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Final Report on the Safety Assessment of Sodium Borate and Boric Acid

Sodium Borate and Boric Acid are used in cosmetics as preservatives, antiseptics, water softeners, pH adjusters, emulsifiers, neutralizers, stabilizers, buffers, or viscosifiers.

Investigators have reported that Sodium Borate and Boric Acid are poorly absorbed through intact skin; however, both compounds are absorbed through abraded, denuded, or burned skin. In a 90-day dermal toxicity study, Boric Acid (25–200 mg/kg/day) was nonirritating and nontoxic when applied to the intact skin of rabbits. Sodium Borate and Boric Acid were relatively nontoxic when tested orally in animals.

A 5% Sodium Borate in water solution was mildly or moderately irritating to the skin of rabbits and guinea pigs, and practically nonirritating when instilled in rabbits' eyes. Acute studies indicated that, at 10% in water, Boric Acid was mildly or moderately irritating to the skin of rabbits and guinea pigs.

Sodium Borate or Boric Acid in the diet of rabbits and rats caused growth retardation. Doses of up to 1.06 g/kg/day Sodium Borate in the diet of male rats exerted toxic effects on the gonads as well as infertility.

Boric Acid was nonmutagenic in the Ames test. Boric Acid induced reduced eye phenocopies and lumpy chromosomal inclusions in *Drosophila melanogaster*. Limited carcinogenic and teratogenic studies did not indicate a statistically significant effect.

In clinical studies, cosmetic formulations containing up to 3.2% Sodium Borate were nonirritating to moderately irritating and nonsensitizing when applied to human skin. Formulations containing up to 2.4% Boric Acid were moderately irritating and practically nonirritating. Photopatch testing of formulations containing 1.1% or 1.7% Sodium Borate were negative.

Based on the increased absorption of Boric Acid by damaged skin as compared to intact skin, as well as the testicular atrophy observed in experimental animals, the Panel concluded that Sodium Borate and Boric Acid, in concentrations $\leq 5\%$, are safe as cosmetic ingredients when used as currently recommended; however, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant or injured skin.

INTRODUCTION

This analysis of Sodium Borate and Boric Acid reviews and supplements the information contained in the Food and Drug Administration's (FDA) *Monograph on Borax, Boric Acid, and Borates.*[1] The monograph summarizes much of the scientific literature on these ingredients published from 1920 to 1978. This analysis includes selected references from the FDA monograph, important documents relevant to cosmetic use and safety dated prior to 1978 but not included in the FDA monograph, and published and unpublished data from 1978 to 1981. Some of the scientific literature provides information on methods and results in boron equivalents of Sodium Borate and Boric Acid. These values are included and, for convenience in comparison of different studies, boron equivalents have also been converted to Sodium Borate and Boric Acid values.

CHEMISTRY

Boric Acid (CAS No. 10043-35-3) is an inorganic acid that conforms to the formula, H_3BO_3. It is also called boracic acid and orthoboric acid. Sodium Borate (CAS No. 1303-96-4) is an inorganic salt that conforms to the formula, $Na_2B_4O_7 \cdot 10H_2O$. It is also called borax and sodium tetraborate.[2] Sodium Borate occurs in pentahydrate and anhydrous forms as well as the decahydrate form.[1,3] The decahydrate is the Sodium Borate that appears in the FDA product formulation computer printout[4] and the use of the name, Sodium Borate, in the chemistry section of this report refers to the decahydrate. In references appearing in other sections of this report the specific Sodium Borate has not usually been identified.

Boric Acid occurs as colorless, odorless, transparent, triclinic crystals or white granules or powder that is slightly oily to the touch. It has a molecular weight of 61.84 and a specific gravity of 1.435. A 0.1 *M* solution of Boric Acid has a pH of 5.1. Boric Acid is stable in air but volatile in steam without decomposition. Its melting point is approximately 171°C when heated in a closed space. With continued heating and higher temperatures, Boric Acid loses water in stages. It becomes metaboric acid, HBO_2, and then pyroboric acid, $H_2B_4O_7$, followed by the oxide, B_2O_3. Boric Acid is soluble in hot and cold water, alcohol, and glycerin. Its solubility in water is increased by citric, hydrochloric, and tartaric acids. It is slightly soluble in acetone and not very soluble in ether.[1,5-8]

Sodium Borate occurs colorless to white, hard, odorless, monoclinic crystals or powder. It is efflorescent in dry air and crystals are often coated with white powder. It has a molecular weight of 381.37 and a specific gravity of 1.73. An aqueous solution of Sodium Borate has a pH of approximately 9.5. When heated rapidly, Sodium Borate has a melting point of 75°C. It becomes anhydrous at 320°C. Sodium Borate is soluble in hot and cold water, and glycerin. It is very slightly soluble in alcohol and is insoluble in acid.[1,5-8]

Zittle[9] has reviewed the reactions of borate with simple polyhydroxyl compounds, polysaccharides, vitamins, enzymes, and viruses. He suggested that the toxic effects of large doses of borate on animals may be explained by the fact that

many biological compounds contain hydroxyl groups in positions favorable for reaction with borate.

Boric Acid occurs naturally as the mineral, sassolite, or may be obtained by acidification of borate minerals, such as kernite, ulexite, colemanite, or tincal. It may be derived by adding hydrochloric or sulfuric acid to a Sodium Borate solution and crystallizing the solution. Boric Acid may be extracted from weak Sodium Borate brines with a kerosine solution of a chelating agent. Borates are stripped from the chelate by sulfuric acid. Boric Acid is purified by recrystallization.[1,6,8] For use in cosmetics, Boric Acid may contain a maximum of 2 ppm arsenic and 20 ppm lead.[5]

Sodium Borate occurs naturally as the mineral, tincal, or may be obtained by treating other minerals, such as kernite, ulexite, and colemanite. It may also be obtained by fractional crystallization of brine containing Sodium Borate. It is purified by recrystallization.[1,6] For use in cosmetics, Sodium Borate may contain a maximum of 3 ppm arsenic and 20 ppm lead.[5]

Qualitative and quantitative determinations of Boric Acid and Sodium Borate may be made by colorimetric procedures,[10-15] atomic absorption spectrophotometry,[16,17] paper chromatography,[18] a flame test,[19] a tumeric paper test,[10] the tumeric paper test after ionophoresis, and titrimetric analysis.[3,11] Positive identification of Boric Acid and Sodium Borate may be made by comparison with published infrared spectra.[5,20]

USE

Cosmetic

Sodium Borate and Boric Acid are widely used as preservatives, antiseptics, water softeners, pH adjusters, emulsifiers, neutralizers, stabilizers, buffers, and viscosifiers in cosmetics. Sodium Borate acts as a stabilizer and emulsifier in cleansing creams and lotions; in these products, Sodium Borate acts as a neutralizing base for beeswax. The Sodium Borate is hydrolyzed and complexed with the free fatty acids of the beeswax to form soaps and in the process, Boric Acid is liberated and functions to buffer any alkalinity which may result from partial hydrolysis of the soaps. Sodium Borate is added to shaving creams to increase their viscosity and is used to adjust the pH of hair sprays and bath preparations. Boric Acid in baby powders acts to buffer talc, which is irritating to skin because of its alkalinity, by forming neutral calcium borate. Additional trace amounts of free Boric Acid in these powders neutralize ammonia-products in wet diapers. After shaving with alkaline soaps, the slightly acidic nature of the skin can be restored by the use of Boric Acid-containing aftershaves.[21]

According to the industry's submission to the FDA in 1981, Sodium Borate and Boric Acid are used in 488 and 142 cosmetic products, respectively (Table 1). A majority of these products contain only 5% or less Sodium Borate or Boric Acid. These two ingredients are used in a variety of product types including bath preparations, hair products, and skin preparations. Products containing Sodium Borate or Boric Acid come into contact with all body surfaces, as well as ocular,

TABLE 1. Product Formulation Data.

Product category[a]	Total no. of formulations in category	Total no. containing ingredient	No. product formulations within each concentration range (%)[a]						
			>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Sodium Borate									
Baby lotions, oils, powders, and creams	56	1	–	–	–	–	–	1	–
Bath oils, tablets, and salts	237	3	–	2	–	–	1	–	–
Bubble baths	475	10	–	6	4	–	–	–	–
Eyeliner	396	14	–	–	–	–	12	2	–
Eye lotion	13	2	–	–	–	–	–	2	–
Eye makeup remover	81	5	–	–	–	–	2	2	1
Mascara	397	24	–	–	–	1	14	9	–
Other eye makeup preparations	230	4	–	–	–	–	–	4	–
Fragrance preparations	191	4	–	–	–	–	–	3	1
Hair conditioners	478	3	–	–	–	–	–	3	–
Hair sprays (aerosol fixatives)	265	1	–	–	–	–	1	–	–
Hair straighteners	64	2	–	–	–	–	2	–	–
Permanent waves	474	16	–	–	–	1	4	11	–
Hair shampoos (noncoloring)	909	2	–	–	–	–	–	2	–
Tonics, dressings, and other hair grooming aids	290	13	–	–	–	–	1	11	1
Wave sets	180	3	–	–	–	–	–	1	2
Other hair preparations (noncoloring)	177	3	–	–	–	1	–	2	–
Other hair coloring preparations	49	3	–	–	–	–	–	3	–
Blushers (all types)	819	2	–	–	–	–	–	2	–
Makeup foundations	740	4	–	–	–	–	–	4	–
Lipstick	3319	1	–	–	–	–	–	1	–
Makeup bases	831	19	–	–	–	–	1	18	–

Other makeup preparations (not eye)	530	1	–	–	–	–	–	1	–
Nail creams and lotions	25	2	–	–	–	–	–	2	–
Bath soaps and detergents	148	1	–	–	–	–	–	–	1
Deodorants (underarm)	239	2	–	–	–	–	–	1	1
Other personal cleanliness products	227	8	4	1	1	2	–	–	–
Aftershave lotions	282	2	–	–	–	–	–	–	2
Shaving cream (aerosol, brushless, and lather)	114	4	–	–	–	–	1	3	–
Other shaving preparation products	29	1	–	–	–	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	144	–	–	–	–	24	111	9
Depilatories	32	1	–	–	–	–	–	1	–
Face, body, and hand skin care preparations (excluding shaving preparations)	823	71	–	–	–	–	3	58	10
Hormone skin care preparations	10	2	–	–	–	–	1	1	–
Moisturizing skin care preparations	747	47	–	–	–	–	3	38	6
Night skin care preparations	219	37	–	–	–	–	–	35	2
Paste masks (mud packs)	171	3	–	–	–	–	3	–	–
Skin lighteners	44	1	–	–	–	–	–	1	–
Skin fresheners	260	12	–	–	–	–	–	8	4
Wrinkle smoothers (removers)	38	4	–	–	–	–	1	3	–
Other skin care preparations	349	1	–	–	–	–	1	–	–
Suntan gels, creams, and liquids	28	5	–	–	–	–	–	5	–
1981 TOTALS		488	4	9	5	5	75	350	40

TABLE 1. (Continued.)

Product category[a]	Total no. of formulations in category	Total no. containing ingredient	No. product formulations within each concentration range (%)[a]						
			>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Boric Acid									
Baby shampoos	35	1	–	–	–	–	–	1	–
Bath oils, tablets, and salts	237	1	–	–	–	–	–	1	–
Eye lotion	13	1	–	–	–	–	1	–	–
Eye makeup remover	81	3	–	–	–	–	2	1	–
Fragrance powders (dusting and talcum, excluding aftershave talc)	483	13	–	–	–	–	11	2	–
Other fragrance preparations	191	1	–	–	–	–	–	1	–
Permanent waves	474	13	–	–	–	–	8	5	–
Hair rinses (noncoloring)	158	1	–	–	–	–	1	–	–
Hair shampoos (noncoloring)	909	13	–	–	–	–	7	6	–
Tonics, dressings, and other hair grooming aids	290	3	–	–	–	–	–	3	–
Wave sets	180	2	–	–	–	–	2	–	–
Other hair preparations (noncoloring)	177	3	–	–	–	–	1	2	–
Hair rinses (coloring)	76	14	–	–	–	1	13	–	–
Other hair coloring preparations	49	3	–	–	–	–	1	2	–
Blushers (all types)	819	2	–	–	–	–	–	2	–
Face powders	555	1	–	–	–	–	–	1	–
Rouges	211	1	–	–	–	–	–	1	–
Makeup fixatives	22	2	–	–	–	–	2	–	–

Mouthwashes and breath fresheners (liquids and sprays)	53	5	–	–	–	–	1	3	1
Bath soaps and detergents	148	1	–	–	–	–	1	–	–
Deodorants (underarm)	239	5	–	–	–	3	2	–	–
Douches	26	5	5	–	–	–	–	–	–
Other personal cleanliness products	227	1	–	–	–	–	–	1	–
Aftershave lotions	282	5	–	–	–	–	2	2	1
Preshave lotions (all types)	29	1	–	–	–	–	–	–	1
Shaving cream (aerosol, brushless, and lather)	114	6	–	–	–	–	2	4	–
Other shaving preparation products	29	1	–	–	–	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	4	–	–	–	–	2	2	–
Face, body, and hand skin care preparations (excluding shaving preparations)	823	5	–	–	–	–	2	3	–
Moisturizing skin care preparations	747	4	–	–	–	–	2	2	–
Night skin care preparations	219	1	–	–	–	–	–	1	–
Paste masks (mud packs)	171	3	–	–	–	–	2	1	–
Skin fresheners	260	17	–	–	–	–	5	11	1
1981 TOTALS		142	5	–	–	4	70	59	4

[a]Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4); see Cosmetic Use section.

Data from Ref. 4.

oral, and vaginal mucosae. Contact with such products can last from seconds to all day; these products may be used daily or occasionally.[4]

The cosmetic product formulation computer printout, which is made available by the FDA, is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations (1979). Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.

A 1979 directive of the European Economic Council (EEC) authorizes a maximum use concentration of Boric Acid in cosmetics of 5% in talcs (with the limitation that it not be used for children aged 3 years or younger), 0.5% in oral hygiene products, and 3% in all other cosmetic products. The EEC's Scientific Committee on Cosmetology concluded that these restrictions were appropriate, but added that the labels on all cosmetic products containing Boric Acid, except oral hygiene products, should contain the warning "not to be used on damaged skins."[22]

Medical

Clinically, Sodium Borate and Boric Acid have been used as irrigants, dressings, antiseptics, buffers, and preservatives. The history of Sodium Borate and Boric Acid in medicine has been reviewed by Kingma.[23]

Sodium Borate and Boric Acid were reviewed by several FDA over-the-counter (OTC) drug panels. Both ingredients have been determined to be safe and effective preservatives in vaginal products and contraceptives at preservative concentrations (less than 1%).[24,25] Sodium Borate and Boric Acid have been judged safe but ineffective topical antifungal agents at concentrations of 5% or less, but not safe at concentrations exceeding 5%.[26] Boric Acid has also been determined safe but ineffective as an ocular anti-infective agent at concentrations up to 5%. An FDA OTC panel also concluded that Sodium Borate and Boric Acid are safe and effective buffers in ophthalmic preparations at concentrations up to 5%.[27] Boric Acid has been found to be unsafe for OTC use as a skin protectant, oral antimicrobial, and anorectal antiseptic. These conclusions were based on Boric Acid's absorption characteristics by damaged skin and oral/anal mucous membranes, as well as its cumulative toxicity and slow elimination.[28-30]

Sodium Borate and Boric Acid have been tested for other clinical uses. In vitro and clinical tests were performed to determine the effect of Sodium Borate on Herpes simplex virus (HSV). Hamster kidney cells were infected with HSV and incubated for 24 h with up to 30 m*M* Sodium Borate. At 20 m*M* or greater, virus replication was completely inhibited. Of 14 patients with HSV cold sores

treated with 4% Boric Acid ointment, 13 reported that treatment helped relieve symptoms. Cold sore duration was decreased from 5.9 to 4.1 days and no adverse effects of Boric Acid treatment were reported.[31]

Swate and Weed[32] successfully inhibited growth of *Candida albicans* in trypticase soy broth with 1%–4% Boric Acid. Boric Acid was fungistatic but not fungicidal. In a clinical test, 40 women infected with vulvovaginal candidiasis each inserted vaginally 600 mg Boric Acid twice daily for two weeks. Each also applied 5% Boric Acid in lanolin to the irritated vulva three times daily as needed. All patients reported relief of symptoms within 48 h; vulvar pruritis was immediately relieved by the Boric Acid ointment. Three of the 40 patients reported a burning, profuse, watery vaginal discharge during therapy. Only two recurrences of candidiasis were reported 30 days after therapy was discontinued. A similar clinical study was performed by van Slyke et al.[33] Intravaginal gelatin capsules containing 600 mg Boric Acid were used daily for 14 days for the treatment of vulvovaginal candidiasis. Cure rates were 92% at seven to 10 days after treatment and 72% at 30 days after treatment. There were no untoward side effects and cervical cytologic features were not affected.

The effect of a Boric Acid/Sodium Borate ophthalmic solution on silver nitrate-induced conjunctivitis was studied in neonates. Eyes were irrigated with the ophthalmic solution immediately after instillation of 1% silver nitrate. Eyes were examined one to 12 h later for irritation. The Boric Acid/Sodium Borate solution did not reduce silver nitrate-induced conjunctivitis when compared with controls.[34]

Sodium Borate and Boric Acid are used or have been tested for medical purposes in many foreign countries. Boric Acid is used in Japanese athlete's foot products to increase the fungicidal properties of the active agents.[35] Five percent Sodium Borate is sprayed on the skin following application of analgesic agents to form a transparent, flexible, water-resistant film.[36] A Boric Acid and menthol mixture is used in East Germany as a nasal unguent.[37] In India, a formulation of "indigenous Indian drugs" and 25% Sodium Borate is reported to be a long-acting (four months) oral contraceptive; it has been reported that the drug acts by inhibiting endometrial alkaline phosphatase and preventing ovum implantation.[38] Skin irritation caused by contact with agricultural pesticides and paronychia (inflammation surrounding the nails) has been treated successfully in Russia by Boric Acid ointments.[39,40] In Russia, Sodium Borate is administered orally to patients with hepatocerebral dystrophy to remove accumulated pathological quantities of copper from the body.[41] An infective agent isolated from Korean patients with epidemic hemorrhagic conjunctivitis was inactivated by exposure to Boric Acid in vitro.[42]

Food

Sodium Borate and Boric Acid are regulated as indirect food additives. They may be used in adhesives, sizes, and coatings for paper and paperboard products and in textiles and textile fibers which come into contact with foods (21 CFR 175.105, 175.210, 176.180, 177.2800, 181.30). Use of Sodium Borate as a direct food additive is prohibited in the U.S.[43]

Sodium Borate and Boric Acid (up to 8%) are effective fungistatic agents for use on vegetables, fruits, and trees.[44-56]

The Federal Register[57] established a tolerance of 8 ppm of total boron in or on citrus fruits. The tolerance is calculated as elemental boron and covers residues from the postharvest applications of Boric Acid and Sodium Borate as fungicides and the naturally occurring boron in the citrus fruits.

In France, the estimated average daily intake of boron (partly as Boric Acid antifungal and antirot agents on fruit and vegetables) is 25 mg per person (range of 3.8 to 41 mg/day).[58]

Pesticide

Sodium Borate and Boric Acid can be used as insecticides to control cockroaches, ants, and flies.[59-62] Oral administration of 2% Boric Acid to cockroaches resulted in impaired digestive ability and death within two days.[63] Studies revealed that 2 ng/ml Sodium Borate damaged all generative cells, completely depressed sperm formation, and destroyed septal cells of cockroach testes cultivated in vitro. Spermatogenesis was not inhibited by 0.1 ng/ml Sodium Borate.[64] Use of Sodium Borate insecticide on fly larvae resulted in considerable morphological deformations of the pupae and prolonged development of the immature flies.[65] Sodium Borate and Boric Acid powders are authorized under the Federal Insecticide, Fungicide, and Rodenticide Act for use as residual insecticides for crack and crevice treatment in food handling areas.[66]

Other Uses

Boric Acid is used for weatherproofing wood and fireproofing fabrics, as a preservative in natural products such as lumber, rubber latex emulsions, leather, and starch products, in manufacturing cements, crockery, porcelain, enamels, optical and sealing glass, textile fiberglass, borates, carpets, hats, soaps, and artificial gems, in printing and dyeing and photography, for impregnating wicks, in electrical condensers, in hardening steel, in washing citrus fruits to prevent mold and in mildew-resistant latex paints. Sodium Borate is used in soldering metals, in manufacturing glazes and enamels, in tanning, in cleaning compounds, in starch and adhesives, as a preservative against wood fungus, in fireproofing fabrics and wood, as a herbicide, in fertilizers, as a rust inhibitor, in photography, in paint, as a component of insulation materials and antifreeze, and as a laboratory reagent.[3,8]

GENERAL BIOLOGY

Antibacterial/Antifungal Properties

Sodium Borate and Boric Acid have weak bacteriocidal properties but have significant bacteriostatic effects in concentrations up to 4%. The antibacterial properties of these ingredients are reviewed by Novak[67] and Zittle.[9]

A 2% concentration of Sodium Borate is bacteriostatic in stored milk samples but does not kill the *Mycobacterium tuberculosis* in the samples.[68] Boric Acid

(0.5%–5%) is an effective bacteriostatic agent and is used to preserve numerous organisms in culture and urine specimens.[69]

The growth of most strains of coagulase positive *Staphylococcus aureus* was inhibited by 1.5×10^{-8} *M* Sodium Borate and sensitivity to Sodium Borate correlated well with lysozyme and α-toxin production.[70] The results of a gelatin liquefaction test suggested that 0.1% Boric Acid may effectively inhibit bacterial proteolytic deterioration in foods.[71] Concentrations of 0.1%–0.5% of Boric Acid with hydroxyacetic acid in bacon stored at high temperatures for 30 days were relatively effective against bacteria but not against fungi. Concentrations of 0.2%–1.0% Sodium Borate in bacon were fungistatic but not bacteriostatic.[72] Bacterial and fungal inocula were added to B complex injectable solutions. A 0.3%–0.5% concentration of Boric Acid was added and the bacteria disappeared in 2 days and the fungi in 28 days. Lower concentrations of Boric Acid were less rapidly effective.[73] Exposure of *Paramecium caudatum* to Boric Acid (0.005%–0.05%) under various conditions resulted in changes in phagocytic activity, decreased cytoplasmic neutral fat, and increased heat resistance.[74-76]

Biochemical Effects

Sodium Borate and Boric Acid affect the activity of a variety of enzymes. The interactions of borate with enzymes have been reviewed by Zittle.[9] Sodium Borate inhibits human, sheep, bovine, and porcine blood arginase (5×10^{-8}–5×10^{-5} *M*);[77] yeast alcohol dehydrogenase (2.5×10^{-4}–7.5×10^{-4} *M*);[78] and yeast, and rat and guinea pig liver glyceraldehydephosphate dehydrogenase (0.003–0.01 *M*) and does not affect rabbit muscle and guinea pig liver lactate dehydrogenase (0.005–0.01 *M*).[79] Boric Acid has been reported to inhibit invertase (1.08 *M*);[80] the oxidation of 5-keto-D-gluconic acid, dehydro-L-ascorbic acid, and 2,3-diketo-L-gulonic acid (0.16–0.4 *M*);[81] the milk enzymes present in commercial liquid rennet, xanthine oxidase and alkaline phosphatase;[82] rat liver, brain, and kidney glucose-6-phosphatase and phosphohexo-isomerase; rat liver and brain phosphoglucomutase (0.12–0.13 *M*);[83] and bovine blood glyceraldehydephosphate dehydrogenase and glucose-6-phosphate dehydrogenase (0.001–0.02 *M*).[84] Boric Acid stimulates rat kidney phosphoglucomutase (0.12 *M*)[83] and ox kidney and hog liver urate oxidase (3.3–100 m*M*)[85] and does not have any effect on bovine blood lactate dehydrogenase (0.01–0.02 *M*).[84] Sodium Borate has been reported to inhibit oxygen uptake (0.033–0.26 *M*),[86] ammonia formation, and glutamine synthesis in guinea pig brain cells (0.05–0.13 *M*).[87] Boric Acid inhibits the spontaneous reduction of methemoglobin in guinea pig blood (0.02 *M*).[84] Sodium Borate (0.02 *M*) inhibited carnitine dehydrogenase, which catalyzes the oxidation of L-carnitine to 3-dehydrocarnitine, in *Pseudomonas aeruginosa*.[88] The activity of o-diphenol oxidase, an enzyme which oxidizes polyhydroxyphenols is competitively inhibited by 4×10^{-4}–4×10^{-3} *M* Sodium Borate.[89] Boric Acid competitively inhibited inactivation of mesentericopeptidase carbamylation by potassium cyanate.[90] In *Methylomonas methylovora* (an obligate methyltroph), Sodium Borate inhibited phenazine methosulfate-linked methamine dehydrogenase activity.[91] Sodium Borate (0.2–4 m*M*) was a reversible competitive inhibitor of β-lactamase I (a penicillinase) from *Bacillus cereus*.[92]

The effect of Borate on RNA biosynthesis was studied in vivo and in vitro by Weser.[93] Two groups of rats were fed low concentrations of Boric Acid. One group received an additional 20 m*M* of Boric Acid injected intraperitoneally prior to the experiment. The incorporation of radiolabeled uridine into liver nuclear RNA was then determined. Uridine was incorporated to a much greater extent in rats with the additional Boric Acid injection. This phenomenon was not observed in normal-diet rats which were injected with Boric Acid. In vitro tests revealed that the activity of DNA-dependent RNA polymerase from whole liver nuclei was enhanced by the presence of 10^{-6}–10^{-5} *M* Boric Acid. Higher concentrations inhibited this enzyme's activity. Similar in vivo results were obtained when using labeled orotic acid as the RNA precursor.[94]

Sodium Borate (0.03 *M*) delayed the establishment of the lac operon repressor in bacterial zygotes by inhibiting RNA transcription and synthesis. Borate inhibition of β-galactosidase was rapid. Induced enzyme synthesis was depressed 53%; however, constitutive synthesis was stimulated 25%.[95]

Jordan and Howell[96] observed that 0.12 *M* Sodium Borate inhibited thromboplastin activity of rat brain microsomal fractions in vitro. This effect resulted in an increased clotting time. The effects of Sodium Borate may have resulted from its complexing with hydroxyl groups of carbohydrates by forming cross-links between hydroxy groups on different disaccharide side chains of the same molecule.

Johnson and Smith[97] determined that Sodium Borate interacts with pyridine nucleotides at the ribose hydroxyl group by affecting the addition of sulfite to the 4-position of the nicotinamide ring. A two-step process for the interaction of NAD-sulfite and Sodium Borate was demonstrated; a change in the rate-determining step occurred with various Sodium Borate concentrations.

Addition of Sodium Borate to the incubation medium resulted in decreased potassium ion content of guinea pig cerebral cortex tissue.[98]

Male rats were given Sodium Borate in their drinking water (3 g/l) for 14 weeks. Cerebral succinate dehydrogenase activity, RNA concentration, and acid proteinase activity increased and NADPH-cytochrome c reductase activity, cytochrome b5 content, and cytochrome P-450 concentration of the liver microsomal fraction decreased at 10–14 weeks. These results support the hypothesis that borate anions are toxic because they interfere with flavin metabolism in flavoprotein-dependent pathways.[99]

Tissue Effects

The effects of Sodium Borate and Boric Acid on various tissues have been studied. Boric Acid has been reported to stimulate myocardial contractility of isolated rabbit heart.[100]

A 5% Boric Acid ointment was applied to the corneas of rabbits and monkeys immediately following lamellar keratectomy. The ointment, which was applied eight times in 24 h, did not inhibit corneal wound healing. In another test, corneal epithelial layers of 10 rats were scraped off. Boric Acid ointment was applied six times in 24 h to one damaged eye of each animal. No different in the rate of re-epithelization was observed between test and control eyes.[101] However, Boric Acid (unknown concentration) was reported to be toxic to corneal

epithelial tissue cultures, destroying them within five to 10 days.[102] The effect of Boric Acid on corneal permeability was studied by Bartsova and Obenberger.[103] Two percent Boric Acid was applied to intact and de-epithelized bovine corneas three times within 10 min. The respective sodium chloride permeability values of treated intact and de-epithelized corneas were 182.5% and 86.1% of control values.

The phagocytosis of *Micrococcus pyogenes albus* by serum polymorphonuclear neutrophils was inhibited by 2%–4% Boric Acid. At 4%, Boric Acid was nontoxic to the cocci but was lethal to all phagocytes.[104]

In another study, the effect of Sodium Borate and Boric Acid on phagocytosis by cutaneous endothelial cells was determined. The two ingredients (0.01%–0.5% in petrolatum and in an emulsifying base containing triethanolamine) were applied to the epilated skin of groups of eight white mice. An india-ink suspension was then injected into the tail vein of each animal. The endothelial cells of the skin capillaries were observed for phagocytosis of india-ink particles at 1, 2, and 24 h. Sodium Borate and Boric Acid did not induce skin phagocytic activity.[105]

When added to embryonic tissue cultures, 1.0 and 0.1 g/l Boric Acid inhibited development to the blastocyst stage in 100% and 50% of the embryos, respectively.[106] (The Panel notes that these concentrations are so high that the significance of the results is questionable.)

Absorption, Storage, and Excretion

Doses of 1.0–2.0 ml of an aqueous jelly and two oleaginous ointments containing less than 3% Boric Acid were applied to approximately 4.3–28 cm^2 of the intact skin of anesthetized rats. There was no to low excretion of boron in their urine. (Boron was measured colorimetrically.) Boric Acid excretion was observed after the application of the jelly and the ointments to damaged skin. Five hours after application, it was observed that more Boric Acid was absorbed from the jelly than from the ointment.[107]

Two cows received 18 to 23 g/day Sodium Borate in their feed for 42 days. Sodium Borate was excreted in the urine, feces, and milk. There was no detectable retention in the body and borate excretion returned rapidly to pre-experiment levels after the experiment.[108]

Rats and guinea pigs were fed diets containing labeled riboflavin with and without Boric Acid additions. There was a greater urinary excretion of riboflavin in the Boric Acid fed animals. In vitro studies with rat blood indicated that borate removes riboflavin from binding sites on serum proteins. Boric Acid toxicity to animals may be partially due to riboflavin depletion.[109]

Sodium Borate and Boric Acid solutions were tested for absorption by intact skin. Occlusive patches containing 5% Boric Acid (aqueous), 5% Boric Acid in urine, 5% Boric Acid in talc, 5% Boric Acid (pH 9), or 8% Sodium Borate were applied to each of six to 12 rabbits for 8 h. The researchers reported that they measured boron concentration in the blood and urine. The results indicated that 5% Boric Acid in water or urine was readily absorbed through intact skin, whereas in talc it was not. Boric Acid in pH 9 buffer was absorbed less than in

water but more than in talc. Sodium Borate in water was also readily absorbed.[110]

In order to determine the effectiveness of Sodium Borate in neutron-capture cancer therapy, 20 mg/kg of boron as Sodium Borate was injected intraperitoneally into groups of tumor-bearing mice. Animals were sacrificed at 72 h and the boron content of various tissues was determined colorimetrically. Tumor-bearing animals had as high a boron concentration in the tumor as in the brain.[111]

Draize and Kelly[112] studied the percutaneous absorption of Boric Acid preparations. Boric Acid, 5% in water, 5% in talc, 12.5% in talc, and undiluted, was applied to intact, abraded, severely burnt, and partially denuded skin of rabbits 1.5 h daily for four days. Boric Acid (15 g) was applied to the intact skin of one human for 4 h. In each test, urinary boron concentrations were determined colorimetrically. "Minimal and insignificant" amounts of Boric Acid were absorbed through intact and abraded skin of rabbits. Severely burnt and partially denuded skin readily absorbed Boric Acid. No increase in boron excretion was observed in the human. The authors concluded that insignificant amounts of Boric Acid are percutaneously absorbed by normal intact skin.

Pfeiffer[113] has studied and reviewed the pharmacology of Boric Acid in humans and in laboratory animals. He determined that, once in the blood, Boric Acid does not remain there, but tends to accumulate in the brain, liver, and fat (in that order). In the brain, the grey matter accumulates more Boric Acid than does the white matter. High amounts of Boric Acid are also found in the spinal cord and sciatic nerve. Nonfatal doses are redistributed over time to the fatty organs of the body. Boric Acid is eliminated slowly in the urine over a period of days, totaling 75%–100% of the ingested dose. Very small amounts may be detected in the feces, saliva, milk, and perspiration. Boric Acid is not absorbed through intact skin but is rapidly absorbed from abraded, denuded, or burned skin, as well as some mucosal surfaces.

A commercial talcum powder that contained 5% Boric Acid was used on the skin of six infants with no to marked diaper rash. Boric Acid was not detected in the urine of any of the infants before powder application. Twenty-four hours after powder application, Boric Acid was present in catheterized urine from the infants with moderate to marked rash and it persisted in the urine for at least 48 h. No Boric Acid was detected in the urine of infants with no to mild diaper rash.[114]

A powder containing 5% Boric Acid was applied seven to 10 times daily for one month to 50 infants with intact and dermatitic skin. The calculated dose was approximately 2.33 g/infant/day. There were 31 control infants; no powder was applied to them. After one month, blood and urine boron concentrations were determined colorimetrically. Only minute amounts of Boric Acid penetrated the skin of the treated infants (including those with rashes) as evidenced by similar boron values in serum and urine of control and test infants.[115]

A talc containing 5% Boric Acid was applied to the buttocks of eight infants 10 times daily for five days. One infant with extensive second-degree burns was similarly tested for three days. Blood and urine boron levels were measured colorimetrically during the experiment and did not differ significantly from the levels measured before or after the experiment in all infants with intact skin. In the burned infant only the urine level of boron was elevated during the experiment.[116]

Wet compresses of Boric Acid were applied to 21 hospitalized patients over several days. Serum Boric Acid levels were significantly increased in only one patient who had kidney damage. Laboratory experiments revealed that rabbits whose kidneys were damaged prior to dermal application of Boric Acid had a significant increase in serum Boric Acid half-life.[117]

Forty women with vulvovaginal candidiasis inserted vaginally 600 mg Boric Acid twice daily for 14 days, and applied 5% Boric Acid in lanolin to any vulval irritation. Serum determinations at 14 days revealed no detectable amounts of Boric Acid in the blood of these women.[32]

An anhydrous, water-emulsifying ointment containing 3% Boric Acid was applied to 31 men in a single application and the amount of boron in their urine was measured at one to nine days later. Sixteen of the men had normal skin and 15 had "diseased" skin. They received 3.1 to 127.3 mg boron (~17.7–727.4 mg Boric Acid). No increase in boron excretion in the urine was observed. Determinations of boron in the urine and blood were made after a single application of the same ointment to three children (3.5 weeks to two months old) with "napkin dermatitis." The children received 6.2 to 10.4 mg boron (~35.4–59.4 mg Boric Acid) and blood and urine boron values of these children and an untreated child (3.5 months old) were determined one to eight days after application. There was no increase in blood concentration or urinary excretion of boron. A water-based jelly containing 3% Boric Acid was applied as a single application to six men, blood boron concentrations were measured 0–24 h later, and urinary boron excretion was measured at 1–9 days later. Three of the men had eczema, two had psoriasis, and one had urticaria. They received 37–89 mg boron (~211.4–508.6 mg Boric Acid). There were significant increases in blood boron concentration on the day of application and in boron excretion in the urine on day two. After Day 2, boron excretion in the urine returned to normal.[118]

Animal Toxicology

Acute Effects

Oral toxicity

The single-dose oral toxicities of aqueous solutions of Sodium Borate and Boric Acid for rats of unspecified strain were determined. The LD50s for Sodium Borate and Boric Acid were 5.66 and 5.14 g/kg, respectively.[119] In another study, Sodium Borate and Boric Acid were administered orally to Sprague–Dawley and Long–Evans rats and the rats were observed for 14 days. The LD50s of Sodium Borate and Boric Acid for male and female Sprague–Dawley rats, and male Long–Evans rats were 4.50 and 3.45 g/kg, 4.98 and 4.08 g/kg, and 6.08 and 3.16 g/kg, respectively. Signs of toxicity included depression, ataxia, convulsions, and death.[120] In the Hodge and Sterner[121] classification of single-dose oral toxicity for rats, Sodium Borate and Boric Acid would be classified as practically nontoxic to slightly toxic.

Acute doses of 45–450 mg/kg boron as Sodium Borate (398.2–3982.3 mg/kg Sodium Borate) were administered orally to male Sprague–Dawley rats. The rats were serially mated and no significant effects on male fertility were observed.[122]

Doses of 0.5–3 g/kg of Boric Acid were administered as single doses to

female mice on the first day of pregnancy. At 3 g/kg, Boric Acid prevented 94% of the embryos from reaching the blastocyst stage of development. Doses of 0.5 and 1.0 g/kg had similar but less significant effects.[106]

The acute oral toxicity of a hair preparation containing 3.2% Sodium Borate was determined in male and female albino rats. The test solution was administered by intubation to groups of 10 rats at doses of 8.72–17.4 g/kg. Animals were observed for 14 days, sacrificed, and were necropsied as were the animals that died during the study. The acute oral LD50 of the hair preparation was 14.1 g/kg, which is indicative of a relatively harmless substance. Results of necropsy revealed the following abnormalities that may have been caused by ingestion of the test material (especially at highest doses): melanuria, diarrhea, polyuria, discolored stomach and intestinal mucosa, discolored gastrointestinal contents, empty urinary bladder, dilated renal pelvis, and testes drawn into the abdominal cavity.[123]

Primary skin irritation

The irritation potential of Sodium Borate and Boric Acid was compared in rabbits and guinea pigs. Ten ml of 5% Sodium Borate (aqueous) and 5 ml of 10% Boric Acid (aqueous) were applied under occlusion to the clipped intact and abraded skin of six rabbits and six guinea pigs. Sites were scored for irritation at 24 and 72 h. Boric Acid resulted in Primary Irritation Indices (PIIs) of 1.7 and 2.1 (maximum score = 8) for rabbits and guinea pigs, respectively. Sodium Borate PIIs were 2.0 and 1.4, respectively. These scores were indicative of mild or moderate skin irritation.[124]

Five percent aqueous solutions of Boric Acid at different pHs had the following effects when applied to the backs of rabbits: at a pH of 3.81 (unadjusted), no irritation; at pHs of 7.38 and 6.86, adjusted with ammonium carbonate, moderate and slight irritation, respectively; at a pH of 7.87, adjusted with sodium hydroxide, slight irritation; at a pH of 8.16, adjusted with ammonium carbonate and an ammonia solution, marked irritation. A 5% Boric Acid solution in freshly passed human urine at a pH of 5.5 resulted in no irritation.[114]

A bath preparation containing 0.4% Boric Acid was tested for primary skin irritation in nine albino rabbits. The material was applied undiluted under occlusion to the shaved intact skin of each animal for 24 h. Sites were scored for irritation at 24 and 72 h. Of the nine animals tested, eight experienced irritation (slight to moderate erythema). The PII was determined to be 1.06 (maximum score = 4), which is indicative of a mild irritant.[125]

Tissue corrosiveness

The effect of a hair preparation containing 3.2% Sodium Borate on the oral and gastrointestinal tissues of rabbits was studied. The undiluted material was applied at a dose of 229 mg/kg to the posterior surface of the tongue of each of four albino rabbits. At 24 and 96 h, two animals were sacrificed; the tongue, adjacent pharyngeal structures, larynx, esophagus, and stomach were removed and examined grossly and microscopically. Corrosiveness of the test material was determined by its effects on these structures. No abnormalities, gross or microscopic, could be attributed to the application of the hair preparation containing Sodium

Borate to the tongues of rabbits; this product was considered to be nonirritating and noncorrosive.[126]

Ocular irritation

A hair preparation containing 3.2% Sodium Borate was tested for ocular irritation in nine albino rabbits. The undiluted material was instilled into one eye of each animal; the other eye served as an untreated control. The eyes of three animals were rinsed with warm water 30 sec after treatment. Eyes were examined at 1, 2, 3, 4, and 7 days. The test substance induced slight conjunctival chemosis in one of three animals in the "rinse" group and in two of six animals in the "no-rinse" group. Irritation subsided in all cases within 72 h. The average ocular irritation index (AOII) for each group was 0.7 (maximum score = 110), indicating that the hair preparation containing 3.2% Sodium Borate was practically nonirritating to the eyes of rabbits.[127]

A bath preparation containing 0.4% Boric Acid was tested similarly in six albino rabbits. In this study, the eyes of all animals were rinsed with warm water 4 sec following instillation of the undiluted test material. The AOII for each day of observation was as follows: Day 1, 36; Day 2, 24; Day 3, 22; Day 4, 11; and Day 7, 2. These results indicate that the product containing 0.4% Boric Acid was moderately irritating when instilled in and rinsed from rabbits' eyes.[128]

Intravenous toxicity

Sodium Borate in saline or distilled water was administered intravenously to mice and the animals were observed for 24 h. The acute intravenous LD50 was reported to be 1.32 g/kg.[129]

A single intravenous injection of 900 mg/kg of Boric Acid in an aqueous solution adjusted to pH 6.5–7.5 with sodium hydroxide was fatal to four of five rabbits. At a dose of 800 mg/kg, one of five rabbits died. Below this dose only a few rabbits died. Albuminuria occurred at doses of 25 mg/kg or greater. At gross and microscopic examinations organs were normal.[114]

The intravenous administration of 75 mg/kg of Boric Acid to rats caused a transient hypotension, whereas in anesthetized dogs, the intravenous administration of up to 300 mg/kg of Boric Acid had no significant effect on respiration, general metabolism, blood pressure, or contractile heart force.[100]

Subcutaneous toxicity

In the rat, the acute subcutaneous LD50 of an aqueous Boric Acid solution adjusted to pH 6.5–7.5 with sodium hydroxide was 1.4 g/kg.[114]

Intraperitoneal toxicity

Sodium Borate was administered intraperitoneally to mice and the animals were observed for 5–12 days. The acute intraperitoneal LD50 was reported to be 2.817 g/kg. After intraperitoneal administration of Sodium Borate to the mice, convulsions usually occurred within 3 h. Trunk muscular contractions and opisthotonic responses were generally observed. General motor activity and respiration rate were depressed for several hours. Mice were frequently observed to have motor activity depression through the second day after administration.

Most deaths occurred within three days following administration. Sodium Borate was dissolved in saline or in water and no differences were observed in the effect of these solutions.[130]

Subchronic Effects

*Oral toxicity**

Aqueous solutions of Sodium Borate and Boric Acid were administered orally to rats in doses of 1 g/kg/day for three weeks. Reduced weight gain was observed with Sodium Borate and Boric Acid administration after one and two weeks, respectively. Signs of toxicity were observed after three weeks; there were significant increases in liver, brain, and kidney RNA and brain and kidney DNA and decreases in liver DNA with both substances.[131]

Four rats were fed a diet containing 1% Boric Acid (approximately 1 g/kg/day) for 27 days. Growth retardation was observed in the rats but there were no other signs of toxicity.[109]

Boric Acid in aqueous solution was administered orally once each day for four days to rabbits. There were no survivors at doses of 850–1000 mg/kg/day. At 800 mg/kg/day there were no deaths among six rabbits but there were severe signs of poisoning, anorexia, weight loss, and diarrhea. There were minor signs observed in animals dosed at 600 and 700 mg/kg/day.[112]

Two cows in midlactation were fed for 42 days on a production ration containing Sodium Borate. Their intake was 18 to 23 g/day (~36–46 mg/kg/day). No adverse effects on the health of the cows was observed. There was no decrease in milk yield.[108]

Sodium Borate and Boric Acid have been studied extensively for their gonadotropic effects following subchronic oral administration. Male rats were allowed free access to drinking water containing 0.3 to 6.0 mg/l of boron as Sodium Borate (~0.37–7.44 mg/kg/day Sodium Borate). Randomly selected animals were studied after 30, 60, and 90 days of treatment. There were no observed reproductive effects or biologically significant changes in the serum chemistry or the weight of the body, testes, prostate, or seminal vesicles. During forced breeding studies, no effect was observed on male fertility.[122]

A dose of 1 g/kg/day of Boric Acid was administered orally to 12 male albino rats for two weeks. The rats were sacrificed and the testes examined. In the convoluted tubules, changes in the nuclei and cytoplasm of spermatocytes and spermatids in the early stages of formation were observed. In some tubules, generative cells were absent. Dystrophic processes included chromatolysis of the nuclei, intensive vacuolation of the cytoplasm, and consolidation of the mitochondrial matrix. The authors concluded that these gonadal disorders are caused by Boric Acid's direct effect on tissue respiration and its prolongation of mitotic division of the spermatogenic epithelial cells.[132,133]

Lee et al.[134] studied the gonadal effects of subchronic Sodium Borate inges-

*Concentrations or total doses reported by investigators were converted to mg/kg/day and are given as approximate values in parentheses. Conversions were based on information given by the investigators or by the use of the conversion chart in: FDA: Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, USA: The Association of Food and Drug Officials of the United States, 1959.

tion. Groups of 18 male rats were placed on diets containing 0–2,000 ppm boron as Sodium Borate (~0–1.06 g/kg/day Sodium Borate). At 30 and 60 days, five rats from each group were mated to assess fertility, 10 rats were used to determine hormone concentrations, and three were used to evaluate enzyme activities, histopathologic changes, and organ weights. Throughout the study, no animals showed signs of systemic toxicity. Body and organ weights, as well as food consumption, were normal. At 1000 and 2000 ppm boron (~0.53 and 1.06 g/kg/day Sodium Borate), the following gonadal effects were observed: reduced testicular weight (60 days); decreased epididymal weight (30 days); reductions in spermatocytes, spermatids, tubular diameter, and numbers of mature spermatozoa (30 days); and germinal aplasia (60 days). Dose-dependent reductions in hyaluronidase, sorbital dehydrogenase, and lactic acid dehydrogenase isoenzyme-x were observed at 30 days. At 2000 ppm boron, increased FSH and LH concentrations were reported; FSH levels were still above normal 12 months post-feeding. Rats given dietary concentrations of 1000 ppm boron for 30 days, 1000 ppm boron for 60 days (~0.53 g/kg/day Sodium Borate), and 2000 ppm boron for 30 days (~1.06 g/kg/day Sodium Borate) were infertile for 3, 4, and 8 weeks post-feeding. Rats receiving 2000 ppm boron for 60 days (~1.06 g/kg/day Sodium Borate) remained infertile throughout the 32-week mating trials. The authors concluded that aplasia was due to the accumulative and cytotoxic effects of boron on germinal tissue in the testes.

Groups of five male and five female rats were fed diets containing 52.5, 175, 525, 1750, and 5250 ppm boron equivalents of Sodium Borate (~46.5, 154.9, 464.6, 1548.7, and 4646 mg/kg/day Sodium Borate) and Boric Acid (~30, 100, 300, 1000, and 3000 mg/kg/day Boric Acid) for 90 days. At the 525 ppm or less boron equivalents of Sodium Borate or Boric Acid, the physical appearance of the rats was normal. Rats fed 1750 and 5250 ppm boron equivalents of Sodium Borate or Boric Acid had rapid respiration, inflamed eyes, swollen paws, and desquamated skin on the paws and tails. These animals were excitable when handled. All male rats had shrunken scrotums during the last weeks of the study. At the 5250 ppm boron equivalent of Sodium Borate and Boric Acid all rats died within three to six weeks, and at necropsy, liver and kidney and lung congestion was observed. These results were also seen with the single rats that died at the 52.5 and 1750 ppm boron equivalents of Sodium Borate. The 525 ppm boron equivalent of Boric Acid did not affect growth, feed consumption, and feed efficiency. These were reduced for rats fed the 1750 ppm boron equivalent of Boric Acid and the 5250 ppm boron equivalent of Sodium Borate and Boric Acid and for male rats fed the 1750 ppm boron equivalent of Sodium Borate. The testes atrophied completely in all males fed the 1750 ppm boron equivalent of Sodium Borate or Boric Acid, and atrophied partially in four of five males fed the 525 ppm boron equivalent of Sodium Borate and in one of five male rats fed the 525 ppm boron equivalent of Boric Acid.[120]

Groups of five male and five female dogs were fed diets containing 17.5, 175, and 1750 ppm boron equivalents of Sodium Borate (~11.6, 116.2, and 1161.5 mg/kg/day Sodium Borate) and Boric Acid (~7.5, 75, and 750 mg/kg/day Boric Acid) for 90 days. During the study, all the dogs were essentially normal in appearance, behavior, elimination, body weight, and food consumption. One male at the 1750 ppm boron equivalent of Sodium Borate died on Day 68 with diar-

rhea, congested kidneys, and severe congestion of the small and large intestine mucosae. Hematologic, blood chemistry, and urine values were all normal except for two males and three females in the 1750 ppm boron equivalent of Sodium Borate group. They had decreased cell volume and hemoglobin values during the study. There were no lesions in dogs fed 175 ppm or less boron equivalents of Boric Acid. At 1750 ppm boron equivalents, both compounds produced severe testicular atrophy in male dogs. Degeneration of the spermatogenic epithelium was generally complete. There was greater red blood cell destruction with Sodium Borate than with Boric Acid.[120]

Dermal toxicity

In a 90-day study, aqueous Boric Acid solutions were rubbed onto the intact skin of rabbits in doses of 25–200 mg/kg/day. No adverse local or systemic toxicity was observed; no abnormal hematologic or microscopic tissue changes attributable to Boric Acid treatment were found.[112]

*Intravenous toxicity**

Rabbits were administered intravenously 100 to 500 mg of an aqueous Boric Acid solution adjusted to a pH of 6.5–7.5 with sodium hydroxide two times a day until death was impending (~22.22 to 156.25 mg/kg). This was 7–10 days for the 100 mg dose and 2–3 days for the 500 mg dose. The rabbits were then sacrificed and necropsied. Kidney damage was observed.[114]

Subcutaneous toxicity

Rats were injected subcutaneously with 10 and 33 mg/kg of an aqueous Boric Acid solution adjusted to pH 6.5 to 7.5 with sodium hydroxide twice a day for two months and for 33 days, respectively. No changes were observed in the body weights of the rats. Male rats were injected subcutaneously with 1.0 g/kg of the same solution daily for 40 days and growth retardation was observed.[114]

Male rats were injected subcutaneously with 2 ml of a 1.5% Boric Acid solution which also contained 0.1% riboflavin each day for 30 days. Because of the increase in body weight of rats during the experiment, the daily dose decreased from 600 to 180 mg/kg. No significant differences were observed in hematologic values. No toxic effects were observed except for a moderate degree of cloudy swelling and some fatty change in the liver. A group of female rats was injected subcutaneously with 12 mg/day of Boric Acid for 21 days. Two of six rats had a prolonged period of diestrus initially, but normal cycles reappeared.[73]

Three dogs were injected subcutaneously with 38–50 mg/kg/day of Boric Acid for 30 days. When the injections were made rapidly, the dogs became unsteady but recovered within a few minutes. No further toxic effects were observed although there was a moderate amount of cloudy swelling of the livers. One dog had mild hyperemia and cloudy swelling of a kidney and another dog had old degenerative changes in a few glomeruli.[73]

An aqueous Sodium Borate solution was injected subcutaneously at a dose of 250 mg/kg/day to six male gerbils for 16 days. Biochemical and histological

*See footnote under Subchronic Effects, Oral Toxicity section.

determinations were then made. During the experiment, no animals showed signs of toxicity. The seminiferous tubules of Borate-treated animals had degenerative changes and reduced diameter. Giant multinucleated cells, germ cell exfoliation, and pyknosis were also observed. Significant increases in acid and alkaline phosphatases resulted from Borate administration. The authors suggested that the increased phosphatase activity was a result of the release of nonspecific phosphatases from the lysosomes of degenerating cells.[135]

*Intraperitoneal toxicity**

Twenty-four rats were injected intraperitoneally with 4 ml of a 4% Boric Acid solution daily for three weeks (~727.3 to 941.2 mg/kg/day). No deaths were reported and no consistent changes in body weights were observed.[73]

Chronic Toxicity

*Oral toxicity**

Groups of 35 male and 35 female rats were given feed containing 117, 350, and 1170 ppm boron equivalents of Sodium Borate (~103.5, 309.7, and 1035.4 mg/kg/day Sodium Borate) and Boric Acid (~66.9, 200, and 668.6 mg/kg/day Boric Acid) for two years. At the two lower concentrations of Sodium Borate and Boric Acid, the rats were essentially normal in appearance and behavior and there were no histologic alterations in their organs. The rats fed the 1170 ppm boron equivalent of both compounds had coarse hair coats, scaly tails, a hunched position, swelling and desquamation of the pads of the paws, abnormally long toenails, inflamed eyelids, and a bloody discharge of the eyes. The scrotums of the males had a shrunken appearance and the testes were atrophic. There was decreased food consumption and retarded growth. At the high level of Sodium Borate, all the rats had a low packed cell volume and low hemoglobin values. This was also true for female rats fed the high level of Boric Acid.[120]

Groups of four male and four female dogs were fed diets containing from 58 to 350 ppm boron equivalents of Sodium Borate (~38.5–232.3 mg/kg/day Sodium Borate) or Boric Acid (~24.9–150 mg/kg/day Boric Acid) for two years. Additional dogs received a 1170 ppm boron equivalent of the two compounds (~776.5 mg/kg/day Sodium Borate and 501.4 mg/kg/day Boric Acid) for 38 weeks. There were no remarkable changes in appearance, behavior, appetite, and elimination, no effects on body weight or food consumption, and no abnormal necropsy findings except for testicular atrophy in the dogs fed the 1170 ppm boron equivalents of the compounds.[120]

Groups of eight male and 16 female rats were fed diets containing 117, 350, and 1170 ppm boron equivalents of Sodium Borate (~103.5, 309.7, and 1035.4 mg/kg/day Sodium Borate) and Boric Acid (~66.9, 200, and 668.6 mg/kg/day Boric Acid) for 14 days and then were mated. Three further generations were observed. The two lower doses of Sodium Borate and Boric Acid had no adverse effects on reproduction. Both male and female rats fed the 1170 ppm boron

*See footnote under Subchronic Effects, Oral Toxicity section.

equivalent of either compound were sterile. The males lacked viable sperm and there was evidence of decreased ovulation in the females.[120]

Boric Acid was administered orally to male rats in doses of 0.015–0.3 mg/kg/day of boron (~0.09 to 1.71 mg/kg/day Boric Acid) for six months. At 0.3 mg/kg boron, increased serum aldolase activity was noted by the second month. At this dose, testicular weight, spermatozoid mobility and numbers, as well as the DNA content of gonadal tissue were all reduced. At 0.05 mg/kg boron (~0.29 mg/kg Boric Acid) spermatozoid counts were reduced. Animals at the two highest doses had reduced liver glycogen and lactic acid levels. The authors concluded that Boric Acid, at doses greater than 0.015 mg/kg of boron for six months, has an adverse effect on the gonads of male rats.[136]

Subcutaneous toxicity

Groups of 10 male rats were injected subcutaneously with 2–25 mg/kg of Boric Acid twice per day, six days a week, for 90 days. There was no decrease in body weights of the rats. The rats were then injected with 200 mg/kg of Boric Acid twice a day for six days. They gained weight and there was no evidence of toxicity. Gross and microscopic examination revealed normal organs.[114]

Intramuscular toxicity

Five puppies received intramuscular injections of a vitamin B complex containing 0.5% Boric Acid three times a week for 12–18 months. Each animal received the equivalent of 0.5 mg/kg/day. No toxic effects were observed in any of the dogs.[73]

Groups of seven male and seven female rats from two consecutive generations received intramuscular injections of a vitamin B complex containing 0.5% Boric Acid three times a week. Since the rats increased in body weight during the course of the experiment, the Boric Acid they received decreased from approximately 3.3–0.7 mg/kg/day. The rats were mated at 75 days of age. The rate of growth, reproductive performance, average number of offspring in litters, and survival of the young were unaffected.[73]

Special Studies

Mutagenesis

Demerec et al.[137] reported that Boric Acid was mutagenic with a membrane method which measured the ability of a chemical to induce back-mutation of a streptomycin-dependent *Escherichia coli* strain. Fifty μg of Boric Acid per ml of agar was spread on the agar surface. However, when this test was repeated using both the method of Demerec et al. and the more sensitive paper-disc assay, in which the disc contained 50 μg of Boric Acid per ml of agar, Boric Acid was nonmutagenic.[138]

Two independent laboratories used the Ames test to study the potential mutagenicity of Boric Acid. Assays were performed in the presence and absence of Aroclor-1254 induced rat or hamster liver microsomes. In all assays from both laboratories, Boric Acid was reported to be nonmutagenic to *Salmonella*.[139]

When added to the medium at concentrations 0.25%–0.50%, Sodium Borate

induced reduced eye phenocopies in *Drosophila melanogaster*. Larvae treated with these borate salts had embryonic malformations.[140]

Drozdovskaya[141] studied the effects of Sodium Borate on the polytene salivary chromosomes of larval *D. melanogaster* flies. At a concentration of 17.5×10^{-4} *M*, Sodium Borate induced lumpy inclusions in most nuclei, grainy chromocenters, and increased chromosomal puff activity. Additionally, increased staining in the nuclei which was the result of increased RNA and DNA content was observed. Rapoport et al.[142] reported that at a concentration of 17.5×10^{-4} *M*, Sodium Borate induced reduced-eye mutations in flies and caused the formation of 22 new puffs on five separate polytene chromosomes. Puffs result from nucleic acid synthesis. Drozdovskaya[143] observed 33 borate-induced puffs in four prepupal salivary chromosomes. One of the puffs occurred in the region of the cytogenic localization "ey" gene phenotype (reduced eyes).

*Carcinogenesis**

The potential genital-tract carcinogenicity of Boric Acid was studied in female mice. One-tenth ml of a 2% Boric Acid in gum tragacanth solution was injected intravaginally into 20 BALB/c mice twice weekly for 50 weeks (~100 mg/kg). Positive and negative controls were used. The positive controls were treated with 7,12-dimethylbenz(a)anthracene (DMBA). One mouse treated with Boric Acid developed a vaginal neoplasm; this was a squamous tumor of low-grade malignancy. None of the other mice developed neoplasms of the genital tract. No tumors developed in 30 untreated controls, whereas 15 of 20 mice treated with DMBA developed tumors.[144]

A carcinogenesis bioassay of Boric Acid is being conducted by the National Cancer Institute. In this test, Boric Acid is being administered in the feed of mice for life. The study was initiated in June 1979.[145]

Teratogenesis

A number of investigators have studied the effects of Boric Acid on chick embryos. The LD50 of Boric Acid injected into chicken eggs when the embryos were 0 to 8 days old was approximately 5 mg/egg.[146] Injection of Boric Acid into chicken eggs has been reported to result in growth inhibition, interference in feather growth and some beak abnormalities,[146,147] leg malformations,[147,148] rumplessness,[149-154] and anemia.[155] Simultaneous administration of riboflavin reduced the teratogenic effects of Boric Acid to chicken eggs.[150-153] Roe et al.[109] reported that the addition of riboflavin to feed decreased the toxicity of Boric Acid administered in the diet to chicks.

Clinical Assessment of Safety

Skin Irritation and Sensitization

It has been reported that "strong" solutions of Boric Acid irritate the skin and turn it red.[156] A case of Boric Acid sensitivity has been reported in the literature.[157] One man used large amounts of Boric Acid ointment to treat boils

*See footnote under Subchronic Effects, Oral Toxicity section.

and with subsequent exposure to Boric Acid developed a papular eruption on his arms and legs.

A cumulative irritancy test was used to study the effect of repeated exposures of a hair preparation containing 3.2% Sodium Borate and a cleansing cream containing 1.7% Sodium Borate on the skin of 12 and 14 subjects, respectively (Table 2). The test material was applied under an occlusive patch to the backs of subjects daily for 21 consecutive days. Sites were scored one hour after patch removal. Applications 4 to 21 of the hair preparation produced erythema and papules in most subjects; the total cumulative irritancy score was 571 (maximum score = 630). The cleansing cream caused slight erythema in two subjects only, resulting in a total irritancy score of 6.4. The investigators concluded that, under the conditions of the study, the hair preparation was a "mild to moderate" cumulative irritant, whereas the cleansing cream was practically nonirritating.[158,159]

The Kligman maximization procedure was used to study the sensitizing potential of a hair preparation containing 3.2% Sodium Borate in 25 subjects (Table 2). The material was initially applied under a 48 h patch to each subject to determine whether sodium lauryl sulfate (SLS) pretreatment was required. The test material was found to be irritating; it was determined that SLS treatment was unnecessary. The undiluted hair preparation was applied under occlusion to one arm of each subject for 48 h. This procedure was repeated every other day for 10 days (five applications). Ten days after removal of the fifth induction patch, a 48 h occlusive challenge patch was applied to a fresh site. Sites were scored at 48 and 72 h. The hair preparation containing 3.2% Sodium Borate induced no irritation during challenge phases of the test; this product was determined to be nonsensitizing when applied to human skin.[160]

In a similar study, the contact-sensitizing potential of a cleansing cream containing 1.7% Sodium Borate was tested in 22 subjects (Table 2). Preliminary irritancy testing revealed no irritation to a 48 h patch containing this product; therefore, skin sites were pretreated with 5% SLS for 24 h prior to application of the initial induction patch. The product was applied under occlusion for 48 h, every other day for 10 days (five applications). Following a 10- to 14-day rest, 48-hour occlusive patches containing the test material were applied to fresh sites (with and without SLS pretreatment). SLS controls were also applied. Sites were scored at 48 and 72 h. More than half of the subjects reacted to SLS treatment (with or without application of test material). No significant irritation was observed at sites tested with the cleansing cream alone. The product containing 1.7% Sodium Borate was nonirritating and nonsensitizing.[161]

A Schwartz–Peck Prophetic Patch Test was used in two separate trials to evaluate the irritancy and sensitizing potential of a cleansing cream containing 1.7% Sodium Borate (Table 2). Open and closed patches containing the undiluted test material were applied to each of 147 subjects (trial 1: 98 subjects/trial 2: 49 subjects) for 48 h. Sites were then scored. Fourteen days later, open and closed 48 h challenge patches were applied to each subject. In both trials, there were no reactions to any of the patches. The cleansing cream containing 1.7% Sodium Borate was nonirritating and nonsensitizing.[162,163]

In a repeated insult patch test (RIPT), 48 h occlusive patches containing an undiluted cold cream (1.0% Sodium Borate) were applied to the backs of 101

TABLE 2. Irritation and Sensitization Tests on Cosmetic Products Containing Sodium Borate or Boric Acid.

Ingredient[a]/ *Product*	*Conc. (%)*	*Test Method*[b]	*No. of subjects*	*Results*	*Comment*	*Ref.*
SB/Hair prep.	3.2	Cumulative irr.	12	Total irritancy score = 571/630	Mild to moderate cumulative irritant	158
SB/Cleansing cream	1.7	Cumulative irr.	14	Total irritancy score = 6.4/630	Practically Nonirritating	159
SB/Hair prep.	3.2	Klig. max. (w/o SLS)	25	No reactions (challenge)	Nonsensitizing	160
SB/Cleansing cream	1.7	Klig. max. (w/SLS)	22	No reactions (induction/challenge)	Nonirritating/Nonsensitizing	161
SB/Cleansing cream	1.7	S-P prophetic	98	No reactions	Nonirritating/Nonsensitizing	162
SB/Cleansing cream	1.7	S-P prophetic	49	No reactions	Nonirritating/Nonsensitizing	163
SB/Cold cream	1.0	RIPT	101	Slight irritation in 2 subjects/ 1 patch induction	Practically nonirritating/ Nonsensitizing	164
SB/Cleansing cream	1.1	RIPT	101	No reactions	Nonirritating/Nonsensitizing	165
SB/Cleansing cream	1.1	S-P prophetic	198	Slight irritation in 1 subject/ induction	Practically nonirritating/ Nonsensitizing	165
BA/. . .	2.4	SIPT	19	Slight irritation in 1 subject	Practically nonirritating	166
BA/Bath prep.	0.4	SIPT	20	Minimal to moderate irritation	Moderately irritating	167

[a]SB = Sodium Borate; BA = Boric Acid; . . . = unknown product.

[b]Cumulative irritancy test: 21 consecutive 24 h patches. Klig. max. (Kligman Maximization Test): initial sodium lauryl sulfate (SLS) pretreatment if substance is nonirritating; 5 48 h induction pathces/10 day rest/1 48 h challenge ± SLS

S-P Prophetic (Schwartz–Deck Prophetic Patch Test): 1 open + closed 48 h induction/14-day rest/1 Open + closed 48 h challenge

RIPT: 10 48 h inductions/14-day rest/1 48 h challenge

SIPT: 1 24 h Patch

subjects, approximately half of whom were "hyper-sensitive" (Table 2). Sites were read at 48 h and the compound reapplied. This procedure was repeated every other day for 3.5 weeks (10 induction applications). After a 14-day rest, a 48 h occlusive challenge patch was applied to a previously untested site; sites were scored at 48 and 96 h. Two subjects reacted with slight erythema to the third induction patch. These were the only reactions observed. The authors concluded that the product containing 1.0% Sodium Borate was practically nonirritating and nonsensitizing.[164]

An RIPT and a Prophetic Patch test were used to determine the irritancy and sensitizing potential of a cream containing 1.1% Sodium Borate in 101 and 198 subjects, respectively (Table 2). The protocols for each test were as described above; however, in the RIPT, both open and closed induction and challenge patches were applied to each subject. In the Prophetic Patch test, one subject experienced minimal irritation to the induction patch; no other reactions to induction or challenge patches were observed. In the RIPT, no reactions (induction or challenge) were elicited by the test product. The results of these two tests indicate that the cream containing 1.1% Sodium Borate is practically nonirritating and nonsensitizing.[165]

A single insult patch test (SIPT) was used to evaluate the irritancy of a product containing 2.4% Boric Acid and a bath preparation containing 0.4% Boric Acid in 19 and 20 subjects, respectively (Table 2). The test material was applied undiluted to the arm of each subject for 24 h. Sites were scored at 24 and 48 h. The product containing 2.4% Boric Acid induced minimal erythema in one subject; no other reactions were observed. This product resulted in a PII of 0.03 (maximum score = 4), which is indicative of a practically nonirritating material.[166] The bath preparation containing 0.4% Boric Acid resulted in a PII of 1.50. Irritation ranged from minimal erythema to bright erythema accompanied by edema, petechiae, or papules. Although this product produced moderate irritation, it was determined to be "significantly milder than a competitive control" product (PII = 1.68) which was simultaneously tested.[167]

Photosensitivity

Photosensitivity studies were included in two of the previous Prophetic Patch tests and the two RIPTs. In the Prophetic Patch tests, challenge sites, treated with 48 h occlusive patches containing the test material, were irradiated with ultraviolet (UVA) (360 nm at a distance of 12 in for 1 min with a Hanovia Tanette Mark I lamp). Sites were scored 48 h later. Two cleansing creams containing 1.7% and 1.1% Sodium Borate were nonphotosensitizing in all of the 98 and 198 subjects tested, respectively, with these procedures.[162,165] In the RIPTs, skin sites treated with test material (under 48 h occlusive patches) were exposed to UVA (360 nm at 12 in for 1 min with a Hanovia Tanette Mark I lamp) following the removal of induction patches 1, 4, 7, and 10 as well as the challenge patch. Sites were scored 48 h after irradiation. Two cleansing creams containing 1.7% and 1.1% Sodium Borate were nonphotosensitizing in all of the 49 and 101 subjects tested, respectively.[163,165]

Chronic Toxicity

Chronic ingestion of mouthwashes containing Boric Acid (concentrations not specified) resulted in diffuse alopecia, as well as central nervous system and gastrointestinal disorders in a woman. Abatement of symptoms and regrowth of hair occurred after the patient avoided all boron-containing products. The authors suggested that hair-loss was a result of Boric Acid's accumulation in the hair follicles and the subsequent toxic effect on the hair bulbs.[168]

Occupational exposure for six years to a soap powder containing 78.6% Sodium Borate resulted in hair-loss in one man. The patient was advised to avoid all contact with the soap powder, and subsequently, hair loss "subsided" and hair growth returned "more or less" to normal.[169]

Intravenous Studies

Seven patients with brain tumors who were receiving neutron-capture therapy were administered intravenously 18.6 to 27.3 g of Sodium Borate (a range of 32–50 mg/kg of boron). In this procedure the boron served as the capture element. A consistent hypoxic type of electrocardiographic abnormality was observed immediately after the injection. When the boron was rapidly excreted or when the dose of boron was less than 50 mg/kg, the electrocardiogram returned to normal within 24–48 h. The researchers suggested that the entrance of boron into myocardial cells in appreciable concentrations produced injury resulting in cell hypoxia.[170]

Ten patients receiving neutron-capture therapy were administered intravenously doses of Sodium Borate up to 20 g (2.12 g boron). The median dose was 25 mg/kg boron and the maximum dose was 46 mg/kg boron. The patients received one to four doses at intervals of two weeks to three months. The immediate symptoms were: intense gastrointestinal stimulation leading to nausea, vomiting, urgent defecation and diarrhea, "mild peripheral vascular collapse", mild mental confusion, and a flushed skin on the face. Later symptoms were: drowsiness, lethargy, and continued gastroirritability. These effects ceased by days three to five and no deaths occurred. Toxic effects were not enhanced by up to four successive intravenous administrations.[171]

Other Clinical Experience

Product panel tests

Two cleansing creams, each containing 1.7% Sodium Borate, were assayed in panel tests. In each study, panelists were given the product and asked to use it daily for two weeks. In a group of 100 subjects, one cream produced no irritation.[172] In the other panel, which included 90 subjects, there was one report of irritation; a subject accidentally instilled some of the cream into her eyes. A stinging sensation was experienced; however, the irritation subsided following eye rinse.[173]

Case reports

Numerous reports of acute Sodium Borate and Boric Acid poisoning appear in the literature. Many of these fatal and nonfatal cases are comprehensively

TABLE 3. Correlation of Experimental, Pathological, Clinical and Laboratory Findings in Boric Acid Poisoning.

Organ or system involved	*Experimental findings*	*Histopathological changes in humans*	*Signs and symptoms*	*Laboratory findings*
Central nervous system	1. Highest organ concentration in the body 2. Neuronophagia, round cell infiltration, and hyper chromatosis 3. Displacement of phosphorus in brain by boron	1. Congestion and edema of brain and meninges 2. Scattered perivascular hemorrhages	Excitement or depression Headache Weakness Signs of meningeal irritation Coma or delirium Convulsions Collapse and cyanosis	Boric acid in cerebrospinal fluid (tumeric test)
Gastrointestinal tract	Small amount excreted by gastrointestinal tract	Vascular congestion Enlarged mesenteric nodes Exfoliative gastroenterocolitis	Vomiting Diarrhea Occasional crampy abdominal pain	Small amounts of boric acid may be demonstrated in feces
Urinary tract	80%–100% excreted in urine Glomerular and tubular drainage with cell degeneration and debris	Cloudy swelling and granular degeneration of tubular cells Rare cortical degeneration Occasional hemorrhagic cystitis	Diminished urine output Rare anuria Pain on micturition	Boric acid in urine Occasional red blood cells, white blood cells, and albumin in urine
Liver	Second highest organ concentration in body Minimal histological changes	Congestion Fatty change Rare parenchymatous degeneration	Rare jaundice	None recorded
Skin	Small amounts excreted in sweat and saliva	Exfoliative dermatitis with loss of keratin layer	Intense erythema with macules and/or papules. Followed by desquamation Rare petechiae	

From Ref. 175.

reviewed by Valdes-Dapena and Arey,[174] Goldbloom and Goldbloom,[175] and Pfeiffer.[113] In many instances, poisoning has been accidental rather than from use as a medication. Many cases have resulted when infants accidentally ingested large quantities of Boric Acid. Use of Boric Acid on burns, wounds, and diaper rash has also accounted for many cases. Mortality is higher in infants and children than in adults. Clinical symptomology and histopathological findings, as well as laboratory and experimental findings, are reviewed by Goldbloom and Goldbloom.[175] A table from their article summarizes these findings (Table 3).

Two additional effects of Boric Acid poisoning should be noted. First, Pinto et al.[176] observed that massive quantities of riboflavin were excreted in the urine of patients with Boric Acid poisoning. These patients had ingested Boric Acid. Second, Fisher,[177] Ducey and Brooke,[178] and Arey[179] observed the presence of intracytoplasmic inclusions in the pancreas of six patients with Boric Acid poisoning. Fisher[177] reported that the round bodies lay within acinar cells and had basophilic granules. Valdes-Dapena and Arey[174] suggested that this histologic finding has diagnostic significance.

Threshold Limit Values

The Threshold Limit Value (TLV) for workroom environments for Sodium Borate set by the American Conference of Governmental Industrial Hygienists[180,181] is 5 mg/m^3 (eight-hour workday, 40-hour workweek) and agrees with the value adopted in both Belgium and the Netherlands. This TLV is thought to "prevent acute irritant effects" over a normal working lifetime.

SUMMARY

This report reviews and supplements the FDA's 1978 *Monograph on Borax, Boric Acid, and Borates* and contains published and unpublished information pertinent to the cosmetic use and biological effects of Sodium Borate and Boric Acid.

These two ingredients are used as preservatives, antiseptics, water softeners, pH adjusters, emulsifiers, neutralizers, stabilizers, buffers, or viscosifiers in cosmetics. According to the industry's submissions to the FDA in 1981, Sodium Borate and Boric Acid are used in over 488 and 142 cosmetic formulations, respectively.

Sodium Borate and Boric Acid have some antibacterial and antifungal activity. Both compounds affect a variety of enzymes from bacteria and animals. Many enzymes are inhibited but some are stimulated.

Most investigators have reported that Sodium Borate and Boric Acid are poorly absorbed through intact skin. Both compounds are absorbed through abraded, denuded, or burned skin, and some mucosal surfaces both in animals and man. In the judgment of the Panel, the absorption of Sodium Borate and Boric Acid through damaged skin is substantially greater than through intact skin. Boric Acid is excreted in the urine, feces, saliva, milk, and perspiration.

Sodium Borate and Boric Acid are relatively nontoxic. The acute oral LD50 of Sodium Borate for rats ranged from 3.45 to 5.14 g/kg. Single oral doses of

450 mg/kg boron as Sodium Borate (3.982 g/kg Sodium Borate) had no effect on the fertility of male rats.

A 5% Sodium Borate in water solution was mildly or moderately irritating to the skin of rabbits and guinea pigs. A hair preparation containing 3.2% Sodium Borate was nonirritating and noncorrosive to the gastrointestinal tract of rabbits when applied to their tongues, relatively harmless to rats when ingested, and practically nonirritating when instilled in rabbits' eyes.

The acute oral LD50 of Boric Acid for rats ranged from 4.50 to 6.08 g/kg. A single oral dose of Boric Acid (3 g/kg) administered to mice on the first day of pregnancy prevented 94% of the embryos from reaching the blastocyst stage of development.

The irritation of rabbit and guinea pig skin by Boric Acid has been investigated. Acute studies indicated that, at 10% in water, Boric Acid is mildly or moderately irritating to the skin of rabbits and guinea pigs; a formulation containing 0.4% Boric Acid was found to be mildly irritating to the skin of rabbits in a similar study. Five percent aqueous Boric Acid solutions adjusted to alkaline pHs were moderately to markedly irritating to the skin of rabbits.

The acute intravenous LD50 to mice of Sodium Borate was 1.32 g/kg and the acute intravenous LD50 to rabbits of Boric Acid was between 800 and 900 mg/kg. A single intravenous dose of 75 mg/kg of Boric Acid resulted in transient hypotension in rats and intravenous doses of up to 300 mg/kg had no effect on the blood pressure of anesthetized dogs. The acute subcutaneous LD50 to rats of Boric Acid was 1.4 g/kg. The acute intraperitoneal LD50 to mice of Sodium Borate was 2.817 g/kg.

Oral doses of 800 mg/kg/day for four days of Boric Acid and 1 g/kg/day for 21–27 days of Sodium Borate or Boric Acid in the diet caused growth retardation in rabbits and rats, respectively. Oral doses of 18–23 g/day of Sodium Borate in the diet for 42 days had no adverse effect on the health of cows. Male rats received 0.3 to 6.0 mg/l of boron as Sodium Borate (~0.37–7.44 mg/kg/day Sodium Borate) in their drinking water for up to 90 days and no adverse effects were noted on male fertility. Boric Acid (1 g/kg/day) was administered orally to male rats for two weeks and testicular atrophy resulted. Doses of 1000 and 2000 ppm boron as Sodium Borate (0.53 and 1.06 g/kg/day Sodium Borate) in the diet for 30 to 90 days exerted toxic effects on the gonads of male rats and the rats were infertile. Testicular atrophy was severe when male rats and dogs were fed a diet containing 1750 ppm boron as Sodium Borate (~1548.7 mg/kg/day Sodium Borate for rats and 1161.5 mg/kg/day Sodium Borate for dogs) or Boric Acid (~1000 mg/kg/day Boric Acid for rats and 750 mg/kg/day Boric Acid for dogs) for 90 days. In a 90-day dermal toxicity study, Boric Acid (25 to 200 mg/kg/day) was nonirritating and nontoxic when applied to the intact skin of rabbits.

Twice daily intravenous administration to rabbits of 100 to 500 mg Boric Acid (~22.22–156.25 mg/kg) resulted in death within 10 days. Subcutaneous injection of up to 33 mg/kg Boric Acid twice daily for two months in rats did not result in any growth rate change. A daily subcutaneous dose of Boric Acid ranging from 180 to 600 mg/kg for 30 days resulted in no adverse effects in male rats. A subcutaneous dose of 1 g/kg of Boric Acid daily for 40 days caused growth retardation in rats. Dogs were injected subcutaneously with 38–50 mg/kg/day of Boric

Acid for 30 days. Rapid injections resulted in unsteadiness but the dogs recovered rapidly and no further toxic effects were observed. Subcutaneous injection for 16 days of 250 mg/kg/day of Sodium Borate did not result in morbidity but did result in degenerative changes in the seminiferous tubules of gerbils. No deaths were reported in rats after the daily intraperitoneal injection for three weeks of a 4% Boric Acid solution (~727.3 to 941.2 mg/kg/day).

Chronic oral toxicity studies in male rats and dogs indicated that a diet containing a concentration of 1170 ppm boron equivalents of Sodium Borate (~1035.4 mg/kg/day Sodium Borate for rats and 776.5 mg/kg/day Sodium Borate for dogs) or Boric Acid (~668.6 mg/kg/day Boric Acid for rats and 501.4 mg/kg/day Boric Acid for dogs) for two years induced testicular atrophy. The dogs showed no others signs of toxicity. Both compounds at this concentration in the diet were toxic to the rats. Another study reported similar results at much lower concentrations of Boric Acid. Ingestion of doses of 0.015–0.3 mg/kg/day boron as Boric Acid (~0.09–1.71 mg/kg/day Boric Acid) by male rats for six months induced changes in the testes.

Subcutaneous injection of rats with 2–25 mg/kg of Boric Acid twice per day, six days a week, for 90 days followed by injection with 200 mg/kg of Boric Acid twice per day for six days did not result in any evidence of toxicity. No adverse effects were observed after puppies were injected with 0.5 mg/kg/day of Boric Acid (in a vitamin B complex) for 12–18 months. Boric Acid (in a vitamin B complex), in a dose of 0.7 to 3.3 mg/kg/day was intramuscularly administered to rats. Reproductive performance, number of offspring in litters, and survival of the young were unaffected.

Boric Acid has been determined to be nonmutagenic in the Ames test. Variable results have been obtained with *Escherichia coli*. Boric Acid induces reduced eye phenocopies and lumpy chromosomal inclusions in *Drosophila melanogaster*.

In a carcinogenesis study, 20 female mice were given Boric Acid (0.1 ml of a 2% solution, ~100 mg/kg) intravaginally, twice weekly for 50 weeks; one developed a vaginal neoplasm of low grade malignancy. The numbers of tumor-bearing animals per positive and negative control groups were 15/20 and 0/30, respectively.

Studies have indicated that Boric Acid is teratogenic when injected into chicken eggs.

In clinical studies, cosmetic formulations containing 1.0%–3.2% Sodium Borate were nonirritating to moderately irritating and nonsensitizing when applied to human skin (620 subjects, total). Products containing 0.4% and 2.4% Boric Acid were moderately irritating and practically nonirritating, respectively (39 subjects, total). Results of photopatch-testing indicate that formulations containing 1.1% or 1.7% Sodium Borate are nonphotosensitizing (446 subjects, total).

Numerous case reports in the published literature pertain to fatal and nonfatal poisonings by Boric Acid and Sodium Borate. The majority of cases occurred prior to 1970 and were the result of accidental ingestion of these ingredients by infants and children. Use of Boric Acid on burned, abraded, or otherwise damaged skin has also accounted for a number of these cases.

DISCUSSION

Boric Acid and its salts have been used widely for decades as weak germicides and bacteriostatic agents partly because of their nonirritating properties. They have been found suitable for application to many delicate membranes including the cornea of the eye. Historically, Boric Acid was considered to be relatively nontoxic. It was widely used in the form of ointments and irrigating solutions and as dusting powders, but because of misuse in certain cases, there have been signs of toxicity. These routinely came from excessive use as irrigating solutions in body cavities, for soaking burn patients and, in rare instances, the application of Boric Acid powder to a diaper rash has been reported to cause fatality (Esplin, D.W., in Goodman and Gilman, 3rd. Edition, quoting Valdes-Dapena and Arey, 1962). Since the recognition in the early 1960s of the toxicities of highly concentrated solutions or nondiluted Boric Acid on the abraded skin, as in diaper rash, fatalities have been eliminated and toxicities have been minimized.

Since Boric Acid is poorly absorbed through intact skin it is concluded that the results of studies on mutagenesis, teratogenesis, and carcinogenesis do not indicate significant cause for concern as related to the judgment of the safety of cosmetics containing low concentrations of Boric Acid. Nevertheless, based on the increased absorption of Boric Acid by damaged skin as compared with intact skin, as well as the testicular atrophy observed in experimental animals after subchronic and chronic administration of Sodium Borate and Boric Acid and after review of the available data on skin irritation and the levels established by the EEC cosmetic comittee and the FDA OTC drug panels, the Panel concludes that a concentration limit of 5% would provide a reasonable degree of safety for the use of these ingredients.

CONCLUSION

The Expert Panel concludes that Sodium Borate and Boric Acid, in concentrations less than or equal to 5%, are safe as cosmetic ingredients when used as currently recommended; however, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant skin or injured skin.

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