; Weeth et al., 1981) as shown by the levels of boron in urine, blood or tissues. In adult human volunteers given a single oral dose of 131 mg B (as boric acid dissolved in water), 94% of the administered dose was excreted in the urine over a 96 hour period (Schou et al, 1984). Similar absorption was observed based on urinary excretion of boron in 6 volunteers drinking a curative spa water with a high boron content (daily dose of 102 mg B) for two weeks (Job, 1973). In another study greater than 90% was absorbed in human volunteers taking in 3% boric acid in an aqueous solution or as a waterless emulsifying ointment spread onto biscuits (Jansen, 1984a). In a series of human volunteer studies conducted in the early 1900s, in which large doses of boric acid were repeatedly administered, approximately 80% of an administered dose was recovered in the urine, while 1% was recovered in the faeces (Wiley, 1904). Reports involving accidental human ingestion, particularly in infants, provide further evidence of oral absorption (Wong, 1964).

Inhaled sodium borate dust is readily absorbed as demonstrated by the blood and urine levels among groups of workers occupationally exposed to various levels of boron (Culver et al., 1993; 1994b). In rats, inhaled boron oxide aerosol was readily absorbed, based on the increased levels of boron excreted in the urine following inhalation exposure (Wilding et al., 1959).

Dermal absorption of borates across intact skin is insignificant in all species evaluated, including human newborn infants (Friis-Hansen et al., 1982), adult humans (Beyer et al., 1983; Hui et al, 1996; Wester et al, 1998), rabbits (Draize and Kelley, 1959), and rats (Nielsen, 1970). Borates have been demonstrated to penetrate damaged or abraded skin (Draize and Kelley, 1959; Nielsen, 1970, Stüttgen et al., 1982). However, the use of an ointment-based vehicle may prevent or reduce the absorption through diseased skin compared to an aqueous jelly based vehicle (Nielsen, 1970 and Stüttgen et al, 1982), although the results by Stüttgen et al. (1982) have a number of flaws and are therefore not conclusive.

Skin absorption data was obtained in human volunteers. Volunteers were dosed on a 900 cm² area (30cm x 30 cm) area of the back with 10B enriched boric acid or disodium tetraborate decahydrate (5% in aqueous solution), or disodium octaborate tetrahydrate (10% in aqueous solution). Twenty-four hours later the residual dose was removed by washing. Boron was measured in the urine (Hui et al, 1996; Wester et al, 1998). The absorption rates are given in Table 2.

Table 2: Dermal Absorption in Humans of boric acid, disodium tetraborate decahydrate and disodium octaborate tetrahydrate

	% Dose Absorbed ± SD	Rate of Absorption Flux µg/cm²/hr	Permeability Constant (Kp) (cm/hr)
Boric Acid (5 %)	0.226 ± 0.125	0.009	1.9 x 10 ⁻⁷
Disodium tetraborate decahydrate (5 %)	0.210 ± 0.194	0.00875	1.8 x 10 ⁻⁷
Disodium octaborate tetrahydrate (10 %)	0.122 ± 0.10	0.00975	1.0 x 10 ⁻⁷

For the purposes of risk assessment, the mean percentage dose absorbed plus the standard deviation is used for skin absorption. However, this is only applicable to small volumes landing on the skin and remaining in contact. For larger volumes on the skin, not all the substance will be available for absorption, therefore the rate of absorption (flux) is more appropriate.

Distribution

There is no evidence of accumulation (Alexander et al. 1951; Forbes et al. 1954; Forbes and Mitchell, 1957; Jansen et al. 1984b; Ward 1987; Treinen and Chapin 1991; Ku et al. 1991; Ku et al. 1993; Culver et al. 1994b) although bone may contain higher levels than other tissues.

Absorbed boron rapidly distributes throughout the body water in humans and animals. In a study of workers occupationally exposed to 10 mg/m³ of airborne disodium tetraborate decahydrate (0.22 mg B/kg/day), there was no progressive accumulation of boron in soft tissues during the working week as measured by blood and urine levels (Culver et al., 1993; 1994b). Similarly, Jansen et al. (1984a, b) concluded from pharmacokinetic studies of human volunteers that there was no tendency for boron to accumulate following a single i.v.dose of 600 mg of boric acid (approximately 105 mg B). Tissue levels of boron generally reached steady-state within three to four days among rats fed boric acid in the diet or drinking water for 28 days (Treinen and Chapin, 1991) or 9 weeks (Ku et al., 1993). Thus, boron does not accumulate in soft tissues with time in either humans or animals.

In both humans and animals, boron levels in soft tissue are comparable to plasma levels, while a greater concentration of boron in bone is observed relative to other tissues. The most complete study of boron distribution conducted to date examined tissue disposition of boron in reproductive organs and other selected tissues in adult male rats fed boric acid, providing approximately 100 mg B/kg bw/day for up to seven days (Ku et al., 1991; 1993). All tissues examined, except bone and adipose tissue, appeared to reach steady state boron levels by three to four days. Bone achieved the highest concentration of boron (2 to 3 times plasma levels), and bone boron levels continued to increase throughout seven days of dietary administration (Ku et al., 1991). In contrast, adipose tissue concentration was approximately 20 % of the plasma level. No other tissues showed any appreciable accumulation of boron over plasma levels. In dogs an accumulation in the brain, liver and fat was reported after a high single dose of 2000 mg/kg bw boric acid (Pfeiffer et al., 1945). However, the accuracy of the analytical procedures is questionable.

Previous studies also show a greater concentration of boron in bone relative to other tissues in humans (Alexander et al., 1951; Forbes et al., 1954;) and rats (Forbes and Mitchell, 1957). Boron levels in a number of tissues have been measured (Abou-Shakra, 1989; Ciba and Chrusciel, 1992; Ward et al, 1987; Sabbioni et al., 1990; Shuler et al., 1990; Minoja et al., 1990; 1994). In mice, boron distribution appeared to be homogenous in the tissues examined, except for higher levels in the kidney (bone was not analysed) (Locksley and Sweet, 1954; Laurent-Pettersson et al., 1992), but higher levels were found in bone in another study (Massie et al., 1990). *In vivo* and *in vitro* studies indicate that boric acid has a strong affinity for cis -hydroxyl groups. This may explain the higher concentrations of boric acid in bone, owing to the binding of to the cis -hydroxyl groups of hydroxyapatite.

Metabolism

Boric acid is not metabolised in either animals or humans, owing to the high energy level required (523kJ/mol) to break the B - O bond (Emsley, 1989). Other inorganic borates convert to boric acid at physiological pH in the aqueous layer overlying the mucosal surfaces prior to absorption. Additional support for this derives from studies in which more than 90% of administered doses of inorganic borates are excreted in the urine as boric acid. Boric acid is a very weak and exclusively monobasic acid that is believed to act, not as a proton donor, but as a Lewis acid, i.e., it accepts OH⁻. Because of the high pKa, regardless of the form of inorganic borate ingested (e.g., boric acid, disodium tetraborate decahydrate or boron associated with animal or plant tissues), uptake is almost exclusively (>98%) as undissociated boric acid.

Excretion

In both humans and animals, boron is excreted in the urine regardless of the route of administration. It is excreted with a half-life of < 24 hours in humans and animals. Boric acid is slowly eliminated from bone.

In humans, 99 % of a single i.v. dose of boric acid was excreted in the urine; the plasma half-life was calculated to be 21 hours using a three compartment toxicokinetic model (Jansen et al., 1984b). Following oral intake of an aqueous solution of boric acid, the urinary recovery was 94 % (Jansen et al., 1984a); more than 50 % of the oral dose was eliminated in the first 24 hours, consistent with the 21 hour half-life in the i.v. study. Sutherland et al. (1998) showed in a boron balance study that only 8% of dietary boron is excreted in faeces. Half-lives of 28.7 hours and mean of 13 hours have also been reported from various poisoning cases (Astier et al., 1988; Litovitz et al., 1988).

Elimination half-lives for animals has not been stated explicitly in the scientific literature, but they can be calculated or estimated from the data in the literature. In mice, assuming first order kinetics for elimination, the half-life was estimated to be approximately one hour, and in rat < 12 hours (Farr and Konikowski, 1963; Ku et al. 1991; 1993). In rabbits, 50 to 66% of an orally administered dose of boric acid was excreted in the urine in the first 24 hours after dosing (Draize and Kelley, 1959). A recent study indicated that the half-life may be only 3 hours (Vaziri et al., 2001) in both pregnant and non-pregnant rats.

The major determinant of boric acid excretion is expected to be renal clearance since boric acid is excreted unchanged in the urine. Rats and mice generally have faster rates of renal clearance than humans since the glomerular filtration rates as a function of body mass are generally higher in rats and mice than in humans.

Clearances of 40.4 ± 3.2 ml/min/1.73m² for sodium tetraborate in male rats and 40 ml /min/1.73m² for boron in mice (Usuda et al., 1998; Farr and Konikowski, 1963) have been reported, although there are methodological and/or analytical limitations in both studies. In more recent studies boric acid clearance rates in non-pregnant rats and pregnant rats ranged from 29.0 ± 5.7 to 31.0 ± 4.5 and from 32.2 ± 5.1 to 35.6 ± 5.7 ml/min/1.73m², respectively (Vaziri et al., 2001).

In humans, Jansen et al (1984b) determined a clearance rate of 55 ml/min/1.73m² following an i.v. dose of 600 mg of boric acid (105 mg B). Farr and Konikowski (1963) also reported a similar value of 39 ml/min/1.73m² in humans given 35 mg B/kg intravenously as sodium pentaborate, although there are methodological and analytical limitations to this 40 year old study. In a more recent study, renal clearance rates in humans were 68.30 ± 35.0 ml/min/1.73m² for pregnant subjects and 54.31 ± 19.35 ml/min/1.73m² for non-pregnant subjects (Pahl et al., 2001). This indicates about 20 –25% greater clearance in pregnant humans.

A comparison of the renal clearance between rats and humans in terms of body surface area indicated that humans clear boric acid slightly faster than rats (~1.7 -1.9 times as fast), while a comparison by bodyweight indicates that humans may clear boric acid more slowly than rats (~ 3 - 4 times slower). This apparent divergence in comparative clearances given per body weight versus surface area between the two species is related to the high surface-to-mass ratio in the rats as compared to the humans and would suggest that there is little difference in the clearance rates. (Pahl et al., 2001; Vaziri et al., 2001).

Table 3: Summary of Toxicokinetics of Inorganic Borates in rats and humans

Absorption	Readily absorbed orally and by inhalation (of respirable particles) Not absorbed dermally except through severely damaged skin
Distribution	Rapidly distributed through body water No accumulation in tissues
Metabolism	Not metabolised Exists mainly as boric acid in whole blood
Excretion	Excreted almost exclusively in the urine Half-life < 24 hours Renal clearance is approximately 3 times faster in rats than humans based on a body weight comparison

Conclusion: Toxicokinetics

There is little difference between animals and humans in absorption, distribution, and metabolism. Differences in renal clearance is the major determinant in the differences between animals and humans, there being an approximate 3 fold difference between rats and humans when based on a bodyweight comparison.

Absorption via the oral route is nearly 100%. Similarly, 100% of inhaled (respired) borates are absorbed across the lung. Dermal absorption through intact skin is extremely low, i.e., <0.3% for boric acid, disodium tetraborate decahydrate and disodium octaborate tetrahydrate.

Acute Toxicity

Acute Oral Toxicity

The borates are in general of low acute oral toxicity in mammals, including rats and mice. An accidental poisoning case in cows and a further study in goats do not suggest that these species are more sensitive to the effects of borates with respect to acute toxicity (Sisk et al., 1988; 1990). The rat LD₅₀ values for the various borates are given in Table 4. No substantial differences in acute rat toxicity were seen in mice and dogs in the limited studies available. However, dogs exhibit an emetic effect in response to high doses of borates. The LD₅₀ in dogs was determined to be > 3980 mg boric acid/kg and > 6150 mg disodium tetraborate decahydrate /kg (administered in a capsule). The dogs vomited shortly after treatment at all doses (158 mg boric acid/kg and 246 mg disodium tetraborate decahydrate/kg were the lowest doses tested). No other adverse symptoms were seen (Keller, 1962; Weir & Fisher, 1972). The main symptoms of toxicity seen in all species tested were CNS depression, ataxia and convulsions

Table 4: Acute Oral Rat LD₅₀ Values

	LD ₅₀ mg/kg rat	Reference
Boric acid	2660 - 4100	Weir & Fisher, 1972; Pfeiffer et al., 1945
Boric oxide (anhydrous boric acid)	> 2000	Denton, 1996a
Disodium tetraborate decahydrate	4500 - 6000	Weir & Fisher, 1972
Disodium tetraborate pentahydrate	3200 – 3400	Reagan and Becci, 1985a
Disodium tetraborate anhydrous	>2000	Denton , 1995, 1996b
Disodium octaborate tetrahydrate	2550	Doyle, 1989a

Humans display different acute symptoms compared with most animals. This is reviewed under Human Data from Poison Control Centres and Literature Cases

Acute Inhalation Toxicity

Low acute inhalation toxicity was observed in those borates tested; the 4 hour LC50 being > 2 mg/l for boric acid, disodium tetraborate decahydrate, disodium tetraborate pentahydrate and disodium octaborate tetrahydrate (Wnorowski 1994a, b, c, d; 1997). The samples were ground in a ball mill for 24 hours ensure that the substance was in a respirable form and the top dose tested ~ 2 mg/l was the highest that was obtainable under the conditions of the tests. Animal observations were limited due to the accumulation of test material on the walls of the exposure chamber.

Acute Dermal Toxicity

As would be expected due to the low skin absorption, the acute dermal toxicity was low for those borates tested, i.e., LD50s were >2 g/kg for boric acid, boric oxide, disodium octaborate, sodium tetraborate decahydrate and sodium tetraborate pentahydrate (Vernot et al., 1977; Reagan and Becci, 1985b,c; Doyle, 1989b; Weiner et al., 1982).

Acute toxicity – other routes

The acute intravenous LD50s of a 5 % aqueous solution of boric acid were 1.78 g/kg and 1.33 g/kg in mice and rats respectively and the subcutaneous LD50s were 2.07 g/kg and 1.2 g/kg for mice and guinea pigs respectively (Pfeiffer et al., 1945).

Conclusion: Acute Toxicity

Boric acid and the sodium tetraborates are of low acute toxicity. Although the acute oral studies were not of modern standards and were performed prior to the introduction of GLP, they are reproducible across a number of studies and species and of acceptable quality. For acute dermal and acute inhalation the studies are of modern GLP standard. LD50 oral rat > 2000 mg/kg; LD50 dermal rat > 2000 mg/kg; LC50 inhalation rat > 2 mg/l.

Corrosivity/Irritation

Skin Irritation

Boric acid and disodium tetraborate decahydrate are used at concentrations of 5% in cosmetics in the US and in talc in Europe, up to 3% in other cosmetics in Europe and up to 0.5% in oral hygiene products in Europe and elsewhere (Beyer et al., 1983; EC, 2000). As expected, inorganic borates are generally not skin irritants or are very mild irritants (Pfeiffer, 1945; Roudabush et al., 1965; Reagan and Becci, 1985d, e; Doyle, 1989c; Young and Doyle, 1973;).

Eye Irritation

Boric acid, boric oxide and disodium octaborate tetrahydrate are not eye irritants in rabbits (Cuperous et al., 1990; Doyle, 1989d,e,f).

For disodium tetraborate pentahydrate an early study indicated severe eye irritation; however, a new sample was tested in two subsequent studies, which revealed only mild irritation (Reagan and Becci, 1989g; Wnorowski, 1996; Cerven, 2000). The initial irritation was thought to be due to the glassy nature of this substance's crystals, rather than the result of a chemical effect. The sample was ground to a fine powder before instillation to reduce the sharp crystals in the sample. In addition the process of manufacture had been changed to produce less glassy crystals. In normal handling and use the large glassy crystals would not be able to enter the eye easily and in addition over 50 years of occupational exposure to borates has indicated no adverse effects on the human eye and in fifty years of occupational exposure to sodium boric acid and sodium tetraborates, no significant adverse effects on the human eye have been observed. Rabbit eye studies are known to overestimate human eye hazard. With disodium tetraborate decahydrate, the eye irritancy observed was reduced significantly when the eyes were rinsed (Reagan and Becci, 1985f; Doyle, 1989g) however, this irritation is thought to also arise from the glassy nature of the crystals of the substance and since it is closely related to the pentahydrate salt it is not treated as an eye irritant since there has been no adverse effects in the human eye. In the interests of animal welfare not more tests were carried out. This data may be read across to disodium tetraborate anhydrous since both this also consists of glassy crystals. No effects in human have been observed.

Boric acid and sodium tetraborates are used at up to 5% in eyewashes in the US, a concentration approaching a saturated solution (Beyer et al., 1973).

Conclusion: Corrosivity/Irritation

Boric acid and sodium tetraborates are not skin irritants. Boric acid is not an eye irritant. The initial irritation seen with sodium tetraborates can be attributed to the abrasive nature of the crystals. No effects have been observed in humans and the sodium tetraborates can be considered as not being irritating to eye.

Sensitisation

No borate tested has displayed skin sensitisation (Wnorowski 1994 e, f, g, h). No evidence of skin sensitisation has been seen in humans exposed occupationally to sodium borates or in a human patch test with a 3% aqueous boric acid solution (Bruze et al., 1995).

Conclusion: Sensitisation

Boric acid and sodium tetraborates are not skin sensitisers on both human and animal studies.

Repeated Dose Toxicity

A number of studies in which rats were fed boric acid or disodium tetraborate decahydrate in their diet or drinking water for periods of 70 - 90 days indicated that the main target organ for toxicity is the testis. As well as testicular atrophy, animals receiving doses of 88 mg B/kg bw/day for 90 days in their diet exhibited weight loss and, at higher doses, rapid respiration, inflamed eyes, swollen paws and desquamation of the skin on the paws (Weir and Fisher, 1972; NTP, 1987). These studies are further discussed under Carcinogenicity and Toxicity to Reproduction.

Conclusion: Repeated Dose Toxicity

The main effects observed were on the testis. These effects and the appropriate NOAEL are discussed under Carcinogenicity and Reproductive Toxicity Section

Genotoxicity

A number of *in vitro* mutagenicity studies, including bacterial mutation assays in *Salmonella typhimurium* and *Escherichia coli*, gene mutation in mammalian cells (L5178Y mouse lymphoma, V79 Chinese hamster cells, C3H/10T1/2 cells), bacterial DNA-damage assay, unscheduled DNA synthesis (hepatocytes), chromosomal aberration and sister chromatid exchange in mammalian cell (Chinese hamster ovary, CHO cells) have been carried out on boric acid, disodium tetraborate decahydrate or disodium octaborate tetrahydrate. No evidence of mutagenic activity was observed (NTP, 1987; Haworth et al., 1983; Landolph, 1985; Bakke, 1991; Stewart, 1991). In addition, no mutagenic activity was seen *in vivo* in a mouse bone marrow micronucleus study on boric acid (O'Loughlin, 1991).

Conclusion: Genotoxicity

Neither boric acid nor the sodium tetraborates are mutagenic either *in vitro* or *in vivo*.

Carcinogenicity

In long term feeding studies on boric acid and disodium tetraborate decahydrate in both rats and dogs, no carcinogenic effects were observed (Weir and Fisher, 1972). Effects observed in the rat studies included lowered food consumption, retarded body weight gain, course hair coats, haunched position, swollen pads, inflamed bleeding eyes and changes in haematological parameters at the highest doses (58.5 mg B/kg bw/day). Testicular effects were observed in both rats and dogs. Testicular atrophy with some interstitial cell hyperplasia was the critical effect seen in a US National Toxicology Program (NTP) bioassay in mice. No carcinogenic effects were observed at doses of boric acid of 75 mg B/kg bw/day and 200 mg B/kg bw/day (NTP, 1987). Effects on survival rate and reduced body weight gain were at the high doses. The testicular effects noted in these studies are discussed in more detail in Reproductive and Developmental Toxicity.

Conclusion: Carcinogenicity

The studies carried out are not to modern standards, nor to GLP. However, they are well performed and reported and are more than adequate to evaluate the carcinogenicity of boric acid and sodium tetraborates. It can be concluded that boric acid and sodium tetraborates are not carcinogenic and there is no concern for a carcinogenic effects in humans.

Reproductive and Developmental Toxicity

High doses of boric acid and disodium tetraborate decahydrate have been found to adversely affect the testis and male fertility and to cause some adverse effects in the developing foetus in animal studies. These are the critical endpoints of toxicity.

Effects on the Testis and Fertility

Effects on the testis have been observed in both sub-chronic and chronic studies in three species: rats, mice and dogs. In rats, a single dose of 175 mg B/kg bw was found to cause reversible disruption of tubular spermiation (Linder et al., 1990), although no such effects were observed after a single dose of 350 mg B/kg (2000 mg boric acid/kg) (Bouissou and Castagnol, 1965).

A comparison of the key NOAELs and LOAELs for reproduction studies is given in Table 5. The effects tend to be similar in all three species, although most data comes from rat studies. The reproductive effects in rats at lower doses and shorter time periods start with reversible inhibition of spermiation. Early effects can be seen after 14 days treatment, at doses around 39 mg B/kg (217 mg boric acid/kg bw/day) but at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects take about 28 days to manifest (Ku et al., 1993). Higher doses lead to testicular atrophy, degeneration of seminiferous tubules, reduced sperm count and a reduction in fertility as seen in a three generation study of boric acid and disodium tetraborate decahydrate in rats at 58.5 mg B/kg bw/day (NOAEL, 17.5 mg B/kg bw/day) (Weir, 1966 a,b; Weir and Fisher, 1972). Similar results were seen in a two-year study of boric acid and disodium tetraborate decahydrate at 58.5 mg B/kg bw/day (NOAEL, 17.5 mg B/kg bw/day) (Weir, 1966 c,d; Weir and Fisher, 1972). In male rats fed disodium tetraborate decahydrate for either 30 or 60 days at 100 or 200 mg B/kg bw/day (NOAEL, 50 mg B/kg bw/day) testis weight

was reduced, testicular germ cells were depleted, selected testicular enzymes were affected and fertility was reduced (Lee et al., 1978). As might be expected, while recovery from inhibition of spermiation occurred at the lower doses, there was no recovery from testicular atrophy when the germ cells were lost.

Fewer data are available for mice and dogs, but the results confirm the findings in rats. In a continuous breeding study of boric acid in mice, a dose-related effect on the testis (testicular atrophy and effects on sperm, motility, morphology and concentration) was noted; fertility was partially reduced at 111 mg B/kg bw/day, and totally reduced at 221 mg B/kg bw/day. Effects on females were minimal. The NOAEL was 27 mg B/kg bw/day (154 mg boric acid /kg bw/day), although at this dose the motility of epididymal sperm was slightly affected without any effect on fertility (Fail et al., 1991). These results are consistent with those in rats.

Data in dogs derives from two very limited two-year feeding studies. Unfortunately, the published study does not reflect the original study reports (Weir, 1966 e, f; 1997 a, b; Weir and Fisher, 1972). In addition, the authors estimated the dietary intakes from standard intake figures. However, the original study reports contained the actual dietary intake allowing a more accurate measure of the dietary intake to be made. These amended figures are used here. Groups of dogs were fed either boric acid or disodium tetraborate decahydrate at doses up to 10.2 mg B/kg bw/day (62.4 mg boric acid/kg bw/day and 84.7 mg disodium tetraborate decahydrate/kg bw/day) in one study and 39.5 mg B/kg bw/day (233.1 mg boric acid/kg bw/day and 373.2 mg disodium tetraborate decahydrate/kg bw/day) in a second study. Only four male dogs per group were used in each study, and animals were sacrificed at various time periods such that observations were reported on groups of only 1 or 2 animals. One boric acid treated and one disodium tetraborate decahydrate treated dog were allowed to recover for three weeks. Some recovery was observed in each dog. Minor histopathological changes such as decreased spermatogenesis remained which was less obvious in the disodium tetraborate decahydrate treated dog. At 39.5 mg B/kg bw/day, testicular atrophy was observed, however the effects in the only one disodium tetraborate decahydrate treated dog investigated at 38 weeks were less severe than those seen in the control dog. Also, testicular atrophy was present in three out of four control dogs, so that the significance of the effect in the treated animals is difficult to assess. The NOAEL was deemed to be 10.2 mg B/kg bw/day. This data is inadequate for risk assessment, but it does confirm the effects seen in other species. Due to the acute toxic effects of borates in dogs, had the LOAEL doses been administered as a single dose then vomiting would have occurred and the study would not have been possible.

Table 5: Comparison of NOAELs and LOAELs for Reproductive Effects

Species	Study Type	NOAEL (mg B/kg bw/day)	LOAEL (mg B/kg bw/day)	Effect at LOAEL	Reference
Rat	9 week dietary study	-	26	Mild reversible inhibition of spermiation	Ku et al., 1993
	3-generation dietary study and 2 year dietary study	17.5	58.5	Testicular atrophy; reduced fertility	Weir, 1966 a, b, c, d Weir and Fisher, 1972
Mouse	Continuous breeding dietary study	27	111	Reduced fertility	Weir and Fisher, 1972
Dog	2 year dietary study	10.2	39.4	Testicular atrophy (also present in control animals)	Weir, 1966 e, f; 1967a,b

Conclusion: Effects on the Testis and Fertility

A dose related effect on the testis was observed in rats and mice with confirmation from limited studies in dogs. Effects start with reversible inhibition of spermiation after 14 days treatment, at doses around 39 mg B/kg, (217 mg boric acid/kg bw/day) although at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects take about 28 days to manifest. Higher doses (58.5 mg B/kg bw/day and above) lead to testicular atrophy, degeneration of seminiferous tubules, reduced sperm count and a reduction in fertility. No recovery from testicular atrophy was observed when the germ cells were lost.

The NOAEL for this endpoint is 17.5 mg B/kg corresponding to 100 mg boric acid/kg/day; 155 mg disodium tetraborate decahydrate/kg and 118 mg disodium tetraborate pentahydrate/kg.

Developmental Toxicity

Only boric acid has been tested in developmental studies. Effects were observed at high doses in rats, mice and rabbits. A comparison of the key NOAELs and LOAELs for developmental studies is given in Table 6.

The majority of studies have been carried out in rats. In two separate studies performed in the same laboratory, rats received a large number of dose levels (approximately 3.3, 6.3, 9.6, 13.7, 25, 28 and 59 mg B/kg bw/day on gestation days 0-20 and 94 mg B/kg bw/day on gestation days 6-15) in feed. The NOAELs for maternal toxicity and developmental effects were 13.7 mg/kg bw/day and 9.6 mg B/kg bw/day, respectively. A reduction in food intake and an increase in relative liver and kidney weight and a reduction in maternal body weight gain at higher doses indicated maternal toxicity. At non-maternally toxic doses, there was a reduction on foetal weight and some skeletal anomalies which, with the exception of shortened 13th rib, had reversed by postnatal day 21 at 13.7 and 28.6 mg B/kg bw/day in a study designed to look at postnatal recovery (Price et al., 1990 1996). At higher maternally toxic doses, other indications of developmental effects were observed, including resorptions and visceral malformations (enlarge lateral ventricles; cardiovascular effects; anophthalmia and microphthalmia and short and curly tails). However, these are likely to have been secondary to the maternal toxicity (Price et al., 1990, 1996; Heindel et al., 1992).

Similar findings were observed in mice receiving estimated doses of 0, 43, 79, and 175 mg B/kg bw/day on gestation days 0-20 in feed. Maternal toxicity was indicated by mild renal lesions and at the highest dose increases in the relative kidney weight and food intake. A NOAEL was not determined for maternal toxicity. The key developmental effects observed were similar to those seen in rats i.e. a reduction in foetal body weight at the mid dose (79 mg B/kg) and an increase in skeletal variations and malformations (missing lumbar vertebrae, fused vertebral arches and short rib XIII) and resorptions at the highest, more maternally toxic dose. The NOAEL for developmental effects in mice was 43 mg B/kg bw/day (Heindel et al., 1992), however, this dose was also a maternally toxic dose.

In rabbits receiving estimated doses of 0, 11, 22 and 44 mg B/kg bw/day by gavage on gestation days 6-19 maternal toxicity was indicated by effects such as an increase in relative kidney weight, increase food intake, vaginal bleeding and an increase in corrected weight gain. Developmental effects were seen only at the top dose, where the majority of the embryos were resorbed and malformations were primarily visceral (major heart and/or great vessel defects), however these effects are likely to be secondary to the maternal toxicity. The only skeletal effect observed was a decreased incidence of rudimentary extra rib on lumbar 1 which was not considered biologically significant. The NOAEL for both maternal and developmental toxicity in the rabbit was 21.8 mg B/kg bw/day (Price et al., 1991).

Table 6: Comparison of NOAELs and LOAELs for Developmental Effects

Species	Maternal NOAEL (mg B/kg bw/day)	NOAEL (mg B/kg bw/day)	LOAEL (mg B/kg bw/day)	Effect at LOAEL	Reference
Rat	13.7	9.6	13.6	Decreased foetal body weight; minor skeletal variations	Price et al., 1990, 1996
Mouse	No NOAEL	43	79	Maternal toxicity; decreased foetal body weight; minor skeletal variations	Heindel et al., 1992
Rabbit	21.8	21.8	43.5	Maternal toxicity; resorptions; Visceral malformations (cardiovascular defects)	Price et al., 1991

Conclusion: Developmental effects

Developmental effects have been observed in three species, rats, mice and rabbits. The most sensitive species appears to be rats, in which the effects observed at non maternally toxic doses include a reduction in foetal body weight and minor skeletal variations which, with the exception of short rib XIII, had reversed by 21 days post natal. The NOAEL for developmental effects is 9.6 mg B/kg.

Effects in Humans

For exposure to borates, a field study by Wegman and associates sought to establish a relationship between level of exposure to borates and various acute symptoms, including irritation, during routine industrial activities (Eisen, et al, 1991; Hu et al, 1992; Wegman et al, 1994; Woskie et al, 1994). In that setting, nasal irritation occurred most frequently, followed by throat, then eye irritation. Wegman and associates also found that smokers reported symptoms less frequently than non-smokers and old workers less frequently than younger workers. However, the study design introduces bias as the workers clearly are aware that they are working with borates and the fact that a study is being carried out would tend to make them more vigilant and over interpret symptoms that may just be due to physical effects of the dust. Of the 2490 reporting periods, there were 136 cases where both the button was pressed and the severity recorded by the technician. In these cases, the exposures were not different from the other 2086 cases when neither the button was pressed nor the severity recorded. This indicates that there was no real irritant effect. Other confounding factors acknowledged by Wegman et al., 1994, are that the severity scale had not been used on other irritant-exposure environments and that true sensory irritants increase in severity rapidly with increasing exposure levels which did not occur in this study. The reported irritation increased only to mild levels and did not increase at all with additional exposure, indicating that the borate dust is not a sensory irritant. The results more closely resembled the expected effects associated with an inert dust. In short, the mild symptoms seen are easily attributable to the physical reaction to exposure to a dust rather than a chemically induced irritant effect by the sodium borates themselves at these exposure levels.

An approach to determine more precisely the acceptable exposure limits based on measurement of responses of volunteers to measured amounts of various dusts was investigated by Cain (Cain et al., 2004) in a human study in which the sensory perception of dusts of sodium tetraborate pentahydrate (Na₂B₄O₇·5H₂O), calcium sulphate (CaSO₄), and calcium oxide (CaO) was investigated. Twelve subjects were exposed to dust particles for 25 min while performing moderate exercise (i.e., riding an exercise bike set at a load of 60 watts). Exposure to carbon dioxide vapour was used to set a reference scale for subjects to judge the feel of the stimulus materials. During exposure, subjects judged level of feel or irritation in the eye, nose, and throat (nasopharynx) at 5-min intervals. The subjects indicated the absence of any feel or irritation by a judgement of zero. At the intervals indicated, heart rate, oxygen saturation, minute ventilation and respiration rate were recorded as well. The results indicated no significant respiratory effects at 14 -15 mg/m³ sodium borate (Cain et al., 2004). This level would also be protective for ocular irritation. This value would also be compatible with the previously published results of the

field studies on borate workers by Wegman and colleagues. Therefore the data supports a limit of 10 mg/m³ (the general nuisance level) for all borates.

Effects on Reproduction

The potential reproductive effects of inorganic borate exposure to a population of workers at a large mining and production facility was assessed using the Standardised Birth Ratio (SBR), a measure of the ratio of observed to expected births. A total of 542 workers completed a reproductive questionnaire. The average exposure for the highest exposure group was 28.4 mg B/day (approximately 0.4 mg B/kg bw/day) for two or more years. The average duration of exposure was 16 years. The number of offspring was actually greater than the US national average, indicating no adverse effects on reproduction in these workers (Whorton et al., 1994).

In a study of a highly exposed population in Turkey, where exposure comes mainly from naturally high levels of B in drinking water (up to 29 mg B/l) as well as from mining and production, no adverse effect has been reported on fertility over three generations (Sayli, 1998; 2001).

Human Data from Poison Control Centres and Literature Cases

There is a large database of accidental or intentional poisoning incidents for humans. Many were the result of accidental use as an antiseptic for irrigating body cavities, treating wounds or as a treatment for conditions such as epilepsy. Such medical uses are now obsolete. Also, accidental misuse in the preparation of baby formula (1 – 14 g in boric acid in the formula) and the topical use of pure boric acid powder for infants has led to poisonings in the past. This database is reviewed in several papers of data from poisoning centres as well as a detailed review of the literature cases from the mid 1800s to the 1970s by Kliegel (Kliegel, 1980; Wong et al. 1964, Litovitz et al, 1988; Goldbloom and Goldbloom, 1953; Valdes-Dapena and Arey, 1962). Humans display different acute symptoms compared with most animals. In the literature, the human oral lethal dose is regularly quoted as 2–3 g boric acid for infants, 5–6 g boric acid for children and 15–30 g boric acid for adults. This data is largely unsubstantiated. In most cases it is difficult to make a good quantitative judgement particularly since medical intervention occurred in most cases and there were often other unrelated medical conditions (Culver and Hubbard, 1996). Of 784 more recent reports of accidental ingestion, none were reported as fatal and 88.3% were asymptomatic. The estimated dose range was 10 mg to 88.8 g (Litovitz et al, 1988). However, a single intake of 30 g of boric acid was fatal in one case (Yoshitaka et al., 1993). Symptoms of acute effects may include nausea, vomiting, gastric discomfort, skin flushing, excitation, convulsions, depression and vascular collapse.

In humans multiple exposure (high levels > 1g) results in various symptoms which may appear singly or together and include dermatitis, alopecia, loss of appetite, nausea, vomiting, diarrhoea, and focal or generalised central nervous system irritation or convulsions. Much data comes from the mid 1800s to around 1940, when boric acid and disodium tetraborate decahydrate were used systematically for a variety of medical conditions including amenorrhoea, malaria, epilepsy, urinary tract infection and exudative pleuritis (Kliegel, 1980). Daily oral doses in adults ranged from 1–14 g per day. Repeated doses in the 6–10 g/day range were given for as long as several weeks. In one extreme case a 28 year old woman ingested around 0.5 g of boric acid (in baby powder) every day for two years and suffered anaemia, which reversed on ceasing ingestion (Adelhardt and Fogh, 1983). Doses greater than 3–5 g/day regularly caused vomiting and/or diarrhoea in the first instance often accompanied by dermatitis and appetite suppression. As the dose became higher and the dosing period longer, symptoms included alopecia, disseminated maculopapular eruption followed by widespread desquamation, focal or generalised central nervous system irritation, and convulsions. The symptoms of dermatitis, nausea, diarrhoea and vomiting symptoms also occurred in some patients receiving doses of 2 g boric acid/day (29 mg boric acid/kg/day) and above. In one such case, reduction of the dose from 2 g/day of boric acid (29 mg boric acid/kg/day) to 1g/day (14 mg boric acid/kg/day) resulted in resolution of the effects (vomiting and dermatitis). In all cases where withdrawal of treatment was reported, recovery occurred with no lasting effects. The lowest recorded adult dose causing symptoms was 2 g/day boric acid (Kliegel, 1980).

In children, where low levels can be estimated (Gordon et al, 1973 and O'Sullivan and Taylor, 1983), infants aged from 6 to 19.5 weeks ingested borax (as a honey-borax mixture which had been applied to pacifiers) for periods of 4 to 12 weeks. The mean intake was 0.98 g boric acid/day (range 0.55g to 2 g) for a 10 kg child. The effects seen, which disappeared on withdrawal of the honey borax mixture, relate to effects on CNS such as convulsions, generalised seizures and focal seizures. There were no dermal effects. Minor occurrences of vomiting and loose stools were also described.

Conclusions: Effects in Humans

A no effect level for humans based on the acute (single intake) and chronic (daily single intake) symptoms of nausea, vomiting and diarrhoea can be established at about 1 g of boric acid/day (2.5 mg B/kg/day). The level at which adverse effects of anorexia, indigestion and exfoliative dermatitis will be seen is 5.0 mg boric acid/kg/day. Although chronic absorption data at these levels is not available in the literature for infants, their responses at high doses are similar enough to the human adult to assume that children are not more sensitive to the effects of borates.

Conclusions

Boron is a ubiquitous element found widely distributed in the environment and is a normal component of a healthy diet. It is an essential micronutrient for plants, and there is evidence to indicate that B is of nutritional importance, if not essential, for mammals. Boron is essential for normal reproduction and embryonic development in frogs and fish (Fort et al., 1998, 1999, 2002; Rowe et al., 1998), and mechanisms for this essentiality are beginning to be revealed (Fort 2002).

Boric acid and sodium borates have low acute toxicity. They are not skin irritants, nor skin sensitisers. Some borates cause eye irritancy in animals due to the glassy nature of the crystals, but in 50 years of occupational exposure no adverse ocular effects have been seen in humans. Borates are absorbed orally and by inhalation. They are very poorly absorbed dermally except through severely damaged skin. Dermal absorption has been shown to be < 0.3% in human studies. They are not carcinogenic or mutagenic.

In human cases of poisoning, via accidental oral intake, acute and chronic symptoms of nausea, vomiting and diarrhoea occur. As the dose became higher and the dosing period longer, symptoms included alopecia, disseminated maculopapular eruption followed by widespread desquamation, focal or generalised central nervous system irritation, and convulsions. A no effect level for humans based on the acute (single intake) and chronic (daily single intake) symptoms of nausea, vomiting and diarrhoea can be established at about 1 g of boric acid/day (2.5 mg B/kg/day).

The most critical endpoints of toxicity are considered to be (1) effects on the testis and fertility in males and (2) developmental effects (in particular, foetal weight reduction). The effects seen occur in three species, rats, mice and dogs for reproductive effects; rats, mice and rabbits for developmental effects. There is good agreement between these species which indicates that there is little species variation in the response. This may be due to the lack of metabolism of boric acid and borates, which tends to reduce interspecies variation.

The critical lowest No Observed Adverse Effect (NOAEL) level for the purposes of risk assessment is 9.6 mg B/kg/day (54 mg boric acid/kg/day; 85 mg disodium tetraborate decahydrate; 46 mg disodium octaborate tetrahydrate/kg/day), based on developmental effects.

The toxicokinetic data indicates that there is very little difference in the way in which humans and rats handle boric acid. Therefore, at the equivalent repeated daily doses in humans that cause reproductive effects in animals, toxic effects (such as vomiting and diarrhoea) are produced which will limit the oral intake by humans. The lowest dose in humans that causes such symptoms is 1.5 –2 and 5 times lower than the lowest LOAEL for reversible, minor developmental effects and for reversible effects on fertility respectively. A 60 kg person would need to consume daily some 3.3 g of boric acid (5.0 g disodium tetraborate decahydrate; 2.7 g disodium octaborate decahydrate) to ingest the same dose level as the lowest animal NOAEL. These equivalent doses would not be encountered, by humans, under any circumstances due to the physical properties of boric acid and to the limited absorption by non-oral routes, except under conditions of serious abuse by deliberate ingestion.



Dr S.A. Hubbard
Rio Tinto Borax
Group Toxicologist

August 12, 2005

References

- Abou-Shakra, F R, Havercroft, J. K. and Ward, N I, (1989), Lithium and Boron in Biological Tissues and Fluids. Trace Elements in Medicine, 6, 142 -146.
- Adelhardt M & Fogh A 1983 Enquiries to a centre for information on poisoning during a period of 12 years (English translation). Boraks – er de farligt (12 ars foresporgslert il giftinformationscentralen) Ugeskr. Laeger. 145 3808 – 3810.
- Alexander, G.V, R. E. Nusbaum, and N. S. MacDonald, The boron and lithium content of human bones, J. Biol. Chem. 192, 489-496 (1951).
- Armstrong TA, Spears JW, Crenshaw TD and Nielsen FH. Boron supplementation of a semipurified diet for weanling pigs improves feed efficiency and bone strength characteristics and alters plasma lipid metabolites. J. Nutr. 130:2575-2581 (2000).
- Armstrong TA, Spears JW and Lloyd KE. Inflammatory response, growth, and thyroid hormone concentrations are affected by long-term boron supplementation in gilts. J. Anim. Sci. 79:1549-1556 (2001).
- Armstrong TA and Spears JW. Effect of boron supplementation of pig diets on the production of tumor necrosis factor- α and interferon- γ . J. Anim. Sci. 81:2552-2561 (2003).
- Astier A, Baud F and Fournier A (1988). Toxicokinetics of boron after an acute accidental intoxication by boric acid. J Pharm. Clin. 7, 57-62.
- Bakke JP, Evaluation of the potential of boric acid to induce unscheduled DNA synthesis in the in vitro hepatocyte DNA repair assay using the male F-344 Rat. SRI International, Menlo Park, CA, Study No. 2389-V500-91; and Amendment 1 to the Original Report, Unpublished Report to US Disodium tetraborate decahydrate (1991).
- Barranco, W.T. Eckhart, C.D. Boric acid acts as a cADPR / RyR antagonist during inhibition of human prostate cancer cell proliferation. FASEB J. April 2004
- Beyer KH, W.F. Bergfeld, W.O. Berndt, R.K. Boutwell, W.W. Carlton, D.K. Hoffmann and A.L. Schroeter, FDA Cosmetic Ingredient Review Expert Panel, Final report on the safety assessment of sodium borate and boric acid, J. Am. Coll. Toxicology 2, 87-125 (1983).
- Bouissou H and R. Castagnol, Action de l'acide borique sur le testicule de rat. Archives des Maladies Professionnelles de Medecin du Travail et de Sécurité Social, T286, 293-306 (1965).
- Brown TF, McCormick ME, Morris DR and Zeringue LK (1989). Effects of dietary boron on mineral balance in sheep. Nutr Res 9, 503-521
- Bruze M, E. Hradil, I-L. Eriksohn, B. Gruberger and L. Widstrom, Occupational allergic contact dermatitis from alkanolamineborates in metalworking fluids, Contact Dermatitis 32, 24 -27 (1995).
- Cain, William S., Alfredo A. Jalowayski, Michael Kleinman, Nam-Soo Lee, Bo-Ryung Lee, I Byung-Hoon Ahn, I Kevin Magruder, Roland Schmidt, Brian K. Hillen, Craig B. Warren, and B. Dwight Culver, (2004). Sensory and Associated Reactions to Mineral Dusts: Sodium Borate, Calcium Oxide, and Calcium Sulfate, Journal of Occupational and Environmental Hygiene, 1: 222–236
- Cerven, D R (2000). Acute eye irritation on rabbits: EPA Reg. No 1624-1, Borax 5 mol., Sodium tetraborate penthydrate Lot #OE26. Study no MB 00-8677.04 MB Research Laboratories, Spinnerstown PA 18968. Unpublished report to US Borax
- Ciba J and Chrusciel A (1992) Spectrophotometric determination of boron in human hair with Azomethine H. Fresenius J Anal Chem. 342, 147-149
- Chen X, Schauder S, Potier N, Van Dorsselaar A, Pelczer I, Bassler BL and Hughson FM. Structural identification of a bacterial quorum-sensing signal containing boron. Nature 415:545-549 (2002).
- Coughlin, J. R. 1998. Sources of human exposure. Overview of water supplies as sources of boron. Biol. Trace Elem. Res. 66(1-3), 87-100.
- Culver BD, Shen P, Taylor TH, Feldstein AL, Anton-Culver H and Strong PL, (1993). Absorption of boron by sodium borate and boric acid production workers. Report to US Borax., August 11, 1993

Culver BD, R.G. Smith, R.J. Brotherton, P.L. Strong and T.M. Gray, Boron. in Patty's Industrial Hygiene and Toxicology, 4th Edition, Volume 2F, Chapter 42, G.D. Clayton and F.E. Clayton eds., John Wiley & Sons Inc., New York, NY, pp 4411-4448 (1994a)

Culver, B.D., P. T. Shen, T. H. Taylor, A. Lee-Feldstein, H. Anton-Culver, and P. L. Strong, The relationship of blood-and urine-boron to boron exposure in borax-workers and the usefulness of urine-boron as an exposure marker, Environ. Health Perspect. 102(7), 133-137 (1994b).

Culver BD and S A Hubbard. Inorganic boron health effects in humans: An aid to risk assessment and clinical judgement. J Trace Elements in Experimental Medicine, 9, 175 -184, 1996

Cuperus, L, Mazur P, Stubblefield S, Opsahl W, Robles H, 1990, Evaluation of the Ocular Irritation of Anhydrous Boric Acid in Rabbits. (P01875). Biological Test Center, Irvine, CA 92714. Unpublished report to US Borax. 25 April, 1990

Denton, S M. (1995). Dehybor anhydrous Borax Acute Oral Study in the Rat. Corning Hazleton (Europe), Harrogate, N Yorkshire, HG3 1PY, Study No 1341/2 -1032. Unpublished Report to Borax Europe Limited, October, 1995.

Denton SM, Anhydrous boric acid. Acute oral study in the rat. Corning Hazleton (Europe), Harrogate, N Yorkshire, HG3 1PY, Study No 1341/9 -1032 and 1341/3-1032, Unpublished Report to Disodium tetraborate decahydrate Europe Limited (1996a)

Denton, S M. (1996b). Dehybor anhydrous Borax Acute Oral Study in the Rat. Corning Hazleton (Europe), Harrogate, N Yorkshire, HG3 1PY, Study No 1341/6-1032. Unpublished Report to Borax Europe Limited, March 1996.

Draize J H and Kelley E A (1959). The urinary excretion of boric acid preparations following oral administration and topical applications to intact and damaged skin of rabbits. Toxicol. Appl. Pharmacol 1, 267-276.

Dourson, M, A. Meier, B. Meek, A. Renwick, E. Ohanian, and K. Poirier, Boron tolerable intake: re-evaluation of toxicokinetics for data-derived uncertainty factors. Biol. Trace Elem. Res. 66(1-3), 453-463 (1998).

Doyle RL, Acute oral toxicity in rabbits of disodium octaborate tetrahydrate. Study No-88-3197-21 Hill Top Biolabs Inc., Miami, Ohio 45147. Unpublished report to US Disodium tetraborate decahydrate (1989a).

Doyle RL, Acute dermal toxicity in rabbits of disodium octaborate tetrahydrate. Hill Top Biolabs Inc., Miami, Ohio, 45147, Unpublished report to US Disodium tetraborate decahydrate (1989b).

Doyle RJ, Primary skin irritation in rabbits of disodium octaborate tetrahydrate. Hill Top Biolabs Inc., Miami, Ohio, 45147. Unpublished report to US Disodium tetraborate decahydrate (1989c).

Doyle RL, Primary eye irritation of boric acid. Hill Top Biolabs Inc., Miami, Ohio 45147. Unpublished report to US Disodium tetraborate decahydrate (1989d).

Doyle RL, Primary eye irritation in rabbits of disodium octaborate tetrahydrate. Hill Top Biolabs Inc., Miami, Ohio 45147. Unpublished report to US Disodium tetraborate decahydrate (1989e).

Doyle RL, Eye irritation study without rinsing in rabbits of disodium octaborate tetrahydrate. Hill Top Biolabs Inc., Miami, Ohio 45147. Unpublished report to US Disodium tetraborate decahydrate (1989f).

Doyle RL, Primary eye irritation of 10 Disodium tetraborate decahydrate Mol. Hill Top Biolabs Inc., Miami, OH 45147. Unpublished report to US Disodium tetraborate decahydrate (1989g).

Draize J H and Kelley E A (1959). The urinary excretion of boric acid preparations following oral administration and topical applications to intact and damaged skin of rabbits. Toxicol. Appl. Pharmacol 1, 267-276

EC Cosmetics Directive - Twenty Fourth Commission Directive 2000/6/EC of 29 February 2000 adapting to technical progress Annexes II, III, VI and VII to Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), Toxicology and reproductive toxicity of some inorganic borates and risk assessment for man., Technical Report No. 63 (1995).

Eckhart, C. D. Boron Stimulates Embryonic Trout Growth. J. Nutrition 128:2488-2493, 1998

Emsley, J. (1989). The Elements. p. 32, Clarendon, Oxford.

- Eisen, E. A., Wegman, D. H., Kriebel, D., Woskie, S. R., & Hu, X. (1991). An epidemiologic approach to the study of acute reversible health effects in the workplace. *Epidemiology*, 2, 264-270.
- European Food Standards Agency (EFSA) : Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid) , The EFSA Journal (2004) 80, 1-22 (Request N° EFSA-Q-2003-018) (adopted on 9 July 2004)
- European Commission. Opinion of the Scientific Advisory Committee concerning toxicologically acceptable parametric value for boron in drinking water. CSTE/96/4/V, February 20, 1996. (EC drinking water directive (98/83/EC)
- Fail PA, J.D. George, J.C. Seely, T.B. Grizzle and J.J. Heindel, Reproductive toxicity of boric acid in Swiss (CD-1) mice: assessment using the continuous breeding protocol, *Fund. Appl. Toxicol.* 17, 225-239 (1991).
- Farr L E and Konikowski T (1963). The renal clearance of sodium pentaborate in mice and men. *Clin. Chem.* 9, 717-726.
- Forbes, R.M. and H. H. Mitchell, Accumulation of dietary boron and strontium in young and adult albino rats, *Arch. Ind. Health* 16, 489-492 (1957).
- Forbes, R.M., A. R. Cooper, and H. H. Mitchell, On the occurrence of beryllium, boron, cobalt, and mercury in human tissues, *J. Biol. Chem.* 209, 857-864 (1954).
- Fort, DJ, Propst, IL, Stover, EL, Strong, PL and Murray, FJ (1998). Adverse reproductive and developmental effects in *Xenopus* from insufficient boron. *Biol Trace Element Res.* 66, 237- 259.
- Fort, DJ, Stover, EL, Strong, PL and Murray, FJ (1999). Chronic feeding of a low-boron diet results in adverse reproductive and developmental effects in *Xenopus laevis*, *IJ Nutr* 129 (11), 2055-2060, 1999
- Fort DJ. Boron deficiency disables *Xenopus laevis* oocyte maturation events. *Biol. Trace Elem. Res.* 85:157-169 (2002).
- Friis-Hansen B, Aggerbeck B and Jansen JA: Unaffected blood boron levels in new-born infants treated with a boric acid ointment, *Fd Chem Toxicol* 20:451, 1982.
- Goldbloom RB, and Goldbloom A: Boric acid poisoning, *J Ped* 43:631, 1953.
- Gordon AS, J.S. Prichard and M.H. Freedman, Seizure disorders and anemia associated with chronic disodium tetraborate decahydrate intoxication, *C.M.A.J.* 108, 719-724 (1973).
- Haworth S, T. Lawlor and K. Mortelmans, Salmonella mutagenicity test results for 250 chemicals, *Environ. Mut. Suppl.* 1, 3-142 (1983).
- Heindel JJ, C.J. Price, E.A. Field, M.C. Marr, C.B. Myers, R.E. Morrissey and Schwetz B A, Developmental toxicity of boric acid in mice and rats, *Fund. Appl. Toxicol.* 18, 266-272 (1992).
- Hu, X., Wegman, D. H., Eisen, E. A., Woskie, S. R., & Smith, R. G. (1992). Dose related acute irritant symptom responses to occupational exposure to sodium borate dusts. *British Journal of Industrial Medicine*, 49, 706-711
- Hubbard SA and F. M. Sullivan, Toxicological effects of inorganic boron compounds in animals: A review of the literature, *J. Trace Elements in Experimental Medicine*, 9, 165 -173 (1996).
- Hubbard SA , Comparative Toxicology of Borates. *Biol. Trace Element Res.* 66, 343-357, 1998.
- Hui, X, Wester, RC and Maibach, HI, (1996) In Vivo Percutaneous Absorption of Boric Acid, Borax and Octaborate Tetrahydrate (DOT) in Man. Unpublished Report to U.S. Borax Inc., Study Number H832-11830-01, November 12.
- Hunt CD, Nielsen FH: Interaction between boron and cholecalciferol in the chick. In McC Howell J, Gawthorne JM, White CL (eds): "Trace Element Metabolism in Man and Animals," (TEMA-4). Canberra, Australia: Australian Academy of Science, 1981, p 597-600.
- IPCS (International Programme on Chemical Safety). "Environmental Health Criteria 204, Boron." World Health Organization, IPCS Working Group, 1998
- Jansen, J.A., J. S. Schou, and B. Aggerbeck, Gastrointestinal absorption and in vitro release of boric acid from water-emulsifying ointments, *Fd. Chem. Toxicol.* 22, 49-53 (1984a).
- Jansen, J.A., J. Andersen, and J. S. Schou, Boric acid single dose pharmacokinetics after intravenous administration to man, *Arch. Toxicol.* 55,64-67 (1984b).

- Job, C., Absorption and excretion of orally administered boron, *Z. Angew. Bader-und Klimaheilkunde* 20, 137-142 (1973).
- Keller JG. Boric acid. Acute Oral Administration -Rats Final Report. Hazleton Laboratories Inc., Falls Church, VA, March 19th 1962 (TX-62-5)
- Kibblewhite MG, Van Rensburg SJ, Laker MC, Rose EF. Evidence for an intimate geochemical factor in the etiology of esophageal cancer. *Environ Res.* 1984 Apr;33(2):370-8.
- Kliiegel, (1980), Bor in biologie, medizin, und pharmazie. Springer-Verlag, Berlin, Heidelberg, New York (ISBN 3-540-934 11-
- Ku, W.W., R. E. Chapin, R. F. Moseman, R. E. Brink, K. D. Pierce, and K. Y. Adams, Tissue disposition of boron in male Fischer rats, *Toxicol. Appl. Pharmacol.* 111,145-151 (1991)
- Ku, W.W., R. E. Chapin, R. N. Wine, and B. C. Gladen, Testicular toxicity of boric acid (BA): Relationship of dose to lesion development and recovery in the F344 rat. *Reprod. Toxicol.* 7, 305-319 (1993).
- Landolph LR, Cytotoxicity and negligible genotoxicity of disodium tetraborate decahydrate ores to cultured mammalian cells. *Am. J. Ind. Med.* 7, 31-43 (1985).
- Lanoue L, Taubeneck M W Muniz J, Hanna L A, Strong P L, Murray F J, Nielsen F H, Hunt C D and Keen C L (1998a). Assessing the effects of low boron diets on embryonic and fetal development in rodents using in vitro and in vivo model systems. *Biol Trace Element Res*, 66, 271 – 298.
- Lanoue L, Strong PL, Hunt CD and Keen CL. Effects of boron deficiency and toxicity on preimplantation mouse embryos. Defining the limits of boron nutrition using an in vitro model. *J. Trace Elem. Exp. Med.* 11:400-401 (1998b).
- Laurent-Pettersson M, Delpech B and Thellier M . The mapping of natural boron in histological sections of mouse tissues by the use of neutron capture radiography. *Histochem. J.* 24, 939-950. (1992)
- Lee IP, R.J. Sherins and R.L. Dixon, Evidence for induction of germinal aplasia in male rats by environmental exposure to boron, *Toxicol. Appl. Pharmacol.* 45, 577-590 (1978).
- Linder RE, L.F. Strader and G.L. Rehnberg, Effect of acute exposure to boric acid on the male reproductive system of the rat, *J. Toxicol. Environ. Health* 31, 133-146 (1990).
- Litovitz T L, Klein-Schwartz W, Oderda G M and Schmitz B F. Clinical manifestations of toxicity in a series of 784 boric acid ingestions. *Am. J. Emerg. Med.* 6, 209-213. (1988)
- Locksley HB and Sweet. Tissue distribution of boron compounds in relation to Neutron-capture Therapy of cancer. *Proc. Soc. Exp. Biol. Med.* 86, 56 –63 (1954)
- Massie HR, Aiello VR, Shumway AE and Armstrong T, (1990). Calcium, iron, boron, collagen and density changes in bone with aging in C57BL/65 mice. *Exp. Gerontol.* 469-481
- McEacham, S.L. and Hunt, C.D. 1998. Dietary boron intakes of selected populations in the United States. *Biol. Trace Elem. Res.* 66(1-3), 65-78.
- Minoia, C., Sabbioni, E., Apostoli, P., Pietra, R., Pozzoli, L., Gallorini, M., Nicolaou, G., Alessio, L. and Capodaglio, E., Trace element reference values in tissues from inhabitants of the European Community I. A study of 46 elements in urine, blood and serum of Italian subjects. *The Science of the Total Environment*, 95, 89-105 (1990)
- Minoia, C, Sabbioni, E, Ronchi, A, Gatti, A, Pietra, A et al. Trace element reference values in tissues from inhabitants of the European Community. IV. Influence of dietary factors. *Sci. Total Environ.* 141: 181-195 (1994).
- Moore, JA and an Expert Scientific Committee. An assessment of boric acid and borax using the IEHR evaluative process for assessing human developmental and reproductive toxicity of agents. *Repro. Toxicol.* 11: 123-160 (1997) and NTIS Technical Report PB96-156005, March, 1995.
- Murray FJ, A human health risk assessment of boron (boric acid and disodium tetraborate decahydrate) in drinking water, *Regul. Toxicol. Pharmacol.* 22, 221- 230 (1995).
- Murray, F.J. A comparative review of the pharmacokinetics of boric acid in rodents and humans. *Biol. Trace Elem. Res.* 66:331-341 (1998).

- Nielsen G H (1970). Percutaneous absorption of boric acid from boron-containing preparations in rats. *Acta. Pharmacol. Toxicol.* 28, 413-424.
- Nielsen FH. 1998. The justification for providing dietary guidance for the nutritional intake of boron. *Biol Trace Elem Res* 66:319–330.
- Nielsen FH, Penland JG. 1999. Boron supplementation of peri-menopausal women affects boron metabolism and indices associated with macromineral metabolism, hormonal status and immune function. *J Trace Elem Exp Med* 12:251–261.
- NTP (National Toxicology Program): Toxicology and carcinogenesis studies of boric acid (CAS No. 10043-35-3) in B6C3F1 mice. US Department of Health and Human Services, National Institute of Health (Technical Report Series No. 324) (1987).
- O'Loughlin KG, Bone marrow erythrocyte micronucleus assay of boric acid in Swiss-Webster mice. SRI International, Menlo Park, CA, Study No. 2389-C400-91, August, 1991, Unpublished Report to US Disodium tetraborate decahydrate (1991).
- O'Sullivan K and M. Taylor, Chronic boric acid poisoning in infants, *Arch. Dis. Childhood* 58, 737-749 (1983).
- Owen E C (1944). The excretion of borate by the dairy cow. *J Dairy Res.* 13, 243-248.
- Pahl, M.V., B.D. Culver, P.L. Strong, F.J. Murray and N. Vaziri. 2001. The effect of pregnancy on renal clearance of boron in humans: A study based on the normal dietary intake of boron. *Toxicological Science* 60, 252-256.
- Penland JG. The importance of boron nutrition for brain and psychological function. *Biol. Trace Elem. Res.* 66:299-317 (1998).
- Pfeiffer CC, L.F. Hallman and I. Gersh, Boric acid ointment. A study of possible intoxication in the treatment of burns, *J. Amer. Med. Assoc.* 128, 266-274 (1945)
- Price C J, Field E A, Marr M C, Myers C B, Morrissey R E and Schwetz B A . Final report on the developmental toxicity of boric acid (CAS No 10043-35-3) in Sprague Dawley rats. NIEHS/NTP (NTP-90-105/NTP-90-105A (and report supplement), Order No. PB91-137570, May (1990)
- Price CJ, M.C. Marr, C.B. Myers, J.J. Heindel and Schwetz BA, Final report on the developmental toxicity of boric acid (CAS No 10043-35-3) in New Zealand white rabbits, NIEHS/NTP Order No. PB92-129550 (1991).
- Price CJ, P.L. Strong, M.C. Marr, C.B. Myers and F.J. Murray, Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. *Fund. Appl. Toxicol.*, 32, 179-193 (1996).
- Rainey C J and L. Nyquist, Multicountry estimation of dietary boron intake, *Biol. Trace Elem. Res.*, 66(1-3), 79-86 (1998).
- Rainey, C. J., Nyquist, L. A., Christensen, R. E., Strong, P. L., Culver, B. D., and Coughlin, J. C. 1999. Daily boron intake from the American diet. *J. Am. Diet Assoc.* 99(3), 335-340.
- Reagan EL and Becci P J. Acute oral LD50 study of 20 Mule Team, lot No. USB-12-84 sodium tetraborate pentahydrate in Sprague-Dawley rats. Food & Drug Research Laboratories, Inc., Waverly, NY 14892-0107, USA. (Unpublished report TX-85-5 of 1 February 1985 to U.S.Borax). (1985a)
- Reagan EL and P.L. Becci, Acute dermal toxicity study of 20 Mule Team lot no. USB-11-84 sodium tetraborate decahydrate in New Zealand white rabbits. Food and Drug Research Laboratories Inc., Waverly, NY 14892, Unpublished report to US Disodium tetraborate decahydrate (1985b)
- Reagan EL and P.L. Becci, Acute dermal toxicity study of 20 Mule Team lot no. USB-12-84 sodium tetraborate pentahydrate in New Zealand white rabbits. Food and Drug Research Laboratories Inc., Waverly, NY 14892, Unpublished report to US Disodium tetraborate decahydrate (1985c).
- Reagan EL and P.L. Becci, Primary dermal irritation study of 20 Mule Team lot no. USB-11-84 sodium tetraborate decahydrate in New Zealand white rabbits. Food and Drug Research Laboratories Inc., Waverly, NY 14892. Unpublished report to US Disodium tetraborate decahydrate (1985d).
- Reagan EL and P.L. Becci, Primary dermal irritation study of 20 Mule Team lot no. USB-12-84 sodium tetraborate pentahydrate in New Zealand white rabbits. Food and Drug Research Laboratories Inc., Waverly, NY 14892. Unpublished report to US Disodium tetraborate decahydrate (1985e).

Reagan EL and P.L. Becci, Primary eye irritation study of 20 Mule Team lot no. USB-11-84 sodium tetraborate decahydrate in New Zealand white rabbits. Food and Drug Research Laboratories Inc., Waverly, NY 14892. Unpublished report to US Disodium tetraborate decahydrate (1985f).

Reagan EL and P.L. Becci, Primary eye irritation study of 20 Mule Team lot no. USB-12-84 sodium tetraborate pentahydrate in New Zealand white rabbits. Food and Drug Research Laboratories Inc., Waverly, NY 14892. Unpublished report to US Disodium tetraborate decahydrate (1985g).

Rooney C, Beral V, Manconochie N, Fraser P, Davies G. Case-control study of prostate cancer in employees of the United Kingdom Atomic Energy Authority. *British Med J.* 307:1391-7, 1993.

Roudabush L, C.J. Terhaar, D.W. Fassett and S.P. Dziuba, Comparative acute effects of some chemicals on the skin of rabbits and Guinea pigs, *Toxicol. Appl. Pharmacol.* 7, 559-565, (1965).

Rowe, RI, Bouzan, C, Nabili, S and Eckhert, CD (1998). Essentiality of boron for vertebrate embryonic development in trout and zebrafish. *Biol Trace Element Res.* 66, 261-270.

Rowe R I and Eckhert C D, (1999). Boron is required for zebrafish embryogenesis. *J Experimental Biol.* 202, 1649 –1654.

Sabbioni E, Nicolaou GR, Pietra R, Beccaloni E, Conni E, Alimonti A and Caroli S, Inductively coupled atomic emission spectrometry and neutron activation analysis for the determination of element reference values in human lung tissue. *Biological Trace Element research*, 26-27, 757-768 (1990)

Samman S, Naghii MR, Lyons Wall PM, Verus AP. 1998. The nutritional and metabolic effects of boron in humans and animals. *Biol Trace Elem Res* 66:227–235.

Sayli, B.S (1998) Assessment of fertility and infertility in boron-exposed Turkish subpopulations. Pt. 2. Evidence that Boron has no effect on human reproduction, *Biol. Trace Elem. Res.* 66, 406–422

Sayli, B.S (2001). Assessment of fertility and infertility in boron-exposed Turkish subpopulations. Pt. 3. Evaluation of fertility among sibs and in 'borate families'. *Biol. Trace Elem. Res.* 81, 255-267.

Schou, J. S., J. A. Jansen, and B. Aggerbeck, Human pharmacokinetics and safety of boric acid, *Arch. Toxicol.* 7, 232-235 (1984).

Shuler TR, Pootrakul P, Yamsukon P and Nielsen FH, (1990). Effect of thalassemia/haemoglobin E disease on macro, trace and ultratrace element concentrations in human tissue. *J. Trace Elem. Exp. Med.* 3, 31-43

Sisk DB, B.M. Colvin and C.R. Bridges, Acute fatal illness in cattle exposed to boron fertilizer. *J. Am. Vet. Med. Assoc.* 196, 943-945 (1988).

Sisk DB, B.M. Colvin, A. Merrill, K. Bondari and J.M. Bowen, Experimental Acute Inorganic Toxicosis in the Goat: Effects on Serum Chemistry and CSF Biogenic Amines. *Vet. Hum. Toxicol.* 32, 205-211 (1990).

Stewart KR, Salmonella/microsome plate incorporation assay of boric acid. SRI International, Menlo Park, CA, Study No. 2389-A200-91, Unpublished report to US Disodium tetraborate decahydrate (1991).

Stüttgen, G, Siebel, Th., and Aggerbeck, B. Absorption of Boric Acid through Human Skin Depending on the Type of Vehicle. *Arch Dermatol Res.* 272: 21-29, (1982).

Sutherland, B., Strong, P.L. and King, J.C. (1998). Determining Human Dietary Requirements for Boron. *Biological Trace Element Research.* 66, 193-204.

Takano J; Noguchi, K; Yasumori, M; Kobayashi, M; Gajdos, Z, Miwa, K, Hayashi, H; Yoneyama, T and Fujiwara, T (2002), Arabidopsis boron transporter for xylem loading. *Nature*, Nov 2002

Treinen K.A. and R. E. Chapin, Development of testicular lesions in F344 rats after treatment with boric acid, *Toxicol. Appl. Pharmacol.* 107, 325-335 (1991).

UK EVM (Expert Group on Vitamins and Minerals), Safe Upper Limits for Vitamins and Minerals, May 2003 (www.foodstandards.gov.uk)

US EPA. 2004. Toxicological review of boron and compounds (CAS No. 7440-42-8) In Support of Summary Information on the Integrated Risk Information System (IRIS) June 2004 U.S. Environmental Protection Agency Washington, DC June 2004, EPA 635/04/052 www.epa.gov/iris

- U.S. Environmental Protection Agency Washington, DC. U.S. Food and Nutrition Board. 2001. Dietary Reference Intakes: Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc., pp. 13-1 - 13-42. Institute of Medicine, Washington, D.C.
- Usuda, K., Kono, K., Orita, Y., Dote, T., Iguchi, K., Nishiura, H., Tominga, M., Tagawa, T., Goto, E., and Shirai, Y. Serum and urinary boron levels in rats of sodium tetraborate. *Arch. Toxicol.* **72**, 468-474 (1998)
- Valdes-Dapena, M-A, and Arey, JB. (1962). Boric acid poisoning: Three fatal cases with pancreatic inclusions and a review of the literature. *J. Pediatrics.* **61**, 531 – 546.
- Vaziri, N.D., F. Oveisi, B.D. Culver, M.V. Pahl, M.E. Anderson, P.L. Strong and F.J. Murray. 2001. The effect of pregnancy on renal clearance of boron in rats given boric acid orally. *Toxicological Science* **60**, 257-263.
- Vernot EH, J.D. MacEwen, C.C. Haun and E.R. Kinkead, Acute toxicity and skin corrosion data for some organic and inorganic aqueous solutions, *Toxicol Appl. Pharmacol* **42**, 417-424 (1977).
- Ward, N.L., The determination of boron in biological materials by neutron irradiation and prompt gamma-ray spectrometry, *J. Radioanal. Nucl. Chem.* **110(2)**, 633-639 (1987).
- Weeth H J, Speth C F and Hanks D R (1981). Boron content of plasma and urine as indicators of boron intake in cattle. *Am. J. Vet. Res.* **42**, 474-477
- Wegman DH, E.A. Eisen, X. Hu, S. Woskie, R.G. Smith and D.H. Garabant, Acute and chronic respiratory effects of sodium borate particulate exposures, *Environ. Health Perspect.* **102**, 119-128 (1994).
- Weiner A S, Conine D L and Doyle R L (1982). Acute dermal toxicity screen in rabbits; Primary skin irritation study in rabbits of boric acid. Ref. 82-028021 of 15 March 1982, Hill Top Research, Inc., Cincinnati, Ohio.
- Weir R J (1966a). Three-generation reproductive study - rats. Sodium tetraborate decahydrate. Final Report. Hazleton Laboratories Inc., Falls Church, VA, July 8th. Unpublished report to US Borax Research Corporation. (TX-66-19)
- Weir R J (1966b). Three-generation reproductive study - rats. Boric acid. Final Report. Hazleton Laboratories Inc., Falls Church, VA, July 8th. Unpublished report to US Borax Research Corporation (TX-66-16)
- Weir R J (1966c). Two-year dietary feeding study - albino rats. Boric acid. Final Report. Hazleton Laboratories Inc., Falls Church, VA, July 8th, 1966 (TX-66-18) and Addendum to Final Report, April 10, 1967 (TX-67-6) Unpublished report to US Borax Research Corporation
- Weir R J (1966d). Two-year dietary feeding study – albino rats. Borax (Sodium tetraborate decahydrate). Final Report (TX-66-21). Hazleton Laboratories Inc., Falls Church, VA, July 8th, 1966 and Addendum to Final Report, April 10, 1967 (TX-67-9). Unpublished report to US Borax Research Corporation
- Weir R J. Two-year dietary feeding -dogs - Boric acid. Hazleton Laboratories Inc., Falls Church, VA, Report to US Borax, 8 July 1966 (TX-66-17) (1966e).
- Weir R J. Two-year dietary feeding -dogs Borax. Hazleton Laboratories Inc., Falls Church, VA and Addendum to Final Report (1967) Report to US Borax, 8 July 1966 (TX-66-20) (1966f)
- Weir R J. 38 week dietary feeding - dogs- Boric acid. Hazleton Laboratories Inc., Falls Church, VA, Report to US Borax, 28 February, 1967 (TX-67-3) (1967a).
- Weir R J. 38 week dietary feeding – dogs Borax. Hazleton Laboratories Inc., Falls Church, VA, Report to US Borax, 28 February, 1967 (TX-67-4) (1967b)
- Weir R J and Fisher R S (1972). Toxicologic studies on borax and boric acid. *Toxicol. Appl. Pharmacol* **23**, 351-364 and related internal reports to US Borax.
- Wester RC, Hui X, Hartway T, Maibach HI, Bell K, Schell MJ, Northington DJ, Strong P and Culver, BD. In vivo percutaneous absorption of boric acid, Borax and disodium octaborate tetrahydrate in humans compared to in vitro absorption in human skin from infinite to finite doses. *Toxicol Sciences* **45** 42-51 (1998)
- WHO, 1998. Guidelines for drinking water quality. 2nd Edition Addendum to Volume 1. Recommendations Boron, pages 4-6 and Addendum to Volume 2 Boron pages 15-29. World Health Organisation, Geneva.

- Whorton MD, J.L. Haas, L.Trent and O.Wong, Reproductive effects of sodium borates on male employees: birth rate assessment, *Occup. Environ. Med.* 51, 761-767 (1994).
- Wiley H W (1904). Influence of food preservatives and artificial colours on digestion and health, I-Boric acid and borax. US Department of Agriculture, Bureau of Chemistry, Bulletin 84, Washington DC, 1-477. Summarised in Jansen WF, The squad that ate poison, *FDA Consumer*, Dec. 1981 - Jan 1982, 6-11.
- Wilding J L, Smith W J, Yevitch P, Sicks M E, Ryan S G and Punte CL (1959). The toxicity of boron oxide. *Am. Ind. Hyg. J* 20, 284-289.
- Wnorowski G, Acute inhalation toxicity limit test on boric acid, Study - 3311. Product Safety Labs, East Brunswick, NJ 08816, Unpublished report to US Borax (1994a).
- Wnorowski G, Acute inhalation toxicity limit on disodium tetraborate decahydrate, Study - 3309. Product Safety Labs, East Brunswick, NJ 08816, Unpublished report to US Borax (1994b).
- Wnorowski G, Acute inhalation toxicity limit on disodium tetraborate pentahydrate, Study - 3307. Product Safety Labs, East Brunswick, NJ 08816, Unpublished report to US Borax (1994c).
- Wnorowski G, Acute inhalation toxicity limit on disodium octaborate tetrahydrate, Study - 3313. Product Safety Labs, East Brunswick, NJ 08816, Unpublished report to US Borax (1994d).
- Wnorowski G, Dermal sensitization test - Buehler method on boric acid, Study - 3310. Product Safety Labs, East Brunswick, NJ 08816. Unpublished report to US Borax (1994e).
- Wnorowski G, Dermal sensitization test - Buehler method on disodium octaborate tetrahydrate, Study - 3312. Product Safety Labs, East Brunswick, NJ 08816. Unpublished report to US Borax (1994f).
- Wnorowski G, Dermal sensitization test - Buehler method on sodium tetraborate decahydrate, Study - 3308. Product Safety Labs, East Brunswick, NJ 08816. Unpublished report to US Borax (1994g).
- Wnorowski G, Dermal sensitization test - Buehler method on sodium tetraborate pentahydrate, Study - 3306. Product Safety Labs, East Brunswick, NJ 08816. Unpublished report to US Borax (1994h).
- Wnorowski, G., Primary Eye Irritation on Neobor Borax 5-mol, Batch # 5L07. Product Safety Labs, US, East Brunswick, New Jersey 08816, Study - 4282. Unpublished report to U.S. Borax. (TX-96-..) (1996).
- Wnorowski, G., (1997), Acute inhalation toxicity limit on boric acid MG Test Product Safety Labs, US, East Brunswick, New Jersey 08816, Study - 5257. Unpublished report to U.S. Borax.
- Woods, W.G. (1994) An introduction to boron: history, sources, uses and chemistry. *Environ. Health Perspect.* 102(7), 5-11.
- Woskie, S. R., Shen, P., Eisen, E. A., Finkel, M. H., Smith, T. J., Smith, R., & Wegman, D. H. (1994). The real-time dust exposures of sodium borate workers: Examination of exposure variability. *American Industrial Hygiene Association Journal*, 55, 207-216
- Young JA, and R.L. Doyle, Corrosivity study on a series of ten materials. 73-630-21, Hill Top Research Inc., Cincinnati, Ohio, 45242. Unpublished report to US Disodium tetraborate decahydrate (1973).
- Yoshitaka I, N. Fujizuka, T. Toshihiko, K. Shimizu, A. Tuchida, S. Yano, T. Naruse and T. Chishiro, A fatal case of acute boric acid poisoning, *Clin. Toxicol.* 31, 345-352 (1993)
- Zhang, Z-F. Winton, J. I. Rainey C. Eckhart C. D. Boron is associated with decreased risk of human prostate cancer. *FASEB J.* 15:A1089 (834.3) 2001