Boric Acid, a Lewis Acid with Unique/Unusual Properties: Formulation Implications

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ABSTRACT

This review provides insight into the use of boric acid as a pharmaceutical, a buffer, and an adjuvant/excipient in pharmaceutical formulations. Boric acid is a Lewis acid whose pKa, 8.92-9.24, varies with concentration due to polymerization above 0.02M, is temperature sensitive, and is minimally sensitive to ionic strength. Boric acid readily reacts with alcohols, especially 1,2-diols, including carbohydrates, amines and thiols. These esters have lower pKa values and rapidly dissociate on dilution. Boric acid can stabilize some materials while catalyzing the degradation of others. It has been used in various dermal, and women's hygiene products because of its mild antibacterial and antifungal activity. In ophthalmic products, it is used as a buffer, an isotonicity agent, and to enhance the protective spectrum of other preservatives. Boric acid has been used reluctantly in parenteral products but appears to be quite safe in low doses. Toxicity, including deaths, has been reported on high exposure in humans, especially children. Animal toxicities have been noted, including drops in male sperm counts. Boric acid is well absorbed on oral dosing and its biological half-life is about 21 hours in humans. It appears appear to accumulate in some tissues especially bone.

INTRODUCTION

The purpose of this short review is to help researchers and formulators considering the use of boric acid understand its unusual and unique properties. While this review attempts to be fairly comprehensive in scope, we have limited references to those which will allow the reader to gain the most insight into this surprisingly complex small molecule. Many of the references quoted provide insight into the early history of boric acid and its properties and usage. A nice summary of the use of boric acid used as an excipient can be found in a document on boric acid/borate by the European Medicines Agency from 2017 available as a pdf document online. (https://www.ema.europa.eu/en/documents/report/boric-acid-borate-used-excipients-report-published-support-questions-answers-boric-acid-borates-used_en.pdf) [1]

Boric acid (Fig. 1) has been used as a buffer, a pharmaceutical in its own right or in combination with various 1,2-diols such as glycerol and mannitol (Aronoff 1975, Azevedo 2012, Boeseken 1949, 1931, Dawber 1988, Hollander 1945, Kose 2009, 2010, Mesmer 1972, Najib 2007, Norrild 1995, Peters 2014, Rietjens 2005, Steinberg 1957, van den Berg 1994, van Duin 1984, 1985, 1986, Woods 1994, Zumreoglu-Karan 2015). [2-21] Its use as a buffer in pharmaceutical formulations is mainly in ophthalmic products and some dermal applications (Sheskey 2017) [22] although it was recently included in a parenteral formulation of bortezomib for injection by Usayapant (2015). [23] It is also has uses in cosmetic, some food, and biocide products.

Insert Figure 1

Claims have been made that the combination of boric acid and mannitol extends the range of preservative protection in preserved multidose ophthalmic eye drops (Chowhan 1996, 1998, Kabra 2015) [24-26] and is known to prevent the crystallization of mannitol (Yoshinari 2003). [27] As will be discussed, the combination also provides better buffering at around physiological pH due to the drop in the pKa value of its mannitol ester (Azevedo 2012), [3] formed *in* situ, compared to boric acid itself.

Of interest is the recent claim that boric acid affects the processing formulatability of the alkyl boronic drug, bortezomib (Usayapant 2015) [23] on freeze-drying allowing an alternative formulation to intravenous Velcade®, which combines bortezomib with mannitol. The boric acid formulation cannot be used for subcutaneous administration since the presence of boric acid does not significantly raise the solubility of bortezomib (unpublished studies from our laboratory), needed for subcutaneous administration.

For perceived safety or other reasons, there appears to have been a reluctance to use the element boron in drug molecules except for the unique ability of one of the natural isotopes of boron, ^{10}B, to capture a neutron to form ^{11}B to treat brain, head and neck tumors, and some bone cancers in the form of Boron Neutron Capture Therapy (BNCT) (Luderer 2015, Barth 2012, Hsu 2011). [28-30] Boric acid itself has been tried in BNCT as have various complex boron containing molecules (Hsu 2011). [30]

While the simplest of the boron containing pharmaceuticals is boric acid (fig. 1), which is the focus here, this review will also provide some understanding into how the properties of boric acid can provide insight into the properties of alkyl and aryl boronic acid drug molecules, which have begun to appear (Yang 2003, Trippier 2010, Leśnikowski 2016). [31-33] For example, in 2003 bortezomib (initially commercialized as Velcade®), an alkyl boronic acid proteasome inhibitor,

was approved for the treatment of multiple myeloma and later mantle cell lymphoma (Adams 2004, Raedler 2015). [34,35] However, Velcade® is actually the boronic acid mannitol ester, an *in situ* formed prodrug of bortezomib produced when bortezomib is freeze dried out of a water/t-butanol mixture in the presence of mannitol (Gupta 2004, 2005). [36,37]

PHYSICOCHEMICAL PROPERTIES

Boric acid as a Lewis acid, Ionization Scheme and pKa Values

Boric acid is a quite weak Lewis acid of pKa variably quoted as 8.92-9.24, see Table 1, with a planar configuration, while its base form, the borate specie, has a tetrahedral configuration, see Fig. 1. Its dissociation constant is temperature, ionic strength (weakly), and unlike most other acids, concentration dependent.

Insert Table 1

Lewis acids do not give up a proton by direct dissociation, as is the case for Brønstead acids, but by either consuming a base like hydroxide ion or by reaction with water with the release of one of a proton of water as illustrated in Fig. 1. This is favorable in boric acid because the boron atom has an empty $2p_Z$ orbital. On reaction with water, some have referred to this as hydrolysis or hydration, and the release of a proton or hydronium ion, the borate specie is formed. The same reaction occurs for boronic acids (Marinaro 2015, Yan 2004). [38,39]

One of the National Bureau of Standards buffers for calibrating pH meters uses borax (Bates, 1964). [40] Borax, also referred to as sodium borate and sodium tetraborate is an interesting

material. It is NOT $NaBO_4H_4$ as the name implies but is generally described as $Na_2B_4O_7{\cdot}10H_2O$ or $Na_2[B_4O_5(OH)_4]{\cdot}8H_2O$. That is, one mole of borax, on dissolution and chemical dissociation, hydrolysis) in water, yields two moles of boric acid, BO_3H_3, or $B(OH)_3$, and two moles of $NaBO_4H_4$, or $NaB(OH)_4$ in dilute solutions, see Fig. 1. Therefore, it is self-buffering since it results in equimolar concentrations, in dilute solution, of both the acid and its base and a pH equal to the pKa or apparent pKa of boric acid at the concentration, and temperature prepared. However, as will be discussed, the pH of a borax solution will vary with concentration, even corrected for ionic strength, due to boric acid/borate polymerization at higher concentrations (Bates 1964), [40] discussion to follow.

Note, the bottom structure for borax illustrated in Fig. 1 is probably inaccurate as it appears as if in the borax is acting as a Brønstead acid with a negative charge residing on the oxygens rather than on the boron. Thus, the confusion on whether borax should be defined as $Na_2B_4O_7{\cdot}10H_2O$ or $Na_2[B_4O_5(OH)_4]{\cdot}8H_2O$. The latter is a more accurate since two of the OH groups added to the neutral borax structure would produce two anionic centers on two boron atoms not oxygens.

While most assume that boric acid behaves only as a Lewis acid, some claim that it can behave as a Brønstead acid (Perelygin 2006, Gilkerson 1957). [41,42] These papers provide little specific support for boric acid as a Brønstead acid but one should not ignore the possibility.

The pKa of boric acid has been variably reported with values ranging from 8.92 to 9.24 (Table 1). Some of the differences are due to temperature, ionic strength and concentration used and the technique dependent, although the pKa should be independent of the technique. It is reasonable to assume that an average pKa value between 9 and 9.2 can describe the pKa range of boric acid in dilute, <0.02M, solution.

The pKa of boric acid is weakly dependent on the ionic strength. Early work by Ingri (Ingri 1962,1962) [43,44] studying the properties of boric acid in 0.1M and 3M $NaClO_4$ showed the pKa changes from 8.98 to 9.00, respectively. A very careful study by Dickson in seawater of varying salinity (5-45 salinity units, grams of salt/Kg of solution) showed that pKa of boric acid decreases with increasing salinity but the ionic strength values of most of his solutions were high compared to physiological conditions (Dickson 1990). [45] For reference, the salinity under physiological conditions has a value of 9.

The temperature dependency of boric acid pKa is illustrated in Table 2 (Owen 1935, Dickson 1990). [45,46] The Dickson data was from a salinity of 5 (ionic strength 0.103). While the values differ, the effect of temperature in both studies parallel each other, with a significant drop in pKa with increasing temperature. Owen described an empirical fit to his data by the equation, $pKa = 9.023 + 8x10^{-5}(76.7-t)^2$, where t is temperature in °C. Dickson also modeled the variation using a less empirical mathematical model. Because of the polymerization of boric acid at higher concentration values (discussion to follow), the temperature dependency of the apparent pKa values for boric acid at higher concentrations is likely to be even more complex.

Insert Figure 1 and Table 2

Boric Acid Ionization Kinetics

Since the ionization of boric acid to its borate specie does not involve a proton transfer reaction from a heteroatom *per se* but hydration of the empty 2pz orbital of the boron atom, one might assume that the kinetics of ionization is not diffusion rate limiting. That is in fact the case, however, while not diffusion rate controlled, as is the case for carboxylic acids and most other

Bronsted acids except for carbon acids (Stella 1979), [47] the half-life for the ionization is in the order of about 0.2-0.7 msec (Ishihara 1994, Waton 1984), [48,49] still fast by most standards.

Boric Acid/Borate Polymerization

Just as water can react with the $2p_Z$ orbital, a second (or more) boric acid molecule/s can react with each other to form, in more concentrated solutions, readily reversible dimeric, trimeric, a cyclic trimeric specie and even more complex specie as shown in Fig. 2. This polymerization accounts for the apparent dissociation constant variation with concentration. Kolthoff and Bosch in 1927 first noted that boric acid polymerizes at higher concentrations (Kolthoff 1927). [50] This was elegantly confirmed experimentally and modeled by Ingri and co-workers (Ingri 1957, 1962, 1962) [43,44,51] who showed that the two major specie of boric acid are monomeric boric acid and, with increasing concentration, its trimeric cyclic anhydride, ($B_3O_3(OH)_3$, and its anion, $B_3O_3(OH)_4^-$), or a boroxine. At even higher concentrations, a third polynuclear complex (at >0.4 M), designated $B_4O_5(OH)_4$ and $B_4O_5(OH)_5^-$ form. Ingri suggested that an even more complex species, including $B_5O_6(OH)_4^-$ and $B_5O_6(OH)_5^{2-}$ are formed, consistent with a known borate salt, ulexite (Ghose 1978). [52] Following the elegant work of Ingri (1957, 1962, 1962), [43,44,51] others have largely confirmed the findings with some differences (Mesmer 1972, Anderson 164). [10,53] Fig. 3 illustrates that even the cyclic boroxine, species, $B_3O_3(OH)_3$ and $B_3O_3(OH)_4^-$, must, on first principles, have predecessors in the linear dimeric and trimeric species. Thus, constants generated ignoring these species are approximations. Mesmer (1972) found that ignoring the linear dimer specie was probably not a good assumption. [10]

Ingri et al, (1957, 1962) [43,44,51] based their findings in careful titration studies. With the advent of high-field carbon and ^{11}B NMR studies, researchers such as Salentine (1983) and

Ishihara (1994), [48,54] were better able to map various borate species including the kinetics of dissociation of various species. Kinetics of dissociation of borate polymeric species, as expected, were concentration dependent for all the specie except for those involving the pentaborate specie to triborate (boroxine) reaction, since this would involve breakdown at the central tetravalent boron center and would not involve free boric acid/borate concentration (Salentine 1983). [54]

Insert Figure 2

While this review is focusing on boric acid, it should be noted that highly water-soluble alkyl and aryl boronic acids can undergo similar polymerization reactions and under dehydrating conditions formation of boroxines (similar to the triborate specie) is very common leading to formulation challenges (Marinaro 2012, Gupta 2004, 2005, Plamondon 2005). [36,37,55-57]

Each boric acid specie, described above have their own unique first pKa values. For example, Ingri (1957, 1962) [43,44,51] estimated the first pKa of boric acid in 0.1M $NaClO_4$ (sodium perchlorate) of 8.98 ± 0.01, while that of the cyclic triborate is 7.29 ± 0.02 and the pentaborate, 6.77 ± 0.10, respectively. Note, these values changed with ionic strength as Ingri determined slightly different values in the presence of 3M perchlorate. The drop in pKa values on association is similar to that seen for boric acid and boronic acids in dilution solution when esters form with alcohols/polyols (Marinaro 2015, Yan 2004, Lopalco 2017). [39,55,58] The increased acidity of boric acid/borax when prepared with glycerin or in the presence of many polyols has been noted as early as the mid-1800's.

Boric Acid as a Buffer

While boric acid has been used as a simple buffer for basic and applied studies, it has a few strengths and a number of limitations.

With a pKa value of around 9-9.2, depending on ionic strength and temperature conditions, boric acid filled a pH gap for which few other buffers are available until the MOPS and MES buffers (3-(N-morpholino)propanesulfonic acid and 2-(N-morpholino)ethanesulfonic acid) buffers introduced by Good et al. in the 1960s became available. [59] Thus, boric acid may be used when pH values above physiological pH conditions, in the range of 8-10, were desired.

A weakness in the use of boric as a buffer is that the pH of a boric acid buffer will change as it is diluted due to dissociation of polymeric species as already discussed. As a buffer, it has really only been used extensively pharmaceutically in ophthalmic formulations and in some dermal products. In ophthalmic formulations, its inclusion is probably more related to its use as a mild preservative, especially when used with a polyol (Chowhan 1996, 1998). [24,25]

Boric Acid is Not Inert

A major weakness, and on occasion, one might consider a strength, of boric acid in solution dosage forms, is that it is not inert. Boric acid can both accelerate and inhibit chemical reactions by reacting with various functional groups (mainly, alcohol, thiols and amines) with the $2p_Z$ orbital of the boron atom, not unlike its reaction with water and with itself i.e., its action as a Lewis acid by reacting with water and self-polymerization at higher concentrations.

Riegelman and Fischer (1962) [60,61] in the 1960s showed that boric acid buffers stabilized epinephrine to oxidation, racemization and reaction with the antioxidant, sodium bisulfite, by reacting with the catechol group of epinephrine to form a cyclic ester as illustrated in Fig.3.

Interesting work by Romanski et al., [62,63] showed that boric acid buffers inhibited the degradation of treosulfan (a prodrug) to its active epoxides by reacting with the *cis*-diol functional groups in treosulfan. Fig. 4 is a simplification of the more complex reaction scheme used by Romanski et al., needed to describe the kinetics of degradation of treosulfan as a function of pH. The half-life of treosulfan at pH 9 and 37°C in the absence of borate buffer (but in the presence of other buffers) is about 4 minutes while in the presence of 0.1 and 0.2M borate buffers, the half-lives are about 35 minutes and 50 minutes, respectively. Romanski et al., actual scheme considers the apparent complex pH dependency of the reaction both in the absence and presence of borate buffers. The scheme and their analysis does not consider, however, the possibility of self-association of boric acid/borate at concentrations greater than 0.02M. To quote Romanaski et al., "*This article provides the example that a borate buffer is "tricky" and may complicate kinetic analysis of drugs.*"

Insert Figures 3 and 4

Oxidative reactions can also be affected by boric acid. Sassetti and Fudenberg (1971) [64] studied the oxidation of alpha-methyldopa, like the earlier studies with epinephrine, to its melanin (polymer of the oxidation product of alpha-methyldopa) and found that melanin formation was inhibited by the presence of borate buffer. This was confirmed by the study of Rembischevski and Gemal later (2001). [65] Riegelman and Fischer (1962) had observed similar results in the oxidation of epinephrine. [60,61]

While the above examples show that boric acid can stabilize some agents it can also accelerate chemical reactions. Capon and Ghosh (1966) [66] found that boric acid buffers

accelerated the hydrolysis of phenyl salicylate as did Hoffman et al., (1972) for the hydrolysis of salicylideneanaline. [67]

Okuyama et al., studied the mechanism of hydrolysis of hydroxy thioesters in the presence and absence of boric acid buffers (Okuyama et al., 1981). [68] They proposed the following reaction scheme to explain their results, Fig. 5. Note, all the ionization and other equilibria were not included here. The reader is directed to the original paper (Okuyama et al., 1981) for further details. [68] The extent of the catalysis is significant. For example, at pH 9, in the presence, 0.04M borate buffer the hydrolysis of 3-hydroxy-3-phenylthiobutanoate, and absence, the hydrolysis half-lives differed by >100 fold.

This same group, and others, studied many cases where boric acid facilitated or inhibited various reactions including cases where acceleration was seen at some pH values while stabilization was seen at other pH values (Matsuda 1984, Nagamatsu 1984, Okuyama 1986, Levonis 2007). [69-72] Since boric acid can react with any alcohol, thio or amine group, one is cautioned that this reactivity can alter the physical and chemical stability (positive or negative) of any molecule in question.

Insert Figure 5

One of the more intriguing examples of boric acid buffer interactions is seen when Usayapant and Bowman (2015) formulated a freeze-dried product of bortezomib, an alkyl boronic acid, to compete with the industry leader, Velcade®. [23] Velcade® is a freeze-dried product of bortezomib formulated with mannitol where the mannitol ester is formed *in situ*. In the case of Velcade®, the formulation results in excellent chemical stability, enhanced solubility and rapid reconstitution of

the freeze-dried cake (Gupta 2004 2005). [36,37] Usayapant and Bowman (2015) achieved similar chemical stability and reconstitution times by freeze-drying bortezomib from a glycine/borate buffer composition. [23] Freeze-drying of bortezomib in the absence of polyols or borate buffer produces the very insoluble boroxine (Marinaro 2012) [55]. On reconstitution in absence of polyols or borate buffer, freezed-dried formulations reconstitute extremely slowly and the formulation is sensitive to oxidation (unpublished results). In the presence of borate buffer, Usayapant and Bowman (2015) claim that boric acid forms various mixed esters (mixed anhydrides) of bortezomib and boric acid during the freeze-drying process, preventing boroxine formation and or crystallization of bortezomib itself. [23] While one might disagree with the assignment of the mixed esters between bortezomib and boric acid illustrated in their patent, the overall effect is signficant as illustrated by the rapid reconstitution times of their freeze-dried formulation/s.

While excellent reconstitution times and stability were achieved, the presence of boric acid does not enhance the equilibrium solubility of bortezomib, thus limiting the administration of this product (Fresenius Kabi USA, LLC) to IV administration while Velcade® can be given IV and SC, because the enhanced solubility of the mannitol ester allows SC administration in a lower more patient friendly fluid volume.

Another example where the reactivity of boric acid is used to effect a change in the physical properties of a material is its ability to inhibit the crystallization of the sugar, mannitol (Yoshinari et al, 2003). [27] Yoshinari proposed that this inhibition of crystallization was due to a physical interaction between added boric acid and mannitol disrupting the crystal packing of mannitol but they probably should not have ignored boric acid chemically reacting with this polyol, presumably producing various esters, especially on freeze-drying where bimolecular

reactions would be enhanced. These ester "impurities" could also have contributed to inhibiting mannitol crystallization.

One cannot emphasize enough that boric/borate buffers are *not* inert and care show be taken in their use both in basic studies and applied formulation studies.

Interaction of Boric Acid with Alcohols and Polyols and Other Substrates

The reaction of boric acid with epinephrine, glycerin, mannitol and many of the examples already mentioned above and referenced are but a few examples of the reactivity of boric acid with 1,2-diols, catechols and polyols. A general reaction scheme used by others is shown in Fig. 6. The reaction of boric with alcohols, and especially 1,2-diols, have been noted for well over a century. Some have referenced to very early papers from 1878 by Klein (*Bull. Soc. Chim*, **29**, 195 (1878) and *Compt. Rend. Acad.* **87**, 826 (1878), which we were not able to access for verification) [73,74] who noted the increased acidity of boric acid in the presence of polyalcohols and sugars (Gilmour 1921) [75] and inhibition of glucose oxidation by borate (Levy 1928). [76] This was quantitated by Mellon and Morris in 1924 when they showed that one could titrate boric acid in the presence of various linear diols, glycerol, erythritol, mannitol and sorbitol resulting in dramatic drops in the apparent pKa value of boric acid and ester mixtures from titrations with mannitol and sorbitol. Of the non-linear sugars, the most effective were fructose and "invert sugar," a mixture of glucose and fructose. Azevedo et al., confirmed these earlier findings in a study of the acid-base titration of boric acid in the presence of increasing mannitol concentrations (Azevedo 2012). [3] While the pKa of boric acid itself was 9.2, the pKa of the mannitol ester was closer to 5, a drop in at least 4+ pKa units. This drop on pKa value was

recently explained by Lopalco et al., for the similar reaction of boronic acids with 1,2-diols (Lopalco 2018) as being largely due to electronic factors. [77]

Insert Figure 6

While most represent the interaction of boric acid as a simple 1:1 ester formation (as represented in Fig. 6), the literature is replete with both speculation and experimental evidence that support more complex structures (Azevado 2012, Steinberg 1957, Boeseken 1931, 1949, Rietjens 2005, Dawber 1988, van be Berg 1994, van Duin 1984 1985 1986, Aronoff 1975, Peters 2014, Gilmour 1921, Pizer 1977). [2-6,13-19,75,78] For example, as discussed, boric acid can polymerize. How do these higher order borates interact with 1,2-diols? In the case of poly 1,2-diols, does boric acid interact in a 1:1 interaction or are polyesters formed?

Historically, one of the most interesting references is that of Boeseken from 1949 titled "The use of boric acid for the determination of the configuration of carbohydrates" where he used the interaction of boric acid with various catechols, linear sugars such as mannitol and smaller 1,2-diol and polyols such as glycerol, ortho hydroxy aromatic acids and then sugars, like glucose, to refine thoughts at the time on the structure of sugars such as glucose, sucrose and mannose etc. in their cyclic and linear forms. [4]

Kose (2009) studied the interaction of boric acid with ascorbic acid, vitamin C, which has two diol groups in its structure and showed that the boric acid ester formed through the *cis*-enediol and minimally through the side chain diol, Fig. 6. [8]

Note, while most papers have focused on the interaction of boric acid with 1,2-diols and hydroxy and thiol carboxylic acids to form cyclic structures, boric acid will react with any

alcohol, thiol or even amine group. Aydohmus (2014) even showed that esters can even be formed between phosphate and borate linked organic molecules (Fig. 6). [79]

PHARMACOKINETICS, DISTRIBUTION, USAGE AND TOXICOLOGY

Pharmacokinetics and Distribution

The pharmacokinetic properties of boric acid have been reported after both intravenous and oral administration in animals and humans (Jansen et al.,1984; Schou, 1984). [80,82] Jansen and coworkers provide the most reliable pharmacokinetic data after intravenous administration in eight adult male subjects and the justification for these studies. They were largely driven to this study as boric acid exposure was seen after subjects were exposed to boric acid containing dermal ointments, napkin women hygiene products and the treatment of vaginal fungal infections with boric acid suppositories (Friis-Hansen 1982, Jansen 1984). [80,81,83]

Boric acid is well absorbed orally in all specie including humans and is fairly evenly distributed in all soft tissues but does show a four-fold accumulation in bone. It has a half-life of under 24 h in humans (Jansen 1984, Moseman 1994, Murry 1998) [80,81,84,85] and is excreted unchanged in the urine (>95%). An IV study in humans showed a terminal half-life of 21.0 ± 4.9 h and a Vd value of about 0.4 L/kg (Jansen et al. 1984). [80,81] Such a long half-life for an apparent fairly polar molecule with a modest Vd value is consistent with efficient renal tubule reabsorption. Elimination is delayed in persons with kidney damage or after administration of cumulative doses.

At least 92% of a single oral dose of boric acid was recovered in the urine of human volunteers [Murray 2004; WHO (World Health Organisation), International Programme on Chemical Safety, Environmental Health Criteria 204: Boron, 1998, Geneva, Switzerland]. [86-88]

Cutaneous absorption through the intact skin was negligible in all the species studied, including rats, rabbits and humans (adults and children). Very little boric acid is absorbed through intact vaginal mucosa (Swate 1974, Van Slyke 1981). [89,90] Intact horny layer provides an effective barrier to percutaneous permeation of boric acid (Dusemund 1987). [91]

No increase in the blood boron level or in the excretion of boron in urine was observed when an anhydrous water-emulsifying ointment containing 3% boric acid was applied once to the healthy skin of men. On damaged skin, systemic penetration of boric acid was demonstrated. Application of an aqueous gel containing 3% boric acid to damaged skin caused an increase in the blood boron level on the day of application and, one day later, a significant increase in boric acid excretion in the urine. Later, the urinary level had returned to normal. (Stüttgen, G., T. Siebel, B. Aggerbeck: *Arch. Derm. Res.* **272**, 21 (1982). [92]

Boric acid is distributed in body fluids and in all soft tissues but does show a four-fold accumulation in bone [WHO, 1998]. [88] High levels of boric acid which are detected in the brain, liver and adipose tissue even after urine levels have returned to control values suggest the presence of some intracellular reservoirs. A complete distribution study was conducted in male rats after administration of 68 mg of boron/kg/day for one week. The study showed that the boron concentrations (3- to 20-fold higher than those in the controls) were similar in all the tissues studied with a steady state (12–30 mg of boron/kg of tissue) being achieved in 3–4 days. It is to be noted that the bone boron concentration was higher (47.4 mg/kg of tissue) and increased throughout the study [Ku 1991; WHO, 1998]. [88,93]

Boric acid is not metabolized in man or in animals (Whiley, H.W. 1904; Pfeiffer, 1945). [94,95] Metabolism of inorganic borates by biological systems is not feasible owing to the excessive energy required to break the boron-oxygen bond (523 kJ/mol). Inorganic complex borate species,

in low concentrations, convert to boric acid at physiological pH in the aqueous layer overlying mucosal surfaces prior to absorption. This is supported by the evidence in both human and animal studies, where more than 90% of the administered dose of borate is excreted as boric acid [WHO, 1998]. [88]

In a study conducted in male rats, it was shown that the boron elimination profile from the bone compartment was different from that for plasma or soft tissue. Intake ranging from 1.4 to 6.8 mg of boron/kg/day for 9 weeks resulted in a dose-dependent increase in the bone boron concentration. The concentration fell off gradually post-treatment and remained higher than that measured in the controls at week 32 post-treatment discontinuation [WHO, 1998, Chapin 1997]. [88,96]

In conclusion, the pharmacokinetic data show that boric acid is very well absorbed following oral administration. Absorption by the cutaneous route is negligible if the skin is intact but significant when applied to damaged skin, particularly in babies. In the body, boric acid is distributed via body fluids, not metabolized and excreted (over 90% of an administered dose) in the urine, independently of the administration route. A summary of its characteristics is reported in Table 3.

Insert Table 3

USAGE AND TOXICOLOGY

In preparing this section of the review on boric acid, we the authors, find ourselves conflicted by the fact that the literature on the medical use of boric acid/borates and their safety contains widely differing opinions on both issues.

Lister in the 1875 is said to have been the first to suggest boric acid/borates as antiseptics and much of their use today still stems from this early history. Yet, Watson in 1945 wrote a paper in the Journal of the American Medical Association (Vol 129, 332-333) entitled "Boric Acid: A Dangerous Drug of Little Value." Thus conflicting reports are not new.

While more modern literature suggests that low to moderate exposure to boric acid/borates is quite safe, Baker and Wilson[122], also in a JAMA paper, point out the lethal toxicity of a 1% solution applied to the skin of a 14 year-old burn patient.

If the reader of this review is left confused on the issue of efficacy and safety of boric acid and its borates, it is recommended that the primary references used here, and others not recited, be consulted

Medicinal Usage

Boric acid is still used widely for both medical and non-medical. Hence, its safety in human depends on the amount that comes in contact intentionally or not and depends on the amount of boron present in the compounds (table 4).

Insert Table 4

Medicinally, boric acid is most commonly present as a tonicity-adjustment agent, buffer, and preservative enhancer in many ophthalmic products. The choice of the appropriate borate-buffer is based on experience. Aqueous solutions of boric acid are also prepared for ophthalmic irrigation to rinse, refresh, and calm irritated eyes and for removal of loose foreign material, air

pollutants (e.g., smog, pollen), or chlorinated water (American Society of Health-System Pharmacists 2011; Drug Information 2011; (EMA report Overview of comments received on the draft 'Questions and answers on boric acid' (EMA/CHMP/619104/2013)). [97-99]

Boric acid and borax have been described as having a "feeble" bacteriostatic action. Their use in ophthalmic preparations is said to enhance the activity of primary preservatives in the formulation by broadening their preservative spectrum. In a series of patents, claims that the presence of 1,2-diols and polyols, especially *D*-mannitol, enhance the antibacterial activity of boric acid in ophthalmic formulations have been made (Kabra, B.P., Jani, R. AQUEOUS PHARMACEUTICAL COMPOSITIONS CONTAINING BORATE-POLYOL COMPLEXES, EP 2 254 549 B1, 2019). [26]

Boric acid in the absence of polyols is largely present in its acidic form (pKa of about 9) in most ophthalmic formulations, while the pKa of a boric acid/polyol ester is closer to 5, meaning that borate species primarily exist around neutral to slightly acidic pH values in the presence of polyols. In medical devices such as in contact lens solutions, boric acid is employed as preservative or preservative enhancer. (Murray, L. 2004) [86,87]

Boric acid, borates and perborates have been used as mild antiseptics or bacteriostats in mouthwashes, burn dressings, and diaper rash powders. However, the effectiveness of boric acid has been brought into question. (Seiler, H.G. 1988) [100] Similarly, they are used in veterinary products as antibacterial and antifungal agents, chiefly in aqueous solutions or powders for external application.

A 3% boric acid solution when applied to deep wounds reduced the time required in intensive care by two-thirds and are said to greatly improve wound healing (Blech MF, Martin C, Borrelly J, Hartemann P. Treatment of deep wounds with loss of tissue: value of a 3 percent

boric acid solution [in French]. Presse Med. 1990;19(22):1050-1052). Yet, Watson in 1945(REF) and Baker and Wilson[122] as well as others have shown that application of such boric acid solutions can be lethal. A 10-12% solution of borax in glycerin, is still sold today for the treatment of various skin maladies (ref), and it has historically been used since the 1800s and has been reported in British Pharmaceutical Codex since 1959 (ref).

Boric acid/borax is found in some women hygiene products and vaginal suppositories for treating fungal infections and vulvovaginal candidiasis albicans. In a study by van Slyke KK et al, after 14 daily intravaginal gelatin capsules containing 600 mg of boric acid powder the cure rates were 92% at 7 to 10 days after treatment and 72% at 30 days. The drug alleviated quickly the signs and symptoms and there were no untoward side effects, and cervical cytologic features were not affected. (Van Slyke KK et al. 1981) [30]

In the past, the boric acid/borates were included in rectal suppositories to treat hemorrhoids (Gilman et al., 1980). [101]

Some have even claimed that boric acid can be preventive and have therapeutic effects in a number of cancers, such as prostate, cervical, and lung cancers and multiple and non-Hodgkin's lymphoma, and may help ameliorate the adverse effects of traditional chemotherapeutic agents. (Pizzorno L., Nothing Boring About Boron, 2015). [102]

Boron Neutron Capture Therapy (BNCT) is used to treat brain, head and neck cancers. The source of the boron atom is only important in BNCT treatment if one wants to have the boron specie accumulate in the tissue undergoing the radiation. That is, it would provide selectivity. With boric acid having an affinity for bone, Hsu et al., looked at the potential of using boric acid and BNCT treatment of osteosarcoma. One hour following IV boric acid, blood levels dropped rapidly and while those in bone were 4-6 times higher compared to blood levels suggesting to the

authors the possibility of boric acid as a boron source for BNCT treatment of osteosarcoma. (Hsu 2011) [30]

In vivo and *in vitro* studies indicate that boric acid has a strong affinity for cis-hydroxy groups. This may explain the higher concentrations of boric acid in bone owing to binding to the cis-hydroxy groups of hydroxyapatite and this may be the mechanism that explains the biological effects, bone affinity, of boric acid. (Murray J. 1998) [85]

Boric acid and some boron compounds have been used as a boron source for some *in vitro* and *in vivo* studies. The results showed that boron effects induced mineralization of osteoblasts, beneficially impacted the body's use of estrogen, testosterone, and vitamin D, significantly improved magnesium absorption and deposition in bone. In a recent human trial, a significant increase in concentrations of plasma boron after supplementation with 102.6 mg sodium tetra borate decahydrate, was coupled with decreased levels of the inflammatory biomarkers (Naghii, 2011) [103] and raised levels of antioxidant enzymes (Pizzorno L., Nothing Boring About Boron, 2015). [102]

Non-medicinal use

Boric acid is found in many products, including fiberglass insulation, ceramics, and glass products, flame retardants, pesticides, fertilizers, household cleaning agents, toiletries, food (as a preservative) and food packaging. (Schubert D; Kirk-Othmer Encyclopedia of Chemical Technology. (1999-2011). New York, NY: John Wiley & Sons; Boron Oxides, Boric Acid, and Borates. Online Posting Date: 15 April 2011][O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, D) [104,105]

These products are applied in aquatic, outdoor and indoor sites. Based on the use patterns, the potential for dermal and inhalation exposure exists. (USEPA/Office of Pesticide Programs;

Reregistration Eligibility Decision Document - Boric acid and its Sodium Salts p.28 (February 1994)) [106] In addition to consumer product exposure, dietary exposure will occur through consumption of food and drinking water. Dietary intake has been estimated to be in the range 0.5-3 mg/B/day (Ramey et al 2002). [107] In January 2001, The U.S. Food and Nutrition Board (FNB), while not suggesting that boron is essential for humans, accepted the nutritional importance for boron and determined a safe Tolerable Upper Intake level, of 20 mg of boron/day. ref

Sodium borate and boric acid have been also widely used in numerous cosmetic products, including makeup, skin and hair care preparations, deodorants, moisturizing creams, breath fresheners, and shaving creams, with concentrations up to 5%. (WHO Environmental Health Criteria Document No. 204 (1998): Boron (7740-42-8) p.49) [88]

In May of 2019 the Official Journal of the European Union published a regulatory update, Regulation 831/2019 (or Omnibus Act), 1 2 (Commission Regulation (EU) 2019/831 amending Annexes II, III and V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products May 2019) of Regulation (EC) No 1223/2009 with very important implications about the use of boric acid evaluated as mutagenic for reproduction (CMR) from Regulation (EC) No 1272/2008 (Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixture GHS/CPL). [108] Under this new Regulations, boric acid was deleted from the list of restricted substances in Annex III to that Regulation and added to the list of substances prohibited in cosmetic products in Annex II. In accordance with the second subparagraph of Article 15(2) of Regulation (EC) No 1223/2009, substances classified as CMR substances of category 1A or 1B may be used in cosmetic products by way of exception where, subsequent to

their classification as CMR substances, certain conditions are fulfilled. In 2013, the Scientific Committee on Consumer Safety (SCCS) issued an opinion (SCCS/1523/13 OPINION ON the safety of boron compounds in cosmetic products) [109] which concluded that some of the boron compounds currently listed in entries 1a and 1b of Annex III to that Regulation are safe for use in cosmetics under certain conditions. However, since no application for a particular use was made and since it has not been established that there are no suitable alternative substances available for the purpose of the relevant uses listed in Annex III to Regulation (EC) No 1223/2009, those boron compounds were deleted from the list of restricted substances in Annex III to that Regulation and added to the list of substances prohibited in cosmetic products in Annex II to Regulation (EC) No 1223/2009.

Boric acid toxicity

The toxicology of boric acid would suggest that it is minimally to mildly toxic in low amounts: LD50 oral rat > 2000mg/kg (Wheir and Fisher 1972; Pfeiffer et al 1945); LD50 dermal rat > 2000 mg /kg (Reagan and Becci 1985 b, c); LD 50 inhalation rat > 2 mg/L (Wnorowski 1994 a, b, c). [94,110-115]

However, a few deaths and not insignificant acute toxicity in both adults and children exposed to high doses have been reported (Corradi 2010, Dourson 1998, Egfjord 1988, Murray 1995, Hubbard 1998, Ishii 1993, Locatelli 1987, Baker 1986, Baker 1963, Watson 1945, Valdes-Dapena 1962, Farfan-Garcia 2016, Hjelm 2019, Stangoulis 1957, Yazbeck 2005). [85,116-129,] Few human control studies have been conducted to directly assess health effects associated with exposure to boric acid. The available data does show that exposure is associated with short-term and reversible irritant effects on the upper respiratory tract, nasopharynx, and eye. High dose exposure can be treated with peritoneal dialysis. Boric acid and sodium tetraborates are not skin

and eye irritants (Reagan and Becci 1989 e, f). [130,131] The initial irritation seen with sodium tetraborates can be attributed to the abrasive nature of crystals (Reagan and Becci 1989 f). [131] No borate tested has displayed skin sensitization in Bheuler studies (Wnorowsky 1994 d, e, f). [132-133] There is no evidence of skin sensitization seen in human exposed occupationally to sodium borate, or in a human patch test with a 3% aqueous boric acid solution (Bruze et al. 1995). [134] Dermal absorption of borate across intact skin is insignificant in all species evalueted, including human newborn infants (Friis-Hansen et al. 1982), [83] adult humans (Beyer et al. 1983, Wester et al. 1998) [135,136] rabbits (Draize and Kelly 1959) [137] and rats (Nielsem 1970). [138] Borate have been demonstrated to penetrate damaged or abraded skin (Draize and Kelly 1959). [137] However, the use of ointment-based vehicle may prevent or reduced the absorbtion compared to an aqueous jelly based vehicle (Stuttgen et al. 1982, Nielsen 1970). [92,138] A study conducted on human volunteers about skin rate absorption is shown in table 5 (Hui et al 1996, Wester et al 1998) [136,139]

Insert Table 5

Unwanted dermatologic effects are more common after chronic or subacute exposures. Skin changes may develop after boric acid ingestion or application of boric acid powder. Erythema and desquamation occurs in 1 to 2 days. Exfoliation that is generalized or localized to the hands, feet or face may occur and has been termed the boiled lobster syndrome. Erythema may be prominent on the buttocks and scrotum. [Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 1322] [140] Application of boric acid powder for diaper rash /produced/ severe erythema of the skin, gastrointestinal symptoms and

deaths in infants. [Goldbloom RB, Goldbloom A; J Pediat 43: 631-43 (1953) as cited in Baselt RC; Biological Monitoring Methods for Industrial Chemicals p. 50 (1980). [141] Long-term chronic exposure to boric acid results in alopecia in adults and seizures have been reported in children. A 32 year old woman who chronically ingested mouthwash containing boric acid over a 7 month period developed progressive hair loss. [Goldfrank, L.R. (ed). Goldfrank's Toxicologic Emergencies. 7th Edition McGraw-Hill New York, New York 2002., p. 1289 [142]

Boric acid has been classified in the reproductive toxicity category 1B H360 (may damage fertility or the unborn child) by the Globally Hazard System. A number of studies in which rats were fed boric acid or disodium tetraborate decahydrate in their diet or drinking for a period of 70-90 days indicated that the main target organ for toxicity is the testis (Wheir and Fisher 1972; NTP 1987). [107,143] These effects are discussed following about carcinogenity and toxicity reproduction. Even though carcinogenicity studies are not conducted with modern standard or in Good Laboratories Practice, they are well performed and reported and more adequate to evaluate the carcinogenicity. It can be concluded that boric acid is not carcinogenic and there is no concern for a carcinogenic effects in humans (Wheir and Fisher 1972; NTP 1987). [107,143]

Effects on the testis have been observed in both sub-chronic and chronic studies in three species: rats, mice and limited dogs, In rats, a singular dose of 175 mg B/Kg, where B/Kg refers to equivalent elemental boron (B) per kilogram body weight, was to cause reversible disruption of tubular sperm formation (Linder et al. 1990), [144] although no such effect were observed after a single dose of 350 mg B/Kg (2000 mg boric acid/Kg) (Boissou and Castagnol 1965), [145] A

comparison of NOELs (No Observed Effect Level) and LOAELs (Lowest Observed Adverse Effect Level) from reproduction studies are shown in Table 6.

Insert Table 6

For developmental toxicity, only boric acid has been tested in animals. Effects were observed at high doses in rats, mice and rabbits. The most sensitive species appears to be rats, in which the effects observed at not maternally toxic doses include a reduction in fetal body weight and minor skeleton variations. The NOAEL for developmental effect is 9.6 mg/B/Kg (Table 7). A number of *in vitro* and *in vivo* mutagenicity studies have been carried out and have concluded that there is no evidence of mutagenic activity for boric acid/borate species. (NTP 1987, Bakke 1991, O'Loughlin 1991) [143,153,154]

Insert Table 7

A number of studies have been carried out in Turkey on workers exposed chronically to borate species in mining operations (Sayli 2003, Duydu 2011, 2012, 2015) and elsewhere (Culver 1994). [154-158] The claim is that workers exposed to boron species show little to no untoward negative effects including drops in sperm counts and reproductive effects that were seen in animal studies.

In one study, Robbins and coworkers (REF) showed that no significant correlations were found between blood or urine boron and adverse semen parameters for workers from high and low environmental boron areas.

Moreover, there have been some epidemiology studies in Turkey comparing family birth rates in boron rich areas with those in lower-boron areas. Some village drinking waters are reported with boron levels as high as 29 ppm boron. No evidence of reproductive toxicity was found in this population. [Krieger, R. (ed.). Handbook of Pesticide Toxicology. Volume 2, 2nd ed. 2001. Academic Press, San Diego, California., p. 1433] [159]

In a separate study, low sperm counts, reduced sperm motility and elevated fructose content of seminal fluids were observed on occupational exposure (10 years or greater) to boron aerosols (22-80 mg/cubic meter) in males engaged in the production of boric acids. ([DHHS/ATSDR; Toxicological Profile for Boron (PB/93/110674/AS) (July 1992). Available from, as of April 25, 2005) [160]

Data regarding developmental and reproductive toxicity showed that the effects on fetal body weight in rat and mouse is mixed. As dose level increased, effects were seen on the bones and testicles in the rat. Increased fetal cardiovascular malformations in the rabbit, testicular atrophy, sterility and lower body weight in the rat are also observed (EMA 2017 Boric acid and borate used as excipients, Heindel J.J. 1994). [1,151] Animal studies on mice and rats showed no evidence of carcinogenicity of boric acid (Weir, R.J. 1972, National Toxicology Program 1987, Boyland E. 1966). [143,151,161] Based on the lack of human data and the limited animal data, boron is not classifiable as to its human carcinogenicity.

Ester formation with riboflavin (vitamin B2), a poly hydroxy compound, seems to play an important part in boric acid intoxication, the mechanism of which is still unknown. The increased excretion of riboflavin in the form of reversibly stable and water-soluble boric acid ester can lead to its deficiency with development of symptoms of intoxication. In experiments with volunteers,

a significant increase in riboflavin excretion in human urine was seen only after administration of oral doses of more than 3 g boric acid (Pinto 1978). [162]

The replacement of intracellular phosphorus with boron in brain tissue has been suggested as a mechanism for the central nervous system effects or boric acid exposure. Analysis of brain tissue from dogs which had been injected with boric acid yielded high levels of boron in the solvent extract but no phosphorus. Moreover, this study described an increase in excretion of phosphate in the urine while the phosphate level in plasma remained constant after intravenous injection of boric acid into dogs. (Pfeiffer 1945) [94]

A large number of studies have described the interaction of borate with numerous enzymes. The effects of boric acid on enzyme activity are ascribed to the formation of complexes with nucleotide triphosphates and monophosphates. (Weser, U., 1968, Kaneshima et al. 1968, Johnson and Smith 1976, Krasovskii et al. 1976) [163,164,165,166]

A 2% solution of boric acid has the same osmotic pressure as the plasma (when determined by a cryoscopic method), so it is isosmotic with the content of red blood cells, although, since boric acid readily crosses cell membranes, this solution causes a rapid hemolysis.

In November 2019, the European Medicines Agency published an Annex to the European Commission guideline on excipients in the labelling and package leaflet for medicinal products for human use. It includes appropriate information in the package leaflet of boron-containing medicinal products especially for the most sensitive populations (pregnant women and children, see Table 8). The most important effect observed in the toxicological studies is considered developmental toxicity in animal models. The Permitted Daily Exposure (PDE) was calculated for adult patients taking into account the minimal risk level determined by the Agency for Toxic Substances and Disease Registry for boron based on developmental toxicity in rodents. Since

infants and children may be exposed to medicinal products containing boric acid or borates, PDE values were derived for this population by extrapolating from the adult PDE on a body surface area basis. Overall, the PDE for boron compounds, including boric acid, is set at 1, 3, 7, and 10 mg of B/day for patients aged 0–2, 2–12, 12–18, and >18 years, respectively (Table 8). (EMA, 2019) [167]

Table 8. Proposal for new information on boric acid and borates in the package leaflet.

Name	**Updated on**	**Route of Administration**	**Threshold**	**Information for the Package Leaflet**	**Comments**
Boric acid (and borates)	09/10/2017	All	1 mg B/day*	Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future.	* 1 mg B (Boron) = 5.7 mg boric acid. See Q&A document (EMA/CHMP/619104/2013) for further calculations. Amount of boron per age group which may impair fertility if exceeded: Age Safety limit < 2 years 1 mg B/day < 12 years 3 mg B/day < 18 years** 7 mg B/day ≥ 18 years** 10 mg B/day ** This amount may also cause harm to the unborn child.
Boric acid (and borates)	09/10/2017	All	3 mg B/day*	Do not give to a child less than 12 years old as this medicine contains boron and may impair fertility in the future.	See comments above.
Boric acid (and borates)	09/10/2017	All	7 mg B/day*	Do not give to a child less than 18 years old as this medicine contains boron and may impair fertility in the future. If you are pregnant, talk to your	See comments above.

				doctor before taking this medicine as it contains boron which may be harmful to your baby.	
Organic mercury compounds e.g.: Phenylmercuric borate		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis) and discolouration.	
Organic mercury compounds e.g.: Phenylmercuric borate		Parenteral	Zero	This medicinal product contains (thiomersal) as a preservative and it is possible that may experience an allergic reaction. Tell your doctor if have/has any known allergies.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99
Organic mercury compounds e.g.: Phenylmercuric borate		Parenteral	Zero	Tell your doctor if you/your child have/has experienced any health problems after previous administration of a vaccine.	Additional statement to be mentioned for vaccines.

CONCLUSION

This review has attempted to provide insight into the physicochemical and biological properties of boric and its borates to help formulators understand their reactivity, strengths and weaknesses as an excipient, a medicinal agent, as well as their safety. While some of the references appear to provide conflicting conclusions about the efficacy and safety of boric acid and its borates as a medicinal agent, a reasonable conclusion is that boric acid and its borates have some modest activity as a preservative, preservative enhancer, antibacterial and antifungal agents. Boric acid and borates appear to be reasonably safe in adults if exposure is low and even higher workplace exposure appears to not cause major health issues. Exposure of babies and very young children to accidental high doses of boric acid/borates can, however, be fatal.

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TABLES

Table 1. Some reported pKa values of boric acid.

pKa	Temperature, °C	Ionic strength	Molar conc	Reference
9.184	25	0.02(?)	0.01 (as borax)	Bates
9.241	25	0.02 (?)	0.01 (as borax)	Manov
9.522	0	0.02 (?)	0.01 (as borax)	Manov
9.134	40	0.02 (?)	0.01 (as borax)	Manov
9.20	RT	NC	0.00132	Najib
9.20	RT	NC	0.05	Azevedo
8.92	25	seawater	0.002	Dickson
9.237	25		As borax	Owen
8.98	25	0.1	<0.02	Ingri

Table 2. Data from Owen (1935) and Dickson (1990) showing the effect of temperature on the pKa (rounded to two decimal places) of boric acid.

Temperature °C	pKa Owen (1935)	pKa Dickson (1990)
0		9.20
5	9.44	9.14
10	9.38	9.07
15	9.33	9.02
20	9.28	8.96
25	9.24	8.92
30	9.20	8.87
35	9.16	8.83
40	9.13	8.79
45		8.74

Table 3. Summary of pharmacokinetics of inorganic borate in rats and humans.

Absorption	Readily absorbed orally and by inhalation (of respirable particles) No dermal absorption except through severely damaged skin
Distribution	Rapidly distributed through body water Some accumulation in bone has been observed
Metabolism	Not metabolized Exists mainly as boric acid in whole blood and urine
Excretion	Excreted almost exclusively in the urine Half-life < 24 hours, approximately 21 hours Renal clearance is approximately three times faster in rats than humans based on a body weight comparison

Table 4. Compounds, molecular formula and conversion factor for the equivalent dose of the element, boron.

Compound	**Molecular Formula**	**Conversion factor for equivalent dose of boron**
Boric acid	H_3BO_3	0.1748
Disodium tetraborate decahydrate	$Na_2B_4O_7 \cdot 10H_2O$	0.1134
Disodium tetraborate pentahydrate	$Na_2B_4O_7 \cdot 5H_2O$	0.1484

Table 5. Percentage dose absorberd, rate of absorption and permeability constant from a 5% boric acid preparation through intact skin after its application to human volunteers.

	% Dose Absorbed ± SD	Rate of Absorption Flux $\mu g/cm^2/hr$	Permeability constant cm/hr
Boric acid (5%)	0.226 ± 0.125	0.009	1.9×10^{-7}

Table 6. Comparison of NOAELs and LOAELs for reproductive effects in rats, mouse and dogs after dietary exposure to borate

.

Species	Study type or duration	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 spermination	(Ku et al. 1993) [93]
Rat	3-generation dietary and 2year dietary study	17.5	58.5	Testicular atrophy; reduced fertility	(Weir and Fisher 1972) [107]
Mouse	Continuous breeding dietary study	27	111	Reduced fertility	(Fail et al. 1991) [146]
Dog	2 year dietary study	10.2	39.4	Testicular atrophy (also present in control animals)	(Weir 1966 a, b) [147,148]

Table 7. NOAELs and LOAELs on developmental effects.

Species	Maternal NOAEL mg(B)/Kg/day	NOEL mg(B)/Kg/day	LOAEL mg(B)/Kg/day	Effect	Reference
Rat	13.7	9.6	13.7	Decreased foetal body weight, minor skeletal variations	(Price et al. 1990, 1996) [149,150]
Mouse	No NOAEL	43	79	Maternal toxicity, decreased foetal body weight, minor skeletal variations	(Heindel et al. 1992) [151]
Rabbit	21.8	21.8	43.5	Maternal toxicity, resorptions, visceral malformations (cardiovascular defects)	(Price et al, 1991)[152]

FIGURES

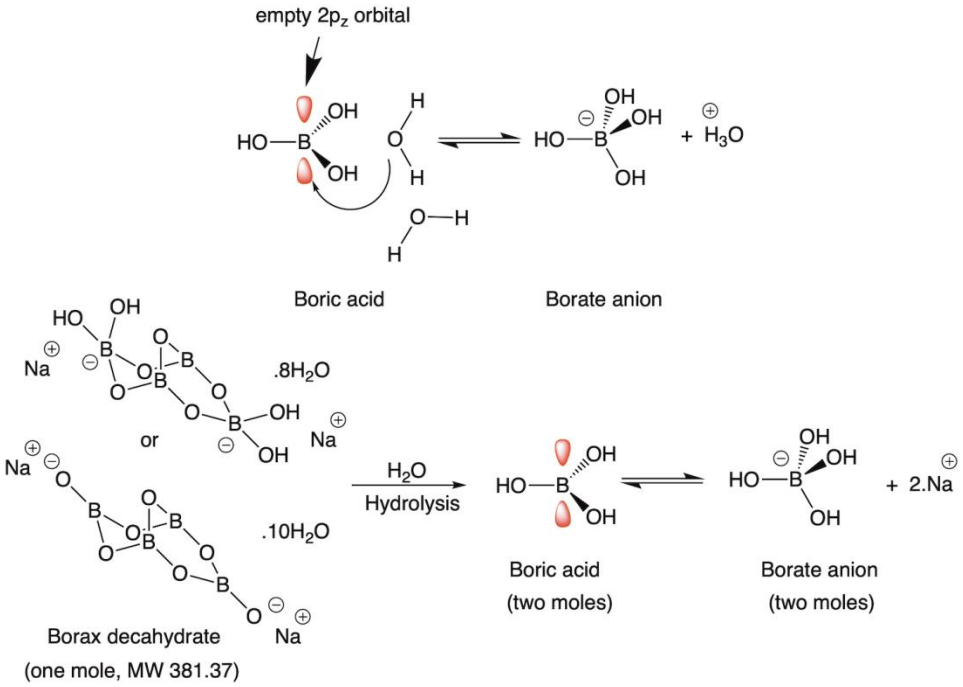

Figure 1. Ionization scheme of boric acid, as a Lewis acid in dilute aqueous solution assuming only monomeric boric acid/borate species present, and the structure and dissociation/hydrolysis of one mole of borax decahydrate (or octahydrate) to two moles of boric acid and two moles mono-borate when dissolved in water.

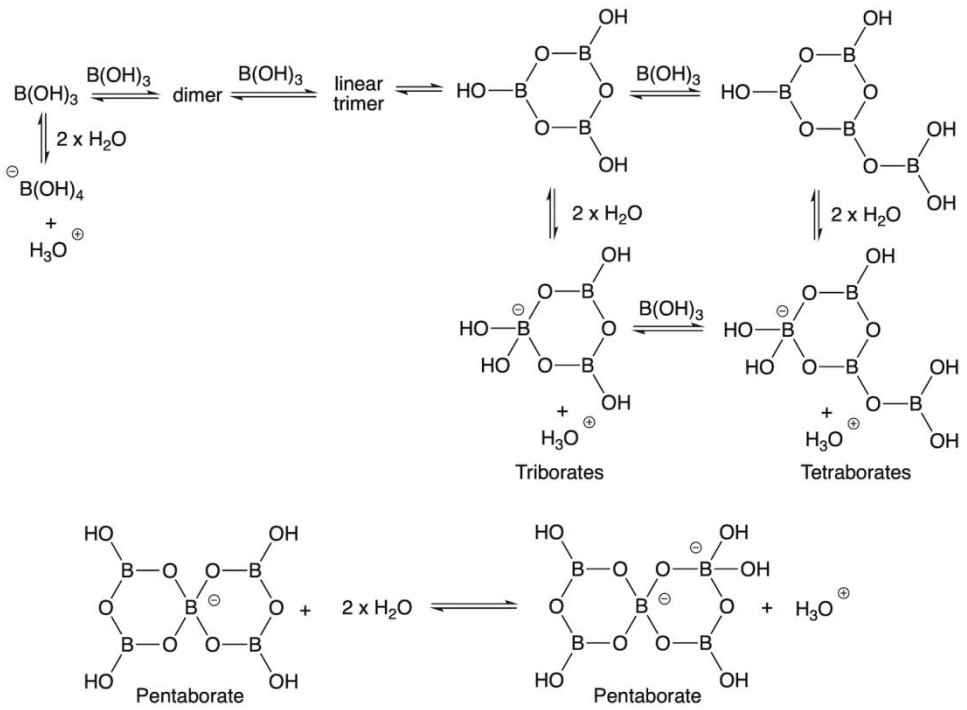

Figure 2. Scheme showing the major species associated with the self-association/polymerization of boric acid/borate with increasing aqueous solutions of greater than 0.02M as described by Ingri and others (refs).

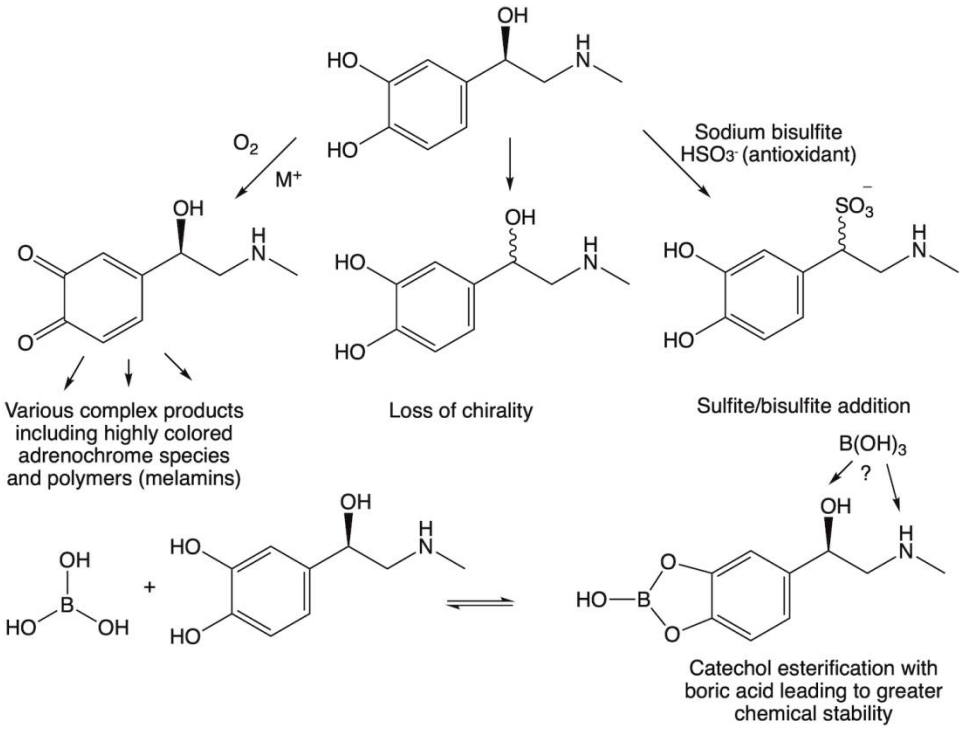

Figure 3. Chemical structures and reactions between epinephrine and boric acid proposed by Riegelman and Fischer (1962a, 1962b) to describe the stabilization of epinephrine by boric acid to oxidation, and reaction with bisulfite.

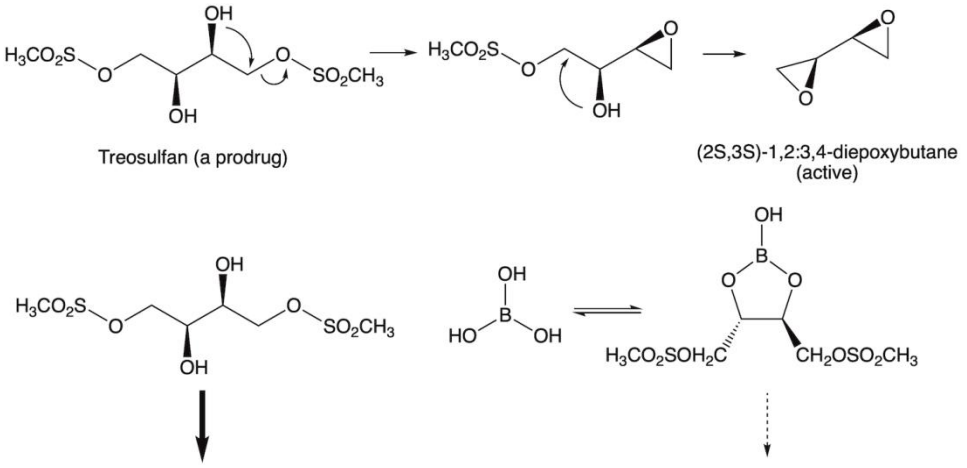

Figure 4. Structure and reactivity of treosufan and its reaction with boric acid resulting in its stabilization at pH values >8 as demonstrated by Romanski et al., (2015, 2017).

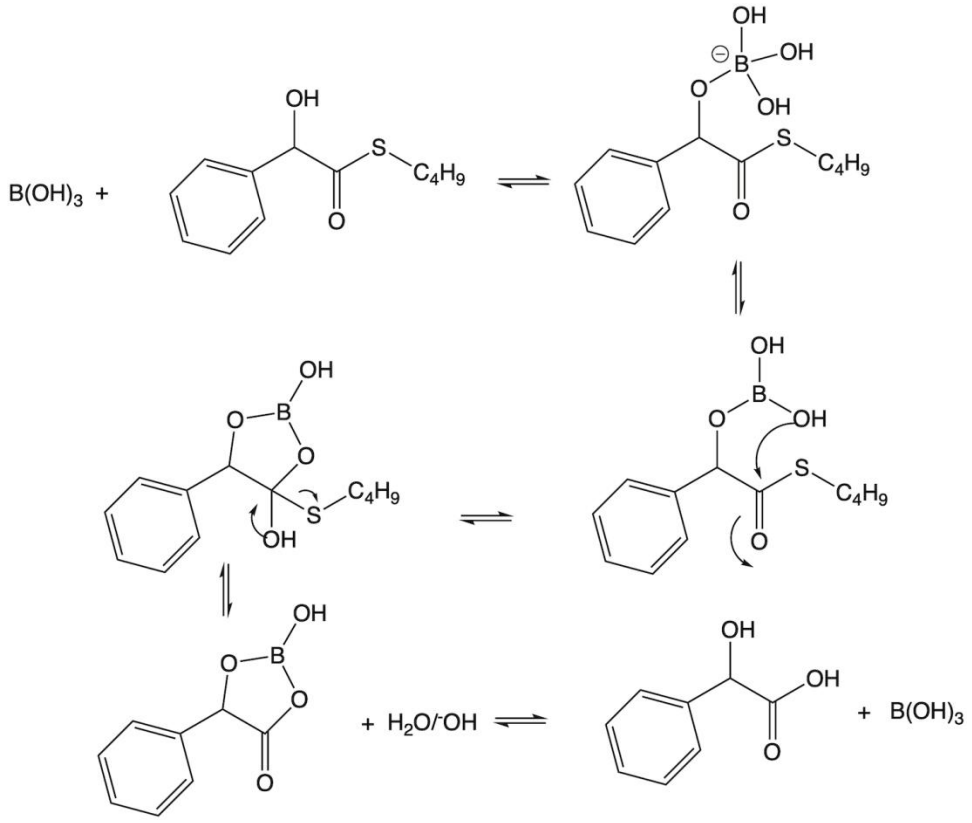

Figure 5. Modification of the reaction scheme proposed for the acceleration of the degradation of 3-hydroxy-3-phenylthiobutanoate in the presence of borate buffer as reported by Okuyama et al., (1981).

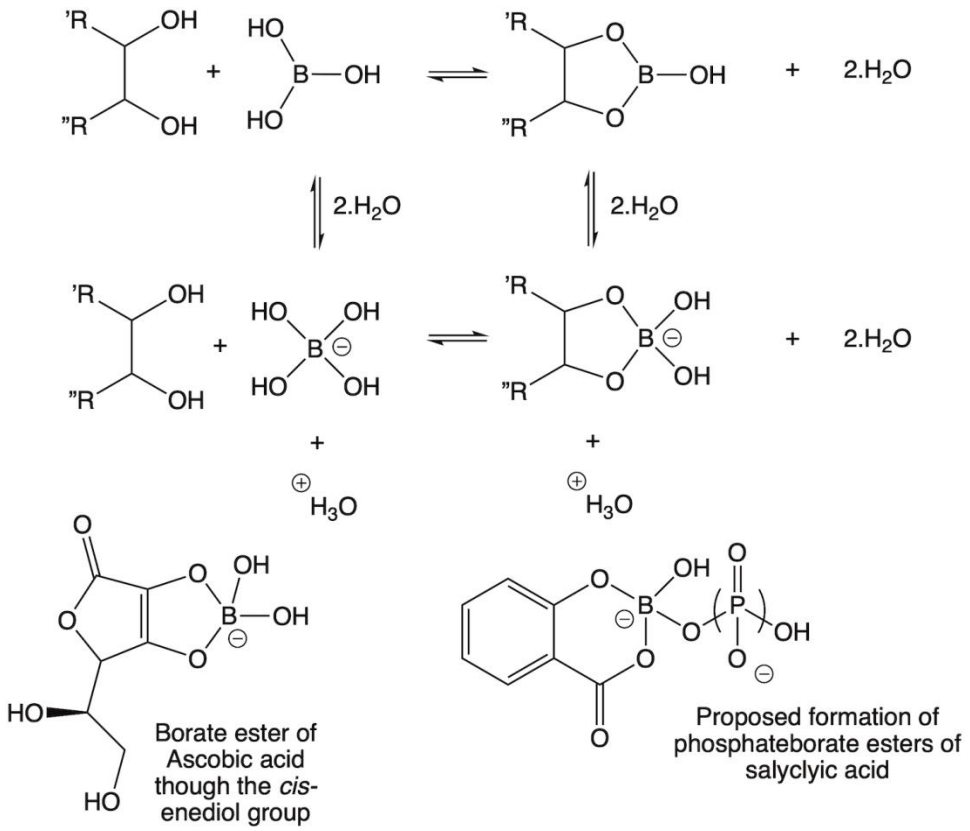

Figure 6. General reaction scheme for cyclic mono-ester formation between a 1,2-diol and boric acid, the primary borate ester initially formed between ascorbic acid and boric acid (Kose 2009), and the proposed structure of the interaction of the hydroxy acid, salicylic acid, boric acid and phosphate (Aydogmus 2014).