Amended Safety Assessment of Sodium Borate and Boric Acid as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date (i.e., **August 31, 2026**) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.*

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: David E. Cohen, M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Temima Nguyen, M.S., Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ALH	amplitude of lateral head
ALP	alkaline phosphate
ALT	alanine transaminase
AMH	anti-Müllerian hormone
AST	aspartate transferase
ATP	adenosine triphosphate
BUN	blood urea nitrogen
CASA	computer-assisted sperm analysis
CCK-8	cell counting kit-8
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
CKD	chronic kidney disease
CLP	classification, labelling and packaging
CMC	carboxymethyl cellulose
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary*
DMBA	7,12-dimethylbenz(a)anthracene
DMSO	dimethyl sulfoxide
E2	estradiol
ECHA	European Chemicals Agency
EC	European Commission
EFSA	European Food Safety Authority
EGFP	enhanced green fluorescent protein
EPA	Environmental Protection Agency
ESC	epididymal sperm count
EST	embryonic stem cell test
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GD	gestation day
GI	gastrointestinal
HCG	human chorionic gonadotropin
HRIPT	human repeated-insult patch test
HSV	herpes simplex virus
ICPMS	inductively coupled plasma mass spectrometry
IEHR	Institute for Evaluating Health Risks
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LH	luteinizing hormone
l.o.	leave-on
LOAEL	lowest-observed-adverse-effect-level
log K_{ow}	octanol-water partition coefficient
MI	mitotic index
MIC	minimum inhibitory concentration
MMAD	mass median aerodynamic diameter
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MOE	margin of exposure
MOS	margin of safety
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NA	not applicable
NIOSH	National Institute for Occupational Safety and Health
NOAEC	no-observed-adverse-effect-concentration
NOAEL	no-observed-adverse-effect-level
NR	not reported
NRU	neutral red uptake
OECD	Organisation for Economic Co-operation and Development

Panel	Expert Panel for Cosmetic Ingredient Safety
PEL	permissible exposure limit
PII	primary irritation index
PND	post-natal day
POD	point of departure
RACB	reproductive assessment by continuous breeding
RD_{50}	50% respiratory rate decrease
REP	relative embryotoxic potency
RI	replication index
RIVM	Netherlands' National Institute for Public Health and the Environment
RLD	Registration and Listing Data
r.o.	rinse-off
SCCS	Scientific Committee on Consumer Safety
SED	systematic exposure dose
SGOT	serum glutamic-oxalic transaminase
SGPT	serum pyruvate transaminase
SLS	sodium lauryl sulfate
STEL	short-term exposure limit
TG	test guideline
TLV	threshold limit values
TSHC	testicular spermatid head count
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
TWA	time-weighted average
US	United States
UV	ultraviolet
VCRP	Voluntary Cosmetic Registration Program
XTT	2,3-bis-(2-methoxy-4-nitro-sulfopenyl)-2H-tetrazolium-5-carboxanilide

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of Boric Acid and Sodium Borate. Boric Acid is reported to function as a buffering agent, cosmetic biocide, and denaturant in cosmetics, and Sodium Borate is reported to function as a buffering agent and fragrance ingredient in cosmetics. The Panel reviewed the relevant data to determine the safety of these ingredients. Accordingly, the Panel issued an amended report with a revised conclusion stating Boric Acid and Sodium Borate are safe in rinse-off products in the present practices of use and concentration described in this safety assessment when used in formulations not intended for application to mucosal surfaces. The Panel also concluded that the data are insufficient to make a determination of safety of these ingredients in leave-on products and in products intended for application to mucosal surfaces.

INTRODUCTION

This assessment reviews the safety of Boric Acid and Sodium Borate (commonly known as borax) as used in cosmetic formulations. According to the *International Cosmetic Ingredient Dictionary* (*Dictionary*), Boric Acid is reported to function as a buffering agent, cosmetic biocide, and denaturant and Sodium Borate is reported to function as a pH adjuster in cosmetics.[1]

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of Sodium Borate and Boric Acid in 1983.[2] Based on the available data presented in the report, the Panel concluded that Sodium Borate and Boric Acid, in concentrations ≤ 5%, are safe as cosmetic ingredients when used as recommended at the time of the safety assessment. However, the Panel noted that cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant skin or injured skin. The Panel first considered a re-review of this report in February 2003[3] and reaffirmed the 1983 conclusion, as published in 2006.[4]

In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports approximately every 15 years, and it has been at least 15 years since the previous re-review was published. Subsequently, the Panel again considered a re-review of these ingredients at its June 2024 meeting. At that meeting, the Panel determined that this safety assessment should be reopened due to a change in the reported use categories, to evaluate new data, and to explore the reasoning for why these ingredients have been banned by the European Union (EU).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted May 2026 for studies dated 2001 forward. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[5,6] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

Summarized excerpts from the initial 1983 report and the 2003 re-review on Sodium Borate and Boric Acid are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. Because the Panel relied on the developmental and reproductive toxicity data from the original report and re-review in the determination of the conclusion of this amended safety assessment, these data were the only information from the previous reports included in a separate table. The remaining information from the previous reports was not included in the tables or the Summary section.

CHEMISTRY

Definition and Structure

According to the *Dictionary*, Boric Acid (CAS No. 10043-35-3; 11113-50-1) and Sodium Borate (CAS No. 1303-96-4 (hydrous); 1330-43-4) are an inorganic acid and an inorganic salt, respectively. These ingredients have chemical structures as shown in Figures 1 and 2, respectively.[1] Boric Acid can also be referred to as boracic acid and orthoboric acid. Sodium Borate is commonly used as the decahydrate.

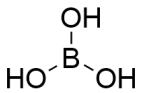


Figure 1. Boric Acid [CIR Staff]

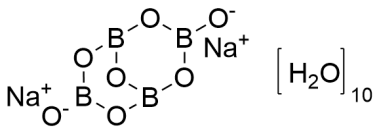


Figure 2. Sodium Borate (decahydrate) [CIR Staff]

Chemical Properties

Boric Acid has a molecular weight of 61.8 g/mol and an octanol-water partition coefficient (log K_{ow}) of 0.175.[7] Sodium Borate (anhydrous) has a formula weight of 201.2 g/mol[8] (or 381.4 g/mol for the decahydrate) and a log K_{ow} of 0.175.[9] Other chemical properties of Boric Acid and Sodium Borate can be found in Table 1.

Natural Occurrence

Boric Acid occurs naturally as the mineral, sassolite, or may be obtained by acidification of borate minerals, such as kernite, ulexite, colemanite, or tincal.[2] *Sodium Borate occurs naturally as the mineral, tincal, or may be obtained by treating other minerals, such as kernite, ulexite, and colemanite.*

Method of Manufacture

Boric Acid may be derived by adding hydrochloric or sulfuric acid to a Sodium Borate solution and crystallizing the solution.[2] *Alternately, Boric Acid may be extracted from weak Sodium Borate brines with a kerosine solution of a chelating agent. Sodium Borate may be obtained via fractional crystallization of brine containing Sodium Borate followed by a recrystallization step for purification.*

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of Boric Acid and Sodium Borate in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption. [10] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

In 2025, RLD obtained from the FDA reported that Boric Acid and Sodium Borate were reported to be in use in 96 formulations and 202 formulations, respectively (Table 2).[11,12] In response to the 2025 Council survey, concentrations of use were only reported for rinse-off products; the maximum concentration of use reported is 3.7% Sodium Borate in skin cleansing formulations (cold creams, cleansing lotions, liquids and pads).[13]

Boric Acid and Sodium Borate are used in products that can be incidentally ingested (mouthwashes and breath fresheners; concentration not reported), products that are applied near the eye (e.g. eye makeup remover; concentration not reported), and in products that may contact mucous membranes (e.g., bath soaps and body washes at up to 0.00016% Boric Acid, feminine wipes; concentration not reported). Boric Acid is also used in sprays; use in deodorant sprays are reported in RLD, but concentration of use are not. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Following the passage of MoCRA, the FDA created a number of new product categories, including "(17) Other preparations (i.e., those preparations that do not fit another category)" (Category 17). CIR and the Panel utilize these product categories to inform, in part, the weight-of-evidence (WoE) in exposure and risk analyses. However, citation of Category 17, alone, as the product use category is uninformative. When a product is co-categorized with both Category 17 and one or more common product use categories (e.g., eye makeup preparations), or other information in the RLD such as the product name are indicative of use type (e.g., "lip balm" is part of the product name), then those uses are accounted for and may be

considered to be part of the "the present practices of use" for those products; as such, the Panel's safety conclusion may be inclusive thereon. Conversely, for instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17 and other information in the RLD is not indicative of use type, the present practices of use for these products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply thereon.

It is possible that some products containing Boric Acid and Sodium Borate may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined therein, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. None of the reported product categories for these ingredients as listed in the RLD include a designation using airbrush application, so it is possible that these ingredients are used with airbrush delivery systems, but not reported as such. Additionally, the concentration of use surveys are conducted based on product categories as stated in the RLD, but airbrush use was not reported in response to the survey. No consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with airbrush technology, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. If these ingredients were to be used in airbrush formulations, the data are insufficient to evaluate the exposure resulting from cosmetics applied in such a manner.

The European Union has included Boric Acid and Sodium Borate in Annex II of Regulation of the European Commission (EC) No 1223/2009, List of Substances Prohibited in Cosmetic Products.[14] Boric Acid and Sodium Borate are classified as category 1B reproductive toxicants.[15]

Non-Cosmetic

Boric Acid and Sodium Borate are widely used in medical, agricultural, and industrial applications, including insecticides and fungistatic agents.[2] Boric Acid has been applied in antiseptics, wound dressings, preservatives, and treatments for skin irritation, conjunctivitis, and athlete's foot, as well as in weatherproofing and fireproofing materials. Sodium Borate has shown antiviral and antifungal activity, particularly against Herpes simplex virus (HSV) and vulvovaginal candidiasis, and has also been explored for use in oral contraceptives and water-resistant films, though it is prohibited as a direct food additive.

According to the Code of Federal Regulations (CFR), Boric Acid and Sodium Borate can be applied to many types of products. Boric Acid is permitted to be used in adhesives (21 CFR 175.105), paper and paperboard coming in contact with dry food (21 CFR 176.180), polymers as an antioxidant or stabilizer (21 CFR 187.2010), and food packaging paper and paperboard products (21 CFR 181.30).[16] In pharmaceuticals, Boric Acid has been listed by the US FDA in approved drug products as an inactive ingredient in products such as auricular (otic) solutions/suspensions, shampoos, and vaginal jellies.[17] Sodium Borate is also acceptable in similar products, but instead of in polymers as an antioxidant or stabilizer, it can be used in acrylate ester copolymer coating (21 CFR.210) and textiles and textile fibers (21 CFR 177.2800).[18] Pharmaceutically, Sodium Borate has been listed by the FDA in approved drug products as an inactive ingredient in products such as auricular (otic) solutions, ophthalmic emulsions, solutions or suspension/drops, and topical creams.[17] When used as an active ingredient in fungicides, herbicides, or insecticides, there is an exemption from the requirement of a tolerance for residues according to 21 CFR 180.1121.

The median dietary boron intakes from food range from 0.87 – 1.35 mg/d in adults.[19] When combined with dietary supplements, the total median boron intake increases to ~1 – 1.5 mg/d. The World Health Organization (WHO) estimates that a safe range for boron intake for adults is 1- 13 mg/d.

The European Food Safety Authority (EFSA) Panel concluded that based on the no-observed-adverse-effect-level (NOAEL) of 9.6 mg boron/kg bw/d, derived from a developmental toxicity study in rats, and an application of an uncertainty factor of 60, a group Acceptable Daily Intake (ADI) of 0.16 mg boron/kg bw/d can be established.[20] Based on these conservative estimates, it is unlikely that the ADI for boron would be exceeded by the use of Boric Acid and Sodium Borate as food additives, as presently authorized.

In the EU, Boric Acid and Sodium Borate are classified under Regulation (EC) No. 1272/2008 on classification, labelling and packaging (CLP) as reproductive toxicants, Category 1B. Following the 17th Adaptation to Technical and Scientific Progress to the CLP Regulation, the generic concentration limit of ≥ 0.3% applies for classification of mixtures containing these substances.[5,21]

TOXICOKINETIC STUDIES

Dermal Absorption

Animal

Occlusive patches with 5% Boric Acid in different mediums (water, urine, talc) or in a pH of 9 buffer were applied to rabbits for an 8-h period.[2] Boron concentrations were measured in blood and urine. Boric Acid in water and urine, but not

in talc, were readily absorbed through intact skin. Absorption of Boric Acid in pH 9 buffer was lower than that of aq. Boric Acid, but greater than when talc was used as the medium. In the same study, occlusive patches with 8% Sodium Borate in water were applied to rabbits for an 8-h period. Sodium Borate was again readily absorbed.

Absorption, Distribution, Metabolism, and Excretion

In Vitro

The in vitro pharmacokinetics of Boric Acid in distilled water over a 24 h period were assessed using three different vehicles: a hydrophobic ointment, water-emulsifying ointment, and water-methylcellulose jelly.[3] There was a 70% release of Boric Acid from the water-methylcellulose jelly in 1 h, eventually leveling off to 90% at 24 h. The release of Boric Acid from the other two vehicles was negligible. In another in vitro study, human skin was mounted on polytetrafluoroethylene diffusion cells before a receptor solution was perfused at a rate of 3 ml/h. Two dose rates were used: an "infinite dose" at 1 ml/cm^2, which is provided throughout the dosing period, and the "finite" dose of 2 µl/cm^2, which mimics the residue that remains on the skin. The concentrations of Boric Acid applied were 0.05, 0.5, and 5% with the infinite dose (1 ml/cm^2) and 5% as the finite dose (2 µl/cm^2). Sodium Borate (5%) was applied as an infinite dose at 1 ml/cm^2. At 1 ml/cm^2, Boric Acid had flux values of 0.25, 0.58, and 14.58 µg/cm^2/h for the 0.05, 0.5, and 5% solutions, respectively. The flux value with 5% Sodium Borate at 1 ml/cm^2 was 8.5 µg/cm^2/h. For the 5% solution of Boric Acid at 2 µl/cm^2, the flux was 0.07 µg/cm^2/h.

Animal

Dermal

Boric Acid

Dermal absorption was tested in rats following application of less than 3% Boric Acid in two oleaginous ointments and in an aqueous jelly; 1 - 2 ml of each were applied to 4.3 - 28 cm^2 intact skin.[2] After 5 h, the data showed that the jelly formulations resulted in more Boric Acid absorbed compared to the ointment; furthermore, it was stated that Boric Acid excretion was observed after the application of the jelly and the ointments to damaged skin. In addition, when their urine was analyzed, there was no- to low-excretion of boron. In another study, the percutaneous absorption of Boric Acid in different preparations (5% in water, 5% in talc, 12.5% in talc, and undiluted) was tested on rabbit skin (intact, abraded, severely burnt, or partially denuded). After a 4-d period where the preparations were applied for 1.5 h daily, the urinary boron concentrations were determined; while there was minimal and insignificant absorption through intact and abraded skin, Boric Acid was readily absorbed through severely burnt and partially denuded skin.

Oral

Boric Acid

It was found that once in the blood, Boric Acid then tends to accumulate in the brain, liver, and fat of animals. In the brain, the grey matter collects more Boric Acid than the white matter. There is also a high amount of Boric Acid in the sciatic nerve and spinal cord observed. Eventually, non-fatal doses will redistribute in the body to fatty organs and the Boric Acid eliminates in the urine at around 75 - 100% of what was ingested. Minimal amounts may be detected in feces, milk, saliva, or perspiration. Boron levels were examined in the plasma, tissue samples, and seminal vesicle fluid in 30 adult male Fisher rats that were fed 9000 ppm Boric Acid (~1575 ppm boron) for 7 d.[3] The control animals received normal feed which contained less than 20 ppm boron. At 1, 2, 3, 4, and 7 d, six control and treatment animals were killed to analyze the boron levels. The boron in the plasma and tissues (liver, kidney, adipose, muscle, large intestine, brain, hypothalamus, testis, epididymis, seminal vesicles, adrenals, and prostate), but not in bone, stabilized after day 2. In the bone, the boron reached a plateau at day 3, increased on day 4, and increased on day 7. The plasma half-life and renal clearance of boron in pregnant and non-pregnant rats were assessed. For the clearance portion of the study, 36 female and 37 timed-pregnant Sprague-Dawley rats were given a low-boron diet of 1.4 mg of Boric Acid/kg (~0.25 boron/kg) the day before being administered a single oral dose of 0.3, 3.0, or 30 mg Boric Acid/kg (~0.052, 0.52, or 5.2 mg boron/kg) via gavage. Body weights were measured 7 d before and on the day of gavage administration while plasma samples were taken at 3 and 15 h after dosing. Urine was collected at 12 h. The clearance was higher in pregnant rats, but not in a statically significant manner. For the half-life portion of the study, 6 pregnant and 6 non-pregnant rats given a single oral dose of 30 mg/kg Boric Acid via gavage and had plasma samples collected every 2-3 h during a 12-h period after dosing. The half-life of Boric Acid was estimated to be 2.9 and 3.2 h in non-pregnant and pregnant rats, respectively. The rate of boron clearance was 6 - 7% higher in pregnant rats, but was not statistically significant.

Sodium Borate

Wistar rats (n = 20) were administered 1 ml of Sodium Borate via gavage at doses ranging from 0 - 0.4 mg/100 g bw as boron.[6] After 24 h, urine samples were collected, and the urinary recovery rate was calculated to be 99.6 ± 7.9%. The excretion and boron dose relationship had a regression coefficient of 0.954, suggesting that it was linear and signifying a 100% bioavailability rate.

Human

Dermal

Topical application of 15 g of Boric Acid for a 4-h period to intact skin of one subject did not lead to an increase in excretion of boron.[2] Talcum powder containing 5% Boric Acid was applied to 6 infants with different levels of diaper rash, ranging from none to marked. For infants that had no-to-mild diaper rash, Boric Acid was not detected in their urine. However, for infants that had a moderate-to-marked diaper rash, Boric Acid was present in their urine for at least 48 h. For a 1-mo study with 50 infants with dermatitic and intact skin, a 5% Boric Acid powder was applied 7 - 10 times a day, amounting to a dose of approximately 2330 mg/infant/d. Compared to the 31 control infants where no powder was applied, only minimal amounts of Boric Acid penetrated the skin of the infants receiving the treatment, including the ones with rashes. The measured boron concentrations in the blood and urine were similar for both groups. In a 5-d study, a talc preparation containing 5% Boric Acid was applied 10 times a day to 8 infants. There was 1 infant that had extensive second-degree burns in the study that was only tested for 3 d. When the boron levels were measured in the blood and urine, infants with intact skin did not have significant differences from before and after the treatment. The burned infant had an elevated level of boron measured in their urine. A study was conducted with 21 hospitalized patients that had wet compresses containing Boric Acid applied for several days. The serum Boric Acid levels only increased significantly for one patient that had kidney damage. Different preparations containing 3% Boric Acid were formulated; an anhydrous water-emulsifying ointment and a water-based jelly. The first preparation was tested in 31 men and 3 children. For the 31 men, there was a single application and the boron concentration in their urine was measured. Sixteen of the men had skin that was classified as normal while the remaining 15 had "diseased" skin. Over the course of this experiment, the men received ~17.7 - 724.4 mg Boric Acid (~3.1 - 127.3 mg of boron), but there was no increase in boron excretion in their urine from day 1 to day 9. For the children, they were characterized as having "napkin dermatitis." They received ~35.4 - 59.4 mg Boric Acid (~6.2 - 10.4 mg of boron), but there was no increase in boron excretion in their urine or blood from day 1 to day 8. Lastly, the 3% Boric Acid water-based jelly was tested on 6 men with different conditions; 3 men had eczema, 2 had psoriasis, and 1 had urticaria. These men received ~37 - 89 mg of boron; this group had a significant increase in boron concentration in their blood on the day of application. They also had an increase in boron excretion on day 2 when analyzing the urine. However, after day 2, the boron excretion normalized.

An anhydrous water-emulsifying ointment containing 3% Boric Acid was applied to 31 male subjects (16 with normal skin and 15 with diseased skin – not further characterized).[3] Depending on the skin type, the subjects would receive either 0 – 127.3 mg of boron (normal skin) or 5.2 – 87.5 mg of boron (diseased skin). Urine samples were collected 24 h before application and 24 h after application; there was no increase in the average boron excretion for either group. The same anhydrous water-emulsifying ointment containing 3% Boric Acid was applied in quantities of 6.2 – 10.4 mg of boron to a group of 3 infants (3.5 wk to 2 mo old). When blood and 24-h urine samples were obtained, the boron concentration in the urine was less than the control. A group of 6 patients with diseased skin (3 eczema, 2 psoriasis, and 1 urticaria) received 42 – 89 mg of boron through a 3% Boric Acid jelly applied to the skin. The blood and 24-h urine samples revealed the mean ratio of boron excretion increased in the blood and urine from day 1 to day 2, indicating an absorption of boron. Aqueous solutions containing boron-10 (naturally occurring isotope of boron)-enriched Boric Acid (5%) and boron-10-enriched Sodium Borate (5%) were applied at a volume of 1.8 ml over a 900 cm^2 area on the skin to groups of 8 male and female subjects with normal skin. The boron-10 in the samples was measured using inductively coupled plasma mass spectrometry (ICPMS) to eliminate dietary boron influences. Urinalysis values were obtained for 4 d before one dose was applied on day 5. Sodium lauryl sulfate solution was applied on day 11 to attempt to irritate the area, before another dose of the Boric Acid or Sodium Borate solutions were applied on day 12. The average boron-10 absorbed through the skin was 4.75 µg, indicating low percutaneous absorption.

In a percutaneous study with human subjects, Boric Acid and Sodium Borate were applied at 5% (in aq. solution) to a 900 cm^2 area on subjects (n=8) for 24 h. [22] When boron concentrations in the urine were measured, there was ~0.23% Boric Acid and ~0.21% Sodium Borate absorbed. When the same study was done in vitro in human skin for Sodium Borate, there was a decrease in absorption at 0.19%.

Oral

Boric Acid

The urinary excretion of Boric Acid in 6 male subjects was measured 96 h after they were orally administered either 750 mg Boric Acid dissolved in water or as much as possible of a 50 g tube of water-emulsifying ointment containing 3% Boric Acid.[3] The urinary recovery was 94% following the oral intake of an aqueous solution of Boric Acid. The measurements did not show a significant difference in urinary excretion between the two vehicles despite a slight delay of excretion in the first 2 h of the ingestion of the ointment. The renal clearance of boron was studied in 32 women, 16 who were pregnant in the second trimester and 16 who were not. The source of boron was dietary and not specified in the study. A blood sample was taken at baseline, 2 h, and 24 h. A urine sample was taken at 2 and 24 h. The boron excretion in pregnant and non-pregnant women was measured to be 1.36 and 1.31 mg/d, respectively. The boron clearances were calculated at the 2 and 24 h mark, and the range was 43.85 – 68.30 ml/min/1.73 m^2.

Mucous Membrane

Boric Acid

In a 14-d study, 40 women with vulvovaginal candidiasis applied 5% Boric Acid in lanolin to areas with irritation in their vulval area and inserted 600 mg of Boric Acid two times each day vaginally.[2] After the end of this study, Boric Acid was not detected in their blood.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The single-dose oral toxicity of Boric Acid and Sodium Borate were determined for rats of an unspecified strain.[2] The median lethal doses (LD_{50}) for Boric Acid and Sodium Borate were 5140 and 5660 mg/kg.[2] The reported LD_{50} values of Sodium Borate ranged from 4500 - 6080 mg/kg in rats. Boric Acid was orally administered to Sprague-Dawley and Long-Evans rats; the LD_{50} for the male and female Sprague-Dawley rats and male Long-Evans rats were 3450, 4080, and 3160 mg/kg, respectively. In the same study, Sodium Borate was orally administered to Sprague-Dawley and Long-Evans rats; the LD_{50} for the male and female Sprague-Dawley rats and male Long-Evans rats were 4500, 4980, and 6080 mg/kg, respectively. The oral LD_{50} of a hair preparation containing 3.2% Sodium Borate was 14,100 mg/kg in male and female albino rats.

The acute toxicity studies for both Boric Acid and Sodium Borate are summarized below and details are provided in Table 3.

Boric Acid[5] and Sodium Borate[6] both had dermal LD_{50} values of >2000 mg/kg (the highest dose tested) in rabbits. In oral studies, LD_{50} values were >2000 mg/kg Boric Acid in rats when administered via gavage.[5] Oral LD_{50} values ranged from >200 - 3401 mg/kg in male rats and >2000 - 3225 mg/kg Sodium Borate in female rats when administered via gavage.[6] The inhalation LC_{50} values in rats were >2 mg/l for Boric Acid (administered via dust and aerosol)[5] and Sodium Borate (administered via dust).[6]

Short-Term Toxicity Studies

In a 4-d study, rabbits were dosed orally with 600 or 700 mg/kg/d aq. Boric Acid; minor signs of toxicity, including anorexia, diarrhea, poisoning (no details), and weight loss, were observed. These effects became severe at 800 mg/kg/d. With 850 - 1000 mg/kg/d, there was 100% mortality.[2] Aq. Boric Acid was administered orally at 1000 mg/kg/d in rats for 3 wk. There was a reduction in weight gain observed in rats dosed with Boric Acid after 2 wk, and signs of toxicity were observed during the 3-wk period. There was a decrease in liver DNA and increases in brain and kidney DNA and liver, brain, and kidney RNA. Growth retardation was observed in a study with 4 rats that were fed a diet with 1% (1000 mg/kg/d) Boric Acid for 27 d. A Sodium Borate aqueous solution was administered at 1000 mg/kg/d in rats for 3 wk.[2] Signs of toxicity were observed during the 3-wk period and at study termination. A decrease in liver DNA and increases in brain and kidney DNA and liver, brain, and kidney RNA were observed. The effects of a 3.2% Sodium Borate hair preparation were studied on the oral and gastrointestinal (GI) tissues of rabbits[2]. Four albino rabbits received undiluted material, 229 mg/kg dose, on the posterior surface of their tongue. At 24 and 96 h, 2 rabbits were killed; the hair preparation was non-corrosive and non-irritating orally or to the GI tissues.

In a 2-wk study, mice (5/sex/group) were fed Boric Acid at 0, 0.62, 1.25, 2.5, 5.0, and 10%.[3] Body weight gains, clinical signs of toxicity, food consumption, and mortality were assessed. For males, mortality was observed in the groups given 2.5% (1/5 mice), 5%, (3/5 mice), and 10% (5/5 mice). In females, mortality was only observed in the group given 10% (4/5 mice). There was some hyperplasia in the forestomach, no changes in food consumption, and a slight decrease in body weights.

Details of the short-term toxicity studies summarized below and are described in Table 4.

A 5-d toxicity study was completed in mice (10/group) given 0.28 mg/250 ml Boric Acid orally via drinking water, which resulted in a mean weight loss and statistically significant changes in some clinical chemistry parameters.[23] In a 7-d study, male albino Sprague Dawley rats were administered 1000 mg/kg/d of Boric Acid orally via drinking water, which led to significant weight loss, edema, an increase in apoptotic cells, and inflammation when compared to the controls.[24] In an oral study, in which Boric Acid was administered via gavage at a dose of 800 mg for 30 d, the rats were killed every 6 d during the exposure period and every 10 d during the recovery period of 109 d.[5] The NOAEL and the lowest observed-adverse-effect-level (LOAEL) were both calculated to be < 800 mg/kg (critical endpoints were not provided). In a study in male albino Sprague Dawley rats (24/group) were given 100, 275, or 400 mg/kg/d of Boric Acid in feed for 45 d, time- and dose-dependent; degenerative changes were observed in kidney tissues.[25]

Subchronic Toxicity Studies

In a 90-d study, aq. Boric Acid solutions were applied to the intact skin of rabbits at doses ranging from 25 - 200 mg/kg/d.[2] No abnormal hematologic or microscopic tissue changes and no systemic or local toxicity were observed. A study was conducted in which groups of 5 male and 5 female rats were fed 52.5, 175, 525, 1750, or 5250 ppm boron as 30, 100, 300, 1000, or 3000 mg/kg/d Boric Acid, respectively, and as ~46.5, 155, 465, 1545, and 4646 mg/kg/d Sodium Borate, respectively, for 90 d. With both test articles, at 1750 and 5250 ppm boron there was the presence of inflamed eyes, swollen

paws, rapid respiration, and desquamated skin on the paws and tails of the rats; all the rats of the 5250 ppm boron groups died within 3 - 6 wk and liver, kidney, and lung congestion were observed at necropsy. In a 90-d study, male rats were provided drinking water that contained 0.3 - 0.5 mg/l of boron (as 0.37 - 7.44 mg/kg/d Sodium Borate); no significant changes in body weights, serum chemistry, reproductive effects, or any other biological changes were observed. Groups of 5 male dogs and 5 female dogs were fed ~7.5, 75, or 750 mg/kg/d Boric Acid or ~11.6, 116.2, or 1161.5 mg/kg/d Sodium Borate (equivalent to 17.5, 175, and 1750 ppm boron, respectively) for 90 d. The dogs initially were all normal in appearance, behavior, body weight, elimination, and feed consumption. By day 68, one male dog in the group fed with 1750 ppm of boron as ~1000 mg/kg Boric Acid died, with congested kidneys, diarrhea, and severe congestion of the large and small intestine mucosa. In this group, 2 male and 3 female dogs had decreased hemoglobin values and cell volume. Otherwise, the rest in the 1750 ppm boron as ~1000 mg/kg Boric Acid group had normal blood chemistry, hematologic, and urine values. At 1750 ppm boron (as ~1000 mg/kg Boric Acid and as ~1548.7 mg/kg/d Sodium Borate), the male dogs had severe testicular atrophy. The spermatogenic epithelium was nearly completely degenerated and there was a higher destruction of red blood cells with Sodium Borate compared to Boric Acid.

In a 13-wk study, mice (10/sex/group) were fed Boric Acid at concentrations of 0, 0.12, 0.25, 0.50, 1, and 2%. [3] *Body weight gain, clinical signs of toxicity, food consumption, and mortality were assessed. The male mice had deaths with 1% (1/10 mice) and 2% (8/10 mice), while the female mice had deaths with the 2% only (6/10 mice). There was some extramedullary hematopoiesis in the spleens, no changes in food consumption, and a slight decrease in body weights in all dose groups. Only mice fed 2% Boric Acid experienced hyperkeratosis or hyperplasia of the forestomach.*

The subchronic toxicity summarized below is described in Table 4.

In a 90-d study, 60 male albino rats were given Boric Acid orally via gavage (0.16 mg/kg/bw) or water as a control.[26] The liver and kidney tissues went under histological examination, and the functions were tested. There was a statistically significant increase in hepatic enzyme leakage (aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP)) and serum renal damage products levels (urea, uric acid, and creatine). There was also depleted antioxidant enzymes and various histopathological perturbations in hepatic and renal tissues were observed.

Chronic Toxicity Studies

In a 2-yr study, groups of 35 male and 35 female rats that were fed a diet that included 117, 350, and 1170 ppm boron as ~70, 200, and 669 mg/kg/d Boric Acid, respectively, and as ~103.5, 310, and 1035 mg/kg/d Sodium Borate, respectively.[2] *The rats in the groups fed 117 and 350 ppm of boron (both as Boric Acid and Sodium Borate) exhibited normal behavior and appearance and no histopathological abnormalities in their organs. The rats that were fed 1170 ppm of boron experienced several signs of toxicity, and bloody discharge from the eyes, inflamed eyelids, desquamation and swelling of the pads of their paws, low hemoglobin values, and low packed cell volume were observed with both test articles.*

The chronic toxicity studies summarized below are described in Table 4.

In inhalation studies, male and female rats were exposed to Boric Acid for 6 h/d, 5 d/wk, at concentrations of 470 mg/m³ for 10 wk (n = 20), 175 mg/m³ for 12 wk (n = 4), or 77 mg/m³ for 24 wk (n = 70), and 3 female dogs were exposed to 57 mg/m³ for 23 wk, via aerosol.[5] There were no signs of toxicity in any of the animals and the no-observed-adverse-effect-concentration (NOAEC) for systemic toxicity in rats was 470 mg/m³, 175 mg/m³ for local effects in rats, and 57 mg/m³ for dogs.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Although data from previous reports are not normally included in a table, due to the considerable amount of past studies, the developmental and reproductive toxicity studies from the original 1983 report and the data from the 2003 re-review have been summarized in Table 5. Overall, Boric Acid and Sodium Borate appeared to have more of an effect on the male reproductive system, while developmental studies reported some adverse effects including reduced growth, skeletal abnormalities, and prenatal loss.

Studies available since these past reports were published, summarized below, are described in Table 6.

Boric Acid was tested at concentrations of 0.019, 0.062, 0.186, or 0.618 mg/ml using primary culture of seminiferous tubules from 20-d-old male Sprague Dawley rats.[5] Cells were analyzed via fluorescence-activated cell sorting (FACS) analysis; Boric Acid resulted in an increase in somatic cell proliferation and a decrease in all the germ cell populations. A revised 96-well embryonic stem cell test (EST) was used to evaluate embryotoxic potency; Boric Acid was "moderately embryotoxic" based on its relative embryotoxic potency (REP) value of 0.001 ± 0.001.[27] Similarly, a survivin-based embryotoxicity assay was performed with 100 µg/ml of Boric Acid.[28] Boric Acid led to a 20% decrease in survivin expression and lower enhanced green fluorescent protein (EGFP) intensities in the D3-CMV-EGFP and D3-SP-EGFP cells, which indicated a moderate embryotoxic effect and cytotoxicity, respectively. In two animal studies, Swiss mice were given Boric Acid via diet at 0 or 9000 ppm.[5] In the first study, FSH (follicle-stimulating hormone) levels increased after 4 wk, luteinizing hormone (LH) increased, testosterone decreased after 2 wk, and gonadotrophin increased 1 - 2 wk afterwards. Boric Acid was suggested to act on Leydig cells to depress testosterone synthesis and/or release. In the second study, the mice were bled weekly for 8 wk by ophthalmic plexus. At wk 9, half were given HCG challenge and half were given saline

where serum was collected for both groups 1 h after. Boric Acid decreased basal concentrations of testosterone and the release of testosterone in response to HCG challenge. In another study, Swiss mice were fed a diet containing 0 - 1262 mg/kg (~0 - 9000 ppm boron) Boric Acid. At 14 wk, there was a reduction in fertility and complete infertility at the 636 mg/kg Boric Acid (4500 ppm boron) and 1262 mg/kg Boric Acid (9000 ppm boron) doses, respectively. At 27 wk, the F_0 generation underwent necropsy after the next generation was born and there was a dose-related reduction in body weight and reproductive organ weight for the F_0 males and at 636 mg/kg Boric Acid (4500 ppm boron), there was decreased kidney and adrenal weights for both sexes. The F_1 mice had normal fertility in the controls and the F_2 pups had a decrease in the adjusted mean body weight. Male and female CD-1 rats were given 0, 120, 400, or 1200 mg/kg Boric Acid via gavage, 3 - 20 or 0 – 20 d before necropsy.[29] Mating occurred between days 8 – 12 and at 1200 mg. There was evidence of testicular toxicity in the males and a reduction in females delivering as well as the number of live pups. In a one-generation study, time-mated female Sprague Dawley rats were delivered a dose of 0, 5, 10, or 20 mg/kg/d of Boric Acid orally via gavage on days 6 - 21 of gestation while the pups received the same dose but from PND 1 - 28.[30] The dams did not have any deaths or signs of maternal toxicity at the doses administered but the pups in the 20 mg/kg/d group had 11 instances of umbilical hernias and a 23% reduction in weight. In a study in which Sprague-Dawley rats were administered Boric Acid via drinking water for 45 d at 100, 275 or 400 mg/kg, the body/testis weights, plasma/testis boron concentrations were measured, and blood samples/testis tissues were collected on days 10, 30, and 45.[5] There was a significant accumulation of boron in the testis in the rats over the course of the study. Pregnant Sprague Dawley rats received 0 or 500 mg/kg of Boric Acid twice a day depending on the block assigned. [5] The 1st block was dosed on GD 6,7, 8, or 9 with the controls receiving only water on GD 9. The 2nd block was dosed on GD 9, 10, or 11 with the controls receiving only water on GD 9 - 11. After being examined, Boric Acid induced axial skeleton malformations and shifted the expression domain for hoxc6 and hoxa6 on GD 13.5. New Zealand white rabbits were given 0, 62.5, 125, or 250 mg/kg via gavage during day 6 – 19 post mating. On day 30 of gestation, the rabbits were terminated and clinical examinations were performed. The maternal rabbits had a LOAEL of 43.5 mg boron/kg (~250 mg/kg Boric Acid) and NOAEL of 21.8 mg boron/kg (~125 mg/kg Boric Acid). At 250 mg/kg Boric Acid, the dams had 90% resorbed vs. the 6% in the controls with an overall 73% complete litter loss. In a different study, rats were exposed to either 9.6 ± 0.5 mg/m^3 or 48.6 ± 1.46mg/ m^3 Boric Acid for 4 h/d for 4 mo. The 9.6 ± 0.5 mg/m^3 group had atrophied testis, reduced spermatozoa, and pathological changes in testis more severity seen in the 48.6 ± 1.46 mg/m^3 group. Wistar albino rats (7 females/group) were administered 0, 1250 or 5000 mg/kg Sodium Borate (~142 and 567 mg/kg boron) orally via gavage for 7, 15, 30, or 60 d.[31] Evaluated endpoints included ovarian weights, serum concentrations of FSH, LH, estradiol (E2), and anti-Müllerian hormone (AMH), histomorphometry measurements, and the ovarian apoptotic index using a terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. As the dose and exposure duration increased, there was a decrease in ovarian weight, LH, E2, and AMH levels and an increase in FSH levels and ovarian apoptosis. Ovarian toxicity associated with boron exposure was dependent on dose and exposure duration with the most effects observed at the highest dose (5000 mg/kg) and longest exposure duration (60 d). In a three-generation study, Sprague Dayley rats (8 males/group and 16 females/group) were fed a diet with Boric Acid or Sodium Borate at doses equivalent to ~0, 5.9, 17.5, and 58.8 mg boron/kg bw/d.[32] After 2–3 wk of treatment at 58.8 mg boron/kg bw/d, females exhibited systemic toxicity and reduced litter production, while males developed testicular atrophy. A NOAEL of 17.5 mg boron/kg bw/d was proposed for female reproductive effects, although the study mentioned limitations in the mating procedure and concluded that the evidence for adverse effects was stronger for male fertility than for female fertility. The LOAEL was identified to be 58.5 mg boron/kg bw/d.

GENOTOXICITY STUDIES

In gene mutation assays, Boric Acid was not mutagenic to Salmonella strains in 2 separate Ames tests, with or without metabolic activation.[2] The mutagenic potential of Boric Acid was also measured by evaluating its ability to induce back-mutation of a streptomycin-dependent Escherichia coli strain, and the test was repeated with a more sensitive paper-disc assay.[2] Boric Acid was non-mutagenic.

The genotoxicity of Boric Acid and Sodium Borate were evaluated in S. typhimurium strains TA98 (frameshift mutant) and TA100 (base pair substitution mutant) in the presence and absence of metabolic activation using a preincubation method at concentrations of 0.01 - 100 µg.[3] After 48 h, both Boric Acid and Sodium Borate did not produce an increase in revertant colonies, which meant that there was no mutagenic activity observed. An assay to test Sodium Borate (as refined borax and borax ores) for mutation to ouabain resistance was performed using C3H/10T1/2 mouse embryo fibroblasts and diploid human foreskin fibroblasts at concentrations ranging from 0.8 - 3.2 mg/ml. For the V79 Chinese hamster cells, a similar assay was used to detect the induction of 8-azaguanine-resistant colonies at concentrations ranging 0.8-3.2 mg/ml for the borax ore and 0.4-3.2 mg/ml for the refined borax. Both the assays did not show significant mutations, and the Sodium Borate (as refined borax and borax ores) were considered at most weakly mutagenic.

Some genotoxicity assays are no longer considered appropriate as standard methods for evaluating genotoxic potential under current OECD guidance. (See https://www.cir-safety.org/cir-findings for the identification of such study types.) Although these assays may be reported in the published literature, unpublished reports, or data submissions, the results from these assays (as identified in the guidance) are of limited interpretability and therefore the studies are not summarized herein.[33-37]

Details of the genotoxicity studies for Boric Acid and Sodium Borate summarized below are described in Table 7.

In a mouse lymphoma gene mutation assay, Boric Acid was not genotoxic in L5178Y cells.[5] In in vitro assays evaluating chromosomal damage, Boric Acid (≤10 µM, 20 ppm, 10,000 µg/l, and 50,000 µg /ml) and Sodium Borate (≤10 µM and 10,000 µg/l) were not genotoxic in micronucleus assays.[5,34-36] Boric Acid and Sodium Borate (≤ 10,000 µg/l) were not genotoxic in a chromosomal aberration assay in human blood cultures.[36] However, Boric Acid did cause an increase in structural and total chromosomal aberrations (but not numerical chromosomal aberrations) in human lymphocytes (≤ 10,000 µg/l).[33] In other genotoxicity studies, Boric Acid was not genotoxic in comet assays performed with Chinese hamster lung fibroblast (V79) cells (at ≤ 200 µM)[38] or with human Sertoli cells (at ≤ 1000 µM),[39] Sodium Borate (150 – 300 µg/ml) produced a statistically significant reduction in the numbers of metaphase plates and metaphase chromosomes in peripheral blood lymphocyte cultures when examined with Giemsa staining and G-banding.[40] In vivo, in a chromosomal damage assay, Boric Acid was not genotoxic in a micronucleus test where mice were given two doses per day for 2 d (≤ 3500 mg/kg) by gavage.[5] To evaluate DNA strand breaks, a comet assay was used for zebrafish (*Danio rerio*) treated with Boric Acid and with Sodium Borate (≤ 64.000 µg/l).[41] Genotoxicity was observed in a dose-dependent manner.

CARCINOGENICITY STUDIES

Oral

Boric Acid

Boric Acid, 2% in gum tragacanth (0.1 ml), was injected intravaginally into 20 BALB/c mice 2 times a week for 50 wk (~ 100 mg/kg).[2] *Positive controls were treated with 7,12-dimethylbenz(a)anthracene (DMBA). One mouse treated with Boric Acid developed a vaginal neoplasm, which was a squamous tumor of low-grade malignancy. No further tumors of the genital tract were observed in treated mice or in 30 untreated controls; tumors developed in 15 out of 20 mice treated with DMBA.*

In a 2-yr study, mice (50/sex/group) were fed Boric Acid at 0, 0.25, and 0.5%.[3] *Body weight gain, clinical signs of toxicity, food consumption, selected organ weights, histopathologic examinations, and mortality were assessed. There was some decrease in food consumption and body weights but these did not appear to be related to mortality, which only occurred mostly in the high-dose group for the male mice. There were hepatocellular and subcutaneous tumors in the low dose group (0.25%), but not in the high dose group (0.5%). There did not appear to be a relationship between the dose and tumor incidence as tumors also occurred in tissues that were not target organs or in the testes. Boric Acid was not considered carcinogenic.*

B6C3F1 mice were fed a diet including 0, 2500, 5000 ppm Boric Acid for 103 wk.[5] There was an increase in testicular atrophy in the male mice, a reduction in body weight during the first year, and reduced survival in all dose groups. However, there was no increase in tumors, which indicated that Boric Acid did not show any evidence of carcinogenicity.

ANTI-CARCINOGENICITY STUDIES

Boric Acid

In several assays, prostate cancer cells (DU-145, LNCaP, and PC-3) were treated with up to 1000 µM Boric Acid.[42] Boric Acid inhibited the proliferation of the DU-145 and LNCaP in a dose-dependent manner. A minimal effect on cell cycle stage distribution and mitochondrial function was observed in DU-145 cells. When compared to Boric Acid concentrations observed in human blood, higher Boric Acid concentrations were required to inhibit proliferation in non-tumorigenic prostate cancer cell lines, such as PWR-1E and RWPE-1, and the cancer cell line PC-3.

OTHER RELEVANT STUDIES

Endocrine Effects

Boric Acid

Groups of 8 female, adult, ovariectomized Sprague-Dawley rats were orally administered Boric Acid at 0, 4, 25, or 75 mg/kg in distilled water (negative control) or 0.1 mg/kg 17β-estradiol (positive control) for 3 d.[43] A statistically significant increase in uterine weights was observed in the high-dose group, which was still lower than that of the positive controls. Serum E2 levels were not statistically significantly different between Boric Acid-treated animals and negative controls. The height of the endometrium and the estrogen receptor density of uterine cells were higher in all Boric Acid-treated groups compared to the negative controls.

Cytotoxicity

Boric Acid

The cytotoxicity studies summarized below are described in Table 8. The effects of Boric Acid on cell proliferation, apoptosis, and oxidative stress were investigated on Jurkat cells using a 2,3-bis-(2-methoxy-4-nitro-sulfopenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay.[44] Boric Acid increased oxidative stress and inhibited Jurkat cell proliferation dose-dependently. Sertoli cells were isolated from eighteen 22-d-old male Sprague-Dawley rats and were exposed to different concentrations of Boric Acid (0.25 - 80 mmol/l).[45] Using cell counting kit-8 (CCK-8) and 3-(4,5-dimethylthiazol-2-yl)-2,5-

diphenyltetrazolium bromide (MTT) assays, it was determined that lower doses (< 0.5 mmol/l) promoted the viability of the Sertoli cells and inhibited apoptosis while higher doses (> 5.0 mmol/l) had toxic effects that inhibited cell viability, accelerated apoptosis, and arrested the cell cycle at the G0/G1 phase. Boric Acid was tested in a study in which oral rinse solutions were formulated to find an alternative to chlorhexidine due to undesirable side effects. [46] The cytotoxicity was evaluated by MTT and LDH assays and the Boric Acid solution had a similar cytotoxicity to chlorhexidine, making it an unfavorable alternative. When Sodium Borate was tested as well, it was less cytotoxic compared to chlorhexidine, making it a favorable alternative. Using the MTT test, cytotoxic effects were studied on U-87 MG glioblastoma cells which were exposed to different concentrations of Boric Acid solution (2.5 - 50 mM).[47] When compared to the control, the percentage viability calculated was 90, 46, and 23% for the 2.5, 25, and 50 mM Boric Acid applications, respectively. A concentration of 50 mM had a fatal effect, and multiplication-preventing could be seen starting in the 25 mM concentration on the U87-MG cells. Using an MTT assay, Boric Acid was tested at 0.00625 - 0.200 ml on the HepG2 and THLE2 cell lines to see the effect on cell viability. [48] The viability of both cell lines was reduced in a dose-dependent manner, with Boric Acid being more cytotoxic in the HepG2 cell line. The IC_{50} for the HepG2 cell line was much lower, at 0.06427 mg/ml, as compared to 0.6128 mg/ml in the THLE2 cell line. An MTT assay also showed that human lymphocyte cell cultures had low proliferation when the cells were treated with 100, 150, 200, 300, and 600 µg/ml Sodium Borate.[37]

Sodium Borate

Sodium Borate (as refined borax and borax ores) was studied in V79 Chinese hamster cells, C3H/10T1/2 mouse embryo fibroblasts, and diploid human foreskin fibroblasts. [3] Solutions were prepared and tested on the cells for 48 h from varying concentrations (depending on the cell type) ranging from 0.0000001 – 3.2 mg/ml[3] before measuring the reduction in plating efficiency. The lowest concentration where cytotoxicity was observed was at 0.02 mg/ml for borax ore in human fibroblasts. However, for refined borax, the lowest was 0.1 mg/ml in C3H/10T1/2 mouse embryo fibroblasts and human fibroblasts. Cytotoxicity increased in a dose-dependent manner as concentration increased.

Antimicrobial Activity

Boric Acid and Sodium Borate have weak bactericidal properties and significant bacteriostatic effects in concentrations up to 4%.[2] When added to in milk samples, Sodium Borate was bacteriostatic at 2% and did not kill Mycobacterium tuberculosis in the samples. Boric Acid is used to preserve urine specimens and organisms at culture at 0.5 - 5% as a bacteriostatic agent. Sodium Borate and Boric Acid exhibited antimicrobial activity in several experimental systems, including inhibition of Staphylococcus aureus growth at 1.5 × 10^{-8} M Sodium Borate, inhibition of bacterial proteolytic deterioration in foods with 0.1% Boric Acid, fungistatic activity with 0.2% - 1.0% Sodium Borate, and elimination of bacteria within 2 d and fungi within 28 d using 0.3% - 0.5% Boric Acid.

The antibacterial activity of Boric Acid and Sodium Borate was tested against cariogenic bacteria using agar well diffusion and microdilution techniques.[46] Boric Acid had larger inhibition zones ranging from 15 - 20 mm and lower minimum inhibitory concentration (MIC) values ranging from 0.156 - 0.625 mg/ml, indicating strong antibacterial activity. Sodium Borate had antibacterial activity with inhibition zones ranging from 14 - 19 mm and an MIC ranging from 0.625 - 1.25 mg/ml. However, due to its smaller inhibition zones and higher MICs, it did not show as strong of antibacterial activity as Boric Acid.

Neurotoxicity

Boric Acid

Male and female Sprague-Dawley rats received a single dose of 0 or 2000 mg/kg Boric Acid, in a vehicle of 1% carboxymethyl cellulose (CMC), via gavage.[5] The total body weight gain in Boric Acid-treated male rats was 16% lower than control rats at the end of a 14-d observation period. There were no changes in mortality or neurohistopathological observations that were noticed. The NOAEL for neurotoxicity was determined to be 2000 mg/kg bw/d.

Immunotoxicity

Boric Acid

In an immunotoxicity study, female B6C3F1 mice (10/group) were treated with 0, 250, 500, 750 or 1000 mg/kg Boric Acid in CMC via gavage for 28 d.[5] Body weight, clinical observations, food consumption, hemolytic plaque formation, and spleen and thymus weight were monitored. No adverse clinical observations were noted, and weight changes and food consumption remained normal. In comparison to the controls, there were no statistically significant decreases in the absolute spleen and thymus weights in the Boric Acid treated group. Although hemolytic plaque formation decreased in a dose-dependent manner, the change was also not statistically significant. Boric Acid was not considered to be immunotoxic.

Effects on Bone Strength

Boric Acid

During a 12-wk exposure period, groups containing 42 male and 6 female F344 rats each were fed a diet containing either 200, 1000, 3000, or 9000 ppm Boric Acid (~1.7, 8.5, 26, and 68 mg/kg boron) to test the effect on bone strength. [3] At weeks 1, 2, 3, 4, 5, 8, and 12, 6 male rats were weighed, killed, and necropsied. The 6 female rats were similarly weighed, killed, and necropsied at week 5. Body weight, serum calcium, phosphorus, and magnesium levels, bone structure, femur breaking strength, and crush resistance were assessed. There was no effect on body weight gain, aside from the males that

consumed 9000 ppm, which had a reduction. For serum levels, calcium, phosphorus, and magnesium all reduced in a dose-dependent manner, but to a maximum of 10%, 84%, and 81% of control levels, respectively. There was no change in the bone microscopic structure or femur breaking strength. However, there was a significant increase in crush resistance for all levels of Boric Acid in the diet for the male rats. Though the same result was observed for the female rats, the increase was not sufficient to be statistically significant.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The irritation potential of Boric Acid and Sodium Borate (10% aq. and 5% aq., respectively) was tested on 6 guinea pigs and 6 rabbits.[2] Approximately 10 ml of the Boric Acid solution and 5 ml of the Sodium Borate solution were applied under occlusion to clipped intact and abraded skin. The primary irritation indices (PIIs) for Boric Acid were 2.1 in guinea pigs and 1.7 in rabbits, and for Sodium Borate were 1.4 in guinea pigs and 2.0 in rabbits. Both test articles were considered to be mildly to moderately irritating. A study was performed in which 5% aq. Boric Acid at various pHs, adjusted to various pH levels using different agents, was applied to the backs of rabbits. No irritation was observed with a solution prepared in freshly passed human urine (pH 5.5) or with the unadjusted solution (pH 3.81). Slight to moderate irritation was observed with solutions adjusted to pH 6.8 and 7.38 using ammonium carbonate, and slight irritation was observed with the solution adjusted to pH 7.87 using sodium hydroxide. Marked irritation was observed with the solution adjusted to pH 8.16 using ammonium carbonate and ammonia solution. In a different study, a bath preparation containing 0.4% Boric Acid was tested in 9 albino rabbits to evaluate primary skin irritation. The formulation was applied to the shaved intact skin for a 24-h period, undiluted and under occlusion. Eight out of 9 rabbits experienced slight to moderate erythema and the PII was 1.06, which indicated that the bath preparation containing 0.4% Boric Acid was a mild irritant.

In clinical irritation studies, a bath preparation containing 0.4% Boric Acid and a product containing 2.4% Boric Acid were tested undiluted in open applications in 2 separate single-insult patch tests using 20 and 19 subjects, respectively.[2] The bath preparation containing 0.4% Boric Acid resulted in a PII of 1.50; irritation ranged from minimal to bright erythema accompanied by edema, petechiae, or papules. The 0.4% Boric Acid bath preparation was considered moderately irritating. The product containing 2.4% Boric Acid induced minimal erythema in 1 subject, with no other reactions, and had a PII of 0.03. Two cleansing creams, each containing 1.7% Sodium Borate, were assayed in separate 2-wk panel tests.[2] One cream produced no irritation in a group of 100 subjects. In the other panel of 90 subjects, there was 1 report of irritation, resulting from incidental contact in the eyes. A stinging sensation subsided after the eyes were rinsed. A 21-d cumulative irritation test was performed to evaluate the effect of occlusive application of a cleansing cream containing 1.7% Sodium Borate and hair preparation containing 3.2% Sodium Borate in 14 and 12 subjects, respectively. The cleansing cream containing 1.7% Sodium Borate caused slight erythema in 2 subjects, resulting in a total irritancy score of 6.4, which was considered non-irritating. Application of the hair preparation containing 3.2% Sodium Borate produced erythema and papules in most subjects. The total cumulative irritancy score was 571 (maximum score = 630); the hair preparation was considered to be a "mild to moderate" cumulative irritant.

To determine sensitization potential, a cream containing 1.1% Sodium Borate was tested in a prophetic patch test using 198 subjects.[2] One subject experienced minimal irritation to the induction patch; no other reactions to the induction or challenge patches were observed. A cleansing cream containing 1.7% Sodium Borate was applied undiluted in open and closed patches in 2 Schwartz-Peck prophetic patch tests. Trial 1 consisted of 98 subjects while trial 2 contained 49 subjects. Since there were no reactions in both trials, the cleansing cream was considered non-sensitizing and nonirritating. A product containing 1% Sodium Borate and a cream containing 1.1% Sodium Borate were non-irritating and non-sensitizing in 2 separate human repeated-insult patch tests (HRIPT) using 101 subjects each. The contact-sensitizing potential of a cleansing cream containing 1.7% Sodium Borate was tested in 22 subjects. Test sites were pretreated with sodium lauryl sulfate (SLS) for 24 h prior to induction. Five occlusive, 48-h applications of the product were made every other day for 10 d; challenge applications were made after a 10 - 14 d non-treatment period to untreated sites (with and without SLS pretreatment). More than half of the test subjects reacted to the SLS treatment; however, non-significant irritation or sensitization was observed at sites tested with the cleansing cream only. In similar maximization test performed in 25 subjects, a hair preparation containing 3.2% Sodium Borate was irritating during induction (SLS pretreatment was unnecessary). No reactions were observed during challenge; the product was considered non-sensitizing.

The dermal irritation and sensitization studies for Boric Acid and Sodium Borate that are summarized below are described in Table 9.

Boric Acid and Sodium Borate were not irritating to rabbit skin when tested at concentrations to up to 95% w/w.[5,6] Neither ingredient was a sensitizer in studies using guinea pigs performed in accord with OECD test guideline (TG) 406.

Photosensitization/Phototoxicity

In 2 separate prophetic patch tests, cleansing creams containing 1.1 and 1.7% Sodium Borate were non-photosensitizing in 198 and 98 subjects, respectively, when 48-h, occlusive challenge applications were irradiated with ultraviolet (UVA; 360 nm at a distance of 12 in for 1 min with a Hanovia Tanette Mark I lamp).[2] In 2 separate HRIPTs, skin sites tested with cleansing creams containing either 1.1 or 1.7% Sodium Borate were exposed to the same UVA irradiation

following the removal of induction patches 1, 4, 7, and 10 as well as the challenge patch. Both cleansing creams containing 1.1 and 1.7% Sodium Borate were non-photosensitizing in all 101 and 49 subjects, respectively.

OCULAR IRRITATION STUDIES

Animal

Boric Acid

The ocular irritation potential of a bath preparation containing 0.4% Boric Acid was evaluated using 6 albino rabbits.[2] Treated eyes were rinsed 4 s after instillation. The product containing 0.4% Boric Acid was considered moderately irritating.

In a 21-d study, 100 mg of Boric Acid were instilled into the conjunctival sac of 6 rabbits.[5] After 24 h, the eyes were rinsed using physiological saline. There was irritation observed but was mostly cleared after a 7-d period. Boric Acid was considered to be a non-irritant.

Sodium Borate

The ocular irritation potential of a hair preparation containing 3.2% Sodium Borate was tested in 9 albino rabbits.[2] The eyes of 3 animals were rinsed 30 s after treatment. The test article induced slight conjunctival chemosis in 1 of 3 animals with rinsed eyes and in 2 of 6 of the animals with unrinsed eyes; the test article was considered non-irritating to rabbit eyes.

A single dose (0.08 ml) of undiluted Sodium Borate was instilled into one eye of 6 New Zealand white rabbits.[5] The treated eyes were not rinsed and were observed for 14 d and were scored for reactions up to 72 h after exposure. The average of the scores collected during the 24, 48, and 72 h periods were the following: corneal opacity (0.22/4), iris (0.22/2), conjunctivae (redness; 2.8/3), chemosis (1.89/4). The test substance was classified as an ocular irritant, based on a mean redness score > 2.

CLINICAL STUDIES

Mucous Membrane Irritation Studies

Inhalation

Sodium Borate

Male subjects were exposed to a mineral dust of 5, 10, 20, 30, or 40 mg/m^3 Sodium Borate, in an exposure dome, via inhalation.[49] Subjects were exposed while lightly exercising during up to 11, 20-min sessions. Three "blank" sessions were used for comparison. The mass median aerodynamic diameter (MMAD) for Sodium Borate particles was determined to be 7.11 ± 1.72 µm. The perceived magnitude of the effect of Sodium Borate was 10 mg/m^3 in the eye and nose, and 5 mg/m^3 for the throat. Nasal secretions, considered the best association with irritation potential, were statistically significantly higher than "blank" exposure at 10 mg/m^3 Sodium Borate exposure, but not at 5 mg/m^3 Sodium Borate exposure.

Case Reports

Dermal

"Strong" solutions of Boric Acid have been reported to cause skin irritation and reddening of the skin (no further details provided).[2] In a case report, a man used a large amount of Boric Acid ointment to treat boils and developed a papular eruption on his arms and legs with repeated exposure to this ointment. Many cases of Boric Acid poisoning, resulting from dermal exposure are seen in infants, in which mortality is higher than in adults.

Oral

The chronic ingestion of mouthwashes containing Boric Acid (concentrations not specified) was reported to result in diffuse alopecia as well as central nervous system and GI disruption in a woman.[2] Symptoms abated and hair regrowth occurred after the patient avoided all boron-containing products. The researchers suggested that hair-loss may have resulted from Boric Acid accumulation in the hair follicles and subsequent toxic effects on the hair bulbs. Acute Boric Acid and Sodium Borate poisoning are frequently reported and mostly result from accidental exposure rather than intentional (medicinal) use. Many cases of Boric Acid poisoning resulting from oral exposure are seen in infants, in which mortality is higher than in adults. Six adult patients that had consumed massive amounts of Boric Acid showed intracytoplasmic inclusions, round bodies within the acinar cells, and had basophilic granules in the pancreas. Additionally, massive quantities of riboflavin were excreted in the urine of patients with Boric Acid poisoning.

A 2-yr-old male ingested 10 g of Boric Acid mixed with flour and had intermittent vomiting 3 h following initial ingestion.[3] After 1 h, serum Boric Acid levels were at 530 µg/ml eventually rising to 580 µg/ml at 7 h. A 28-yr-old female ingested ~297 g of an insecticide containing 99% Boric Acid. In 1 h after ingestion, the patient experiencing vomiting and underwent a gastric lavage, activated charcoal, and a cathartic for treatment. When the patient's blood Boric Acid level was measured 2 h post-ingestion, it was measured to be 49 µg/ml. A 35-yr-old woman had spontaneous vomiting and facial flushing 30 min after ingesting 80 g of Boric Acid in a fungicidal preparation. For treatment, syrup of ipecac, activated charcoal, and a cathartic were used. The measurement of the patient's blood Boric Acid level was 2320 µg/ml in the first

hour after ingestion and eventually decreased to 1360 µg/ml at 13 h. A 72-yr-old woman accidentally ingested 2 doses of Boric Acid (45 g) as a result of dispensing error which produced diarrhea and vomiting at the first dose and vomiting at the second dose. She had non-pruriginous erythema on her face and upper half of her thorax and underwent a gastric enema. The patient also developed a 7-d fever but recovered at 12 d. When the boron concentration was measured in the plasma, it started at 64 µg/ml, decreased to 37 µg/ml at 10 h, and eventually to 2 µg/ml in 5 d. For the urinary excretion, it began at 250 µg/ml and increased to 1000 µg/ml at 24 h, leveling off at 1400 – 1450 µg/ml at 3 – 6 d. An 82-yr-old woman accidently ingested a homemade insecticide containing milk, sugar, onion, flour, and 250 g of Boric Acid. The woman had diarrhea and vomiting within 3 h and was semi-conscious around 24 h. Within 3 d of ingestion, the patient was comatose and was experiencing a fever and high blood pressure. The patient eventually developed inflammation of the skin and mucous membranes with her blood pressure falling until she died 8 d after ingestion. A 45-yr-old male experienced nausea, vomiting, diarrhea, and dehydration after ingesting 2 cups of Boric Acid dissolved in water. After 2 d, he had hypotension, metabolic acidosis, renal failure, a generalized erythematous rash, and superficial skin abrasions when brought into the hospital. Vasopressors and intravenous fluids were used as treatment but were unsuccessful. Although atrial fibrillation developed, the patient died 17 h after admission due to the cardiovascular collapse secondary to electromechanical dissociation. The blood Boric Acid was measured to be 420 µg/ml 52 h after ingestion. A 77-yr-old male ingested 30 g of Boric Acid as a treatment for hiccups but exhibited vomiting, diarrhea, erythema on the face and trunk when arriving at the hospital. The patient also developed acute renal failure and underwent charcoal hemoperfusion and hemodialysis. The blood Boric Acid level went from 37.7 µg/ml to 25.3 µg/ml with the treatment, but the patient eventually died of cardiac insufficiency. A group of 7 infants suffering from seizures from pacifiers dipped in a proprietary mix of Sodium Borate (borax) and honey were brought to the hospital. Only 4 of the infants had vomiting, loose stools, and irritability. The other 3 infants had their blood boron levels measured, which were 2.6, 8.5, and 8.4 µg/ml. These levels were higher than the average (0.21 µg/ml) measured in 15 infants not receiving boron in their diet.

Details of the case reports and other clinical reports referencing Boric Acid and Sodium Borate summarized below are described in Table 10.

Following dermal exposure to 2% Boric Acid solution, a 2-yr-old girl had symptoms that included erythema, lesions, crusting, edema, erosions, and exudation.[50] Adults aged 56, 82, and 88-yr reported oral ingestion of 6 - 300 g Boric Acid that resulted in localized irritation, headache, nausea, vomiting, thrombocytopenia, altered mental state, anemia, elevated transaminases, impaired renal clearance, diarrhea, and hypotension, and dermal findings similar to those observed following topical exposure.[51-53]

Occupational Exposure

A man experienced hair-loss when exposed to a soap powder containing 78.6% Sodium Borate in an occupational setting for 6 yr.[2] *The hair loss symptoms subsided when the patient avoided all contact with the soap powder. The previous threshold limit value (TLV) for workroom environments for Sodium Borate set by the American Conference of Governmental Industrial Hygienists (ACGIH) was 5 mg/m^3, for an 8-h workday, and 40-h workweek. This value agreed with that of Belgium and the Netherlands and was thought to "prevent acute irritant effects" over a normal working lifetime. Workers were evaluated at a plant that manufactured Boric Acid from borax (Sodium Borate) and boron oxide from Boric Acid.* [3] *When the total particulates were measured in the exposure areas, it ranged from 1.2 – 8.5 mg/m3 with a mean of 4.1 mg/m3. At the time, the ACGIH had a TLV of 10 mg/m^3 where the levels of measured areas of the plant would occasionally exceed. Despite this, exposed workers experienced statistically significant increases in dryness of the mouth, nose, and throat, eye irritation, sore throat, and productive cough. In workers at a borax mining and refining plant, mean dust exposures were categorized as: low (0.9 mg/m^3), medium (4.5 mg/m^3), and high (14.6 mg/m^3). Information was gathered on the workers' respiratory symptoms and smoking history via a questionnaire. A chest radiograph and pulmonary function tests were conducted but did not show a pattern of abnormalities. However, the questionnaire revealed that workers exposed above 4.4 mg/m^3 of the Sodium Borate had chronic bronchitis and a productive cough. An additional occupational exposure study involving 79 exposed and 27 unexposed workers found that daily and short-term peak particulate exposures were linearly associated with acute respiratory and ocular irritation symptoms. Continuous particulate and event monitoring further supported the relationship between Sodium Borate exposure and irritant responses, although electronic event monitoring produced a high rate of false-positive recordings.*

Reproductive toxicity indicators were measured in the blood and semen of 204 production plant workers at a Boric Acid plant.[54] Subjects were classified according to their blood boron concentration as controls (< 0.0000485 mg/g), low- (> 0.0000485 - 0.0001 mg/g), mid- (> 0.0001 - 0.00015 mg/g), or high-dose (> 0.00015 mg/g) exposure. No statistically significant differences in mean levels of sperm concentration, motility, or morphology parameters were observed between control and exposed groups. A dose-dependent increase in FSH, LH, and testosterone levels was also not observed with increased blood boron concentrations. There was a statistically significant correlation between blood boron concentrations and sperm tail % intensity values.

The time-weighted averages (TWA) set by ACGIH for inhalable particulate matter are 2 mg/m^3 (TLV- TWA) and 6 mg/m^3 (TLV-short-term exposure limit (STEL)).[55] California's Division of Occupational Safety and Health set an 8-h permissible exposure limit (PEL)-TWA of 5 mg/m^3. The National Institute for Occupational Safety and Health (NIOSH) TWA-STEL for borates, tetraborates, and sodium salts (Sodium Borate; CAS No. 1330-43-4, anhydrous) is 1 mg/m^3.[56]

EPIDEMIOLOGICAL STUDIES

Details of the epidemiological studies referencing Boric Acid and Sodium Borate summarized below are described in Table 11.

During a 3-yr period, 190 women exposed to boron in their drinking water had blood boron concentrations ranging from 0.000075 - 0.000328 µg boron/g. There were no adverse events in induced abortion, spontaneous abortion (miscarriage), stillbirth, infant death, neonatal death, early neonatal death, preterm birth, congenital anomalies, sex ratio, and birth weight. In a study with 177 mothers during pregnancy, the amount of boron was measured from the maternal serum and maternal blood before pregnancy (30 - 447 µg/l and 27 - 322 µg/l) and after pregnancy (47 - 624 µg/l and 66 - 750 µg/l), respectively.[57] After birth, the infant urinary boron content was measured at 0 - 3 mo (105 - 9200 µg/l) and 3 - 6 mo (389 – 15,068 µg/l). There was an inverse association of infant urinary boron on the weight, length, and head circumference of an infant in the first 6 mo. The amount of boron was measured in the dietary food/fluids, workplace inhalable dust, blood, semen, and urine from boron workers and controls.[58] From this data, three groups in the study were created which included boron workers (n=66), the workers from high boron areas as the community comparison (n=59), and the workers from low boron areas as the control (n=67). Semen parameters were also determined such as apoptosis, aneuploidy, DNA breakage, morphology, motility, sperm concentration, and total sperm count. The average blood boron, semen boron, and boron in the urine ranged from 47.9 – 499.2 ppb, 214 – 785.6 ppb, and 2.0 – 16.7 mg/l across the control, community comparison, and boron worker groups. There were no significant correlations between the semen parameters or blood boron concentration. In a study with 1000 men working in boron mining or processing in China, the mean daily boron intake and the semen was analyzed (sperm density, total sperm count, semen quality, sperm zinc, motility) of the following groups were taken; boron workers (n= 75), boron workers at a plant with heavy boron contamination of water (n=16), the local community (sample size not mentioned), and remote background controls (sample size not mentioned). The mean daily boron intake was measured to be 31.3, 125, 4.25, and 1.40 mg boron/d, respectively.[59] There was not a statistically significant difference in the semen characteristics between the exposure groups.

RISK ASSESSMENT

Margin of exposure (MOE) is a quantitative ratio calculated for cosmetic ingredients by dividing the point of departure (POD) obtained for an ingredient in an animal experiment by the estimated systemic exposure dose (SED) for the ingredient in humans, generally according to US Environmental Protection Agency (EPA) and EC Scientific Committee on Consumer Safety (SCCS) guidelines. An MOE value greater than 100 has traditionally been considered an indication of safety. The basis for this MOE value of 100 comes from two multiplication factors: a 10-fold factor for extrapolating data from test animals to human being (interspecies extrapolation), and an additional 10-fold for differences among the human population (intraspecies extrapolation). Notably, the MOE value is sometimes referred to as the margin of safety (MOS) despite the parameters being definitionally different.

The Panel considered that Boric Acid-containing intimate wash products may be applied to the genital area and may result in vaginal mucosal exposure, particularly in light of the reproductive and developmental toxicity potential of Boric Acid. Accordingly, CIR staff performed an MOE calculation for rinse-off bath/body wash products as a conservative estimate for intimate wash use with potential genital-area exposure.

The exposure parameters are presented in Table 12. The calculation was based on the maximum reported concentration of 0.00016% Boric Acid in body washes,[13] a daily body wash use amount of 25.5 g/d,[60] and a retention factor of 0.01. In the absence of mucous membrane absorption data, 100% absorption of the retained amount was assumed as a conservative estimate of potential systemic exposure from genital-area/mucous membrane contact with these product types. Based on these assumptions, the calculated SED was 0.0000068 mg/kg bw/d. Because this calculation assumes 100% mucous membrane absorption of the retained product amount, it likely overestimates systemic exposure from rinse-off body wash use. A refined estimate could scale the body wash use amount to the adult genital exposed area of 637 cm^2,[61] thereby limiting the mucous membrane absorption assumption to the relevant intimate-area exposure. However, because product use may not scale directly with exposed surface area, this refined area-based approach remains uncertain and may warrant application of an additional uncertainty factor. When an NOAEL of 55 mg/kg bw/d (derived from an oral developmental study in time-mated female Sprague-Dawley rats; details provided in Table 5),[62] was used, the resulting MOE was 8,088,235. This MOE is substantially greater than 100 and is considered protective.

In addition, the 2025 RLD reported 1 use of Boric Acid in douches and 7 uses of Boric Acid in disposable wipes;[11,12] these product categories are associated with intimate-area exposure. Exposure inputs for intimate hygiene (disposable) wipes and douches are available.[61] However, concentration of use data were not reported for these product types, thus precluding calculation of an MOE for these uses. The available maximum concentration of 0.00016% from the Council survey reported for rinse-off body wash/shampoo-type products should not be assumed to apply to douches or disposable wipes. If such concentration of use data becomes available, additional MOE calculations could be performed.

SUMMARY

Boric Acid is reported to function in cosmetics as a buffering agent, cosmetic biocide, and denaturant while Sodium Borate functions as a pH adjuster. The Panel first reviewed these ingredients in 1983 concluding that both ingredients are

safe as cosmetic ingredients at concentrations ≤ 5%. In February 2003, the Panel reaffirmed the 1983 conclusion in a re-review, which was published in 2006. In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In June 2024, the Panel determined that this safety assessment should be re-opened for re-evaluation due to reported bans by the European Union on the use of Boric Acid and Sodium Borate.

In 2025, RLD obtained from the FDA reported that Boric Acid and Sodium Borate were reported to be in use in 96 formulations and 202 formulations, respectively. In response to the 2025 Council survey, concentrations of use were only reported for rinse-off products; the maximum concentration of use reported is 3.7% Sodium Borate in skin cleansing formulations (cold creams, cleansing lotions, liquids and pads).

Wistar rats (n = 20) received a 1 ml dose of Sodium Borate via gavage at doses ranging from 0 - 0.4 mg/100g bw as boron. After 24 h, urine collection revealed a urinary recovery of 99.6 ± 7.9%. The excretion and boron dose relationship had a regression coefficient of 0.954, indicating a highly linear correlation and 100% bioavailability rate. In an in vivo percutaneous study, Boric Acid and Sodium Borate were applied at 5% (in aq. solution) to a 900 cm^2 area on subjects (n=8) for 24 h. Boron concentrations indicated there was ~0.23% Boric Acid and ~0.21% Sodium Borate absorbed. When done in vitro in human skin for Sodium Borate, there was a decrease in absorption at 0.19%.

Boric Acid and Sodium Borate both had dermal LD_{50} values of >2000 mg/kg (the highest dose tested) in rabbits. In oral studies, LD_{50} values were >2000 mg/kg Boric Acid in rats when administered via gavage. Oral LD_{50} values ranged from >200 - 3401 mg/kg in male rats and >2000 - 3225 mg/kg in female rats when administered via gavage. The inhalation LC_{50} values in rats were >2 mg/l for Boric Acid and Sodium Borate.

A 5-d toxicity study was completed in mice (10/group) given 0.28 mg/250 ml Boric Acid orally via drinking water, which resulted in a mean weight loss and statistically significant changes in some clinical chemistry parameters. In a 7-d study, male albino Sprague Dawley rats were administered 1000 mg/kg/d of Boric Acid orally via drinking water, which led to significant weight loss, edema, an increase in apoptotic cells, and inflammation when compared to the controls. In an oral study, in which Boric Acid was administered via gavage at a dose of 800 mg for 30 d, the rats were killed every 6 d during the exposure period and every 10 d during the recovery period of 109 d. The NOAEL and LOAEL were both calculated to be < 800 mg/kg (critical endpoints were not provided). In a study in male albino Sprague Dawley rats (24/group) were given 100, 275, or 400 mg/kg/d of Boric Acid in feed for 45 d, time- and dose-dependent; degenerative changes were observed in kidney tissues.

In a 90-d study, 60 male albino rats were given Boric Acid orally via gavage (0.16 mg/kg/bw) or water as a control. The liver and kidney tissues went under histological examination, and the functions were tested. There was a statistically significant increase in hepatic enzyme leakage (AST, ALT, and ALP) and serum renal damage products levels (urea, uric acid, and creatine). There was also depleted antioxidant enzymes and various histopathological perturbations in hepatic and renal tissues were observed.

In inhalation studies, rats were exposed to Boric Acid for 6 h/d, 5 d/wk, at concentrations of 470 mg/m^3 for 10 wk (n = 20), 175 mg/m^3 for 12 wk (n = 4), or 77 mg/m^3 for 24 wk (n = 70), and 3 female dogs were exposed to 57 mg/m^3 for 23 wk, via aerosol. There were no signs of toxicity in any of the animals and the NOAEC for systemic toxicity in rats was 470 mg/m^3, 175 mg/m^3 for local effects in rats, and 57 mg/m^3 for dogs.

Boric Acid was tested at concentrations of 0.019, 0.062, 0.186, or 0.618 mg/ml on the primary culture of seminiferous tubules coming from 20-d-old male Sprague Dawley rats. After the cells were analyzed via fluorescence-activated cell sorting (FACS) analysis, Boric Acid had resulted in an increase in somatic cell proliferation and a decrease in all the germ cell populations. A revised 96-well EST was used to evaluate embryotoxic potency; Boric Acid was "moderately embryotoxic" based on its REP value of 0.001 ± 0.001. Similarly, a survivin-based embryotoxicity assay was performed with 100 µg/ml of Boric Acid. Boric Acid led to a 20% decrease in survivin expression and lower EGFP intensities in the D3-CMV-EGFP and D3-SP-EGFP cells, which indicated a moderate embryotoxic effect and cytotoxicity, respectively. In two studies, Swiss mice were given Boric Acid via diet at 0 or 9000 ppm. In the first study, FSH levels increased after 4 wk, LH increased, testosterone decreased after 2 wk, and gonadotrophin increased 1 - 2 wk afterwards. Boric Acid was suggested to act on Leydig cells to depress testosterone synthesis and/or release. In the second study, the mice were bled weekly for 8 wk by ophthalmic plexus. At wk 9, half were given HCG challenge and half were given saline where serum was collected for both groups 1 h after. Boric Acid decreased basal concentrations of testosterone and the release of testosterone in response to HCG challenge. In a 27 wk study, Swiss mice were administered via diet which included Boric Acid ranging from 0 - 1262 mg/kg (~0 - 9000 ppm boron). At 14 wk, there was a reduction in fertility and elimination at the 4500 ppm (636 mg/kg Boric Acid) and 9000 ppm (1262 mg/kg Boric Acid) doses, respectively. At 27 wk, there was a reduction in body weight and reproductive organ weight for the males and at 4500 ppm (636 mg/kg Boric Acid), there was decreased kidney and adrenal weights for both sexes. Male and female CD-1 rats were given Boric Acid via gavage 3 - 20 and 0 – 20 d before necropsy at 0, 120, 400, or 1200 mg. Mating occurred between days 8 – 12 and at 1200 mg. There was evidence of testicular toxicity in the males and a reduction in females delivering as well as the number of live pups. In a one-generation study, time-mated female Sprague Dawley rats were delivered a dose of 0, 5, 10, or 20 mg/kg/d of Boric Acid orally via gavage on days 6 - 21 of gestation while the pups received the same dose but from PND 1 - 28. The dams did not have any deaths or signs of

maternal toxicity at the doses administered but the pups in the 20 mg/kg/d group had 11 instances of umbilical hernias and a 23% reduction in weight. In a study in which Sprague-Dawley rats were administered Boric Acid via drinking water for 45 d at 100, 275 or 400 mg/kg, the body/testis weights, plasma/testis boron concentrations were measured, and blood samples/testis tissues were collected on days 10, 30, and 45. There was a significant accumulation of boron in the testis in the rats over the course of the study. Pregnant Sprague Dawley rats received 0 or 500 mg/kg of Boric Acid twice a day depending on the block assigned. The 1st block was dosed on GD 6,7, 8, or 9 with the controls receiving only water on GD 9. The 2nd block was dosed on GD 9, 10, or 11 with the controls receiving only water on GD 9 - 11. After being examined, Boric Acid induced axial skeleton malformations and shifted the expression domain for hoxc6 and hoxa6 on GD 13.5. New Zealand white rabbits were given 0, 62.5, 125, or 250 mg/kg via gavage during day 6 – 19 post mating. On day 30 of gestation, the rabbits were terminated and clinical examinations were made. The maternal rabbits had a LOAEL of 43.5 mg B/kg (~250 mg/kg Boric Acid) and NOAEL of 21.8 mg B/kg (~125 mg/kg Boric Acid). At 250 mg/kg Boric Acid, the dams had 90% resorbed vs. the 6% in the controls with an overall 73% complete litter loss. In a different study, rats were exposed to either 9.6 ± 0.5 mg/m^3 or 48.6 ± 1.46mg/ m^3 Boric Acid for 4 h/d for 4 mo. The 9.6 ± 0.5 mg/m^3 group had atrophied testis, reduced spermatozoa, and pathological changes in testis more severity seen in the 48.6 ± 1.46 mg/m^3 group. Wistar albino rats (7 females/group) were administered 0, 1250 or 5000 mg/kg Sodium Borate (~142 and 567 mg/kg boron) orally via gavage for 7, 15, 30, or 60 d. Evaluated endpoints included ovarian weights, serum concentrations of FSH, LH, estradiol E2, and AMH, histomorphometry measurements, and the ovarian apoptotic index using a TUNEL assay. As the dose and exposure duration increased, there was a decrease in ovarian weight, LH, E2, and AMH levels and an increase in FSH levels and ovarian apoptosis. Ovarian toxicity associated with boron exposure was dependent on dose and exposure duration with the most effects observed at the highest dose (5000 mg/kg) and longest exposure duration (60 d). In a three-generation study, Sprague Dayley rats (8 males/group and 16 females/group) were fed a diet with Boric Acid or Sodium Borate at doses equivalent to ~0, 5.9, 17.5, and 58.8 mg boron/kg bw/d. After 2–3 wk of treatment at 58.8 mg boron/kg bw/d, females exhibited systemic toxicity and reduced litter production, while males developed testicular atrophy. A NOAEL of 17.5 mg boron/kg bw/d was proposed for female reproductive effects, although the study mentioned limitations in the mating procedure and concluded that the evidence for adverse effects was stronger for male fertility than for female fertility. The LOAEL was identified to be 58.5 mg boron/kg bw/d.

In a mouse lymphoma gene mutation assay, Boric Acid was not genotoxic in L5178Y cells. In in vitro assays evaluating chromosomal damage, Boric Acid (≤10 µM, 20 ppm, 10,000 µg/l, and 50,000 µg /ml) and Sodium Borate (≤10 µM and 10,000 µg/l) were not genotoxic in micronucleus assays. Boric Acid and Sodium Borate (≤ 10,000 µg/l) were not genotoxic in a chromosomal aberration assay in human blood cultures. However, Boric Acid did cause an increase in structural and total chromosomal aberrations (but not numerical chromosomal aberrations) in human lymphocytes (≤ 10,000 µg/l). In other genotoxicity studies, Boric Acid was not genotoxic in comet assays performed with Chinese hamster lung fibroblast (V79) cells (at ≤ 200 µM) or with human Sertoli cells (at ≤ 1000 µM), Sodium Borate (150 – 300 µg/ml) produced a statistically significant reduction in the numbers of metaphase plates and metaphase chromosomes in peripheral blood lymphocyte cultures when examined with Giemsa staining and G-banding. In vivo, in a chromosomal damage assay, Boric Acid was not genotoxic in a micronucleus test where mice were given two doses per day for 2 d (≤ 3500 mg/kg) by gavage. To evaluate DNA strand breaks, a comet assay was used for zebrafish (*Danio rerio*) treated with Boric Acid and Sodium Borate (≤ 64.000 µg/l). Genotoxicity was observed in a dose-dependent manner.

B6C3F1 mice were fed 0 - 5000 ppm Boric Acid through their diet for 103 wk. There was an increase in testicular atrophy in the male mice, a reduction in body weight and reduced survival in all dose groups. There was not an increase in tumors, which indicated that Boric Acid did not show any evidence of carcinogenicity.

In several assays, prostate cancer cells (DU-145, LNCaP, and PC-3) were treated with up to 1000 µM Boric Acid. Boric Acid inhibited the proliferation of the DU-145 and LNCaP in a dose-dependent manner, with minimal effects on cell cycle stage distribution and mitochondrial function in DU-145 cells. Higher Boric Acid concentrations were required to inhibit proliferation in non-tumorigenic prostate cancer cell lines, such as PWR-1E and RWPE-1, and the cancer cell line PC-3 compared to concentrations in the human blood.

Boric Acid was orally administered to groups of 8 female, adult, ovariectomized Sprague-Dawley rats from 0 - 75 mg/kg, distilled water (negative control), or 0.1 mg/kg 17β -estradiol (positive control) for 3 d. Compared to the positive controls, the statistically significant increase in uterine weights in the high-dose group was lower. Serum E2 levels were not statistically significantly different between Boric Acid-treated animals and negative controls. Compared to the negative controls, the height of endometrium and estrogen receptor density of uterine cells were higher in all Boric Acid-treated groups.

The effects of Boric Acid on cell proliferation, apoptosis, and oxidative stress were investigated on Jurkat cells using an XTT assay. Boric Acid increased oxidative stress and inhibited Jurkat cell proliferation dose dependently. Sertoli cells were isolated from eighteen 22-d-old male Sprague-Dawley rats and were exposed to different concentrations of Boric Acid (0.25 - 80 mmol/l). Using CCK-8 and MTT assays, it was determined that lower doses (< 0.5 mmol/l) promoted the viability of the Sertoli cells and inhibited apoptosis while higher doses (> 5.0 mmol/l) had toxic effects that inhibited cell viability, accelerated apoptosis, and arrested the cell cycle at the G0/G1 phase. Boric Acid was tested in a study in which oral rinse solutions were formulated to find an alternative to chlorhexidine due to undesirable side effects. The cytotoxicity was

evaluated by MTT and LDH assays and the Boric Acid solution had a similar cytotoxicity to chlorhexidine, making it an unfavorable alternative. When Sodium Borate was tested as well, it was less cytotoxic compared to chlorhexidine, making it a favorable alternative. Using the MTT test, cytotoxic effects were studied on U-87 MG glioblastoma cells which were exposed to different concentrations of Boric Acid solution (2.5 - 50 mM). When compared to the control, the percentage viability calculated was 90, 46, and 23% for the 2.5, 25, and 50 mM Boric Acid applications, respectively. A concentration of 50 mM had a fatal effect, and multiplication-preventing could be seen starting in the 25 mM concentration on the U87-MG cells. Using an MTT assay, Boric Acid was tested at 0.00625 - 0.200 ml on the HepG2 and THLE2 cell lines to see the effect on cell viability. The viability of both cell lines was reduced in a dose-dependent manner, with Boric Acid being more cytotoxic in the HepG2 cell line. The IC_{50} for the HepG2 cell line was much lower, at 0.06427 mg/ml, as compared to 0.6128 mg/ml in the THLE2 cell line. An MTT assay also showed that human lymphocyte cell cultures had low proliferation when the cells were treated with 100, 150, 200, 300, and 600 µg/ml Sodium Borate.

The antibacterial activity of Boric Acid and Sodium Borate was tested against cariogenic bacteria using agar well diffusion and microdilution techniques. Boric Acid had larger inhibition zones ranging from 15 - 20 mm compared to 14 - 19 mm for Sodium Borate. Boric Acid also had lower MIC values ranging from 0.156 - 0.625 mg/ml compared to 0.625 - 1.25 mg/ml for Sodium Borate. Due to smaller inhibition zones and higher MICs, Boric Acid had a stronger antibacterial activity than Sodium Borate.

Male and female Sprague-Dawley rats received a single dose of 0 or 2000 mg/kg Boric Acid, in a vehicle of 1% CMC, via gavage. The total body weight gain in Boric Acid-treated male rats was 16% lower than control rats at the end of a 14-d observation period. The NOAEL was determined to be 2000 mg/kg Boric Acid as it did not result in neurohistopathological effects or changes in mortality.

In an immunotoxicity study, female B6C3F1 mice (10/group) were treated with 0 - 1000 mg/kg Boric Acid in CMC via gavage for 28 d. Body weight, clinical observations, food consumption, hemolytic plaque formation, and spleen and thymus weight were monitored. No adverse clinical observations were noted, and weight changes and food consumption remained normal. The spleen and thymus weight decreases were comparable to the controls and not statistically significant. Although hemolytic plaque formation decreased in a dose-dependent manner, the change was also not statistically significant. Boric Acid was not considered to be immunotoxic.

Boric Acid and Sodium Borate were not irritating to rabbit skin when tested up to at concentrations to up to 95% w/w. Neither ingredient was a sensitizer in studies using guinea pigs performed in accord with OECD TG 406.

In a 21-d study, 100 mg of Boric Acid were instilled into the conjunctival sac of 6 rabbits.[5] After 24 h, the eyes were rinsed using physiological saline. There was irritation observed but was mostly cleared after a 7-d period. Boric Acid was considered to be a non-irritant. Undiluted Sodium Borate (0.08 ml) was instilled into one eye of 6 New Zealand white rabbits and were observed for 14 d without rinsing. The mean score reactions were the following: corneal opacity (0.22/4), iris (0.22/2), conjunctivae (redness; 2.8/3), chemosis (1.89/4). Due to Sodium Borate having a mean redness score > 2, it was classified as an ocular irritant.

Male subjects were exposed to a mineral dust of 5 - 40 mg/m^3 Sodium Borate in an exposure dome via inhalation. The MMAD for Sodium Borate particles was determined to be 7.11 ± 1.72. The perceived magnitude of the effect of Sodium Borate was 10 mg/m^3 in the eye and nose and 5 mg/m^3 for the throat. Nasal secretions increased significantly compared to the "blank" exposure at 10 mg/m^3 Sodium Borate exposure, but not at 5 mg/m^3 Sodium Borate exposure.

Following dermal exposure to 2% Boric Acid solution, a 2-yr-old girl had symptoms that included erythema, lesions, crusting, edema, erosions, and exudation. Adults aged 56, 82, and 88 yr reported oral ingestion of 6 - 300 g Boric Acid that resulted in localized irritation, headache, nausea, vomiting, thrombocytopenia, altered mental state, anemia, elevated transaminases, impaired renal clearance, diarrhea, and hypotension, and dermal findings similar to those observed following topical exposure.

Reproductive toxicity endpoints were evaluated in the blood and semen of 204 production workers at a Boric Acid plant. Subjects were classified according to their blood boron concentration as controls (< 0.0000485 mg/g), low- (> 0.0000485 - 0.0001 mg/g), mid- (> 0.0001 - 0.00015 mg/g), or high-dose (> 0.00015 mg/g) exposure. There were no statistically significant differences in the mean levels of sperm concentration, motility, or morphology parameters, nor were any dose-dependent responses observed in FSH, LH, and testosterone levels with increasing blood boron concentrations. However, there was a statistically significant correlation between blood boron concentrations and sperm tail % intensity values.

The ACGIH has established the TLVs for inhalable particulate matter as 2 mg/m^3 (TLV-TWA) and 6 mg/m^3 (TLV-STEL). California's Division of Occupational Safety and Health set an 8h PEL-TWA of 5 mg/m^3. The NIOSH TWA-STEL for borates, tetraborates, and sodium salts (Sodium Borate; CAS No. 1330-43-4, anhydrous) is 1 mg/m^3.

During a 3-yr period, 190 women exposed to boron in their drinking water had blood boron concentrations ranging from 0.000075 - 0.000328 µg boron/g. There were no adverse events in induced abortion, spontaneous abortion (miscarriage), stillbirth, infant death, neonatal death, early neonatal death, preterm birth, congenital anomalies, sex ratio, and birth weight. In a study with 177 mothers during pregnancy, the amount of boron was measured from the maternal serum and

maternal blood before pregnancy (30 - 447 µg/l and 27 - 322 µg/l) and after pregnancy (47 - 624 µg/l and 66 - 750 µg/l), respectively.[57] After birth, the infant urinary boron content was measured at 0 - 3 mo (105 - 9200 µg/l) and 3 - 6 mo (389 – 15,068 µg/l). There was an inverse association of infant urinary boron on the weight, length, and head circumference of an infant in the first 6 mo. The amount of boron was measured in the dietary food/fluids, workplace inhalable dust, blood, semen, and urine from boron workers and controls. From this data, three groups in the study were created which included boron workers (n=66), the workers from high boron areas as the community comparison (n=59), and the workers from low boron areas as the control (n=67). Semen parameters were also determined such as apoptosis, aneuploidy, DNA breakage, morphology, motility, sperm concentration, and total sperm count. The average blood boron, semen boron, and boron in the urine ranged from 47.9 – 499.2 ppb, 214 – 785.6 ppb, and 2.0 – 16.7 mg/l across the control, community comparison, and boron worker groups. There were no significant correlations between the semen parameters or blood boron concentration. In a study with 1000 men working in boron mining or processing in China, the mean daily boron intake and the semen was analyzed (sperm density, total sperm count, semen quality, sperm zinc, motility) of the following groups were taken; boron workers (n= 75), boron workers at a plant with heavy boron contamination of water (n=16), the local community (sample size not mentioned), and remote background controls (sample size not mentioned). The mean daily boron intake was measured to be 31.3, 125, 4.25, and 1.40 mg boron/d, respectively. There was not a statistically significant difference in the semen characteristics between the exposure groups.

CIR staff performed an MOE calculation for Boric Acid as used in body washes at 0.00016%. When assuming 100% absorption, the resulting MOE was 8,088,235; this value is substantially greater than 100 and is considered protective.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusions of previously issued reports approximately every 15 years. In 1983, the Panel published a final report on Boric Acid and Sodium Borate, concluding that these ingredients are safe for use in cosmetic products up to a concentration of 5% and should not be used on infant or injured skin. A re-review was initiated in 2003 (and published in 2006) which reaffirmed the conclusion from the original report. However, in 2024, another re-review was considered, and this report was reopened due to a change in the reported use categories, to evaluate new data, and to explore the reasoning for why these ingredients have been banned by the EU. After evaluation of previous and new data (including 2025 RLD), and in accordance with the product categories and concentrations of use identified in the Use section and Use table, the Panel issued a revised conclusion stating that Boric Acid and Sodium Borate are safe in rinse-off products in the present practices of use and concentration described in this safety assessment when used in formulations not intended for application to mucosal surfaces, and that the data are insufficient to make a determination of safety of these 2 ingredients in leave-on products and in products intended for application to mucosal surfaces.

The CIR staff calculated an MOE of 8,088,235 for rinse-off bath/body wash products to estimate potential genital-area exposure. The MOE was considered protective due to the value being greater than 100. However, this estimation is not a substitute for an MOE for products intended for application to mucosal surfaces (e.g., douches, mouthwashes).

The Panel also discussed the potential for increased absorption through damaged, abraded, or otherwise compromised skin. In particular, the Panel noted reports of increased absorption through burned or denuded skin and the detection of Boric Acid in the urine of infants with diaper rash, suggesting that disruption of the dermal barrier may enhance systemic exposure to Boric Acid and Sodium Borate.

The Panel discussed the issue of incidental inhalation exposure resulting from this ingredient. Inhalation toxicity data suggested that Boric Acid and Sodium Borate resulted in low acute inhalation toxicity in rats (LC_{50} >2 mg/l); repeated inhalation to Boric Acid in rats or dogs at $\leqslant$ 470 mg/m^3 did not cause systemic toxicity. Additionally, the Panel noted that the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/ particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded that if this ingredient is used in airbrush formulations, the data are insufficient to support safe use when applied with such delivery system.

Additionally, at least 1 use for the ingredients reviewed in this assessment is reported in the RLD under Category 17, "other preparations." For instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17,

and other information in the RLD is not indicative of use type, the present practices of use for such products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply thereon.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Boric Acid and Sodium Borate are safe in rinse-off products in the present practices of use and concentration described in this safety assessment when used in formulations not intended for application to mucosal surfaces, and that the data are insufficient to make a determination of safety of these ingredients in leave-on products and in products intended for application to mucosal surfaces.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Boric Acid		
Physical Form	Triclinic crystals or granules/powder	[2]
Color	Colorless or transparent (crystal form) or white (granule/powder form)	[2]
Odor	Odorless	[2]
Molecular Weight (g/mol)	61.84	[2]
Specific Gravity	1.44	[2]
Vapor pressure (mmHg @ 25ºC)	1.6×10^{-6}	[7]
Melting Point (ºC)	171	[2]
Boiling Point (ºC)	300	[7]
Water Solubility	Freely soluble in hot and cold water, alcohol, and glycerin	[2]
Other Solubility	Slightly soluble in ether; not soluble in ether	[2]
log K_{ow}	0.175	[7]
Disassociation constants (pKa @ 25 ºC)	9.24	[7]
Sodium Borate		
Physical Form	Hard, monoclinic crystals or powder	[2]
Color	White	[2]
Odor	Odorless	[2]
Formula Weight (g/mol)	381.4 (decahydrate); 201.2 (anhydrous)	[2]
Specific Gravity	1.73	[2]
Vapor pressure (mmHg @ 20ºC)	0	[8]
Melting Point (ºC)	75	[2]
Boiling Point (ºC)	1,575	[8]
Water Solubility	Freely soluble in hot and cold water	[2]
Other Solubility	Slightly soluble in alcohol; insoluble in acid	[2]
log K_{ow} (@ 20ºC)	0.175	[9]

Table 2. Frequency and concentration of use according to likely duration and exposure and by product category

	Boric Acid		Sodium Borate	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)[11,12]	% (2025)[13]	RLD (2025)[11,12]	% (2025)[13]
Totals*	**96**	**0.00006-0.00016**	**202**	**0.0019-3.7**
summarized by likely duration and exposure**				
Duration of Use				
Leave-On	*64*	*NR*	*205*	*NR*
Rinse-Off	*45*	*0.00006-0.00016*	*57*	*0.0019-3.7*
Diluted for (Bath) Use	*NR*	*NR*	*25*	*NR*
Unknown	*13*	*NR*	*10*	*NR*
Exposure Type				
Baby Products	NR	NR	NR	NR
Children's Makeup	NR	NR	NR	NR
Eye Area	4	NR	3	NR
Incidental Ingestion	4	NR	7	NR
Mucous Membrane	52	0.00016	50	NR
Incidental Inhalation-Spray	24[a]; 14[b]	0.00016[a]	111[a]; 102[b]	NR
Incidental Inhalation-Airbrush	NR	NR	NR	NR
Incidental Inhalation-Powder	14[b]	NR	102[b]	NR
Dermal Contact	82	0.00006-0.00016	264	3.7
Deodorant (underarm)	2 (spray)	NR	2 (not spray)	NR
Hair - Non-Coloring	5	0.00016	14	0.0019
Hair-Coloring	NR	NR	3	NR
Nail	7	NR	1	NR
Other Preparations (Unknown Exposure Type)	13	NR	10	NR
as reported by product category				
Bath Preparations				
Bath Oils, Tablets, and Salts	NR	NR	25	NR
Eye Makeup Preparations (not children's)				
Eye Makeup Remover	3	NR	2	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	1	NR	1	NR
Hair Preparations (non-coloring)				
Hair Conditioners	NR	NR	1 (l.o.)	NR
Rinses (non-coloring)	NR	NR	2	NR
Shampoos (non-coloring)	4 (r.o.)	0.00016 (r.o.)	6 (r.o.)	0.0019 (r.o.)
Tonics, Dressings, Other Hair Grooming Aids	NR	NR	1	NR

Table 2. Frequency and concentration of use according to likely duration and exposure and by product category

	Boric Acid		Sodium Borate	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)[11,12]	% (2025)[13]	RLD (2025)[11,12]	% (2025)[13]
Other Hair Preparations	1	NR	3 (l.o.); 1 (r.o.)	NR
Hair Coloring Preparations				
Hair Bleaches	NR	NR	2	NR
Other Hair Coloring Preparation	NR	NR	1	NR
Makeup Preparations (not eye or children's)				
Foundations	NR	NR	1 (traditional application)	NR
Lipstick and Lip Glosses	3	NR	NR	NR
Manicuring Preparations				
Nail Creams and Lotions	1	NR	NR	NR
Nail Polish and Enamel	1	NR	NR	NR
Nail Polish and Enamel Removers	1	NR	NR	NR
Other Manicuring Preparations	4	NR	1	NR
Oral Hygiene Products				
Dentifrices	NR	NR	4	NR
Mouthwashes and Breath Fresheners	1	NR	1	NR
Other Oral Products	NR	NR	2	NR
Personal Cleanliness				
Bath Soaps and Body Washes	14	0.00016	6	NR
Deodorants (underarm)	2	NR	2	NR
Douches	1	NR	NR	NR
Feminine Deodorants	7 (l.o.); 3 (r.o.)	NR	NR	NR
Disposable Wipes	7	NR	NR	NR
Other Personal Cleanliness Products	11 (l.o.); 5 (r.o.)	NR	12 (r.o.)	NR
Shaving Preparations				
Aftershave Lotions	5	NR	NR	NR
Shaving Creams (aerosol/brushless/lather)	NR	NR	2	NR
Skin Care Preparations				
Cleansing	8	NR	9	3.7
Face and Neck (excluding shaving preps)	1 (l.o.); 4 (r.o.)	0.00006 (r.o.)	31 (l.o.); 5 (r.o.)	NR
Body and Hand (excluding shaving preps)	2 (l.o.); 4 (r.o.)	NR	4 (l.o.); 3 (r.o.)	NR
Foot Powders and Sprays	NR	NR	9	NR
Moisturizing	12	NR	88	NR
Night	NR	NR	11	NR
Paste Masks (mud packs)	NR	NR	2	NR
Other Skin Care Preparations	3 (l.o.)	NR	50 (l.o.); 1 (r.o.)	NR
Other Preparations (i.e., those preparations that do not fit another category)	13	NR	10	NR

NR – not reported

*The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.

**Likely duration and exposure are derived from survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 3. Acute toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Protocol	Results	Reference
			DERMAL			
Boric Acid	physiological saline	New Zealand White rabbit (5/sex/group; both sexes)	2000 mg/kg	Skin of rabbits was abraded; test substance was applied dermally for 24 h.	LD_{50} > 2000 mg/kg bw; no acute dermal toxicity.	[5]
Sodium Borate	NR	New Zealand White rabbit (5/sex/group; both sexes)	2000 mg/kg	Rabbit skin was clipped of fur before test substance was applied dermally for 24 h.	LD_{50} > 2000 mg/kg bw; no acute dermal toxicity.	[6]
			ORAL			
Boric Acid	corn oil	rats (5/sex/group; both sexes)	200 and 2000 mg/kg	OECD TG 401 (acute oral toxicity); Test substance was administered via gavage	2000 mg/kg resulted in deaths of 2 males; no deaths for groups administered 200 mg/kg; LD_{50} > 2000 mg/kg	[5]
Boric Acid	corn oil	rats (5 males/dose)	1540 and 2600 mg/kg	Test substance was administered via gavage to groups of 5 fasted rats at specified doses.	LD_{50} > 2600 mg/kg bw; no deaths.	[5]
Sodium Borate	corn oil	rats (5/sex/dose; both sexes)	200 and 2000 mg/kg	OECD TG 401 (acute oral toxicity); Test substance administered via gavage	LD_{50} > 200 mg/kg bw for males; 40% of the male rats died at 2000 mg/kg. LD_{50} > 2000 mg/kg bw for females.	[6]
Sodium Borate	corn oil	rats (5/males/dose)	1600 and 2500 mg/kg	OECD TG 401 (acute oral toxicity); Test substance administered via gavage	LD_{50} > 2500 mg/kg bw; no deaths	[6]
Sodium Borate	NR	Sprague-Dawley rats (5/group; both sexes)	1000, 1495, 2236, 3344 and 5000 mg/kg	OECD TG 401 (acute oral toxicity); Test substance administered via gavage	LD_{50} combined: 3305 (2403 - 4207) mg/kg. LD_{50} males: 3401 (2056 - 4746) mg/kg. LD_{50} females: 3225 (2007 - 4443) mg/kg.	[6]
			INHALATION			
Boric Acid	NR	Sprague-Dawley rats (5/sex/dose; both sexes)	2 mg/l	OECD TG 403 (acute inhalation toxicity); test substance administered via dust for inhalation	No deaths; some ocular/nasal discharge & hunched posture during first 1.5 h of exposure.	[5]
Boric Acid	NR	rats (5/sex/dose; both sexes)	2 mg/l	OECD TG 403 (acute inhalation toxicity); test substance administered via aerosol	LC_{50} > 2.03 mg/l; no deaths; some ocular discharge, hypoactivity, and hunched posture during first 30 min of exposure.	[5]
Sodium Borate	NR	Sprague-Dawley rats (5/sex/dose; both sexes)	2 mg/l	OECD TG 403 (acute inhalation toxicity); test substance administered via dust for inhalation	LC_{50} > 2.04 mg/l	[6]

LD_{50} – median lethal dose; LC_{50} – median lethal concentration; NR – not reported

Table 4. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
				ORAL			
Boric Acid	drinking water	mice (10/group)	5 d	0 and 0.28 mg/250 ml	Mice treated via drinking water. Mice were weighed on days 0 and 5. After a 5-d period, feces and urine outputs were recorded. Total body weight changes were measured. Once the mice were killed, their major organs were examined for histopathologic changes. Additional evaluations included fecal volume, fecal bile acid content, blood biochemistry parameters, total urine output, and urinary urobilinogen levels.	Control group – 0.09% weight gain Study group – 28.1% weight gain, statistically significant increase in cholesterol, LDL, AST, ALT, LDH, amylase, and urobilinogen levels compared to controls.	[23]
Boric Acid	water	male albino Sprague Dawley rats (30 in study group, 10 in control group)	7 d	0 and 1000 mg/kg/d	Rats treated via drinking water. At the end of the study, body and organ weights were measured, and tissues were isolated in the study and control groups before undergoing histopathological examination.	The study group had a significantly significant weight loss in the kidneys, liver, testes, and overall body weight. Compared to the controls, there was the presence of edema in the interstitial area of the tissue of the testes, thickening of the basal membrane in the seminiferous tubules, inflammatory cell infiltration in the kidney tissue in the interstitium. There was also an increase in edema rate, amount of apoptotic cells in testicular tissue and Leydig cells, when compared to the controls.	[24]
Boric Acid	NR	rats (n=50)	30 d	0 and 800 mg	Test substance administered via gavage; animals killed every 6 d during exposure period (30 d) then 10 d during recovery period (109 d). Control was untreated.	The NOAEL and LOAEL were both < 800 mg/kg	[5]
Boric Acid	NR	male albino Sprague Dawley rats (n=8)	45 d	0, 100, 275, or 400 mg/kg	Rats treated orally via feed. On the 10th, 30th, and 45th day of the study, 8 rats from each of the treated groups and 8 control rats were killed to retrieve kidney tissues. Weight, boron concentration, and histopathological changes were determined.	Compared to the controls, all test groups had accumulation of boron in the kidney tissue with a statistically significant decrease in kidney boron concentrations from 30 to 45 d. Across the test groups, histopathological changes in kidney tissue were dose and time dependent; degenerative changes detected in all test groups on days 10 and 30, with increased degeneration on day 45.	[25]
Boric Acid	water	Sprague-Dawley rats (n=24)	45 d	0, 100, 275 or 400 mg/kg	Test substance administered via drinking water; body/testis weights, plasma/testis boron concentrations were measured; blood samples/testis tissues collected on days 0, 30, and 45. Control was untreated.	Significant accumulation of boron in testis associated with histopathological changes.	[5]

Table 4. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Boric Acid	NR	male albino rats (n=60)	90 d	0 and 0.16 mg/kg	Test substance was administered via gavage. Water was used as a control. Liver and kidney functions and tissues were examined.	Depleted antioxidant enzymes. Increase in hepatic enzyme leakage (aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP)) and serum renal damage products levels (urea, uric acid, creatine). Various histopathological perturbations were observed in hepatic and renal tissues including granular degeneration in renal tubular cells, moderate shrinkage of glomeruli, congestion of intertubular blood vessels, and interstitial edema.	[26]
					INHALATION		
Boric Acid	NR	albino rats (both sexes; n= 70, 4, and 20 for following doses 77, 175, and 470 mg/m³, respectively)	24 wk	77 - 470 mg/m³	All the animals were exposed via aerosol for 6 h/d for 5 d/wk 20 rats exposed for 10 wk, 470 mg/m³ 4 rats exposed for 12 wk, 175 mg/m³ 70 rats exposed for 24 wk 77 mg/m³	No signs of toxicity in any of the animals; -NOAEC of 470 mg/m³ for systemic toxicity -NOAEC of 175 mg/m³ for local effects due to irritation of noses of rats.	[5]
Boric Acid	NR	female dogs (n=3)	23 wk	57 mg/m³	Animals were exposed via aerosol for 6 h/d for 5 d/wk for 23 wk	No signs of toxicity in any of the animals; NOAEC of 57 mg/m³	[5]

ALT – alanine transaminase; AST – aspartate transferase; CMC - carboxymethyl cellulose; LDH – lactase dehydrogenase; LDL - low-density lipoprotein; LOAEL – lowest-observed-adverse-effect-level; NOAEC – no-observed-adverse-effect-concentration; NOAEL - no-observed-adverse-effect-level; NR – not reported

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
				GENERAL DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES		
				IN VITRO		
Boric Acid	*NR*	*Sertoli-germ cell cocultures from Fischer 344 rats*	*1st experiment: 0.1, 0.3, 1.0, 3.0, or 10 mM* *2nd experiment: 0, 0.1, 0.3, 1.0, 3.0, or 10 mM*	*In the first experiment, the cocultures of Sertoli cells and germ cells were exposed to Boric Acid for 72 h.* *In the second experiment, the Sertoli-germ cell cocultures were treated with Boric Acid or a control for 72 h. The lactate, pyruvate, and ATP levels were determined.*	*1st experiment: There were no germ cell loss or morphologic changes in the treated cells.* *2nd experiment: Results indicated that the cocultures exposed to 3 and 10 mM Boric Acid had a significant decrease in lactate and pyruvate levels as well as a slight significant decrease in cellular ATP levels.*	[3]
				MALE REPRODUCTIVE EFFECTS		
				ANIMAL		
				ORAL		
Boric Acid	*NR*	*Male Fisher 344 rats (n=6/group/week)*	*0, 3000, 4500, 6000, and 9000 ppm*	*Test material was administered orally for 9 wk through feed. Six rats/dose group killed weekly; testes were removed and examined microscopically; TSHC and ESC performed.*	*Mildly inhibited spermiation (Grade 1) was found in the 3000 ppm group. The 4500 ppm group had severe and widespread inhibition of spermiation (Grade 2). In the highest dose groups (6000 and 9000 ppm), an initial increase of TSHC occurred before a progressive and profound decrease in epididymis weight, ESC, testis weight, and TSHC. This reflected severe inhibition of spermiation that progressed (dose and time dependently) to Grade 6 atrophy.*	[3]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
Boric Acid	*NR*	*Male Fischer rats Control group (n=30) Treatment group (n=36)*	*0 and 9000 ppm (w/w)*	*Test material was administered orally for 28 d. On days 4, 7, 10, 14, 21, and 28, six of the treated and four of the control rats were killed and had their right testis removed before undergoing light and electron microscopy.*	*By day 7, half of the treated rats had an inhibition in spermiation in ~10 - 30% of stage IX tubules, with all treated animals eventually showing inhibited spermiation in all stage IX and X tubules by day 10. Day 10 also revealed the presence of condensed spermatid nuclei undergoing degradation near the basement membrane in the Boric Acid treated rats only. At 28 d, there was evidence of advanced epithelial disorganization, cell exfoliation, cell death, and luminal occlusion for the treated rats.*	[3]
Boric Acid	*NR*	*Male Fischer rats Control group (n=10) Treatment group (n=10)*	*0 and 9000 ppm (w/w)*	*Test material was administered orally for 28 d. Observations were made on days 4, 7, 10, and 28 after dosing and a serum testosterone analysis was performed.*	*There was a significant decrease in basal testosterone levels on day 4 that continued until day 28.*	[3]
Boric Acid	*NR*	*Young adult male rats (6/dose/wk)*	*0, 3000, 4500, 6000, and 9000 ppm*	*Test material was administered orally for 9 wk before the rats were killed each week (6/dose group). Body and organ weights, boron measurements, clinical chemistries, histologic exams, and sperm parameters were evaluated.*	*In the 3000 and 4500 ppm groups, spermiation was inhibited with no atrophy. Both groups had a significant decrease in the number of epididymal sperm and increase in bone boron until wk 5, with no boron accumulation in the testes. The testes became atrophic and did not recover for up to four spermatogenic cycles. When comparing the studies on mice and rats, the rats were more sensitive to Boric Acid. The target for male effects appeared to be during the sperimiation process but was unclear between the elongated spermatids or the Sertoli cells. The dose rate seemed to be related to spermiation. The NOAEL and LOAEL for reduced male fertility were 1000 and 4500 ppm, respectively.*	[3]
Boric Acid	*NR*	*6 male rats*	*9000 ppm*	*Test material was administered orally; rats were killed on days 4, 7, 10, 14, and 28; histopathology and sperm parameters were evaluated.*	*On day 7, the first lesion appeared in some rats, and they had an inhibition of sperm release which progressed in severity. Eventually, there was the release of immature germ cells and disorganization of the epithelium. On day 28, some of the atrophic tubules contained residual spermatogonia and somatic Sertoli cells only.*	[3]
Boric Acid	*NR*	*male rats (number not specified)*	*0.02 -1.71 mg/kg/d Boric Acid (0.015 - 0.3 mg/kg/d boron)*	*Test material was administered orally for 6 mo. No further details available.*	*Rats dosed with 1.71 mg/kg/d Boric Acid experienced a reduction in DNA content of gonadal tissue, testicular weight, and spermatozoid mobility and numbers. At 0.29 mg/kg/d Boric Acid, spermatozoid counts decreased. The changes observed with the two highest doses of boron were attributed to a decline in lactic acid and liver glycogen levels. For any male rats that received more than 0.02 mg/kg/d of Boric Acid for a 6-mo period, there was an adverse effect on the gonads.*	[2]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
Boric Acid	*Distilled water*	*male Wistar rats (20/male/group)*	*0, 50, 150, and 500 mg/kg/d*	*Test material was administered orally for 3 wk before mating with untreated female rats (10/female/group). After 3 wk, the non-mated male rats were killed before undergoing histopathological examination and having the sperm undergo CASA to observe ALH, beat cross frequency, curvilinear velocity, linearity, percent mobile, and straight-line velocity. For the morphological examination, the sperm was analyzed for the presence of a head, amorphous head, flection in the neck or tail region, and other qualities if seen.*	*Compared to the control, males in the 150 mg/kg group had lower epididymis weights and decreased percent motility, while the beat cross frequency of the head and sperm linearity values were comparable to the control. The 500 mg/kg group experienced the lowest testis and epididymis weights, suppressed body weight, a death, and a slight increase in beat cross frequency and a slight decrease in linearity. Both groups (150 and 500 mg/kg) had a dose-dependent decrease in sperm and dose-dependent decrease in sperm and mean ALH values, decrease in percent motile and a decrease in curvilinear and straight-line velocities. The total number for the 150 mg/kg group consisted of tail abnormalities while the 500 mg/kg group had the most abnormalities with the majority located in the head. The LOAEL for sperm count reduction was 150 mg/kg/d while the NOAEL was 50 mg/kg/d.*	[3]
Boric Acid	*NR*	*male Wistar rats (6/treatment group)*	*125, 250, and 500 mg/kg*	*Test material was administered orally for 2 or 4 wk. At 2 or 4 wk, the rats were killed, male reproductive organs (testes and epididymides) were weighed, sperm number and motility rates determined, and examinations were performed under light microscopy.*	*At 4 wk, a significant decrease in sperm number was observed in the 500 mg/kg group. The sperm motility decreased in the 250 and 500 mg/kg groups. For the 500 mg/kg group, there was a retention of step 19 spermatids stages IX-XI observed in the testes of almost all of the treated rats at both 2 and 4 wk.*	[3]
Boric Acid	*distilled water*	*male Wistar rats (6/treatment group)*	*0, 300, or 500 mg/kg*	*Test material was administered orally for 2 or 4 wk. Control rats received distilled water for 4 wk. No further details available.*	*At 2 wk, the 500 mg/kg group had a decrease in testis weights while both groups had exfoliation of round spermatids, increased numbers of residual body-like structures in the seminiferous tubules, and retention of step 19 spermatids. At 4 wk, there was a significant decrease in testis and epididymis weights for both groups and the histopathological changes were similar to the 2 wk results. The only difference was that the 500 mg/kg group had diffuse atrophy of seminiferous tubules.*	[3]
Boric Acid	*NR*	*male albino rats (n=12)*	*1000 mg/kg/d*	*Test material was administered orally for 2 wk. After necropsy, the rat testes were examined microscopically.*	*Changes in the nuclei and cytoplasm of spermatocytes and spermatids in the early stages of formation were observed in convoluted tubules. 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 researchers concluded that Boric Acid directly caused these gonadal disorders via tissue respiration and prolongation of mitotic division of spermatogenic epithelial cells.*	[2]
Boric Acid	*NR*	*8 male Sprague-Dawley rats*	*0, 250, 500, 1000, or 2000 mg/kg*	*Test material was administered orally for 14 d, and the rats were killed for analysis.*	*The 1000 mg/kg group had degrees of retention of Step 19 spermatids at the lumen of Stage IX-XII and atypical cytoplasmic lobes of Step 19 spermatids in Stage VIII. These effects were also found in the 2000 mg/kg group, but at a higher frequency, with one rat having reduced numbers of Step 15-19 spermatids. When considering the retention of Step 19 spermatids, the NOAEL was 500 mg/kg and the LOAEL was 1000 mg/kg.*	[3]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
Boric Acid	*NR*	*24 Sprague-Dawley rats (6/treatment)*	*0 or 2000 mg/kg*	*Test material was administered orally via gavage for 57 d. On days 2, 14, 27, or 57, six control and six treated rats were killed and tissues were examined microscopically.*	*On day 14, there were enlarged distorted cytoplasmic lobes of Step 19 spermatids in Stage VIII seminiferous tubules. Day 28 post treatment resulted in 4 out of 6 rats having retention of Step 19 spermatids at the lumen of seminiferous epithelium through Stage X. At 57 d post-treatment, there were no changes in 4 out of 6 rats. However, the other 2 rats had retention of Step 19 spermatids into Stage X.*	[3]
Boric Acid	*NR*	*6 rats (sex not specified)*	*2000 mg/kg*	*Test material was administered orally on day 0 twice for total dosage of 2000 mg/kg via gavage. The rats were killed on day 2 or 14, and the epididymis, prostrate, seminal vesicles, and testis excised.*	*Using video analyses and sperm suspensions, abnormalities were noted such as head separation, misshapen head, abnormal flagellum, or a normal head containing degenerative flagellar defects.* *On day 14, the presence of stage VIII distorted enlarged residual bodies, retention at the lumen and base of Step 19 spermatids in Stages IX to XIII, and testicular debris at the proximal caput were observed. Sperm counts significantly decreased on day 2 and significantly increased on day 14. Day 14 also revealed that caput sperm morphology was abnormal, but no further details were given.*	[3]
Boric Acid	*NR*	*male and female rats (5/sex/group)*	*30, 100, 300, 1000, or 3000 mg/kg/d Boric Acid (~52.5, 175, 525, 1750, or 5250 ppm boron)*	*Test material was administered orally to for 90 d. No further details available.*	*Male rats experienced complete testicular atrophy at 1000 mg/kg Boric Acid (~1750 ppm boron)* *There was partial atrophy in 1 out of 5 males given 300 mg/kg Boric Acid (corresponding to 525 ppm boron).*	[2]
Boric Acid	*NR*	*male and female dogs (4/sex)* *Additional dogs (number and sex not specified)*	*25 - 150 mg/kg/d (~58 - 350 ppm boron)* *501 mg/kg/d (~1170 ppm boron)*	*Test material was administered orally for 38 wk. No further details available.*	*Male dogs developed testicular atrophy when given 501 mg/kg/d Boric Acid (~1170 ppm boron). Otherwise, there were no significant changes to the appearance, appetite, behavior, body weight, elimination, or feed consumption of dogs.*	[2]
Sodium Borate	*drinking water*	*male rats (n=10)*	*0.37 - 7.4 mg/kg/d*	*Animals were randomly selected for study after 30, 60, or 90 d of treatment. Body weights and testis, prostate, and seminal vesicles weights were measured. The serum levels of sodium, potassium, chloride, carbon dioxide, total proteins, albumin, calcium, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), glucose, serum glutamic-oxalic transaminase (SGOT), and serum glutamic-pyruvate transaminase (SGPT) were also measured.*	*No reproductive effects or biologically significant changes in the weight of testes, prostates, or seminal vesicles were observed. Additionally, no effects on male fertility were observed in subsequent forced-breeding studies.*	[2]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
Sodium Borate	*in feed*	*male rats (n=18)*	*0 - 1060 mg/kg/d of Sodium Borate (0 - 2000 ppm boron)*	*Test material was administered orally via diet. At 30 and 60 d, the rats were split up to assess fertility, hormone concentrations, and enzyme concentrations.*	*At 530 - 1060 mg/kg/d of Sodium Borate (1000 - 2000 ppm of boron), there was decreased epididymal weight, spermatocytes, spermatids, tubular diameter, and number of mature spermatozoa after 30 d.* *At 60 d, there was germinal aplasia and a reduction in testicular weight.* *There was an increased FSH and LH concentration at 1060 mg/kg/d Sodium Borate (2000 ppm boron) with the FSH levels remaining elevated for 12-mo post-feeding. The rats became infertile for 3-, 4-, and 8-wk post feeding with 530 mg/kg/d Sodium Borate (1000 ppm boron) for 30 d or 60 d, as well as 1060 mg/kg/d of Sodium Borate (2000 ppm boron) for 30 d .* *For the rats that received the largest amount of 1060 mg/kg/d of Sodium Borate (2000 ppm boron) for 60 d, they remained infertile during the mating trials, which were 32 wk. The authors attributed testicular aplasia to the cumulative and cytotoxic effects of boron on germinal tissue.*	[2]
Sodium Borate	*drinking water*	*male Sprague-Dawley rats*	*399.2 - 3982.3 mg/kg Sodium Borate (45 – 450 mg/kg boron)*	*Sodium Borate was administered orally after mating. No further details available.*	*There were no significant effects on male fertility identified.*	[3]
Sodium Borate	NR	*male and female rats (5/sex/group)*	*46.5, 154.9, 464.6, 1548.7, and 4646 mg/kg/d Sodium Borate (~52.5, 175, 525, 1750, or 5250 ppm boron)*	*Test material was administered orally to for 90 d. No further details available.*	*Male rats experienced complete testicular atrophy at 1548.7 mg/kg Sodium Borate (~1750 ppm boron).* *There was partial atrophy in 4 out of 5 males 464.6 mg/kg Sodium Borate (corresponding to 525 ppm boron).*	[2]
Sodium Borate	NR	*4 male and 4 and female dogs* *Additional dogs (number and sex not specified)*	*38.5 - 232 mg/kg/d (~58 - 350 ppm boron)* *776.5 mg/kg/d (~1170 ppm boron)*	*Sodium Borate was administered orally for 38 wk. No further details available.*	*Male dogs developed testicular atrophy when given 776.5 mg/kg/d Sodium Borate (~1170 ppm boron). Otherwise, there were no significant changes to the appearance, appetite, behavior, body weight, elimination, or feed consumption of dogs.*	[2]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
COMBINED REPRODUCTIVE EFFECTS						
ANIMAL						
ORAL						
Boric Acid	*NR*	*male and female CD-1 mice*	*0, 1000, 4500, and 9000 ppm* *Predicted to give 110 mg/kg and 182 mg/kg, 598mg/kg and 846 mg/kg, and 1260 mg/kg and 1660 mg/kg Boric Acid to males and females, respectively.*	*RACB protocol was performed; oral administration*	*Fertility decreased in a dose-dependent manner, with the 1000 ppm group being comparable to the control and the 9000 ppm group being infertile. Over time, the following metrics decreased; the number of female mice producing litters, average number of litters per pair, live pups per litter, proportion of pups born alive, the weight of pups born alive, and live pup weight adjusted for litter size. When looking at crossover mating, there was reduced fertility in males from the 4500 ppm group mated with the control females. However, when the control males mated with the 4500 ppm female group, the average number of litters per pair was the same as the control but the average dam weight on postnatal day 0 was lower for females that produced litters and the live pup weight adjusted for litter size significantly decreased. Fertility trials of the F1 animals demonstrated that the 1000 ppm and control groups were similar except the 1000 ppm group had estrous cycles significantly shorter than controls and fewer ambiguous vaginal smears. The NOAEL for parental generation was 1000 ppm (LOAEL was 4500 ppm) for reduced male fertility and Boric Acid was considered a reproductive toxicant for male mice.*	[3]
Boric Acid	*in feed*	*male rats (n=8)* *female rats (n=16)*	*70, 200, and 6696 mg/kg/d (~117, 350, and 1170 ppm boron)*	*Test material was administered orally via diet for 14 d before mating; 3 generations were observed*	*70 and 200 mg/kg/d Boric Acid (~117 and 350 ppm boron) did not have any adverse effects on reproduction. However, for the group fed 6696 mg/kg Boric Acid (~1170 ppm boron), the males were unable to produce viable sperm and the females had decreased ovulation, leading to sterility in both sexes.*	[2]
Boric Acid	*in feed*	*male rats (20/treatment group)* *female rats (10/treatment group)*	*0, 50, 150, and 500 mg/kg/d*	*Test material was administered orally via diet for 3 wk prior to mating until mating was confirmed. 10 males from each group mated with 10 untreated females. At GD 13, the female rats were killed and necropsied and the number of corpora lutea, dead embryos, implants, and live embryos were counted. The 10 unmated males underwent a sperm morphological examination as histopathological examination.*	*The male rats in the 500 mg/kg group did not impregnate any of the female rats. For the female rats in the 150 mg/kg group, the number of implants and live embryos were lower and had a higher pre-implantation loss rate compared to the control. Regarding the reduced number of implants and live embryos, the LOAEL was 150 mg/kg/d while the NOAEL was 50 mg/kg/d. For the unmated males, males treated with 150 and 500 mg/kg/d had head and tail abnormalities. For the males treated with 500 mg/kg/d, they had multinucleated giant cells in the tested and atrophy of the seminiferous tubules.*	[3]
Sodium Borate	*in feed*	*male rats (n=8)* *female rats (n=16)*	*103.5, 310, and 1035 mg/kg/d (~117, 350, and 1170 ppm boron)*	*Test material was administered orally via diet for 14 d before mating; 3 generations were observed*	*Rats of the 103.5 and 310 mg/kg/d Sodium Borate (~117 and 350 ppm boron) groups did not have any adverse effects on reproduction. However, for the group fed 1035 mg/kg Sodium Borate (~1170 ppm boron), the males were unable to produce viable sperm and the females had decreased ovulation, leading to sterility in both sexes.*	[2]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
			EMBRYOTOXIC/TERATOGENIC EFFECTS			
			IN VITRO			
Boric Acid	*NR*	*male rat embryos*	*0, 28.6, 57.2, or 85.8 µg/ml*	*Embryos were exposed to Boric Acid in vitro for 48 h, or to for 24 h followed by control serum for 24 h.*	*Embryos exposed to 57.2 µg/ml had decreased head length, while the 85.8 µg/ml group additionally had decreased crown-rump length, developmental score, somite number, and somite width (somites 3 - 13).* *Embryos exposed to Boric Acid for 24 h followed by control serum for 24 h had somite measurements comparable to controls.*	[3]
			ANIMAL			
			ORAL			
Boric Acid	*in feed*	*male and female Swiss CD-1 mice*	*0, 1000, 4500, or 9000 ppm*	*In an RACB study, the test material was administered orally via diet to both males and females. The mice cohabited for 14 wk. All pups were evaluated. The mid-dose group (4500 ppm) was mated with the controls. After delivery, the F0 mice were killed and necropsied. Once the F1 mice were reared to sexual maturity, they were fed the same diet given to their parents (F0 mice), and mated to non-siblings within same dose groups as above. Following delivery, the F1 mice were killed and necropsied.*	*The 1000 ppm group had similar results to the control (~4.7 litters per cohabiting pair) in fertility, while the 9000 ppm group had no litters. In the 4500 ppm groups, the mean litter size and adjusted live pup weight decreased.*	[3]
Boric Acid	*NR*	*pregnant female CD-1 mice (160 assigned to 10 groups)*	*0 and 400 mg/kg (twice daily)*	*Test material was administered orally via gavage twice daily .* *Controls treated with distilled water on GD 6 – 8 or only GD 6, GD 7, or GD 8* *Boric Acid treated groups were on GD 6 – 8 or only GD 6, GD 7, GD 8, GD 9, or GD10.* *Skeletal and gross fetal examinations were performed.*	*In all treatment groups (minus GD 9 and 10 that were not included in statistical analysis due to lack of concurrent controls), there was a decrease in average fetal weight. For the group that was treated with Boric Acid from GD 6 - 8, there was a reduction in rib length and observations of fused/branched ribs in the thoracic region and agenesis of the 13th rib.*	[3]
Boric Acid	*NR*	*timed-pregnant CD-1 mice (n=26, 10/dose and 6 controls)*	*0, 500, and 750 mg/kg*	*Test material was administered orally via gavage once a day until GD 17Skeletal and gross fetal examinations were performed. Controls were given distilled water.*	*Upon examination, the 13th rib length significantly decreased for both treatment groups.*	[3]
Boric Acid	*NR*	*CD-1 mice (number not specified)*	*0 and 750 mg/kg (twice daily)*	*Test material was administered orally via gavage on GD 8 twice daily. Skeletal and gross fetal examinations were performed.*	*There was the presence of exencephaly, misshapen vertebrae, rudimentary ribs, unilateral lumbar vertebrae, fused arches, fused ribs, agenesis of the ribs and lumbar vertebra.*	[3]
Boric Acid	*NR*	*CD-1 mice (number not specified)*	*0 and 750 mg/kg*	*Test material was administered orally via gavage on GD 7. Skeletal and gross fetal examinations were performed.*	*There were differences in the unilateral thoracic vertebrae and cervical ossifications compared to the control as well as an increase in arches, fused ribs, and hemivertebra.*	[3]
Boric Acid	*in feed*	*time-mated Swiss CD-1 mice (n=26 - 28/group)*	*248, 452, and 1003 mg/kg/d*	*The test material was given orally in feed GD 0 - 17. Maternal toxicity endpoints included food/water consumption, body weight, liver/kidney weights, kidney histology, uterine weight, and signs of toxicity, while developmental toxicity included embryonal/fetal weight and structural variations/malformations.*	*The highest dose group had a statistically significant decrease in maternal weight gain and increase in the percentage of adversely affected implants/litter, litters with one or more adversely affected implants, and resorptions/litter for treated group. The developmental toxicity LOAELs and NOAELs were 452 and 248 mg/kg/d for mice (fetal weight reduction), respectively.*	[3]
Boric Acid	*NR*	*female mice (number not specified)*	*500 - 3000 mg/kg*	*Female mice were dosed orally with the test material on GD 1.*	*Boric Acid suppressed development to the blastocyst stage in 94% of embryos at 3000 mg/kg. Groups who had doses of 500 and 1000 mg/kg had similar results, but the effects were less significant.*	[2]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
Boric Acid	*in feed*	*time-mated female Sprague-Dawley rats (60/group)*	*0, 0.025, 0.075, 0.1 or 0.2%*	*Test material was administered orally via diet from GD 0 – 20. Maternal and developmental evaluations included organ/body weights, implantation and resorption parameters, fetal and pup viability, and external, visceral, and skeletal examinations.*	*For the maternal effects, there was a slight increase in the relative maternal right kidney weight in the 0.2% Boric Acid group on GD 20. Live litter size, implantation sites/litter, ovarian corpora lutea/dam, preimplantation loss/litter, and offspring viability were unaffected. There was a decrease in fetal body weights for the 0.1 and 0.2% dose groups. but did not persist through the postnatal period. There did not appear to be a dose-response relationship for external malformations (occurred in < 0.5% fetuses or pup/group on GD 20 and PND 21) or visceral malformations. Despite the percentage of fetuses with skeletal malformations/litter having a significant increase trend, the overall incidence of skeletal variations was unaffected. The short rib XIII did not have a dose-response relationship and concentrations below 0.2% Boric Acid did not appear to be treatment-related. For fetal weight reduction, the NOAEL was 0.075% (55 mg/kg/d) and the LOAEL was 0.1% (75 mg/kg/d) of Boric Acid. For skeletal effects, there was a NOAEL of 0.1% (76 mg/kg/d) and LOAEL of 0.2% (145 mg/kg/d).*	[3,62]
Boric Acid	*in feed*	*180 female Sprague-Dawley rats (23-32/group; 169 were pregnant)*	*0, 0.025, 0.05, 0.075, 0.1, or 0.2% (~0, 3, 6, 10, 13, or 25 mg boron/kg bw/d)*	*Test material was administered orally via diet from GD 0 – 20.*	*With increasing dietary concentrations of Boric Acid, average blood boron concentrations increased. Maternal blood boron concentrations correlated with dietary Boric Acid intake and embryo/fetal toxicity. On GD 20, the average fetal body weight per litter in both sexes significantly decreased when exposed to 0.1 or 0.2% Boric Acid. The 0.075% group had a blood concentration of ~1.27 µg/g, while the 0.1% group had a blood concentration of ~1.53 µg/g.* *The developmental NOAEL was 10 mg boron/kg/d (0.075% Boric Acid) while the LOAEL was 13 mg boron/kg/d (0.1% Boric Acid)*	[3]
Boric Acid	*deionized water*	*pregnant female rats (11 – 14/group)*	*0 or 500 mg/kg*	*Test material was administered orally via gavage twice daily on GD 5 - 9, 6 - 9, or 6 - 10 while the control received the vehicle on GD 5 - 10. Maternal deaths, decreased maternal body weight, increased resorption rates, and decreased fetal weights were observed in all treated groups.*	*The group receiving Boric Acid on GD 5 - 9 had the most severe effects with evidence of abnormal bone fusions, agnathia, anophthalmia/microphthalmia, brachygnathia, cleft lip or palate, craniorachischisis, domed head, encephalocele, exencephaly, rachischsis, scoliosis, and sternoschisis. Groups exposed on GD 5 - 9 and 6 – 10 had the absence or shortening of the 13th rib.*	[3]
Boric Acid	*deionized water*	*pregnant female rats (11 – 13/group)*	*0 or 500 mg/kg*	*Test material was administered orally via gavage in single-day exposures during gestation. The rats were split into two blocks (11-13/group) where they were treated on GD 6, 7, 8, or 9 in the first block or were dosed on GD 9, 10, or 11 in the second block, while controls received the vehicle during the corresponding gestational periods.*	*No clinical signs of toxicity or mortality were noted after the single-day dosing, although body weight significantly decreased in all groups except for the GD 10 group. There was also a slight increase in post-implantation loss and alterations in the number of vertebrae, ribs, or sternebrae. GD 8 and GD 9 groups had a low incidence of cervical ribs, while the GD 9 group had 90% of the fetuses having six cervical vertebrae. The GD 10 group had a 60% incidence of fetuses with <13 ribs and an increased incidence of <6 sternebrae.*	[3]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
Boric Acid	*deionized water*	*pregnant female rats (3-5/group) and the pups*	*0 or 500 mg/kg*	*Test material was administered orally via gavage in single-day exposures during gestation (GD 8, 9, or 10). After the pups were delivered, they were evaluated on PND 1, 7, 14, 21, and 28, with skeletal and visceral examinations performed on PND 28.*	*There were no significant effects on pup weight or mortality in the GD 9 group, but the 6 cervical vertebrae phenotype was observed among 100% of the PND 28. For the GD 10 group, there was an increase in postnatal mortality during PND 1 - 7. For offspring in the GD 8 group, the pup weights decreased on PND 21 and PND 28. At PND 28, surviving pups also exhibited significant incidences of cervical ribs, fused, or small vertebrae.*	[3]
Boric Acid	*in feed*	*time-mated Sprague Dawley rats (n=26 - 28/group),*	*0, 78, 163, and 330 mg/kg/d (GD 0 - GD 20)* *539 mg/kg/d (GD 6 – 15)*	*The test material was given orally in feed. Maternal toxicity endpoints included food/water consumption, body weight, liver/kidney weights, kidney histology, uterine weight, and signs of toxicity from daily observations, while developmental toxicity included embryonal/fetal weight and structural variations/malformations.*	*All the treatment groups had a significantly higher percentage of litters containing one or more adversely affected implants compared to the control. The 163 and 330 mg/kg/d groups experienced a significant increase in the percentage of adversely affected implants/litter. For the 330 and 539 mg/kg/d groups, there was statistically significant decrease in maternal weight gain during GD 0 – 20 and GD 6 – 15, respectively. The developmental toxicity LOAELs and NOAELs were 78 and <78 mg/kg/d for rats (fetal weight reduction)*	[3]
Boric Acid	*deionized water*	*pregnant female rats (3-5/dose)*	*0, 100, 200, 400, or 800 mg/kg*	*Test material was administered orally via gavage daily from GD 6 – 9. Maternal organ/body weights and fetal skeletal examinations were evaluated.*	*No maternal toxicity or significant effects on fetal viability were observed, although the 800 mg/kg group had significantly reduced fetal weight compared to the control. Skeletal findings included shortened 13th ribs, increased cervical ribs, and incidence of a 14th thoracic rib in the 400 and 800 mg/kg groups.*	[3]
Boric Acid	*NR*	*New Zealand rabbits (n=18 - 23/group)*	*62.5, 125, or 250 mg/kg/d*	*The rabbits were artificially inseminated and received the test material via gavage during GD 6 – 19. Maternal toxicity endpoints included food/water consumption, body weight, liver/kidney weights, kidney histology, uterine weight, and signs of toxicity from daily observations, while developmental toxicity included embryonal/fetal weight and structural variations/malformations.*	*There was an increase in corrected maternal weight change at 125 and 250 mg/kg/d in the rabbits. However, the high dose group had a decrease in feed consumption, body weight, and uterine weight as well as a high rate of resorption and proportion of doses with complete prenatal loss. There was an increase in overall incidence of malformed fetuses at the highest dose. The developmental toxicity LOAELs and NOAELs were 250 and 125 mg/kg/d for rabbits (prenatal mortality and malformations).*	[3]

ALH - amplitude of lateral head displacement; ATP - adenosine triphosphate; BUN - blood urea nitrogen; CASA - computer-assisted sperm analysis; ESC - epididymal sperm count; FSH - follicle stimulating hormone; GD – gestational day; LH - luteinizing hormone; LOAEL - lowest-observed-adverse-effect-level; NOAEL - no-observed-adverse-effect-level; NR – not reported; PND – postnatal day; RACB - reproductive assessment by continuous breeding; SGOT - serum glutamic-oxalic transaminase; SGPT - serum glutamic-pyruvate transaminase; TSHC - testicular spermatid head count

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Test System	Dose/Concentration	Procedure	Results	Reference
			IN VITRO			
Boric Acid	NR	primary culture of seminiferous tubules from 20-d-old male Sprague Dawley rats	0.019, 0.062, 0.186, or 0.618 mg/ml	Assay using Bio-Alter® technology to mimic in vivo conditions. At 7 and 14 d, cells were recovered to be counted and go under FACS analysis to assess number of somatic cells, pre-meiotic cells (spermatogonia), meiotic cells (young spermatocytes, late pachytene spermatocytes, secondary spermatocytes) and post-meiotic cells (round spermatids). Cadmium was used as the positive control.	Boric Acid induced an increase in somatic cell proliferation and decreased the populations of all the studied germ cells.	[5]
Boric Acid	DMSO	murine derived embryotic stem cells (D3)	NR	Revised 96-well EST to determine embryotoxic potency.	Boric Acid had an REP value of 0.001 +/- 0.001, which indicated that it was moderately embryotoxic.	[27]
Boric Acid	DMSO	mESCs	0.1 mg/ml	survivin-based embryotoxicity assay	Boric Acid decreased survivin expression ~20% in 3 d, indicating a moderate embryotoxic effect. Also lowered EGFP in D3-CMV-EGFP and D3-SP-EGFP cells, meaning a cytotoxic effect.	[28]
			ANIMAL			
Boric Acid	NR	Swiss CD1 male mice (n=20/dose)	0 or 9000 ppm	Test substance was administered via diet for 8 wk. Controls were untreated. Basal serum concentrations of LH and FSH were determined. The effect on testosterone and gonadotropin was also examined.	FSH increased after 4 wk. LH concentrations also increased, but not as significantly. Testosterone decreased after 2 wk with gonadotropin increasing 1-2 wk later. Boric Acid is suggested to act on Leydig cells to depress testosterone synthesis and/or release.	[5]
Boric Acid	NR	Swiss mice (20 males/group)	0 or 9000 ppm	Test substance was administered via diet. Controls were untreated. Animals were bled weekly for 8 wk by ophthalmic plexus. At wk 9, half were given HCG challenge and half were given saline where serum was collected for both groups 1 h after.	Boric Acid decreased basal concentrations of testosterone and the release of testosterone in response to HCG challenge.	[5]
Boric Acid	NR	Swiss mice (both sexes; number not specified)	0, 1000, 4500 or 9000 ppm boron (as ~ 0, 152 636, or 1262 mg/kg Boric Acid)	Reproductive Assessment by Continuous Breeding Protocol; Test substance is administered via diet for 27 wk before the mice undergo mating and necropsy. Observations were continued through two generations.	F_0 mice: -At 14 wk, fertility was reduced at the 4500 ppm and there was complete infertility at the 9000 ppm doses. -At 27 wk, the F0 generation underwent necropsy after the offspring were born. There was a dose related reduction in body and reproductive organ weights and changes in sperm for the F0 males. At 4500 ppm, both sexes in the F_0 generation had decreased kidney and adrenal weights. Controls had normal fertility in F_1 mice and the adjusted mean bw in F_2 pups decreased for this group.	[5]
Boric Acid	NR	Swiss CD-1 rats (10/sex/dose)	0, 120, 400 and 1200 mg	Males: gavage administration from days 3-20 before necropsy. Body/organ weights were measured and histopathology was performed on the males. Females: gavage administration from days 0-20 before necropsy. Body/organ weights, number of females delivering, litter size, and number of implantation sites were collected for the females. Mating occurred days 8-12 for both sexes.	Boric Acid reduced testis weight after 19 d of dosing. At 1200 mg, males experienced reduced testis weight and significant testicular toxicity. At this dose, there was also a significant reduction in the number of females delivering and number of live pups.	[29]

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Test System	Dose/Concentration	Procedure	Results	Reference
Boric Acid	NR	Sprague-Dawley rats (8 males/group; 16 females/group)	Boric Acid amount was not specified but was equivalent to 0, 5.9, 17.6, and 58.8 mg/kg boron)	Test substance was administered orally via diet. Controls were untreated. Clinical examinations and gross pathology were observed.	After 2–3 wk of treatment at 58.8 mg boron/kg bw/d, females exhibited systemic toxicity and reduced litter production, while males developed testicular atrophy. A NOAEL of 17.5 mg boron/kg bw/d was proposed for female reproductive effects, although the study mentioned limitations in the mating procedure and concluded that the evidence for adverse effects was stronger for male fertility than for female fertility. The LOAEL was identified to be 58.5 mg boron/kg bw/d.	[32]
Boric Acid	water	time-mated female Sprague-Dawley rats and their pups (8 dams/group)	0, 5, 10, or 20 mg/kg/d	Gavage administration to the dams on days 6 - 21 of gestation. Once pups were born, pups also went under gavage administration from PND 1-28.	No deaths or signs of maternal toxicity were observed in the dams at all doses. On PND 7, the 20 mg/kg dose group had 11 instances of umbilical hernias. On PND 28, in the same group, Boric Acid resulted in statistically significant lower postnatal weights with a 23% reduction compared to the controls.	[30]
Boric Acid	double-distilled deionized water	Sprague-Dawley rats (both sexes, number not specified)	0 and 500 mg/kg	Test substance was administered via gavage twice a day to pregnant Sprague-Dawley rats. There were 2 blocks: 1st block (rats dosed on GD 6,7, 8, or 9 with controls receiving the vehicle only on GD 9) 2nd block (rats dosed on GD 9, 10, or 11) with controls receiving the vehicle only on GD 9-11). Rats were examined afterwards for toxicity.	A comparison of both blocks indicated that Boric Acid induced axial skeleton malformations and shifted the expression domain for 2 genes (hoxc6 and hoxa6) on gestation day 13.5.	[5]
Boric Acid	water	New Zealand White rabbits (30 females/group)	0, 62.5, 125, and 250 mg/kg Boric Acid (~10.9, 21.8, 43.5 mg/kg boron)	OECD TG 414 (Prenatal Developmental Toxicity Study); test substance was administered via gavage during day 6-19 of gestation where they were killed on day 30 of gestation. Controls were untreated. Clinical examinations were made post-mortem.	Maternal rabbits had decreased feed intake and maternal body weight. There was vaginal bleeding at 250 mg/kg of Boric Acid, with no live fetuses at termination. LOAEL: 250 mg/kg bw Boric Acid (~43.5 mg B/kg bw) NOAEL: 125 mg/kg bw Boric Acid (~21.8 mg B/kg bw) For the dams, 250 mg/kg bw Boric Acid led to 90% of the litter being resorbed compared to 6% for controls, and a 73% complete litter loss.	[5]
Sodium Borate	NR	Sprague-Dawley rats (8 males/group; 16 females/group)	Sodium Borate amount was not specified but was equivalent to 0, 5.9, 17.6, and 58.8 mg/kg boron)	Test substance was administered orally via diet. Controls were untreated. Clinical examinations and gross pathology were observed.	After 2–3 wk of treatment at 58.8 mg boron/kg bw/d, females exhibited systemic toxicity and reduced litter production, while males developed testicular atrophy. A NOAEL of 17.5 mg boron/kg bw/d was proposed for female reproductive effects, although the study mentioned limitations in the mating procedure and concluded that the evidence for adverse effects was stronger for male fertility than for female fertility. The LOAEL was identified to be 58.5 mg boron/kg bw/d.	[32]
Sodium Borate	NR	Wistar albino rats (7 females/group)	0, 1250 and 5000 mg/kg (~142 and 567 mg/kg boron)	Test substance was administered orally via gavage for 7, 15, 30, or 60 d. Evaluated endpoints included ovarian weights, serum concentrations of FSH, LH, estradiol, and anti-müllerian hormone (AMH), histomorphometry measurements, and the ovarian apoptotic index using a Terminal deoxynucleotidyl transferase dUTP Nick End Labeling (TUNEL) assay.	As the dose and exposure duration increased, there was a decrease in ovarian weight, LH, E2, and AMH levels and an increase in FSH levels and ovarian apoptosis. Ovarian toxicity associated with boron exposure was dependent on dose and exposure duration with the most effects observed at the highest dose (5000 mg/kg) and longest exposure duration (60 d).	[31]

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Test System	Dose/Concentration	Procedure	Results	Reference
INHALATION						
Boric Acid	NR	rats (12 males/group)	9.6 ± 0.5 and 48.6 ± 1.46 mg/m^3	Animals were exposed via aerosol in cages for 4 h/d for 4 mo. Controls were untreated. Histological examinations were performed.	9.6 ± 0.5 mg/m^3 group had atrophied testis, reduced spermatozoa, and pathological changes in testis; severity greater in the 48.6 ± 1.46 mg/m^3 group.	[5]

AMH - anti-müllerian hormone; EGFP - enhanced green fluorescent protein; EST – embryonic stem cell test; FACS – fluorescence activated cell sorting; FSH – follicle stimulating hormone; GD – gestational day; HCG – human chorionic gonadotropin; LH – luteinizing hormone; mESCs – mouse embryonic stem cells; LOAEL – lowest observed-adverse-effect-level; NOAEL - no-observed-adverse-effect-level; PND – post-natal day; REP - Relative Embryotoxic Potency; TUNEL - terminal deoxynucleotidyl transferase dUTP nick end labeling assay.

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
IN VITRO						
Gene Mutation						
Boric Acid	NR	1000-5000 µg /ml	Mouse lymphoma L5178Y cells	OECD TG 476 (In vitro mammalian cell gene mutation test); mammalian cell gene mutation assay (time not specified)	Increase in mutations at the thymidine kinase locus was not significant.	[5]
Chromosomal Damage						
Boric Acid	distilled water	0, 0.25, 0.5, 1, 2, 5, 10, or 20 ppm	human blood cultures	Micronucleus assay; cells were treated for 72 h Controls were untreated	Not genotoxic	[34]
Boric Acid	NR	0, 2.5, 5, or 10 µM	human lymphocytes	Micronucleus assay; cells were treated for 72 h Also completed with titanium dioxide (1, 2, 3, 5, 7.5, or 10 µM) Controls were untreated, positive controls treated with DMSO	Boric Acid did not cause an increase in micronuclei formation. The addition of 2.5, 5, or 10 µM Boric Acid significantly reduced titanium dioxide-induced genotoxicity but did not inhibit micronuclei formations in 5 – 10 µM doses of titanium dioxide.	[35]
Boric Acid	water	0, 5000 and 10,000 µg/l	human blood cultures	Micronucleus assay; cells were treated for 72 h Also completed with vanadium (IV) tetraoxide (5000, 10,000, and 20,000 µg/l) Negative controls were untreated, positive controls treated with mitomycin C.	Boric Acid did not cause an increase in micronuclei formation. Boric Acid decreased vanadium-induced genotoxicity.	[36]
Boric Acid	NR	0-50,000 µg /ml	Peripheral blood lymphocyte cultures	Mammalian cell micronucleus test (time not specified)	Not genotoxic.	[5]
Boric Acid	water	0, 5000 and 10,000 µg/l	human blood cultures	Chromosomal aberration assay; cells were treated for 72 h Also completed with vanadium (IV) tetraoxide (5000, 10,000, and 20,000 µg/l) Negative controls were untreated, positive controls treated with mitomycin C.	Negative. Boric Acid decreased vanadium-induced genotoxicity.	[36]
Boric Acid	DMSO	0, 400, 600, 800, 10,000 µg/ml	human lymphocytes	Chromosomal aberration assay; cells were treated for 24 and 48 h Negative control was a solvent control (DMSO), positive controls treated with mitomycin C.	Structural and total chromosomal aberrations were induced at all test concentrations and durations. Boric Acid did not cause numerical chromosomal aberrations.	[33]

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
Sodium Borate	NR	0, 2.5, 5, or 10 µM	Human lymphocytes	Micronucleus assay; cells were treated for 72 h Also completed with titanium dioxide (1, 2, 3, 5, 7.5, or 10 µM) Controls were untreated, positive controls treated with DMSO	Sodium Borate did not cause an increase in micronuclei formation. Sodium Borate significantly reduced titanium dioxide-induced genotoxicity but did not inhibit micronuclei formations in 5 – 10 µM doses of titanium dioxide.	[35]
Sodium Borate	water	0, 5000 and 10,000 µg/l	Human blood cultures	Micronucleus assay; cells were treated for 72 h Also completed with vanadium (IV) tetraoxide (5000, 10,000, and 20,000 µg/l) Negative controls were untreated, positive controls treated with mitomycin C.	Sodium Borate did not cause an increase in micronuclei formation. Sodium Borate decreased vanadium-induced genotoxicity.	[36]
Sodium Borate	water	0, 5000 and 10,000 µg/l	Human blood cultures	Chromosomal aberrations assay; cells were treated for 72 h Also completed with vanadium (IV) tetraoxide (5000, 10,000, and 20,000 µg/l) Negative controls were untreated, positive controls treated with mitomycin C.	Negative Sodium Borate decreased vanadium-induced genotoxicity.	[36]
				Other (e.g., DNA Strand Breaks)		
Boric Acid	NR	0, 3, 10, 30, 100, or 200 µM	Chinese hamster lung fibroblast (V79 cells)	Alkaline comet assay; cells were treated for 16 h. Negative control was untreated, positive control treated with hydrogen peroxide	Not genotoxic.	[38]
Boric Acid	NR	0, 0.5, 1, 5, 10, 50, 100, 500, or 1000 µM	human Sertoli cells	Alkaline comet assay; cells were treated for an unspecified time. Negative control was untreated, positive control treated with hydrogen peroxide	Not genotoxic. There was not a significant difference in DNA damage between the treated groups and control groups.	[39]
Sodium Borate	NR	0, 150, 200, or 300 µg/ml	Human lymphocyte cell cultures	Giemsa staining and G-banding; cells were treated for 72 h; controls were untreated	A statistically significant reduction in the numbers of metaphase plates and metaphase chromosomes was observed in cells treated with 150 µg/ml (57.2%), 200 µg/ml (50.8%), and 300 µg/ml (42.3%). Sister chromatid separation was found in the 0.3 mg/ml group, compared to controls.	[40]
				IN VIVO		
				Chromosomal Damage		
Boric Acid	distilled water	0 - 3500 mg/kg	Swiss Webster mice, both sexes	OECD TG 474 (mammalian erythrocyte micronucleus test) - time not specified; mice given 2 doses/d for 2 d via gavage	not genotoxic.	[5]
				Other (e.g., DNA Strand Breaks)		
Boric Acid	aquarium water	0, 1000, 4000, 16,000, or 64,000 µg/l	Zebrafish *Danio rerio*, both sexes	Comet assay; animals were treated for 24, 48, 72, or 96 h. Peripheral erythrocytes were drawn from the caudal vein and were analyzed. Negative controls were untreated, positive controls treated with ethyl methanesulfonate.	Genotoxicity was observed in response to Boric Acid in a dose-dependent manner. DNA damage was highest at 24 and 96 h of exposure to all test concentrations.	[41]
Sodium Borate	aquarium water	0, 1000, 4000, 16,000, or 64,000 µg/l	Zebrafish *Danio rerio*, both sexes	Comet assay; animals were treated for 24, 48, 72, or 96 h. Peripheral erythrocytes were drawn from the caudal vein and were analyzed. Negative controls were untreated, positive controls treated with ethyl methanesulfonate.	Genotoxicity was observed in response to Sodium Borate in a dose-dependent manner. DNA damage was highest at 24 and 96 h of exposure to all test concentrations.	[41]

Table 8. Cytotoxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
Boric Acid	Serum free medium	Jurkat cells	0, 100, 300, 500, 700, 800, 850, 900, 1000, and 1500 µg/ml	2,3-bis-(2-methoxy-4-nitro-sulfopenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay; cells were treated for 24, 48, and 72 h; controls were untreated.	Boric Acid increased oxidative stress and inhibited Jurkat cell proliferation dose-dependently.	[44]
Boric Acid	NR	HepG2 cell line THLE2 cell line	0.00625, 0.0125, 0.025, 0.050, 0.100, and 0.200 ml	MTT assay; cells were treated for 24 h Positive control was cisplatin.	The viability of both cell lines was reduced in a dose-dependent manner with Boric Acid being more cytotoxic in the HepG2 cell line. Its IC50 for the HepG2 cell line was much lower at 0.06427 mg/ml vs. 0.6128 mg/ml in the THLE2 cell line.	[48]
Boric Acid	NR	0, 3, 10, 30, 100, or 200 µM	Chinese hamster lung fibroblast (V79 cells)	NRU assay; cells were treated for 18 h. Positive and negative controls not mentioned.	Not cytotoxic in tested concentrations.	[38]
Boric Acid	water	HGF-1	0, 0.312, 0.625, 1.25, 2.5, 5, 10 mg/ml	MTT assay; cells were treated for 24 h Negative controls were untreated; positive controls treated with chlorhexidine.	The cytotoxicity of the Boric Acid solution was similar to the positive control	[46]
Boric Acid	water	HGF-1	0, 0.312, 0.625, 1.25, 2.5, 5, 10 mg/ml	LDH assay; cells were treated for 24 h Negative controls were untreated; positive controls treated with chlorhexidine.	The cytotoxicity of the Boric Acid solution was similar to the positive control	[46]
Boric Acid	NR	U-87 MG glioblastoma cells	0, 2.5 mM, 25 mM, and 50 mM	MTT assay; cells were treated for 48 h controls were untreated	The MTT assay revealed that the percentage viability calculated was 90%, 46%, and 23% for the 2.5mM, 25 mM, and 50mM boron applications. At 50 mM was considered fatal and the cells had issues multiplying at the 25 mM concentration. Boric Acid had a cytotoxic effect on the U-87 MG glioblastoma cells.	[47]
Boric Acid	NR	Primary rat Sertoli cells	0.25, 0.5, 1, 5, 10, 40, and 80 mmol/l	MTT assay; cells were treated for 24 h	Lower doses of Boric Acid, specifically doses below 0.5 mmol/l, promoted the viability of the Sertoli cells and inhibited apoptosis. Higher doses at 5.0 mmol/l or above had toxic effects that inhibited cell viability, accelerated apoptosis, and arrested the cell cycle at the G0/G1 phase	[45]
Boric Acid	NR	Primary rat Sertoli cells	0.25, 0.5, 1, 5, 10, 40, and 80 mmol/l	CCK-8 assay; cells were treated for 24 h Controls were untreated	Lower doses of Boric Acid, specifically doses below 0.5 mmol/l, promoted the viability of the Sertoli cells and inhibited apoptosis. Higher doses at 5.0 mmol/l or above had toxic effects that inhibited cell viability, accelerated apoptosis, and arrested the cell cycle at the G0/G1 phase	[45]
Boric Acid	0.1% sterile water	human Sertoli cells	0, 0.5, 1, 5, 10, 50, 100, 500, or 1000 µM	NRU assay; cells were treated for 18 h. Negative control was untreated, positive control treated with SDS solution	Not cytotoxic in tested concentrations.	[36]
Sodium Borate	NR	human lymphocyte cell cultures	0, 100, 150, 200, 300, and 600 µg/ml	MTT assay; cells were treated for 24 h	MTT assay showed that cultures exposed to Sodium Borate had low proliferation.	[37]
Sodium Borate	water	HGF-1	0, 0.312, 0.625, 1.25, 2.5, 5, 10 mg/ml	MTT assay; cells were treated for 24 h Negative controls were untreated; positive controls treated with chlorhexidine.	The cytotoxicity of the Sodium Borate solution was less than the positive control.	[46]
Sodium Borate	water	HGF-1	0, 0.312, 0.625, 1.25, 2.5, 5, 10 mg/ml	LDH assay; cells were treated for 24 h Negative controls were untreated; positive controls treated with chlorhexidine.	The cytotoxicity of the Sodium Borate solution was less than the positive control.	[46]

CCK-8 - cell counting kit-8; LDH – lactase dehydrogenase; MTT - 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NR – not reported; NRU – neutral red uptake

Table 9. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
ANIMAL						
Boric Acid	physiological saline	0.5 g	New Zealand White rabbit (n=10)	Test substance applied to abraded and intact skin for 24 h. Observations made within 72 h.	Scored average of 0 for edema and 0.105 for erythema under Draize system. Classified in US in Toxicity Category IV (slight or no irritation). PDII was 0.1/4.	[5]
Boric Acid	NR	100 mesh (concentration not specified)	Rabbit (n=6)	Test substance applied to abraded and intact skin for 4 h. Observations were made at 24 and 48 h.	Test substance was non-corrosive.	[5]
Sodium Borate	Physiological saline	0.5 g	New Zealand White rabbit (n=60)	Test substance applied to skin for 4 h. Observations made within 72 h.	Test substance was non-irritating.	[6]
SENSITIZATION						
ANIMAL						
Boric Acid	distilled water	0.4 g (95% w/w)	Hartley guinea pigs (n=60)	OECD TG 406 (skin sensitization); positive control was dinitrochlorobenzene	Non-sensitizing Faint erythema, otherwise no adverse effects.	[5]
Sodium Borate	distilled water	0.4 g (95% w/w)	Hartley guinea pigs (n=60)	OECD TG 406 (skin sensitization); positive control was dinitrochlorobenzene	Non-sensitizing No adverse effects.	[6]

NR – not reported

Table 10. Case reports

Ingredient	Subjects	Protocol/Study Description	Results	Reference
Boric Acid	2-yr-old female	Patient was brought in to the pediatrician after experiencing erythema on her cheeks for a 2-mo period. Her symptoms worsened for 14 d when her parents treated her with 2% Boric Acid applied via wet dressings 10x a day.	Withdrawal from Boric Acid and treatment including 0.1% dexamethasone and 5 ml of cetirizine solution for 6 d allowed for the erythema and lesions to resolve after a 2 wk period.	[50]
Boric Acid	82-yr-old male	Clinical observations and serum/urinary concentrations were measured for a patient admitted to the hospital after accidentally ingesting 300 g of Boric Acid.	The patient showed signs of agitation, headache, nausea, and vomiting without signs of renal dysfunction.	[51]
Boric Acid	56-yr-old male	Clinical observations, skin exam, and histopathologic evaluation were made day 9 post-ingestion on patient was history of suicidal tendencies that ingested 2 cups of roach killer with Boric Acid.	Skin exam showed erythema, desquamation, and hemorrhagic crusting of the lips and conjunctival edema with a clear white orbital exudate. Histopathologic evaluation showed mostly intact epidermis with parakeratosis, alternating orthokeratosis, superficial exfoliation, vacuolar alteration of basal layer, and scattered keratinocytes in all levels of epidermis. Serum boron level was 34,000 µg/l. Patient also experienced persistent, severe ileus, worsening thrombocytopenia, acute renal failure, altered mental state, anemia, and elevated transaminases.	[52]
Boric Acid	88-yr-old female	Clinical observations and serum concentrations were measured for a patient admitted to the hospital after accidentally ingesting 6 g of an eye irritation solution containing Boric Acid.	Patient had mild erythema in face and chest, diarrhea, nausea, and hypotension. Patient received continuous hemofiltration 16 h after ingestion for 48 h. After 45 d in the hospital, the patient's serum creatine level returned to baseline (11 µg/ml) and chronic kidney function remained stable. The study suggested that the ingested dose was below the lethal range of 15 – 20 g, but the patient's impaired renal clearance likely led to the prolonged systemic exposure and toxicity.	[53]

Table 11. Epidemiological studies

Ingredient	Subjects	Protocol/Study Description	Results	Reference
Boric Acid	Females (n= 199), specifically mothers and their children	Mother-child cohorts were studied on their exposure to boron through drinking water during pregnancy to evaluate the pre- and postnatal boron exposure and its effect on infant anthropometry. Adjustments were made in the study to account for the lithium and arsenic exposure that were also present in the drinking water. Blood and urine were retrieved to determine blood boron concentrations and how participants fit into different exposure groups. Reproductive outcomes were assessed for 3 yr. Environmental exposure only; low exposure group: < 0.0001 mg/B/g, medium exposure group: 0.0001 -0.00015 mg B/g, high exposure group: > 0.00015 mg B/g	Individual blood boron concentrations ranged from 0.000000328 to 0.000000075 mg B/g in the blood. Adverse events from boron exposure were not observed on induced abortion, spontaneous abortion (miscarriage), stillbirth, infant death, neonatal death, early neonatal death, preterm birth, congenital anomalies, sex ratio, and birth weight.	[57]
Boric Acid	Females (n=177)	The boron concentration of drinking water during this study ranged from 377 - 16076 µg/l. The amount of boron in ranges is included below before and after pregnancy. *Before pregnancy* • Maternal serum: 30 - 447 µg/l • Maternal blood: 27 - 322 µg/l *After pregnancy* • Maternal serum: 47 - 624 µg/l • Maternal blood: 66 - 750 µg/l • Infant urinary boron content: o 0 - 3 mo: 105-9200 µg/l o 3 - 6 mo: 389-15068 µg/l Infant weight, length, and head circumference were measured at birth, 0-3 mo, and 3-6 mo.	Infant urinary boron was inversely associated with the infant weight, length, and head circumference during the first 6 mo.	[63]
Boric Acid	Males (n= 192)	The amount of boron was measured in the dietary food/fluids, workplace inhalable dust, blood, semen, and urine from boron workers and controls. From this data, three groups in the study were created which included boron workers (n=66), the workers from high boron areas as the community comparison (n=59), and the workers from low boron areas as the control (n=67). Semen parameters were also determined such as apoptosis, aneuploidy, DNA breakage, morphology, motility, sperm concentration, and total sperm count.	The average blood boron, semen boron, and boron in the urine ranged from 47.9 – 499.2 ppb, 214 – 785.6 ppb, and 2.0 – 16.7 mg/l across the control, community comparison, and boron worker groups. There were no significant correlations between the semen parameters or blood boron concentration.	[58]
Boron (exposure was not specified from either Boric Acid or Sodium Borate)	Males (n=1000)	In a study with men working in boron mining or processing in China, the mean daily boron intake and the semen was analyzed (sperm density, total sperm count, semen quality, sperm zinc, motility) of the following groups were taken; boron workers (n= 75), boron workers at a plant with heavy boron contamination of water (n=16), the local community (sample size not mentioned), and remote background controls (sample size not mentioned).	The mean daily boron intake was measured to be 31.3, 125, 4.25, and 1.40 mg boron/d, respectively. There was not a statistically significant difference in the semen characteristics between the exposure groups.	[59]

Table 12. MOE calculations for Boric Acid in body wash products

Product Type	Area of Application	Body Weight (kg)	Surface Area (cm^2)[64,65]	Retention factor[66]	Conc. of Boric Acid (%)[13]	Estimated Daily Amount Applied (g/d)[60]	Calculated Systemic Amount of Applied Boric Acid (mg/d)	SED* (mg/kg bw/d)	NOAEL† (mg/kg bw/d)[62]	MOE
Rinse-off (Body wash)	Body area	60	16,900	0.01	0.00016	25.5 (90^{th} percentile)	0.000408	0.0000068	55	8,088,235

* The SED was calculated assuming 100% mucous membrane absorption, which represents a highly conservative estimate for potential genital-area exposure from a body wash/intimate wash use scenario. A refined estimate could scale the body wash use amount to the adult genital exposed area of 637 cm^2,[61] thereby limiting the mucosal absorption assumption to the relevant intimate-area exposure. However, because product use may not scale directly with exposed surface area, such a refinement would introduce additional assumptions and was not applied.
†NOAEL was derived from an oral developmental study in rats, based on reduced fetal body weight and increased skeletal variations observed at higher doses.

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