EVALUATION OF THE HEALTH ASPECTS OF BORAX
AND BORIC ACID AS FOOD PACKAGING INGREDIENTS

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Prepared for
Bureau of Foods
Food and Drug Administration
Department of Health and Human Services
Washington, D.C.

Contract No. FDA 223-78-2100
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report, one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior-sanctioned food substances as food ingredients, is being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-78-2100 with the Food and Drug Administration (FDA), U.S. Department of Health and Human Services. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshaling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances (SCOGS), were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using borax and boric acid as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (Handler, 1978), which summarizes the world's scientific literature from 1920 through 1978. To ensure completeness and currency as of the date of this report, this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of April 25, 1980 (45 FR 27992-27995) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using borax and boric acid as food packaging ingredients. The Select Committee received a request for a hearing from the U.S. Borax Research Corporation, Anaheim, CA, which was subsequently withdrawn. No other requests were received and no hearing was held.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (Office of the Federal Register, 1980b) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA recognizes further [21 CFR 170.30] (Office of the Federal Register, 1980b) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO reviewed and evaluated the available information on borax and boric acid in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with FDA's
guidelines, relied primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. This report is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act. The Committee anticipates that its conclusions will be reviewed as new information becomes available.
II. BACKGROUND INFORMATION

Boron is a trivalent element comprising about 0.001% of the earth's crust (The Merck Index, 1976). It is widely distributed in plant and animal tissues and is known to be essential for plant growth (Underwood, 1977). Boron has been detected in cow milk in concentrations which appear to vary with the intake of boron by the animal (Fenner and Archibald, 1958; Owen, 1944), although the levels found in milk are small when compared to the amount excreted in the urine (Owen, 1944). Hamilton et al. (1972/1973) reported that the element is found in small amounts in human tissues (Table 1). Feeding studies have not shown boron to be an essential nutrient for animals (Hove et al., 1939; Orent-Keiles, 1940), but Schwarz (1974) has suggested that because boron is ubiquitous in animal tissues and possesses properties expected of an essential element, it should be classified "under special consideration" for trace element function. Dietary analyses have indicated that approximately 3 mg boron is contained in a USDA "moderate cost" food plan supplying 4200 kcal (Zook and Lehmann, 1965).

Boron does not occur in nature in its elemental form, but rather as boric acid in some volcanic spring waters and elsewhere as its salts, primarily borax and colemanite (Weast, 1979).

Boric acid (H₃BO₃) occurs as colorless, odorless, transparent crystals or as a white granular powder. It is readily soluble in water, ethanol, and glycerol (The Merck Index, 1976). It is stable at ordinary temperatures (The National Formulary XIV, 1975), has a melting point of approximately 171°C, and becomes volatile with steam (The Merck Index, 1976).

Borax (Na₂B₄O₇) is found as such in arid areas or as a component of uxeelite, colemanite, or kernite (Weast, 1979). In its anhydrous form, borax is a white crystalline substance. The salt is hygroscopic and, upon hydration, becomes a hard crystalline compound. Borax is soluble in water and glycerol, but insoluble in alcohol (The Merck Index, 1976).

Three borate salts, sodium metaborate (NaBO₂), sodium perborate (NaBO₂·H₂O₂·3H₂O), and sodium pentaborate (Na₂B₁₀O₁₆·10H₂O) are commonly known. Like boric acid and borax, they are soluble in water and glycerol (The Merck Index, 1976). Health aspects of these three salts are not evaluated in this report.

Boron compounds have many industrial uses. Boric acid is used in the production of ceramics, glass products, boron alloys, and flameproof finishes for textiles, in the hardening of steel, and in the formation of welding and brazing fluxes (The Merck Index, 1976). Traditionally, it has been used as an eyewash and as an antiseptic in pharmaceutical preparations, although it has been shown to have limited bacteriostatic activity (Harvey, 1975).
Table 1. Boron Distribution in Human Tissues (Hamilton et al., 1972/1973)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Concentration μg/g wet weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.4</td>
</tr>
<tr>
<td>Liver</td>
<td>0.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.6</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.1</td>
</tr>
<tr>
<td>Lung</td>
<td>0.6</td>
</tr>
<tr>
<td>Lymph node</td>
<td>0.6</td>
</tr>
<tr>
<td>Brain</td>
<td>0.06</td>
</tr>
<tr>
<td>Testis</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Borax has many and closely related uses in industry and in households. With soaps and detergents it is widely used as a cleaning product. In cosmetics it is often an ingredient of products requiring a mild alkali and preservative (The Merck Index, 1976), and is in some abrasive cleansers for control of acne (Cureton and Torrens, 1976). Either alone or with boric acid, it is used as a flame-retardant in textiles, lumber, hardboard, plywood, and acoustical tile and as a preservative for wood products and adhesives. It is also a component of commercial fertilizers, herbicides, and insecticides (The Merck Index, 1976).

Borax and boric acid are prior-sanctioned ingredients authorized for use in adhesives, sizes, and coatings in the manufacture of paper and paperboard products used in food packaging [21 CFR 181.30] (Office of the Federal Register, 1980b). Under prior sanction, borax has been used as a preservative in the packaging of meat for export [9 CFR 318.8] (Mehurin, 1958; Office of the Federal Register, 1980a), providing this use was at the request of and under the limitations of the receiving country. However, Steinmetz (1979) indicated that use of borax has been discontinued during the last 25-30 years due to rapid advances in refrigerated facilities for processing and shipping of meat products for export. Although the Joint FAO/WHO Expert Committee on Food Additives (1962, 1967) has stated that boric acid should not be used as a food additive, boric acid and borax may be used in some countries as direct food ingredients, particularly in caviar (Brunstad, 1969; Holak, 1972). Because their use as direct GRAS ingredients is not permitted in foods either produced in or imported by the United States, this report will not address direct addition of boric acid and borax to foods.

Use of borax and boric acid is also authorized as regulated indirect food additives when these compounds are used as components of paper and paperboard in contact with dry food [21 CFR 176.180] or as components of adhesives in articles intended for use in packaging, transporting, or holding food [21 CFR 175.105]. Borax also may be used as an adjuvant in textiles and textile fibers used as articles or components of articles intended for use in producing, manufacturing, packaging, processing, preparing, treating, transporting, or holding dry food [21 CFR 177.2800] (Office of the Federal Register, 1980b).

A residue tolerance of 8 ppm boron on or in citrus fruit is specified [40 CFR 180.271] (Office of the Federal Register, 1979) when boric acid or borax is applied as a post-harvest fungicide. This tolerance level includes boron occurring naturally in the citrus fruit. A tolerance of 30 ppm of boron in or on cottonseed is set to cover residues from application of the defoliant, desiccant, and herbicide sodium borate (including sodium metaborate and sodium tetraborate) plus naturally occurring boron in cottonseed [40 CFR 180.271]. Boric acid is also cleared as an inert ingredient of pesticides when it is used as a sequestранt [40 CFR 180.1001].
III. CONSUMER EXPOSURE DATA

The amount of borax used in conjunction with starch in adhesives for corrugated boxboard and laminated paperboard may be projected from an estimate for such use in 1972 (Russell, 1973). For that year he calculated that 420 million pounds (191 million kg) of starch were used in production of adhesives and that 5-20% borax was added to the starch to improve its adhesive properties. The annual rate of increase in use of starch for production of adhesives was estimated to be 4.6%. By assuming the average rate of addition of borax to these starch adhesives to be 12.5%, the estimated use in 1978 of borax in corrugated boxboard and laminated paperboard would be approximately 6,862,500 pounds (3,119,300 kg). This figure would translate to a daily per capita usage of about 0.04 g for all paperboard and boxboard products manufactured. Because only a fraction of the boxboard and paperboard containing borax-starch adhesives is used for food packaging, and because migration of borax from such packaging would be small, the figure of 0.04 g borax (0.004 g boron) per day from this source far exceeds that of actual consumer exposure.
IV. BIOLOGICAL STUDIES

Absorption, metabolism, and excretion

Oral administration of 15-88 mg boron per kg body weight (as borax) to guinea pigs and rabbits resulted in excretion of 64% of the dose in 24 hours, with the remainder excreted during the next 4 days (Akagi et al., 1962). Measurement by this group (Akagi et al., 1963) of boron distribution in guinea pigs after oral administration of borax (140 mg boron per kg) indicated that concentrations in brain, liver, and kidney peaked 2-3 hours after administration and then decreased steadily over the remainder of a 24-hour period. Phosphorus levels in brain and liver fell to about 80% of initial values for about 4 hours after the borax administration, and then returned to normal by the end of 24 hours. Phosphorus levels in the kidney were not affected by the treatment (Akagi et al., 1963). Direct titration of boric acid in the urine of dogs established that "practically all" of the boron present was in the form of boric acid (Pfeiffer et al., 1945), suggesting that the compound is probably not converted to other metabolites.

Pham-Huu-Chanh and coworkers (1975) compared the effects of boric acid upon respiration, systemic hemodynamics, and general metabolism in isolated perfused rabbit hearts and in anesthetized rats and dogs. Boric acid (0.2, 1, 2, 10, and 20 mg) caused a moderate (5-25%) increase in the force of contraction of the isolated rabbit heart. In male Wistar rats injected intravenously with 75 mg boric acid per kg body weight, arterial blood pressure dropped slightly for a short time. Respiration, cardiac contractile force, systemic hemodynamics, and general metabolism of the dogs were not affected by intravenous injection of as much as 300 mg boric acid per kg.

Studies by Wiley (1907) indicated that human adults ingesting a single dose of 3 g or more of boric acid rapidly excreted 82-100% of the compound in the urine. Only traces were excreted in the feces and sweat. Essentially complete excretion of oral doses of boric acid in the urine was confirmed by balance studies in humans in which 95% of the boron (dietary plus boric acid) administered on days 3, 4, and 5 was excreted in the urine by day 7 (Kent and McCance, 1941). A more recent dietary study (Tipton et al., 1966) reaffirmed that approximately 98% of 350-420 µg boron ingested daily in foodstuffs was excreted through the kidney, while less than 2% was excreted in the feces. Actual balance figures for the 30-day period showed the subjects to be in slightly negative balance (that is, they excreted more boron than they consumed from food during this period).
Absorption of boric acid through skin has been measured with varying results. Although Kahlenberg and Barwasser (1928), Mulinos et al. (1953), Ochterner (1911), and Tan (1970) reported absorption of boric acid through intact human skin, other investigators, using better analytical procedures, have established that intact skin does not allow absorption in humans and rabbits (Draize and Kelley, 1959; Fisher et al., 1955; Pfeiffer et al., 1945). However, it is readily absorbed through irritated or damaged skin (Mulinos et al., 1953; Pfeiffer et al., 1945), and numerous reports indicate that sufficient boric acid may be absorbed by this route to cause toxicity in infants (Abramson, 1949; Brooke, 1954; Brooke and Boggs, 1951; Fellows et al., 1948; Grant and Wegner, 1948; Hallett, 1955; Marks, 1954; Rosen and Haggerty, 1956) and children (Baker and Wilson, 1963; Skipworth et al., 1967). Boric acid absorbed through damaged skin is excreted unchanged (Draize and Kelley, 1959).

Acute toxicity

Data from studies of acute toxicity of boric acid and borax administered by several routes are summarized in Table 2. Verbitskaya (1975) reported oral LD$_{50}$ values for both compounds in rats, mice, rabbits, guinea pigs, and dogs. Her data indicated that guinea pigs, rabbits, and dogs were more sensitive to these substances and that both sexes appeared to be affected similarly.

Weir and Fisher (1972) determined oral LD$_{50}$ values of borax and boric acid in Sprague-Dawley and Long-Evans rats (5 per group) and in mongrel dogs. The compounds were administered to the fasted rat by stomach intubation. The Sprague-Dawley rats received the compounds as 5% aqueous methyl cellulose suspensions, while the Long-Evans rats received the compounds dissolved in distilled water. The LD$_{50}$ values for the two strains varied somewhat (Table 3) and signs of toxicity reported by these authors included depression, ataxia, convulsions, and death. Both sexes were affected equally by treatment with the boron compounds. In dogs given 1.5-6.5 g borax per kg body weight or 1-4 g boric acid per kg, emesis occurred within 1 hour of administration. Dogs given the boric acid or borax survived the 14-day observation period.

Data for rabbits given four daily consecutive oral doses of boric acid indicated the LD$_{50}$ to be 800 mg/kg. Signs of toxicity in this species included anorexia, weight loss, and diarrhea (Draize and Kelley, 1959).

Several investigations have been reported on the diminution of borate toxicity by glucose. Easterday and Farr (1961) injected mice intravenously with a normally toxic amount of borax and varied the concentration of glucose. The least toxic ratios were 1:1.5 and 1:2 borax:glucose. At these ratios, the intravenous
Table 2. Acute Toxicity (LD$_{50}$) of Boric Acid and Borax in Animals

<table>
<thead>
<tr>
<th>Species</th>
<th>Route of administration</th>
<th>Dosage g/kg</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>p.o.</td>
<td>2.9-4.4</td>
<td>Verbitskaya, 1975</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>2.9-4.4</td>
<td>Verbitskaya, 1975</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>2.6</td>
<td>NIOSH, 1976</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>4.75-5.58</td>
<td>Smyth et al., 1969</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>3.16-4.08</td>
<td>Weir and Fisher, 1972</td>
</tr>
<tr>
<td>Rat</td>
<td>s.c.</td>
<td>1.4</td>
<td>Mulinos et al., 1953</td>
</tr>
<tr>
<td>Rat</td>
<td>i.v.</td>
<td>1.3</td>
<td>NIOSH, 1976</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>p.o.</td>
<td>1.9</td>
<td>Verbitskaya, 1975</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>s.c.</td>
<td>1.2</td>
<td>NIOSH, 1976</td>
</tr>
<tr>
<td>Rabbit</td>
<td>p.o.</td>
<td>1.9</td>
<td>Verbitskaya, 1975</td>
</tr>
<tr>
<td>Rabbit</td>
<td>p.o.</td>
<td>0.8</td>
<td>Draize and Kelley, 1959</td>
</tr>
<tr>
<td>Dog</td>
<td>p.o.</td>
<td>1.9</td>
<td>Verbitskaya, 1975</td>
</tr>
</tbody>
</table>

Boric acid

<table>
<thead>
<tr>
<th>Species</th>
<th>Route of administration</th>
<th>Dosage g/kg</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>i.v.</td>
<td>1.77</td>
<td>Easterday and Farr, 1961</td>
</tr>
<tr>
<td>Mouse</td>
<td>p.o.</td>
<td>4.3-6.4</td>
<td>Verbitskaya, 1975</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>4.3-6.4</td>
<td>Verbitskaya, 1975</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>5.66</td>
<td>Smythe et al., 1969</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>4.5-6.08</td>
<td>Weir and Fisher, 1972</td>
</tr>
<tr>
<td>Rat</td>
<td>p.o.</td>
<td>2.6</td>
<td>NIOSH, 1976</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>p.o.</td>
<td>2.7</td>
<td>Verbitskaya, 1975</td>
</tr>
<tr>
<td>Rabbit</td>
<td>p.o.</td>
<td>2.7</td>
<td>Verbitskaya, 1975</td>
</tr>
<tr>
<td>Dog</td>
<td>p.o.</td>
<td>2.7</td>
<td>Verbitskaya, 1975</td>
</tr>
</tbody>
</table>
Table 3. Acute Toxicity (LD$_{50}$) Values for Boric Acid and Borax in Rats (Weir and Fisher, 1972)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Sex</th>
<th>Body weight g</th>
<th>Mean g/kg</th>
<th>Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boric acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M*</td>
<td>267-310</td>
<td>3.45</td>
<td>2.95-4.04</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>F*</td>
<td>206-248</td>
<td>4.08</td>
<td>3.64-4.56</td>
</tr>
<tr>
<td>Long-Evans</td>
<td>M†</td>
<td>85-118</td>
<td>3.16 (est.)</td>
<td></td>
</tr>
<tr>
<td>Borax</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M*</td>
<td>267-310</td>
<td>4.50</td>
<td>4.14-5.01</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>F*</td>
<td>206-248</td>
<td>4.98</td>
<td>4.31-5.76</td>
</tr>
<tr>
<td>Long-Evans</td>
<td>M†</td>
<td>85-118</td>
<td>6.08</td>
<td>3.54-10.40</td>
</tr>
</tbody>
</table>

*Sprague-Dawley rats received the compounds as 0.5% aqueous methyl cellulose suspensions.

†Long-Evans rats received the compounds as water solutions.
LD₅₀ estimate for borax increased from 1320 to 1770 mg/kg. Glucose also decreased the toxicity of sodium pentaborate and sodium tetraborate administered intravenously and intraperitoneally (Easterday and Hamel, 1963).

**Short-term studies**

Frost and Richards (1945) injected weanling male rats (six per group) subcutaneously with 30 mg boric acid in aqueous solution daily for 30 days. At the beginning of the study, the injections provided 600 mg boric acid per kg body weight, and at the end, 180 mg boric acid per kg. Urinalyses, blood chemistry measurements, and gross pathology at necropsy were reported to be normal. Female rats injected subcutaneously for 21 days with 12 mg boric acid per day (60-70 mg boric acid per kg) had normal estrous cycles. Dogs injected intravenously with 38-50 mg boric acid per kg daily for 30 days showed no adverse changes in body weight, blood or urine composition, or in gross pathology at necropsy. The daily dosages given to these dogs would be equivalent to 2.7-3.5 g boric acid in a 70 kg human.

In the same year, Pfeiffer et al. (1945) determined the effects in rats and dogs of boric acid administered subcutaneously, orally, and cutaneously. In growth studies, five groups of 20-24 "immature" rats were given boric acid in drinking water. Boric acid concentrations of 0.25% and higher (0.25% representing an intake of about 350 mg/kg body weight per day) slowed growth, but caused no pathologic lesions or adverse changes in blood composition. In four dogs injected subcutaneously twice a day for 45 days with 100 mg boric acid per kg, Pfeiffer et al. (1945) found no changes in hemoglobin concentration, or in erythrocytes or leucocytes. Urinary excretion of boric acid, however, did not reach a plateau until after 14-18 days' administration, at which time 85% of the injected boric acid was being excreted. This finding was interpreted as indicating that boric acid was probably accumulating in the organs of these dogs. Analyses of organs of two dogs treated with boric acid ointment for 25 and 33 days (one dog for a skin wound, the other for a third degree burn of approximately the same size) showed high concentrations of boric acid. During this time, brain tissue of each of the two dogs accumulated 212 and 247 mg boric acid per 100 ml tissue; liver, 107 and 18 mg per 100 ml; and adipose tissue, 30 and 60 mg per 100 ml.

Inhalation of boric acid aerosols (9.6 or 48.6 mg/m³) by male rats for 4 hours per day for 4 months indicated dose-related adverse changes in morphological characteristics of the spermatogenic epithelium in comparison with control rats. Rats exposed to both levels of boric acid aerosol were not able to impregnate female rats in estrus. Although mating was observed, vaginal smears showed the absence of spermatozoa (Tarasenko et al., 1972).
In another subchronic study, Dixon et al. (1976) administered borax to male rats in drinking water. Concentrations of boron in the water were 0.3, 1.0, or 6.0 ppm. Based upon an average intake of 35 ml per day, the maximum intake of boron was estimated by the authors to be 840 μg/kg body weight. After 30, 60, and 90 days consumption of the borax solutions, no significant differences were found in body weights, weights of testes, prostate, or seminal vesicles, or in clinical serum chemistry measures as compared with control animals. Fructose and zinc levels, plasma concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH), and acid phosphatase activity in the prostate were not affected by this treatment.

Weir and Fisher (1972) fed for 90 days, diets containing borax or boric acid supplying 52.5, 175, 525, 1750, and 5250 ppm boron to male and female Sprague-Dawley rats initially weighing 81 to 119 g. These diets provided daily boron intakes of approximately 2.6, 8.8, 26, 88, and 260 mg/kg body weight, respectively. The highest level (5250 ppm) was unequivocally toxic; all animals fed this diet died within 3-6 weeks. Growth, physical appearance, and food intake of animals consuming diets containing up to 525 ppm boron appeared normal throughout the study. Although slight increases in organ weights were observed in females fed 52.5 ppm boron as borax or boric acid and in males fed 175 ppm boron as borax, organ weights of rats fed 525 ppm boron were similar to controls. Histologic examination of testes showed partial atrophy in some males fed 525 ppm boron as borax or boric acid and arrest of spermatogenesis in one animal fed borax at this level. Rats provided diets supplying 1750 ppm boron had decreased food consumption and decreased growth. Organ weights were generally lower in this group; organ to brain weight ratios, a measure considered by the authors to indicate organ damage, were considerably decreased. Complete atrophy of the testes and abnormalities of the adrenals were found when tissues of these animals were examined for morphological differences.

Weir and Fisher (1972) also fed diets containing borax or boric acid supplying 17.5, 175, or 1750 ppm boron to male and female beagle dogs (five per group) for 90 days. Daily intakes of boron were approximately 0.4, 4.4, and 44 mg/kg body weight, respectively. The only effect in animals on the diet containing 17.5 ppm boron (as borax) compared with untreated controls was a significantly decreased spleen to body weight ratio in males. In males fed the diet containing 175 ppm boron as boric acid, a decrease in the ratio of testes to body weight was observed, but no histological changes were noted. No significant changes in organ weights were seen in the female dogs at this same level. Dogs fed 1750 ppm boron as borax had greater ratios of brain to body weight; dogs given this level of boron as boric acid had increased liver to body weight ratios. Decreased hematocrit values and hemoglobin concentrations were found in some dogs fed 1750 ppm boron as borax. Histological evidence of red blood cell
destruction (presence of hemosiderin in liver, spleen, and kidney cells) was found in these animals. Microscopic examination of testes and spermatogenic epithelium of dogs fed the same concentration indicated that these tissues had undergone severe atrophy. Thyroid and adrenal tissue also showed signs of histological changes.

Effects of boric acid and borax on protein and nucleic acid content of brain, liver, and kidney in 3-month-old male albino rats were investigated by Dani et al. (1971). Rats were administered 1000 mg boric acid or borax per kg body weight in aqueous solution daily by stomach tube until the rats showed signs of toxicity (a maximum of 3 weeks). Both substances slowed the growth of the rats, with borax causing greater growth depression. Concentrations of DNA increased in brain and kidney but decreased in liver of these rats. Simultaneously, concentrations of RNA increased in the three tissues when either boron compound was administered. Concentrations of protein and nitrogen in tissues of these animals followed no predictable pattern, being increased in some instances and decreased in others.

Stimulation of RNA synthesis by boric acid in livers of male Sprague-Dawley rats was confirmed by measurement of 6-14C-labeled orotic acid incorporation into RNA. RNA synthesis was greatly increased in livers of animals injected intraperitoneally, whereas stimulation was less marked in livers of rats fed a diet containing 1 ppm boron (as boric acid) for 6 weeks. DNA synthesis, as measured by incorporation of 6-3H-labeled thymidine, was not increased by either route of boric acid treatment, but the authors attributed this finding to the long time interval (10 hours) before the DNA concentration was measured (Weser, 1967).

Roe et al. (1972) demonstrated that one of the mechanisms of action in boric acid toxicity may be through formation of complexes with riboflavin. Boric acid has long been known to form complexes with compounds having two adjacent hydroxyl groups in cis-positions such as glucose, riboflavin, and ascorbic acid (Zittle, 1951). More recent in vitro kinetic and equilibrium studies have shown that borate reacts with the ribose moiety of nicotinamide adenine dinucleotide (NAD) and nicotinamide mononucleotide (NMN) (Johnson and Smith, 1976). Inclusion of 1% boric acid in diets containing no riboflavin, or very low levels of the vitamin, impaired growth in rats and guinea pigs. The growth retardation was less severe when boric acid was omitted from the diet. Inclusion of boric acid in the diet provided daily intakes of about 1000 mg/kg body weight for rats and 400 mg/kg for guinea pigs. Excretion of 14C-labeled riboflavin was greater in rats fed boric acid, although the capacity of the liver to retain the vitamin was not changed by the presence of boric acid. Administration of excess riboflavin to chicks given boric acid mitigated the signs of toxicity, easy pluckability and excessive loss of feathers (Roe et al., 1972).
Long-term studies

In a study of effects of oral administration of trace minerals, male and female Swiss mice of the Charles River strain (54 per group) were given drinking water containing 5 ppm boron (0.44 mg/kg body weight) as sodium metaborate for 2 years (Schroeder and Mitchener, 1975). Body weights of male mice differed significantly from controls only at 90 days of age, and body weights of females did not differ significantly at any time during the treatment. Life span or incidence of tumors were not affected.

Weir and Fisher (1972) fed diets containing 117, 350, or 1170 ppm boron (6, 18, and 60 mg/kg body weight) as borax or boric acid to groups of 35 male and 35 female Sprague-Dawley rats for 2 years. Rats fed the diets supplying 1170 ppm boron showed the following signs of toxicity after 2 months: "coarse hair coats, scaly tails, a hunched position, swelling and desquamation of the pads of the paws, abnormally long toenails, shrunken appearance of the scrotum of the males, inflamed eyelids and bloody discharge of the eyes." The frequency of these abnormalities increased during the first year, but then remained fairly constant. Histologic examinations of atrophied testes of the male rats fed 1170 ppm boron showed degenerated seminiferous epithelium and decreased tubular size. Hemoglobin concentrations and hematocrit values were significantly lower in both male and female rats fed 1170 ppm boron as borax, but were lower only in female rats fed this level of boron as boric acid. Composition of urine samples was not affected by administration of either compound. No signs of toxicity were reported in the rats on diets containing 117 and 350 ppm boron.

These investigators (Weir and Fisher, 1972) also fed diets containing 58, 117, or 350 ppm boron (1.5, 3, or 9 mg/kg body weight) as borax or boric acid to groups of four male and four female beagle dogs for 2 years. After these levels of boron produced no observed adverse changes in appearance, behavior, appetite, or elimination, additional groups of dogs were fed diets containing 1170 ppm boron for 38 weeks. The only adverse effect noted at this level of intake was testicular degeneration and cessation of spermatogenesis. After 38 weeks of boron ingestion, two male dogs were fed the control diet for 25 days. Based on observation of one of these animals, the testicular atrophy and cessation of spermatogenesis appeared to be reversible.

Mutagenicity and carcinogenicity

Demerec et al. (1951) reported that boric acid (concentration 1.5-4.0%) had the capacity to induce back-mutation from streptomycin dependence to nondependence in Escherichia coli. However, Iyer and Szybalski (1958), using two modifications of this procedure, found that boric acid caused no significant mutagenic activity.
In a lifetime study, random-bred Swiss mice of the Charles River CD strain were administered sodium metabolate (5 ppm boron or 0.44 mg boron per kg body weight) in drinking water. The life span of animals exposed to this level of sodium metabolate was not significantly affected, and incidence of tumors was not increased by this treatment (Schroeder and Mitchener, 1975).

Teratogenicity studies

Studies of teratogenic effects of boric acid on chick embryos are extensive. A summary of these studies follows, although it is recognized that the results have limited relevance to mammalian systems. Landauer (1952, 1954) injected 2.5 mg boric acid into yolk sacs of chick embryos at 24 hours after fertilization or 1.0, 2.5, or 3.5 mg boric acid at 96 hours. Rumpleness (absence of all tail vertebrae and related structures) occurred after injection at 24 hours incubation. Injection at 96 hours produced decreased body size, shortening of the lower beak, facial coloboma, and cleft palate in embryos examined on the thirteenth day of incubation. Incidence of these abnormalities and mortality increased as the dose of boric acid was increased. Newly-hatched chicks treated with boric acid at 96 hours of incubation had an increase in "curled toe paralysis," an abnormality associated with riboflavin deficiency during embryonic development. Landauer and Clark (1964) demonstrated that administration of riboflavin with the boric acid greatly decreased the incidence of these abnormalities in chick embryos.

Other experiments (Landauer, 1953) indicated that simultaneous administration of substances forming complexes with boric acid (D-ribose, D-sorbitol hydrate, or pyridoxine·HCl) also decreased mortality and the incidence of defects resulting from boric acid administration to chick embryos.

Histological examination of 3-day embryos treated with 2.5 mg boric acid at 24 hours (Goldie and Stierholz, 1964) indicated that the neural tube, notochord, and tailbud were affected by exposure to boric acid at this stage of development. A more recent study (Schowing et al., 1976) indicated that these histologic effects were present when much smaller doses (200 µg per egg) were injected after 28 hours of incubation.

Other adverse effects in chick embryos included delayed erythrocyte maturation (Sherman and Fox, 1955) and lowered hemoglobin and hematocrit values (Rosky et al., 1957).

Ridgway and Karnofsky (1952) calculated LD50 doses of boric acid for chick embryos at 4 and 8 days incubation. At 4 and 8 days, the LD50 values for administration by the yolk sac route were 5 and 7 mg per egg. By the chorioallantoic membrane route, the 8th day LD50 was 5 mg per egg. Abnormalities in embryos examined at 18 days were paleness, edema, and retardation of feather growth.
Studies of teratogenicity of boric acid in mammalian species were not found. It is known, however, that boric acid is transferred across the placentae in rats (Hove et al., 1939).

Reproduction studies

In a study of reproduction over three generations, male and female rats were fed diets containing borax or boric acid which supplied 117, 350, or 1170 ppm boron (6, 18, and 60 mg/kg body weight) (Weir and Fisher, 1972). Dietary treatment began 14 weeks before mating of the parent generation and continued for the entire study. Reproductive performance in rats fed diets containing 117 or 350 ppm boron was not impaired, and gross defects in tissues of these parents or their weanling offspring were not detected. Rats fed the diets containing 1170 ppm boron did not reproduce. Apparently reproductive organs of both sexes were adversely affected. Testes of male rats were atrophied and viable spermatozoa were not found. Attempted mating of females consuming the diets containing 1170 ppm boron with control males did not produce offspring. Examinations of ovaries of these groups indicated that ovulation was probably reduced.

Preliminary studies of specific alterations in reproductive capacity of male rats were reported by Dixon et al. (1976). Borax was administered as single oral doses of 45, 150, and 450 mg boron per kg body weight and as subchronic levels in drinking water (0.3, 1.0, and 6.0 ppm boron as borax) for 30, 60, or 90 days. Daily boron intakes were approximately 40, 140, and 840 μg/kg. Profiles of spermatogenic cell types and fertility determined by serial mating were not affected by these acute doses. In the short-term studies, normal ranges were found for weights of testes, prostate, and seminal vesicles, for specific activity of acid phosphatase and levels of fructose and zinc in the prostate, and for plasma levels of LH and FSH.

More specific and extensive short-term studies of reproductive effects in male rats fed borax in diets containing 500, 1000, or 2000 ppm boron (25, 50, and 100 mg/kg body weight) for 30 or 60 days were reported by Lee et al. (1978). Animals fed the diet containing 500 ppm boron were not adversely affected but animals fed diets containing 1000 or 2000 ppm boron had fewer germinal cells and decreased diameters of seminiferous tubules. As these cellular changes occurred, plasma levels of FSH and LH increased while plasma testosterone remained unchanged. Levels of enzyme activities also reflected the morphological changes in the gonadal tissues: specific activities of hyaluronidase, sorbitol dehydrogenase, lactate dehydrogenase, and isozyme-X were reduced, while specific activities of glyceraldehyde-3-phosphate and malate dehydrogenases were increased. These abnormalities became more severe as levels of boron and length of exposure increased. Fertility patterns indicated that males exposed at 1000 ppm boron for
30 and 60 weeks had markedly reduced fertility rates for 3 and 4 weeks, respectively, after termination of boron consumption. Exposure to 2000 ppm for 30 weeks produced significantly reduced fertility for 8 weeks, which was only partially reversed during weeks 9-12. Treatment at this level for 60 days produced total infertility for at least 32 weeks after boron treatment was terminated. Mating behavior was normal in all animals, and litter size was not reduced by boron treatment when pregnancy occurred.

Human studies

In order to study the nutritional effects of food preservatives commonly used at that time, Tunnicliffe and Rosenheim (1901) administered borax and boric acid to three children, ages 2½-5 years. Two of the children were described as "healthy" and the third was described as "delicate, being convalescent from pneumonia." Increasing doses of boric acid (0.5, 0.66, and 1.0 g per day) were given to each child for 7 days and constant doses of borax (1.5 g per day) were given for 5 days following boric acid administration. Both compounds were dissolved in the daily milk allowance of the children. Body weights of the children increased slightly during the periods of boric acid and borax consumption. Nitrogen balance remained positive and urinary phosphorus excretion was not greatly affected. Although the total cumulative dose of boric acid was 4.5 g and that of borax was 7.5 g, the investigators did not report any adverse signs in these children.

Many cases of fatal poisoning of infants have occurred when boric acid or borax was used in ignorance of their harmful effects when applied to injured skin, or accidentally substituted for another substance in feeding. Estimates of toxic exposures for infants range from 1-3 to 5-6 g (Fellows et al., 1948).

For many years boric acid was used for antiseptic purposes in baby powders. In an instance of fatal poisoning by the absorption of boric acid through injured skin, Hallett (1955) reported that a baby had developed "blisters" around the buttocks and upper thighs, leaving a raw, underlying surface exposed. Boric acid powder was applied at every diaper change. After a few days the baby died. The concentrations of boric acid in the liver and kidneys were 0.564% and 0.403%, respectively. These levels are approximately 10 times the recognized lethal concentrations for these organs.

In an incident in an American hospital, a flask of 3% boric acid was mistakenly substituted for distilled water in the preparation of infant formulas. Four infants were affected; only one survived. The signs displayed by these infants included fussiness, vomiting, diarrhea, dehydration, and an exfoliative dermatitis characterized by a "scalded skin" or "boiled lobster" appearance (Rubenstein and Mushet, 1970).
Occurrence of toxic signs, including convulsions, abnormal electroencephalograms (EEG), and normocytic hypochromic anemia resulting from feeding mixtures of borax and honey to two infants, was described by Gordon et al. (1973). Over the course of 12 weeks, one infant consumed about 125 g borax (about 323 mg/kg body weight per day) from a mixture containing 10.5% borax; the other received approximately 9 g of boric acid (about 64 mg/kg per day) in a 5-week period. Borate intoxication was confirmed in the first infant by the presence of abnormally high levels of boric acid in the blood and urine. These parameters were not measured in the second infant, but in both cases the convulsions ceased and the EEG returned to normal after the boric acid and borax were withdrawn.

Fisher (1957) and Valdes-Dapena and Arey (1962) attributed intracytoplasmic inclusions in the pancreas of infants to boric acid poisoning. However, Sanusi et al. (1975) reported this pathological abnormality in an infant without boric acid poisoning and questioned the value of this lesion as a method of diagnosis.

A number of adults have also been severely injured, some fatally, by single large doses of boric acid or borax. As reviewed by Fellows et al. (1948), the lethal doses seem to vary considerably. However, the median is thought to be more than 15-20 g in adults.

Pinto et al. (1978) analyzed urine samples of fourteen 14-month- to 90-year-old persons in New York City, who had accidentally or purposely ingested boric acid or commercial borax products. Ingestion by some of the adults was estimated to be as much as 10 g. Collection of the urine samples began as early as 4 hours or as late as 54 hours following ingestion. Urinary riboflavin concentrations (µg riboflavin per mg creatinine) were compared to percentiles of normal values of riboflavin excretion of the Ten-State Nutrition Survey, 1968-1970. Analyses of complete 24 hour or random urine samples indicated that riboflavin excretion of patients ingesting boric acid was in the 62-100th percentile rankings established in the Ten-State Survey. In one patient, the urine sample collected 4 hours after boric acid ingestion contained more than twice the level of riboflavin designated as the 100th percentile level for that group. By 8 hours after ingestion, the level of urinary riboflavin had dropped almost to the 100th percentile level. Urinary riboflavin concentrations continued to fall over a 40-hour period to levels which were not detectable. In a second patient from whom urine samples were collected beginning 19 hours after boric acid ingestion, urinary excretion of riboflavin followed the same pattern.

Pinto and coworkers (1978) then attempted to determine the minimal amount of boric acid that would increase the urinary excretion of riboflavin. Three normal healthy male subjects (ages
30-41 years) consumed 3 g boric acid dissolved in 200 ml water following an overnight fast. An isocaloric diet containing 1.5 mg riboflavin was provided for 3 days preceding and on the day of boric acid administration. Baseline levels of riboflavin excretion were determined during the first 3 days. Riboflavin excretion was not increased by administration of 3 g boric acid in the volunteers. The authors concluded that a single dose of more than 3 g boric acid would be required to increase urinary excretion of riboflavin.

Effects of large doses of borax injected intravenously into patients being given neutron capture therapy for brain tumors were studied by Locksley and Farr (1955). Ten patients received from one to four injections of borax before neutron capture therapy treatments given at intervals of 2 weeks to 3 months. Each dose ranged from 14-20 g borax (1.5-2.0 g boron). Nausea and emesis occurred within 2 minutes of borax injection and urgent defecation and micturition with incontinence were frequently experienced. Changes were also reported in electrocardiograms (ECG) of seven patients given 19-27 g borax (32-50 mg boron per kg body weight) intravenously before neutron capture therapy (Conn et al., 1955). Sinus tachycardia developed 5-10 minutes after the borax injection and persisted for several hours. Changes in the S-T segment of the ECG followed soon after the tachycardia developed and continued for as long as 24-48 hours. These ECG changes, the authors theorized, occurred as a result of ischemia caused by the entry of boron into myocardial cells.

Effects of chronic inhalation of boric acid in male workers aged 30-40 years who were occupationally exposed to boric acid fumes for 10 or more years were studied (Tarasenko et al., 1972). Use of a questionnaire to determine male sexual function indicated that the 28 workers tested reported "a lowering of sexual activity and a general level of sexual disruption" in comparison to a control group of 10 men of the same age range not exposed to boric acid. Examination of the seminal fluid in six of the workers exposed to boric acid indicated a reduced ejaculate volume in four men, fewer spermatozoa in five, a reduced number of mobile sperm cells in two, a reduced fertilizing ability of the spermatozoa in four, and an increased concentration of fructose in the sperm of five of the men. Despite the reported differences of spermatozoa, the number of pregnancies among the wives of these men did not differ from the number in the wives of the control group.

Effects on metabolism

Roush and Norris (1950) reported that activity of riboflavin-dependent xanthine oxidase was decreased in the presence of borate buffer (0.016 M). Similar concentrations of borate buffers (Eppstein, 1962) also inhibited the in vitro hydrolysis of bovine growth hormone and human serum albumin by α-chymotrypsin. Sodium
tetraborate at concentrations greater than $5 \times 10^{-8} \text{M}$ reduced the activity of arginase from ovine, porcine, bovine, and human erythrocytes (Kalab et al., 1964). Although the authors reported that the sodium tetraborate reacted with the carbohydrate portion of the enzyme, addition of glucose to the assay medium did not alleviate inhibition of this enzyme.

Ganguli et al. (1963) found that boric acid (0.5 ml of a 5% solution) inhibited glucose-6-phosphatase and phosphohexose isomerase in liver, brain, and kidney of adult male rats. Phosphoglucomutase activity was also decreased by boric acid in liver and brain, but was stimulated in kidney of these animals. Later studies (Misawa et al., 1966) of enzymes active in carbohydrate metabolism in liver and muscle showed that borate (0.01 M) reduced activity of glyceraldehyde phosphate dehydrogenase in livers of rats and guinea pigs, resulting in an accumulation of fructose-1, 6-diphosphate, and fructose-6-phosphate. Addition of glucose, sorbose, ribose, mannose, or glycerol did not reverse this inhibition. Activity of lactate dehydrogenase in liver of guinea pigs or muscle of rabbits was not affected by borate.

Weser (1966) showed that epinephrine reacted with borate in excess at pH 7-8.5. Further experiments showed that borate inhibited the usual epinephrine-induced activation of dephosphorylase to phosphorylase in perfused livers of dogs.

Kaneshima et al. (1968) determined that borate inhibited an in vitro nitrite-induced reduction of methemoglobin in guinea pig red blood cells. Addition of NADH but not NADPH to the medium improved the reduction rate of methemoglobin. Examination of effects of borate on NAD- and NADP-dependent enzymes in bovine erythrocytes showed that glyceraldehyde phosphate dehydrogenase was inhibited by borate while lactate dehydrogenase and glucose-6-phosphate dehydrogenase were not affected.

Borax reduced the in vitro uptake of oxygen by brain cells of guinea pigs when a substrate was not added to the assay system (Trautner and Messer, 1953). When glucose was present in amounts that would maintain the normal respiration rate of the brain tissue, addition of borate in amounts 50-100 times this amount of glucose did not slow oxygen uptake for approximately 90 minutes. Fructose at 4-6 times the concentration of glucose also counteracted the inhibitory effects of borate. Mannitol was ineffective in this role.

Addition of sodium borate to a mince of guinea pig cerebral tissue decreased formation of ammonia and glutamine when glucose was not included in the phosphate-Ringer assay system. Borate also lowered the production of glutamine in the presence of glucose, L-glutamate, and added ammonia, compounds ordinarily promoting glutamine synthesis (Messer and Trautner, 1955).
V. OPINION

Boric acid and borax are widely used in industry and they are components of some household articles. Boron is an essential nutrient for most plants and is a common component of fruits, but there is little evidence to suggest that it is essential in human or animal nutrition. Boric acid and borax are absorbed from the alimentary tract and distributed throughout the body before being excreted. Little is known of human tolerance, but it is estimated that the amount of boron entering food by migration from packaging materials and ingested by the average person is small compared to that ingested as a normal component of food.

In the past, use of borax as a preservative in meats for export was allowed, providing this use was at the request of and under the limitations of the receiving country. However, it is understood by the Select Committee that this practice has been discontinued and that there is no authorized use of borax or boric acid in domestic foods.

Boric acid and borax are prior-sanctioned substances for use as components of paper and paperboard products that may be used in packaging food, thus having limited GRAS status. The amount that may migrate to food from such packaging materials is not accurately known, but the daily amount is presumed to be no higher than a few milligrams per person. On the basis of all the evidence, such amounts are surely much smaller than necessary to produce any harmful effects.

Based on these considerations, the Select Committee concludes that:

There is no evidence in the available information on boric acid and borax that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public as they are now used in the manufacture of paper and paperboard products for food packaging at levels that are now current or that might reasonably be expected in the future.
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