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

Status:	Draft Tentative Amended Report for Panel Review
Release Date:	May 22, 2026
Panel Meeting Date:	June 15-16, 2026

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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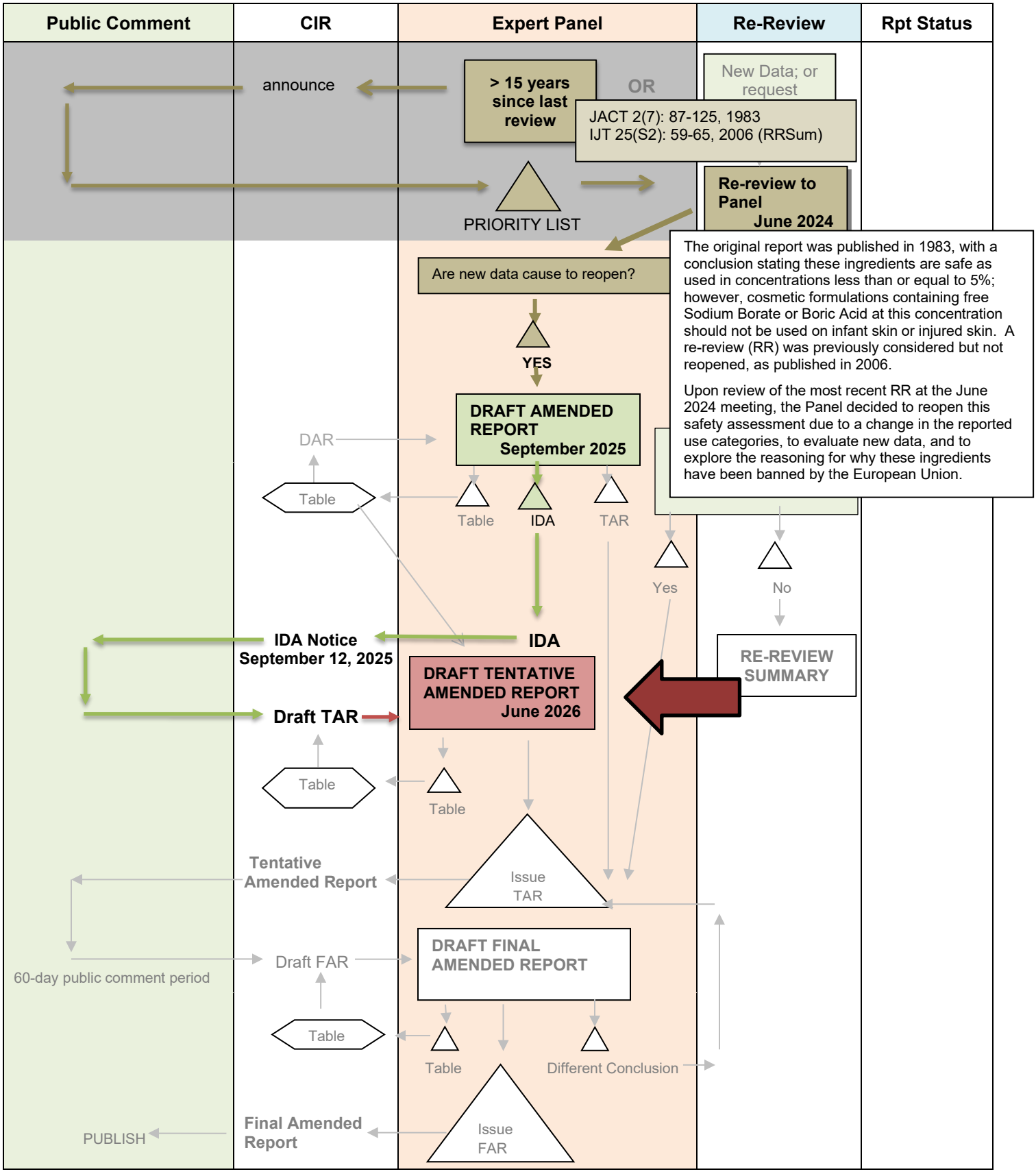
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Sodium Borate and Boric Acid

MEETING June 2026



The original report was published in 1983, with a conclusion stating these ingredients are safe as used in concentrations less than or equal to 5%; however, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant skin or injured skin. A re-review (RR) was previously considered but not reopened, as published in 2006.

Upon review of the most recent RR at the June 2024 meeting, the Panel decided to reopen this safety assessment 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.

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Temima Nguyen, M.S., Scientific Analyst/Writer, CIR
Date: May 22, 2026
Subject: Amended Safety Assessment of Sodium Borate and Boric Acid as Used in Cosmetics

Enclosed is the Draft Tentative Amended Report on the Safety Assessment of Sodium Borate and Boric Acid as Used in Cosmetics (It is identified as *report_SodiumBorate_062026* in the report package). At the September 2025 meeting, the Panel determined that the data were insufficient to support the safety of these cosmetic ingredients, and issued an Insufficient Data Announcement (IDA) with the following data needs:

- Margin of exposure (MOE) calculations for cosmetic uses that result in mucosal and vaginal exposures.
- Mucosal absorption data
- Vaginal absorption and total application surface area data
- Maximum concentration for Sodium Borate in products applied near the eye area, that result in mucous membrane exposure, and in douches
- Maximum concentration for Boric Acid when used in products applied near the eye

Since the IDA was issued, CIR has not received any of the requested data, as mentioned in the table below.

The data from the original 2003 re-review document (*RRdata_SodiumBorate_062026*) has been included in the current amended report for the Panel to review; please note, the previous edition did not include this information due to time constraints. The 2003 re-review data, median dietary boron intakes, generic concentration limit in the EU, relevant data from the SCCS 2010 Opinion on Boron Compounds that was not featured previously, a study evaluating reproductive toxicity in female Wistar albino rats, and a case study on a 88-yr-old female that ingested Boric Acid are highlighted in yellow to assist in your review.

In addition, the use table, which previously contained both VCRP and RLD, has been converted to include 2025 RLD only. Since the re-review for Boric Acid and Sodium Borate, when comparing the number of uses according to 2023/2002 VCRP data, the 2023 VCRP data decreased for both Boric Acid (from 77 to 8) and Sodium Borate (from 280 to 30). The maximum concentrations of use also decreased for Boric Acid since the 2003 re-review of these ingredients (from 2% to 0.00016%). However, for Sodium Borate, there was an increase in maximum concentration (from 3 to 3.7%).

In our analysis of each product reported in the RLD with a categorization of "(17) Other preparations (i.e., those preparations that do not fit another category)," Boric Acid and Sodium Borate both had 1 product that was co-categorized as “(03) Eye makeup preparations (other than children's eye makeup preparations).” According to the submitted names, 4 of the Boric Acid products consist of a cuticle oil, gel polish remover, gel polish remover and cuticle oil, and a nail treatment. However, for 5 of the reported formulations exclusively categorized as '(17) Other preparations,' neither the product type nor the area/route of exposure is obvious from the information submitted to the RLD. For 3 of the Sodium Borate products, the submitted names indicate the products consist of 2 teeth whitening products and a powdered hand cleaner. Information reported for 4 Boric Acid and 6 Sodium Borate products in the '(17) Other preparations,' category suggests that those submitted products might not be considered to be cosmetic products in the US. We have sent a request to our colleagues in the FDA's OCAC for clarification.

Based on the equivocal relevance of certain genotoxicity study methods, CIR staff have excluded sister chromatid exchange (SCE) assays from this report.

Comments received from the Council prior to the September 2025 meeting on the Draft Amended Report have been addressed (*PCPCcomments_SodiumBorate_062026* and *response-PCPCcomments_SodiumBorate_062026*).

Additional supporting documents for this report package include a flow chart (*flow_SodiumBorate_062026*), report history (*history_SodiumBorate_062026*), data profile (*dataprofile_SodiumBorate_062026*), search strategy (*search_SodiumBorate_062026*), transcripts from the recent meeting at which reopening this report was discussed (*transcripts_SodiumBorate_062026*), and minutes from the meetings at which the original reports were discussed (*originalminutes_SodiumBorate_062026*).

A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider and discuss the data (or lack thereof) and be prepared to issue a Tentative Amended Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

A table is provided below to indicate data insufficiencies and availability of the requested data.

Data Insufficiency	Has data been received?	If so, provide details.
Margin of exposure (MOE) calculations for cosmetic uses that result in mucosal and vaginal exposures	No	
Mucosal absorption data	No	
Vaginal absorption and total application surface area data	No	
Maximum concentration for Sodium Borate in products applied near the eye area, that result in mucous membrane exposure, and in douches	No	
Maximum concentration for Boric Acid when used in products applied near the eye	No	

Boric Acid & Sodium Borate History

December 1982

1st Review / Draft Report: The Expert Panel concludes that Sodium Borate and Boric Acid, in concentrations less than or equal to 5%, are safe as cosmetic ingredients when used as currently recommended; however, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant skin or injured skin.

1983

Final report was published.

February 2003

Dr. Belsito mentioned that new data on Boric Acid & Sodium Borate has entered published literature since 1983 and that they should consider beginning the process of considering whether the final report should be reopened.

June 2003

Dr. Belsito expressed concern for male reproductive effects and relation to use concentrations & dermal absorption. Since the reference to not using the ingredients on damaged skin was posted in the original conclusion, the Panel concluded that absorption would not be an issue. The Panel voted unanimously in favor of not reopening the Final safety assessment on Sodium Borate and Boric Acid.

2006

Re-review was published affirming conclusion from 1983.

June 2024

Re-review considered, the Panel decided to reopen due to the European ban (EU Annex II) and new information (cosmetic uses, inhalation toxicology, ocular irritation, case reports).

September 2025

Draft report reviewed and the Panel issued an Insufficient Data Announcement (IDA) for the following information:

- Margin of exposure (MOE) calculations for cosmetic uses that result in mucosal and vaginal exposures.
- Mucosal absorption data
- Vaginal absorption and total application surface area data
- Maximum concentration for Sodium Borate in products applied near the eye area, that result in mucous membrane exposure, and in douches
- Maximum concentration for Boric Acid when used in products applied near the eye

Boric Acid & Sodium Borate Data Profile* – June 2026 – Writer, Temima Nguyen																														
	Use				Toxico-kinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	New Rpt	Old Rpt	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Boric Acid	X	O	O	O	X	O	O		OX	X	O	OX	X		OX	OX	X		O		OX	O		X				OX		OX
Sodium Borate	X	O	O	O	X	O	OX		OX	X		OX			OX	OX	X				OX	O		X	O	O		OX		OX

* “X” indicates that new data were available in this category for the ingredient; “O” indicates that data from the original assessment were available

Boric Acid and Sodium Borate

Ingredient	CAS #	PubMed	FDA	CompTox	ChemPort	NIOSH	NTIS	NTP	FEMA	EU	ECHA	SIDS	SCCS	AICIS	FAO	WHO	Web
Boric Acid	10043-35-3 11113-50-1	√	√*	√	√	NR	√*	√*	NR	√	√	√*	√	√*	NR	√*	√
Sodium Borate	1303-96-4 (hydrous) 1330-43-4	√	√*	√	√	√	√*	√*	NR	√	√	√*	√	√*	NR	NR	√

NR- not reported; √* - data is available, but is not new or relevant

Search Strategy (from 2001 onwards)

Pubmed
((boric acid) OR (10043-35-3)) AND (toxicity) - from 2001 - 3000/12/12 - 410 hits/ 12 useful
((sodium borate) OR (borax)) OR (1303-96-4) AND (toxicity) from 2001 - 3000/12/12 - 116 hits/ 1 useful

Web
boric acid dermal irritation – 2,300,000 hits/ 2 useful
borax dermal irritation – 362,000 hits/ 0 useful

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- CompTox: https://comptox.epa.gov/dashboard/chemical/pubmed-abstract-sifter/DTXSID3039242; https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data#LM
- eChemPortal: https://www.echemportal.org/echemportal/
- DeepDyve: https://www.deepdyve.com/
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf; https://dps.fda.gov/omuf/monographsearch
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-sa fety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Kimberly Norman, Ph.D., DABT, ERT
Industry Liaison to the CIR Expert Panel

DATE: September 2, 2025

SUBJECT: Draft Amended Report: Amended Safety Assessment of Sodium Borate and Boric Acid as Used in Cosmetics (draft prepared for the September 8-9, 2025, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft amended report, Safety Assessment of Sodium Borate and Boric Acid as Used in Cosmetics.

Key Issues

The Cosmetic Use sections of CIR reports correctly states: "Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting)." Unfortunately, this report (in the memo, Cosmetic Use section, Summary) says there was a higher frequency of use reported to the RLD compared to the VCRP. Although the numbers may be higher, the total number of products reported to the RLD is much greater than reported to the VCRP. As is done in other CIR reports, the numbers reported to the VCRP and RLD should be included in the CIR report without any comparative language.

Many studies from the 2003 re-review should be added to the current report on Boric Acid and Sodium Borate, but especially the studies concerning dermal penetration, testicular effects, dermal case reports, and the 1997 risk assessment by Moore et al.

Perhaps as a separate section, it would be helpful to have more information about normal levels/average intakes of boron, such as median dietary intakes of 0.87-1.35 mg boron/day from NIH and the WHO tolerable upper limit of 20 mg boron/day. These values may be useful to provide perspective to exposures to boron from cosmetic products containing Boric Acid or Sodium Borate.

Additional Considerations

Cosmetic Use – Based on Table 2, the RLD lists Boric Acid as being in two spray deodorants.

Therefore, it is not clear why the incidental inhalation paragraph states: "could possibly be in cosmetic sprays and powders", using a general term when more specific details should be stated.

Please correct: "List of Substances Prohibited by Cosmetic Products" ("by" should be "in"). The description of CMR substances is not accurate. Category 1B does not just relate to "toxic to reproduction", there are also category 1B carcinogens and mutagens. In this case, Boric Acid and Sodium Borate have been classified as category 1B reproductive toxicants.

Non-Cosmetic – When describing permitted uses listed in the CFR, please describe them as permitted uses rather than "is used", unless there is other evidence that it is actually used.

Dermal Absorption, old report summary – Were there any differences among the different mediums that were used?

ADME, oral, Sodium Borate; Summary – Please add % associated with the urinary recovery rate.

ADME, Human, Dermal, old report summary – Did some studies really measure Boric Acid in the urine, or was it boron that was measured?

Short-Term, old report summary – Please be more specific than "poisoning" in describing effects observed.

Please revise the following: "A Sodium Borate aqueous solution was administered at 1000 mg/kg/d in rats for 3 wk signs of toxicity during the 3-wk period…" Is the dose, the amount of the aqueous solution or the amount of Sodium Borate?

Short-Term; Summary – What species was used in the gavage study in which animals were treated with 800 mg Boric Acid/kg/day? It says: "the [?] were killed every 6 d during the oral study".

Subchronic – Please state how liver and kidney functions were tested. Please correct: "serum renal damage products levels"

DART, old report summary – Please correct: "five in sex" to "five per sex". Please add the value for Boric Acid and Sodium Borate when it says a concentration of boron "equivalent to Boric Acid" (or Sodium Borate).

DART – In the studies in Swiss mice, please state which sex (or both) were treated. Rather than "test subjects" (which implies humans), please state the species that was treated.

At the end of the DART section, it would be helpful to include information from the summary of the ECHA dossier. The ECHA dossier summary states that the testes are the main target of boron and that the NOAEL for fertility is 17.5 mg boron/kg bw/day or 100 mg Boric Acid/kg bw/day (cited to Wier 1966 a, d).

Genotoxicity, In Vitro – What concentrations were tested in the sister chromatid exchange and micronucleus assays? The following sentence needs to be revised: "Boric Acid an[d] Sodium Borate [were] not genotoxic in sister chromatid exchange (SCE) assays or micronucleus assays." (add what is in the brackets; add the tested concentrations).

Carcinogenicity, Oral – Please state the duration of the observation period in the 10-week Boric Acid study in B6C3F1 mice.

Cytotoxicity – Please provide a reference for the MTT assay in human lymphocyte cell cultures exposed to Sodium Borate.

Neurotoxicity – Although the study authors may have called the single 2000 mg/kg dose a NOAEL for neurotoxicity of Boric Acid, because no other doses were used and because it was it was a single dose study, it would be better just to say that the single dose did not result in neurohistopathological effects, and not to call the dose a NOAEL.

Immunotoxicity – The immune system is very complex. Please state what was studied in the immunotoxicity study.

Dermal Irritation and Sensitization – In the text, please include some indication of the concentrations tested in the dermal irritation and sensitization studies.

Ocular Irritation, Sodium Borate – What timepoints do the mean score reactions represent?

Mucous Membrane Irritation, Inhalation, Sodium Borate – Please state the units for MMAD (μm).

Case Reports, Dermal – The studies of women and blood boron concentrations and birth outcomes (references 44, 45) are not case studies with dermal exposure. They are epidemiology studies. The number of subjects and the maternal blood boron levels should be stated for the second study.

Sodium Borate and Boric Acid – March 2026 – Temima Nguyen	
Subject: Draft Amended Report: Amended Safety Assessment of Sodium Borate and Boric Acid as Used in Cosmetics (draft prepared for the September 8-9, 2025, meeting) **Comment Submitter:** Kimberly Norman, Personal Care Products Council **Date of Submission:** September 2, 2025	
Comment	**Response/Action**
The Cosmetic Use sections of CIR reports correctly states: "Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting)." Unfortunately, this report (in the memo, Cosmetic Use section, Summary) says there was a higher frequency of use reported to the RLD compared to the VCRP. Although the numbers may be higher, the total number of products reported to the RLD is much greater than reported to the VCRP. As is done in other CIR reports, the numbers reported to the VCRP and RLD should be included in the CIR report without any comparative language.	Addressed.
Many studies from the 2003 re-review should be added to the current report on Boric Acid and Sodium Borate, but especially the studies concerning dermal penetration, testicular effects, dermal case reports, and the 1997 risk assessment by Moore et al.	Addressed.
Perhaps as a separate section, it would be helpful to have more information about normal levels/average intakes of boron, such as median dietary intakes of 0.87-1.35 mg boron/day from NIH and the WHO tolerable upper limit of 20 mg boron/day. These values may be useful to provide perspective to exposures to boron from cosmetic products containing Boric Acid or Sodium Borate.	Addressed.
Cosmetic Use – Based on Table 2, the RLD lists Boric Acid as being in two spray deodorants. 2 Therefore, it is not clear why the incidental inhalation paragraph states: "could possibly be in cosmetic sprays and powders", using a general term when more specific details should be stated.	Addressed.
Please correct: "List of Substances Prohibited by Cosmetic Products" ("by" should be "in"). The description of CMR substances is not accurate. Category 1B does not just relate to "toxic to reproduction", there are also category 1B carcinogens and mutagens. In this case, Boric Acid and Sodium Borate have been classified as category 1B reproductive toxicants.	Addressed.
Non-Cosmetic – When describing permitted uses listed in the CFR, please describe them as permitted uses rather than "is used", unless there is other evidence that it is actually used.	Addressed.
Dermal Absorption, old report summary – Were there any differences among the different mediums that were used?	This data was already provided in the report.
ADME, oral, Sodium Borate; Summary – Please add % associated with the urinary recovery rate.	Addressed.

Sodium Borate and Boric Acid – March 2026 – Temima Nguyen	
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ADME, Human, Dermal, old report summary – Did some studies really measure Boric Acid in the urine, or was it boron that was measured?	"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." This summary mentioned "Boric Acid" only. The original full paper is not available. "A study conducted with 21 hospitalized patients 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." This summary mentioned serum Boric Acid only. The original full paper is not available. The rest of the studies measured boron content.
Short-Term, old report summary – Please be more specific than "poisoning" in describing effects observed.	The original full paper did not go into detail on what the "poisoning" effects were.
Please revise the following: "A Sodium Borate aqueous solution was administered at 1000 mg/kg/d in rats for 3 wk signs of toxicity during the 3-wk period…" Is the dose, the amount of the aqueous solution or the amount of Sodium Borate?	Addressed. The original report says 1g/kg/day of the aqueous solution and there is no other information mentioned. The citation appears to go to a paper that does not match the study.
Short-Term; Summary – What species was used in the gavage study in which animals were treated with 800 mg Boric Acid/kg/day? It says: "the [?] were killed every 6 d during the oral study".	Addressed. Rats were the species. No other information was given.
Subchronic – Please state how liver and kidney functions were tested. Please correct: "serum renal damage products levels"	Addressed.
DART, old report summary – Please correct: "five in sex" to "five per sex". Please add the value for Boric Acid and Sodium Borate when it says a concentration of boron "equivalent to Boric Acid" (or Sodium Borate).	Addressed.
DART – In the studies in Swiss mice, please state which sex (or both) were treated. Rather than "test subjects" (which implies humans), please state the species that was treated.	Addressed.
At the end of the DART section, it would be helpful to include information from the summary of the ECHA dossier. The ECHA dossier summary states that the testes are the main target of boron and that the NOAEL for fertility is 17.5 mg boron/kg bw/day or 100 mg Boric Acid/kg bw/day (cited to Wier 1966 a, d).	Addressed.

Sodium Borate and Boric Acid – March 2026 – Temima Nguyen	
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Genotoxicity, In Vitro – What concentrations were tested in the sister chromatid exchange and micronucleus assays? The following sentence needs to be revised: "Boric Acid an[d] Sodium Borate [were] not genotoxic in sister chromatid exchange (SCE) assays or micronucleus assays." (add what is in the brackets; add the tested concentrations).	Addressed. Micronucleus assay: • Boric Acid - ≤ 10 µM, 20 ppm, 10,000 µg/l • Sodium Borate - ≤ 10 µM, 10,000 µg/l SCE assay: • Boric Acid - ≤ 10 µM, 20 ppm, 10,000 µg/l • Sodium Borate - ≤ 10 µM, 600 µg/ml, 10,000 µg/l
Carcinogenicity, Oral – Please state the duration of the observation period in the 10-week Boric Acid study in B6C3F1 mice.	According to the ECHA website, the study appears to have an observation period of 103 weeks. This is not explicitly mentioned, but they highlight observations at wk 63, 84, and 101. Also, there was a typo. It should be "103 wk," not "10 wk". This was corrected in the report.
Cytotoxicity – Please provide a reference for the MTT assay in human lymphocyte cell cultures exposed to Sodium Borate.	Addressed.
Neurotoxicity – Although the study authors may have called the single 2000 mg/kg dose a NOAEL for neurotoxicity of Boric Acid, because no other doses were used and because it was it was a single dose study, it would be better just to say that the single dose did not result in neurohistopathological effects, and not to call the dose a NOAEL.	Addressed.
Immunotoxicity – The immune system is very complex. Please state what was studied in the immunotoxicity study.	Addressed.
Dermal Irritation and Sensitization – In the text, please include some indication of the concentrations tested in the dermal irritation and sensitization studies.	Addressed.
Ocular Irritation, Sodium Borate – What timepoints do the mean score reactions represent?	Addressed. The timepoints were based off the scores from the 24, 48, and 72 h periods.
Mucous Membrane Irritation, Inhalation, Sodium Borate – Please state the units for MMAD (µm).	Addressed.
Case Reports, Dermal – The studies of women and blood boron concentrations and birth outcomes (references 44, 45) are not case studies with dermal exposure. They are epidemiology studies. The number of subjects and the maternal blood boron levels should be stated for the second study	Addressed.

JUNE 2024 PANEL MEETING – RE-REVIEW/DECISION TO REOPEN

Belsito Team – June 3, 2024

DR. BELSITO: So, then we're going to move on to boric acid. This is also a re-review. So, the Expert Panel first published our review in the safety of boric acid and sodium borate in '83. Concluded that in concentrations less than or equal to five percent they were safe in cosmetic ingredients when used as currently recommended, as described in a safety assessment. However, cosmetic formulations containing free sodium borate or boric acid at this concentration should not be used on infant skin or injured skin. The Panel previously considered a re-review of this report in 2003 and reaffirmed that conclusion. It was published in 2006. Because it's been 15 years since the re-review, we're being asked to look at it again. Again, the literature was scoured in 2024 April for any data since 2001.

So, a number of studies evaluating repeated oral tox, reproductive tox, potential hormonal, immunologic, neurotoxic effects, various case reports were found. Data on approved non-cosmetic uses, acute inhalation toxicity, in vitro genotox, occupational exposure were found for both boric acid and boric sulfate [sodium borate]. Ocular irritation study in sodium borate was classified as a ocular irritant in rabbit eyes was found. But more importantly, both are included on the European Union Annex II List of Substances Prohibited in Cosmetic Products.

MS. RAJ: Just wanted to add that the reason (inaudible) why they were put on the ban (inaudible) was because there was (inaudible) recorded use (inaudible) because I tried to look up the reasoning for why that (inaudible) toxicological or a scientific basis.

DR. BELSITO: Okay. Also, we have a table of current and historical use. 2023 VCRP data has sodium borate listed as 30 reported uses a boric acid eight, which is a significant decrease. Max reported concentrations for sodium borate to PCPC in 2022 was 0.78 percent in other shaving preparations, down from 20 percent in bath soaps and detergents, which would be diluted three percent during use, as reported in 2002. Highest reported leave-on concentration in 2002 was boric acid at 2% in eye makeups. Boric acid has no reported concentrations of use in 2022. The use categories haven't changed significantly. Again, frequency and concentration have gone down.

So, my overall conclusion looking at this is, despite discrete decrease to use in concentration, that we should reopen it to look at the new DART and genotoxic effects. We also heard why the EU has banned it, but I thought we should reopen it.

DR. RETTIE: Yeah, I agree to reopen. There's --

DR. BELSITO: A lot of data.

DR. RETTIE: There's a lot of new data there. I thought we need to perhaps clarify what we're looking at here. Structurally, borax itself seems to be sodium tetraborate. Sodium borate can be monomeric or trimeric. And I wasn't clear on what we were considering here or what we needed to consider in our report. Do we need to consider all salt forms?

DR. KLAASSEN: I don't know if any of you are old enough, but isn't this what Ronald Reagon used to advertise on television?

DR. BELSITO: Borax, yeah.

DR. KLAASSEN: Is that the same thing as this?

DR. BELSITO: No. I think borax was sodium borate, if I remember. Boric acid is actually used as an eyewash, or used to be.

DR. KLAASSEN: Oh, yeah?

DR. BELSITO: Yeah. It used to be used as an eyewash for styes.

DR. HELDRETH: The *Dictionary* monograph has sodium tetraborate as a technical name, so that puts borax in as a potential part of that ingredient of sodium borate.

DR. KLAASSEN: Well, there's a lot of new data, no question about it. I guess my concern is it's not used.

DR. BELSITO: Well, it is used.

DR. KLAASSEN: Well, according to the information we have here --

DR. BELSITO: It is used.

DR. KLAASSEN: Oh, I'll take it back then.

DR. BELSITO: We have the number of uses have decreased. Concentration of use has. No, Preethi was saying she thought the EU banned it because there were no reported uses in cosmetics, but we're getting --

DR. EISENMANN: It's a 1B reproductive toxicant in Europe.

DR. BELSITO: Okay.

DR. EISENMANN: Based on ECHA. So, that automatically bans it unless SCCS reviews it, and industry did not request that it get review, as far as I understand. So, it's been banned because of the 1B.

DR. BELSITO: Okay.

DR. EISENMANN: And industry is not supporting it.

DR. BELSITO: So, then I think we misunderstood Preethi's statement. So, it was banned because of the data shown, and it was a reproductive toxicant. It wasn't supported by industry to submit further studies.

DR. EISENMANN: Correct.

DR. BELSITO: Okay. But we have data that it is being used; and we have concentrations of use; and we have new DART and genotoxicity data. I think we need to look at it and determine is it safe for use.

DR. KLAASSEN: Good.

DR. RETTIE: You learn lots of stuff in this Panel. Do you know why it's called ten mule train borax, the stuff you put in your --

DR. BELSITO: I don't think we need to discuss that, Allan, really.

DR. RETTIE: -- wash.

DR. BELSITO: We have huge reports coming up.

MS. RAJ: Just wanted to add, DR. BELSITO, in the previous review discussion, there was mention that due to (inaudible) was a concern. That was the Panel's previous --

DR. BELSITO: I understand, Preethi, but we have a ton of new information. We're reopening it. Okay.

MS. RAJ: No problem.

DR. BELSITO: Okay. Any other comments. Paul?

DR. SNYDER: I concur --

DR. BELSITO: I mean, we have whole discussions that may change completely based upon the new data that we look.

DR. SNYDER: I concur with the reopen.

DR. BELSITO: Okay.

Cohen Team – June 3, 2024

DR. COHEN: Boric acid and sodium borate was first published in 1983 and the Panel concluded it was safe as a cosmetic ingredient at concentrations less than or equal to five percent. However cosmetic formulations containing free sodium borate and boric acid at this concentration should not be used on infant skin and injured skin. The Panel considered a re-review in 2003 to reaffirm the original conclusion. There's a number of studies evaluating repeated low dose oral toxicity, reproductive tox through various routes, hormonal, immunologic, neurotox effects and case reports were found.

There's an ocular irritation study in which sodium borate was classified as an ocular irritant to rabbit eyes. It's included in the European Union Annex II list of prohibited substances in cosmetic products. In 2023 the VCRP has sodium borate in 30 reported uses and boric acid in 8. That's substantially down from 2002 and in 2022 we had a reported max concentration of 0.78 percent for sodium borate in shaving preparations down from 20 percent in bath soaps and detergents from 2002.

The highest reported leave on concentration for boric acid in eye ointments was 2% in 2002. Boric acid has no reported concentration of use in 2022. So, we have a lot of relevant data that's been presented to us, and we also have European information, and this seems like an awful lot for a re-review summary. So, perhaps we reopen this?

DR. ROSS: I agree. I thought a lot of new data, EU Annex II. You know, our existing conclusion, as you said here, was pretty high concentration, 5%. So, I think just like the last one we can and should reopen it.

DR. BERGFELD: The driving force is the European ban. I don't think we should be of discordance without an explanation.

DR. ROSS: I think so.

MS. RAJ: I'd just like to mention though that these ingredients have been under, I think it's called a reproductive 1B category and they were not reported as being used in REACH which is why they were put on this ban list. Not necessarily because there was any toxicologic concern, but they weren't reported to be in use, and I think that's general procedure that they get put on the ban list.

DR. ROSS: (Inaudible) sense.

DR. COHEN: So, when they don't have reported uses, they're on the ban list.

DR. ROSS: We like it. We like it.

DR. COHEN: We run the report for a year and then wait two more years.

MS. RAJ: I'm just the messenger.

MS. FIUME: We've received no data. We received no data when you were asking for the REACH dossiers is when they end up on the ban list if no one has submitted data for an ingredient.

DR. COHEN: Okay.

DR. ROSS: There's a novel idea.

MS. FIUME: So just, since I'm always looking at the writer side of it, I know there's a lot of information but it's an information that would change your conclusion and needs full discussion.

DR. COHEN: I think so. I think this one would.

MS. FIUME: Knowing that the reproductive effects were discussed in the discussions of the previous reports.

DR. ROSS: You've got new inhalation tox data, you've got new developmental tox data, positive in high dose, you've got genotox data -- and most of that's negative by the way, but some's positive. The ocular's negative. You've got some estrogenic-like effects. But the major reason for reopening I still think is the EU Annex II. That's a good point.

DR. COHEN: And also, we have max use concentrations way less than there were in the past and is this 5% correct or not? I'm not sure.

DR. ROSS: I don't want to reopen it but I'm not sure we don't have much of a choice.

MS. FIUME: My concern was not there's a lot of information, there's a lot of different information, is different just because I know sometimes it'll go that route. It's like, no, we're all good.

DR. COHEN: Where we go safe as used on the initial report.

MS. FIUME: I'm just watching for the Panel -- for the writer work. I'm sorry. I wasn't questioning your decision.

DR. COHEN: No, no. I completely get it.

DR. ROSS: It needs to be questioned.

DR. COHEN: The conclusion. The conclusion is five percent.

DR. TILTON: Yeah, I agree. I mean, there's a lot of new developmental tox data and then the conclusion is very specific relative to use concentration and recommendations. So, I don't feel like I can just reaffirm without reviewing the data. We get into these situations where there's no reported concentrations and that always makes it difficult but --

MS. FIUME: So, it is possible to note that it's been two years since the concentrations were requested and it was noted those (inaudible) concentration of use data, is there something. I guess there is some. I'm saying that without looking at the table. There's not a lot, okay.

DR. COHEN: One of these skin irritation studies was five percent boric acid in freshly passed human urine. A PH of 5.5 resulted in no irritation. Who signed up for that one?

MS. FIUME: Oh my god.

DR. COHEN: It'd be nice to update this, I think. We may get a different response. Wilma, what are you thinking?

DR. BERGFELD: I'm thinking you're sort of around the border of what to do. I think, in that case, open it and figure it out. I think that the ban is important to respond to and I think to establish how we did that 5% when the studies were up to 3.2% in the old document. How did we get to 5%? I was trying to figure that out. But it doesn't matter. We have to clarify the concentration. Though I'd happen to know that boric acid in (inaudible) are used as a pharmaceutical agent by GYN.

DR. COHEN: It's a (inaudible).

DR. BERGFELD: As a pharmaceutical agent in GYN for a variety of vaginal infections, et cetera.

DR. COHEN: Yeah. There may be more data out there.

DR. BERGFELD: Yeah. Okay. So, we're reopening for concentration. Basically, ask for concentration, and studies and then European ban to describe that. Those two things, is that it?

DR. COHEN: Yeah. But we also have this injured skin and infant skin. It's an old conclusion.

DR. BERGFELD: So, clarify infant skin, okay.

DR. COHEN: Yeah. I don't know if --

DR. BERGFELD: Damaged skin.

DR. COHEN: Yeah.

DR. BERGFELD: Yep. Okay.

DR. COHEN: Okay.

DR. BERGFELD: I mean, at high doses it's extremely toxic. I've seen the results of it in patients. Vaginal mucosal becomes white, and sheds, exfoliates, painful.

DR. COHEN: It's like a chemical peel.

DR. BERGFELD: Yeah. That's it.

Full Panel – June 4, 2024

DR. COHEN: First published Boric Acid and Sodium Borate in 1983. The Panel concluded that in concentrations less than or equal to five percent are safe as cosmetic ingredients when used as currently recommended. However, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used in infant skin or injured skin.

The Panel re-reviewed this report in February 2003 and reaffirmed the original conclusion. There are a number of additional studies that were presented in this dossier. And I'll describe some of those a little bit later. This is in the European Union Annex II listed as substances prohibited in cosmetic products. The reported frequency and concentration of use has significantly decreased for both ingredients. In 2022 Boric Acid had no reported concentration of use, but the VCRP had Sodium Borate at 30 uses and Boric Acid at 8 uses.

So for the following reasons, one, new FDA data not in the original report on its uses and inactive ingredient under various conditions that would be cosmetic uses, Boric Acid on the EU Annex List II, new inhalational tox data, new ocular irritation data, and some case reports of serious illnesses and death, our motion is to reopen.

DR. BELSITO: Second.

DR. BERGFELD: Any discussion? Seeing none, I'll call the question. All those in favor raise your hand.

DR. BELSITO: Paul?

DR. SNYDER: I concur.

DR. BERGFELD: And moving on to the next ingredient, DR. BELSITO with Butoxyethanol.

SEPTEMBER 2025 PANEL MEETING – DRAFT AMENDED REPORT

Belsito Team – September 8, 2025

DR. BELSITO: Okay. So, we can begin Boric Acid and Sodium Borate. So, this is a Draft Amended Report on the safety of Sodium Borate and Boric Acid as used in cosmetics. We first reviewed this in 1983. And we concluded that Sodium Borate and Boric Acid in concentrations of less than five percent are safe as cosmetic ingredients when used as currently recommended.

Then we re-reviewed it in 2003 and reaffirmed the 1983 conclusion as published in -- 1983 wasn't published until 2006? No, that can't be right.

The data from the '83 report are summarized in this but not from the 2003 re-review. But that was just a couple of DART studies, which I think should easily be able to be brought in to this. I think they are important because DART will be our endpoint.

Anyway, it's been 15 years since the report was published, and so we're looking at this. And, In June of 2024, we looked at it and decided to reopen it to explore the reasoning why the ingredients were banned in the E.U.

According to the 2023 VCRP data, Sodium Borate was reported in 30 formulations, Boric Acid in 8. And in 2002, these were much increased, 280 and 77, respectively. 2024 RLD data, Boric Acid and Sodium Borate are in 40 and 144 formulations. Highest concentration of use in 2002 was two percent in conditioners for Boric Acid and three percent Sodium Borate in a paste mask.

And 2025 concentrations of use from the Council show that all of them are reported in rinse-off products with a maximum concentration of 0.00016 percent for Boric Acid in shampoo and bath soap and body waters, and for Sodium Borate 3.7 percent. So, really Sodium Borate is the endpoint here at 3.7.

So, the reason we reopened it was to try and understand the ban in Europe. And have we resolved that? Is it now considered category 1B there, Monice?

MS. FIUME: Temima, were you able to find any of that information this morning?

MS. NGUYEN: So, that's what I still see. I did find some other sources that I think are slightly more updated, but it's a little confusing, honestly. There was a lot of back and forth with, at least, the Annex 2 and Annex 3. But, at least for the 1B, that still seems consistent, at least on my end. But I can keep on looking into that.

DR. BELSITO: Well, if it's 1B, then it means it's banned. And, Allan, you said you found a report saying it was 1B. Allan, you're muted.

DR. RETTIE: Yeah. That wasn't me that found the 1B report.

DR. BELSITO: Oh, I thought, when we were discussing what I sent out--

DR. RETTIE: I didn't reply to that.

DR. BELSITO: Okay. Temima, where are you finding the 1B? Are you able to share that?

MS. NGUYEN: Yes. Let me share my screen. I can also share the link, too, just in case the font's a little --

DR. BELSITO: Okay.

MS. NGUYEN: Oh, wait, the chat turned off. Okay. I will just share my screen. Okay. Can you see my screen, or is it taking a little bit still?

DR. BELSITO: No. Yeah. There it is. You're just going to need to increase the size.

MS. NGUYEN: Okay. Yeah. That's a bit much. Sorry. Okay. Oh, my goodness. It's either going to be -- okay, here it is. So, this is the section that I was looking at.

DR. BELSITO: But that's Section 1A and 1B of Annex 3.

MS. NGUYEN: Right. How I interpreted this originally when I was doing the report, is that they were amending Annex 3. So, then they would put Boric Acid on Annex 2. So, that's how I interpreted this portion. And then, I did find -- I think you would still see my screen -- this, where they added Boric Acid to Annex 2.

DR. BELSITO: Yeah. So, Annex 2 is not necessarily a ban. There can be restrictions. And, if you could just increase the size of your screen.

MS. NGUYEN: Does that work?

DR. BELSITO: Yeah.

MS. NGUYEN: Okay.

DR. BELSITO: So, that's just the chemical names, and it doesn't go on. But, if it's Annex 2B, then that's the information I have. Right, Monice? It's listed in Annex 2B, and then it's given restrictions not to be used in children less than three and concentration limits for different product uses.

MS. FIUME: I think that's correct. I think where the confusion comes in, it's a CMR category 1B, which I think is different than the EC categories. Correct? Because the first Page that Temima was showing, that Section 18, says Boric Acid has been classified as a CMR substance of Category 1B.

DR. BELSITO: Right, but of Annex 3.

MS. FIUME: Right. And then says, should be deleted from the list of restricted substances on Annex 3 and be added to Annex 2.

DR. BELSITO: Right.

MS. FIUME: So, I think you're correct, Don. Right. That we just need to correct that with the limits and say that it's prohibited except for the conditions laid down.

DR. BELSITO: Right. Yeah. So, what it is, is that 1A and 1B indicates out of the class where it's coming in. So, 1B of the DART effects. I don't remember what 1A is, but then that caused them to move it down to Annex 2. And then, if they couldn't come up within a margin of exposure in Annex 2 which was safe, then it would move into Annex 1, which is a total ban in cosmetics, which it hasn't done.

So, they've just put restrictions like an age restriction and concentration restrictions. So, it's not completely banned, it's just, I guess you could say, banned in children less than three years of age and restricted in concentrations depending upon use for above three.

MS. FIUME: So, we will make that correction in the report before the next version is posted.

DR. BELSITO: Yeah. Yeah. And then, of course, we need to do our own margin of safety. I don't think we can rely on the EU's. So, in the introduction, we'll need to correct the third paragraph where it says that these were banned. I think it should say were restricted by the EU. You see where I'm at, Temima?

MS. NGUYEN: Let me make sure I'm going to the right section. I think there was confusion.

MS. FIUME: What page is it?

DR. BELSITO: PDF Page 14, the last sentence in the introduction.

MS. NGUYEN: The last sentence starting right before Chemistry?

DR. BELSITO: No, the third paragraph of the introduction on Page 14. So, the fourth paragraph above the Chemistry. It says, in accordance with its procedures, the Panel evaluates blah, blah, blah, blah.

MS. NGUYEN: Uh-huh.

DR. BELSITO: And to evaluate new data and explore the reason why these ingredients have been restricted in cosmetics by the EU.

MS. NGUYEN: Okay. Right. Okay. I will make that.

DR. BELSITO: And it should be in cosmetics because the restrictions don't necessarily apply to non-cosmetic uses.

MS. NGUYEN: I think, originally, I was confused because the link would always say a list of substances prohibited, and I guess I kind of interpret that as banned. But it's good to know that that doesn't mean banned.

DR. BELSITO: Yeah. It is very confusing because I went back and forth trying to find this as well.

MS. NGUYEN: Yeah.

DR. BELSITO: And then, in response to some of the comments from Women's Voices For The Earth, on PDF Page 15, we do mention that these are used in feminine washes and wipes. So, we don't ignore it. We just don't have a concentration of use, which I think, again, when we get to data needs, is going to be an issue because it is reported to be used. And that's the third paragraph in the Cosmetic Use section.

Yeah. So, as I mentioned, 1B is a reprotoxicant. I don't know what 1A is, but that's going to be, I think, our endpoint here. In PDF Page 16, the bottom of the page, it says eventually non-fatal doses will redistribute in the body to fatty organs, and the Boric Acid eliminates in the urine at around 75 to 100 percent of what was ingested. I didn't follow that. So, if it redistributes to fatty organs then eventually it gets out of the body from the fatty organs. Is that it?

MS. NGUYEN: I think that's how I interpreted this. This was from the previous report. And I believe I tried to make the statement a little more cohesive, but I was honestly a little confused too. So, I can look back at that one.

DR. BELSITO: Yeah.

DR. KLAASSEN: Yeah. I also had a problem with that. And I kind of wondered if this was more of a hypothesis than data. It didn't even make sense to me that this compound would kind of concentrate in fatty tissues. That whole business there is -- yes. If you can, look into that in more detail.

DR. SNYDER: It was referenced in Reference 2. It says about being eliminated in urine. So, it should be available.

DR. RETTIE: Yeah. Volatile anesthetics that redistribute into fatty tissues, eliminated in the urine. So, I don't know that there's a disconnect there.

MS. FIUME: I wonder if it's terminology because it's from the original report, and it was a 1950 reference.

DR. BELSITO: And how is it stated in the original report, Monice?

MS. FIUME: Exactly as summarized, that it's redistributed.

DR. BELSITO: Exactly as it's written?

MS. FIUME: Yes.

DR. BELSITO: So, maybe if it says, redistributed in the body to fatty organs and then eliminated in the urine at around 75 to 100 percent of what was ingested, would that make more sense? So, there's a high amount of Boric Acid in the sciatic nerve and spinal cord area. Eventually, non-fatal doses will redistribute in the body to the fatty organs and then be eliminated in the urine at around 75 to 100 percent of what was ingested. Would that make more sense?

“There’s a high amount of Boric Acid in the sciatic nerve and spinal cord observed. Eventually, non-fatal doses will redistribute in the body to the fatty

organs and then be eliminated in the urine at around 75-100 percent of what was ingested."

DR. KLAASSEN: See, I don't even think it would be distributed to fatty tissues.

DR. RETTIE: I agree with Curt. It's highly water soluble.

DR. BELSITO: Well, I have that issue too, but that 1950 report says it does, right, Monice? Is that what you're saying?

MS. FIUME: So, because I can't compare back and forth, I'll read what's in the original report.

DR. BELSITO: Okay.

MS. FIUME: And you can tell me if it's what's stated. It says, "Non-fatal doses are redistributed over time to the fatty organs of the body. Boric Acid is eliminated slowly in the urine over a period of days, totaling 75 to 100 percent of the ingested dose."

DR. KLAASSEN: But is this from the original manuscript?

MS. FIUME: From the original CIR report.

DR. KLAASSEN: Okay. Can we go back to the real reference?

MS. FIUME: I'll try and find it. It's a 1950 Citation, so sometimes those become a little challenging to find, but we will look.

DR. KLAASSEN: Yeah.

DR. BELSITO: What is the Citation?

MS. FIUME: So, it's Bulletin NASH. I don't know what the abbreviations, Natl Form Comm. So, Bulletin National Formulation Communications, maybe something? I don't know what the abbreviation stands for. Let me see if I Google it.

DR. RETTIE: Is that Reference 2, Monice?

MS. FIUME: So, Reference 2 is the original CIR report because that's what we cite when we're doing the old data.

DR. RETTIE: So, there's no Citation for what we're discussing right now, then, included at the moment?

DR. BELSITO: They're reading it.

MS. FIUME: So, it is a 1950 Citation.

DR. BELSITO: It's 1950. Are there authors?

MS. FIUME: Pfeiffer, P-F-E-I-F-F-E-R, one author. It's in the Bulletin of the National Formulary Committee.

DR. BELSITO: It's not even in Columbia Library, at least The Journal. Let me see if there's anything on PubMed, but I doubt it. Doesn't sound like it's. So, it's P-F-E-I-F-F-E-R?

MS. FIUME: Yes. So, that's the only author listed in the CIR report. But, when I Googled the title it was Pfeiffer and Jenney, J-E-N-N-E-Y.

DR. BELSITO: So, P-F-E-I-F-F-E-R and Jenney, J-E-N-N-E-Y?

MS. FIUME: Yeah, P-F-E-I-F-F-E-R. Yeah. And Jenney, J-E-N-N-E-Y, 1950.

DR. BELSITO: Wrote a lot of papers.

MS. FIUME: And the paper was 23 pages long.

DR. BELSITO: And what was the title?

MS. FIUME: The Pharmacology of Boric Acid and Boron Compounds.

DR. BELSITO: Okay. So, it is Boric Acid. No, it's not listed in PubMed. Not surprising given The Journal. So, good luck because you'd have to go through --

I mean, The Journal is not in the Columbia Library. They're pretty exhaustive.

MS. FIUME: Yeah. I don't know how.

DR. BELSITO: National Library of Science?

MS. FIUME: We can check there.

DR. KLAASSEN: Or you can send a memo to PubMed and see if they have it someplace.

DR. KLAASSEN: We're not going to get it today.

DR. BELSITO: No. No, it's something to look into because we have our doubts that it redistributes to fat. But we'd like to see the primary reference.

DR. KLAASSEN: Right.

MS. NGUYEN: We'll try our best to find it.

DR. BELSITO: Okay. And then, the first paragraph on Sodium Borate and then on PDF Page 17, again, I was a little bit confused. It says that the excretion and Boron dose relationship had a regression coefficient of 0.954, suggesting that it was linear, suggesting 100 percent bioavailability. So, I get the linear regression coefficient of 0.954. What does suggesting 100 percent

bioavailability have to do with the linear excretion of this material?

MS. NGUYEN: Let me try to pull up the source again.

DR. KLAASSEN: It really doesn't. What that really means is that this is first order kinetics, but it doesn't mean that it is 100 percent. Whatever percent it is, it's consistent with the doses. So, it's a first order process.

DR. BELSITO: Go ahead, Allan.

DR. RETTIE: While we're on this section, I was a bit confused about the dermal absorption verbiage that's just above what we're looking at. The ADME data that's described, most of it really quite old, seems to contradict itself as the absorptions described variously as ready absorption to no absorption, which is a wide span.

So, I just wondered if there's something in there that's maybe miscommunicated that would help us harmonize the absorption information because in human, at least the human data that I could see that I thought was maybe a little more up to date, the absorption is described as minimal to none for humans.

DR. BELSITO: That paragraph, Allan, is intact and abraded skin was minimal and insignificant.

DR. RETTIE: Yeah.

DR. BELSITO: Significant absorption was through burnt skin or severely denuded skin. So, basically, you're putting the compound into the dermis in the lower layers and directly onto the vasculature. So, you don't have a barrier. You don't have a stratum corneum barrier. You don't have an epidermis.

DR. RETTIE: So, this was in so that you could make a distinction? This was put in or left in so you could make a distinction about healthy versus non-healthy skin in the old report?

DR. BELSITO: Right.

DR. RETTIE: Got it.

DR. BELSITO: And you see some of that come up later in case reports of toxicity being put on burn patients where they had issues.

DR. RETTIE: But, all the way up at the top, in the first paragraph under dermal absorption, animal patches, 8 percent Sodium Borate, and various solvents, aqueous, urine, talc, were applied in rabbits for eight hours. And it was readily absorbed by the intact skin of the rabbits.

DR. BELSITO: Where are you?

DR. RETTIE: I'm on PDF 16, the first paragraph under toxicokinetic studies taken from the old report. It ends with Sodium Borate was readily absorbed by the intact skin of the rabbits.

DR. KLAASSEN: Here under ADME, animal dermal?

DR. BELSITO: No, under toxicokinetic dermal.

DR. RETTIE: Under toxicokinetic studies, PDF 16, halfway down the page, a little more than half.

DR. BELSITO: So, 5 percent Boric Acid in water was most readily absorbed through the intact skin, followed by 5 percent Boric Acid and pH9 buffer.

DR. RETTIE: Yeah. That's where I'm at.

DR. BELSITO: The 5 percent Boric Acid and talc mixture was not easily absorbed. The same study was completed using 8 percent Sodium Borate occlusive patches. Well, pH9 is not the pH of the skin. That's going to be irritant. And I don't know what it's going to do to the skin, but it's going to cause some degree of burn, whether first or second.

DR. RETTIE: Okay. So, that 9 in parenthesis is the pH rather than the reference, I guess. Yes. I didn't read that.

DR. BELSITO: I presume it’s pH (audio skip) because the reference is two.

DR. RETTIE: Got it. So, pH9 would mimic the burn situation you see, and I get that.

DR. BELSITO: It would mimic damaged skin. I don't know how much it would burn the skin, but it would be pretty significant. But I don't understand the talc and water.

DR. RETTIE: That's okay. That kind of harmonizes it for me, now that I understand what's being said.

DR. BELSITO: Okay. So, to go back to my point about the excretion and Boron dose relationship, at a regression coefficient suggestion that was linear

suggesting a hundred percent bioavailability, how do we wordsmith this, Curt? You were saying that it's --

DR. KLAASSEN: Okay. Where do you see that, Don?

DR. BELSITO: On PDF Page 17.

DR. KLAASSEN: Okay.

DR. SNYDER: Where you were stating it was first order kinetics is all that was.

DR. BELSITO: Right.

DR. KLAASSEN: This is human dermal. Which line?

DR. BELSITO: No, it's Wistar rat and Sodium Borate. It's the first paragraph on PDF 17.

DR. KLAASSEN: Oh, okay.

DR. BELSITO: I just said it, regression coefficient.

DR. KLAASSEN: I think that's just wrong. You know, someone doesn't know his pharmacokinetics.

DR. BELSITO: So, what would you say? Had a regression coefficient of 0.954 suggesting first order kinetic elimination?

DR. KLAASSEN: Yeah. Yep. Let's say, at the lowest dose, you get 5 percent excreted. And, at the next dose, you get 5 percent excreted, and a higher dose, 5 percent excreted, that's going to give you a linear. But it was 5 percent, not 100 percent. So, if we can change it to that, that's what it should be. That's first order kinetics.

DR. BELSITO: Okay. You got that, Temima?

MS. NGUYEN: Yes. Yeah, I made a note. Thank you for letting me know on that one. It was an ECHA study, so I don't know if they missed out on anything, but I appreciate the catch.

DR. BELSITO: So, again, just for consideration for Discussion, what we're seeing is that on damaged skin there can be issues with absorption. And right below that, for human dermal it said, for infants that had mild to moderate diaper rash, Boric Acid was present the urine for at least 48 hours, suggesting increased absorption on infants.

So, that will be an issue that we might want to say, as we did -- what was it initially? Was it PEGs, not to be used on damaged skin?

DR. SNYDER: I believe you're correct, Don.

DR. BELSITO: Yeah. So, we might want to say something about damaged skin here in the Discussion, and also with the dermal absorption and pH9, through abraded skin as well or through burnt skin, and potentially denuded skin.

DR. RETTIE: So, I'd like to go back to that first paragraph on PDF 16 where we were talking about the different pHs.

DR. BELSITO: Yeah.

DR. RETTIE: I just think that doesn't read very well. And that the final sentence from the old report, “was readily absorbed by the intact skin of the rabbits,” is misleading unless we kind of clarify what goes before. As I'm reading it, different mediums, aqueous, pH control, urine, probably about pH6 where talc comes in, or pH9.

It seems to me the aqueous or even the urine medium for 8 percent Borate should not provide ready absorption from intact skin. I'm just confused by the way it's written.

DR. KLAASSEN: I guess I don't have a problem how it's written, I have a problem with the data. I can't believe that in intact skin, in a rabbit, this is going to be readily absorbed. Now, what the word readily is, I don't know. But, in my mind, readily means over 50 percent.

DR. RETTIE: Yes.

DR. KLAASSEN: And I would guess it's more like 5 percent. So, that whole paragraph, I have questions with the data.

DR. BELSITO: Yeah. You could also look at readily as time, right? It might be 5 percent, but it occurs quickly. But, first of all, that study is with occlusion, right?

DR. RETTIE: Yes.

DR. BELSITO: And occluded urine we know is an irritant. That's the whole cause for diaper rash.

DR. RETTIE: But just aqueous, occluded aqueous, and the absorption seems a little lot to me.

DR. BELSITO: No. But it's hard for me to interpret an absorption study that's done under occlusion because that's not the way a cosmetic is applied.

MS. FIUME: So, again, it's written as was in the original report. The original Citation was a 1958 Citation, so we can see if we can obtain that.

I think, to give some clarity as to why you're seeing it in talc and maybe also why it was under occlusion, is because in looking, I think in the Use section of the original report, it states that Boric Acid in baby powders acts to buffer talc, which is irritating to skin because of its alkalinity by forming neutral calcium Borate. So, I have a feeling that's why it was tested with talc and probably why it was tested under occlusion.

DR. BELSITO: Good point, Monice.

DR. RETTIE: Yeah.

MS. FIUME: But, again, we can try and obtain that Citation to see if there's any additional information in it that would be useful for the Panel.

DR. BELSITO: Yeah.

MS. NGUYEN: I'll try to look for that.

MS. FIUME: No luck Tamima?

MS. NGUYEN: For the specific Citation?

MS. FIUME: Oh, I thought you said you tried to look for it -- sorry -- not I will look for it.

MS. NGUYEN: Oh, no. I'm just making a note that I'm going to try to look for it. Because I know that sometimes even when I was writing the report, if I didn't understand something, I would look and I couldn't find it. So, I'll look again.

MS. FIUME: Thank you.

DR. BELSITO: Under short-term toxicity, Tamima, this is PDF 17, as well, the last paragraph; it says, in a four-day study and rabbits were dosed, it should be in rabbits that were dosed.

MS. NGUYEN: Okay.

DR. BELSITO: And then, on PDF 18, the third paragraph which starts with a five-day toxicity study was completed in mice, it says that the lowest observed adverse effect were both calculated to be less than 800 milligrams per kilogram. What was the endpoint for that LOAEL based on?

MS. NGUYEN: Let's see. It's the sentence -- I just want to make sure. It starts with the NOAEL and the lowest observed?

DR. BELSITO: Right. “Were both calculated to be less than 800 milligrams per kilogram.”

MS. NGUYEN: Let me see. Do you mind if I look at this later, only because I have a lot of tabs up, and I think my computer's slowing down.

DR. BELSITO: Yeah. Not a problem.

MS. NGUYEN: Okay.

DR. BELSITO: So, I think, if we're doing a margin of exposure on these, probably the NOAEL we would look at comes from the chronic tox study, a two-year study. Would people agree? Rats in the groups, fed 117 and 350 parts per million of Boron, exhibited normal behavior and no histopathological abnormalities? Just something to think about if we're looking for endpoints to base a margin of exposure on.

DR. KLAASSEN: Yes. I think that's reasonable.

DR. SNYDER: Yeah. I agree. That would be the best study.

DR. BELSITO: And, just to point out that we do, again, on Page 118, we have a chronic inhalation study, so we just may want to pay attention to our respiratory boilerplate. In this case, I don't think it changes anything because, basically, there were no tracheobronchial effects like there were with -- I forget which ingredient that caused irritation. And our respiratory boilerplate didn't really address that.

MS. FIUME: Don, to go back to your question about that 800 milligrams; the study doesn't give the critical endpoints, it just states the less than 800.

DR. BELSITO: Okay. So, maybe a parentheses to say endpoints not given?

DR. SNYDER: Endpoints not provided or not, yeah, stated.

MS. NGUYEN: Okay, I can add that. Thanks for finding that, Monice.

DR. BELSITO: Then PDF Page 19, the second line, it says male and female rats with five in sex. I assume that means five of each sex.

MS. NGUYEN: Yes. Yeah, that was a typo.

DR. BELSITO: And then, PDF, again, Page 19, ten lines, it says that serum levels were assessed, the reproductive effects, blah, blah, blah. Serum levels of what? Were they serum levels of Boron, I presume?

MS. NGUYEN: That's what I believe. I can double check in the original report since this is from there.

DR. BELSITO: And then, the immunotoxicity, this is PDF 22. It just says Boric Acid was not immunotoxic. Do we know what the endpoints were? What they looked for to determine it wasn't immunotoxic?

MS. NGUYEN: I will take a look. That might be also another study that I'm not sure if they included that. So, I will take a look for that one.

DR. BELSITO: And then, in our Discussion, when we get to it, clearly these can be irritating. So, caution should be, formally, to not be irritating, and then caution about use in products for damaged skin in the Discussion.

In that same one in the dermal irritation, fifth line down, this is looking at Boric Acid. There was no irritation at the two lowest pH levels, moderate to slight

at the next to highest, and marked irritation at the highest pH.

And the pHs were ranging from 3.81 to 8.16. Sort of like, if you have Boric Acid, as you go up on the pH, it should be converted more to like a Borate, right? Wouldn't it be less irritating and maybe more irritating at the lower pH levels? It just seemed counterintuitive to me. If you're saying something, Allan, you're muted.

DR. RETTIE: I was wondering if we had a PKA listed for Boric Acid. It might help there. Doesn't look like we do.

MS. NGUYEN: For Boric Acid, there is one on the table, Table 1, 9.24.

DR. RETTIE: 9.24, yeah. That's the one I just found.

MS. NGUYEN: Yeah.

DR. RETTIE: Yeah.

DR. BELSITO: So, you think this irritation would be correct, Allan?

DR. KLAASSEN: Well, I guess my question, Don, is do you think irritation is correlated with lipid solubility or not? I guess I've never thought about this before.

DR. BELSITO: I mean, one of the things is that irritant are materials that can defat the skin. I mean, soap and water is the most common cause of chronic cumulative irritation.

DR. KLAASSEN: Okay.

DR. SNYDER: But we're dealing with that by saying, when formulated to be non-irritating.

DR. BELSITO: Right. I'm just wondering about the statement. I don't have any issue with the fact that these are going to be irritant or potentially irritant. It's just that when I read it, it seemed counterintuitive to me that if you take Boric Acid at the lowest pH levels, where it's going to be Boric Acid, it's less irritating than as you go up the pH. But I'm not a chemist, so I don't know.

DR. RETTIE: Well, all I say about that is, of course, at higher pH we have more of it deprotonated. So, the acid form would be less. Does that coincide with what

you think, Don, with regard to irritation due to the acid itself?

DR. BELSITO: Yeah. That's what I assumed, but it's just my assumption. But, if that's what they reported, that's what they reported. I would just check to make sure that we have that correct. In the end, I think we still need to say non-irritating in our Conclusion.

DR. KLAASSEN: Right. That's probably all that's necessary.

MS. FIUME: So, in the original report, the Boric Acid was adjusted with various other compounds, such as ammonium carbonate or sodium hydroxide?

DR. BELSITO: Yeah. So, it was adjusted before it was tested at those pHs. Or the adjustments caused the pH shifts.

MS. FIUME: So, it appears it was adjusted ahead of time. It's difficult. The results just say at pH of 7.38 and 6.86, adjusted with ammonium carbonate. So, it sounds like it may have been adjusted before it was applied.

DR. RETTIE: Yes.

MS. FIUME: Again, a 1953 Citation, so might be difficult to obtain the original.

DR. BELSITO: Just read that sentence again, Monice.

MS. FIUME: Okay. So, I'll read the whole sentence. It says, "5 percent aqueous solutions of Boric Acid at different pHs had the following effects when applied to the backs of rabbits; at a pH of 3.81 unadjusted, no irritation; at pHs of 7.38 and 6.86, adjusted with ammonium carbonate, moderate and slight irritation, respectively; at pH of 7.87, adjusted with sodium hydroxide, slight irritation."

DR. BELSITO: So, the pHs were caused by the adjustment with the ammonium carbonate and the sodium hydroxide, is how I'm understanding it.

MS. FIUME: It says 5 percent aqueous solutions of Boric Acid at different pHs.

DR. BELSITO: Right. So, the 5 percent aqueous Boric Acid was then buffered up to whatever with ammonium carbonate. And then, in the next study, buffered up to

whatever with sodium hydroxide. And the last study was buffered up to what with what?

MS. FIUME: So, 7.87 was buffered up with sodium hydroxide, 8.16 pH was adjusted with ammonium carbonate and an ammonia solution.

DR. BELSITO: Yeah.

MS. FIUME: And that caused the marked irritation.

DR. BELSITO: Right. So, the starting material was five percent benzoic acid and water. And then the pHs were adjusted with those compounds, is what I'm understanding. I mean, that's what they got. That's the report. Didn't make sense to me, but that's what they found, so I'm not going to argue with it.

The third paragraph down, with a sensitization potential, a cream of 1.1 percent of Sodium Borate was tested in prophetic patch testing in 198 subjects. Cleansing cream with 1 percent Sodium Borate was non-irritating. Yeah.

So, the third sentence, this is a cleansing cream containing 1.7 percent Sodium Borate, was non-irritating and non-sensitizing when applied undiluted in open an closed patch test and two Schwartz prophetic patch tests in separate trials. Do we know what the number of volunteers were in those trials?

MS. NGUYEN: Since this was from the original report, the only number that's listed for this one is the 198 subjects.

DR. BELSITO: Okay. So, we don't know the subjects in the second?

MS. NGUYEN: Let's see. No, it doesn't clarify. I mean, it does say one subject experienced minimal irritation to the induction patch, but it doesn't outright say how many volunteers were in the original.

DR. BELSITO: No. The one subject with the irritation was a 1.1 percent Borate and prophetic patching. And then, the sentence after that is a different study; it's a cleansing cream with 1.7 percent Sodium Borate.

MS. NGUYEN: Oh, sorry.

DR. BELSITO: Non-irritating and non-sensitizing when applied to open and closed, and two Schwartz prophetic patch tests performed in separate trials. It doesn't say the number.

MS. NGUYEN: For this one, 147. So, I can include that?

DR. BELSITO: Yeah.

MS. NGUYEN: Okay.

DR. BELSITO: And then, in the paragraph below this -- and it may simply have been poor use of language, the paragraph that starts with, "to determine sensitization potential, a cream containing 1.1 percent Sodium Borate." The third line up in that paragraph.

So, this is an HRIPT. It says, "no significant irritation was observed at sites tested with a cleansing cream only." Really, an HRIPT, you'd see sensitization -- irritation, but the goal of those studies is really sensitization.

So, I just wonder if we were using irritation and sensitization interchangeably, which is incorrect. So, it would be really, "no significant irritation or sensitization was observed." But I don't know what the original report said, and whether we're allowed to change the language.

MS. FIUME: Don, I'm sorry. I not finding -- I missed where that sentence was because I have a feeling this is something I may have questioned as well, when I originally reviewed it.

DR. BELSITO: So, this is PDF Page 22, third paragraph from the bottom that starts with, to determine sensitization potential, a cream containing 1.1 percent Sodium Borate. Are you on that paragraph?

MS. FIUME: Yes.

DR. BELSITO: Okay. If you go to the bottom of that paragraph, the third sentence up. So, this was an HRIPT with 48-hour occlusions every other day for 10 and then a challenge patch. It just says, no significant irritation was observed at sites tested with a cleansing cream only. Then, an HRIPT is looking at sensitization.

I mean, irritation would be observed as well. But the real endpoint of that study is sensitization. So, I'm just wondering if we misused the term irritation.

MS. FIUME: So, in the original CIR report, it does say no significant irritation was observed at sites with the cleansing cream alone. The product containing 1.7

percent Sodium Borate was non-irritating and non-sensitizing.

DR. BELSITO: Okay. We should include, then, no significant irritation or sensitization was observed, right?

MS. FIUME: Yes.

DR. BELSITO: So, after all of that, when we got to the Discussion, I said formulate to be non-irritating, caution in products that may be applied to damaged skin, and insufficient for concentration of use in feminine hygiene products and intimate wipes. And then, we need to calculate a margin of exposure for the -- either we can use chronic oral or for DART effects, which are really, I guess, what we're concerned about.

And I don't remember what the NOAEL was for the DART. Paul, do you know the NOAEL for the DART?

DR. SNYDER: No, I don't see that, Don.

DR. BELSITO: It's certainly, interestingly higher.

DR. RETTIE: Is that the NTP study, 1991?

DR. BELSITO: The chronic oral. Which one are you talking about?

DR. RETTIE: I'm just looking at my notes here, which are now full. Just provides a NOAEL of 110 milligrams per kilogram per day, but I don't have the details there.

DR. BELSITO: Yeah. I think that's the chronic oral. Right? No, chronic oral was 350 parts per million of Boron.

DR. SNYDER: The NOAELS for the development are on Table 5. Look at Table 5.

MS. FIUME: PDF Page 34.

DR. SNYDER: Yeah.

DR. BELSITO: Oh, yeah. 21.8 milligrams per kilogram body weight. That's the problem when the tables are separated. My notes appear after the document.

MS. FIUME: I know. We tried incorporating them in text, it didn't flow very well. As we made edits, it would mess up where the tables were.

DR. BELSITO: Right.

DR. SNYDER: I certainly like looking at the tables because it's very easy to go there, and it's right to what you want to know.

MS. FIUME: Yeah.

DR. BELSITO: Right. Okay. Since we're on tables, under Inhalation, PDF Page -- I guess it's, 32, for the Boric Acid. The 90-day inhalation in rats, it says that hepatic enzymes leakage and serum renal damage product levels. What are serum renal damage products?

MS. NGUYEN: I think for this one --

DR. KLAASSEN: It's often creatinine.

DR. BELSITO: Well, I assume BUN and creatinine.

DR. KLAASSEN: Yeah.

DR. BELSITO: Does it say in the report?

MS. NGUYEN: I'm going to take a look. Might have to make a note on this. Sorry, my computer is acting so slow.

DR. BELSITO: No. That's okay.

MS. FIUME: I think I may have found it. I believe you said for the renal tissues.

MS. NGUYEN: Yes. And I believe it's the report named Toll-like receptors by Abd-Elhakim.

DR. KLAASSEN: Abd-Elhakim.

MS. NGUYEN: Yeah.

MS. FIUME: So, for the renal tissues, malondialdehyde, superoxide dismutase and catalase, and reduced glutathione, is what they were looking at.

DR. BELSITO: Okay. Well, I think it's important to include that because most people would assume it's BUN and creatinine, like Curt and I did.

DR. SNYDER: Yeah. So, those are for renal damage, not for functional, right?

DR. BELSITO: Right.

MS. FIUME: So, yes. But they did look at creatinine in uric acid, AST, ALT, and ALP as well.

DR. BELSITO: Well, AST and ALP would be liver.

MS. FIUME: Oh, sorry. Yes, but we will clarify -- we will make sure that we spell out exactly what was looked at and affected.

DR. BELSITO: Great. And then, on PDF Page 33, this is on developmental and repro effects under Animal

Oral. The last study on that page, Swiss mice, number not specified it says, “reproductive assessment by continuous breeding protocol. Test substance is administered in the diet for 22 weeks before mating and continues the birth of the two generations.” Something's missing there; “And continued through the birth of two generations?”

DR. SNYDER: Yeah. I would think it was a two-generation study, Don. You're right. So, it'd be through the two generations. Yeah. It was a two-generation study. Yeah.

DR. BELSITO: And continued through? How would you wordsmith that? And continue through the birth of two generations?

DR. SNYDER: Yeah. That's the way I would read it. Yeah. Continued for 27 weeks and through the two generation.

DR. BELSITO: And through two generations. Okay. Yeah. And then, I highlighted that NOAEL of 21.8 milligrams Boron per kilograms of body weight as the NOAEL for the DART. That's what we previously discussed on Page 34 of the PDF.

DR. SNYDER: Well, I think we've given her quite a laundry list of things to clarify and to add. So, I think it's pretty thorough.

DR. BELSITO: Just a few more, Paul. On PDF Page 38, the dermal irritation and sensitization studies, where you say Boric Acid physiological saline and that it's given at 0.5 grams in the first and third study listed, do we know what that concentration translated to?

MS. NGUYEN: I can double check on that one. This thing is taking so long.

DR. BELSITO: It's not applied as solid substance since it's dissolved in saline, right?

MS. NGUYEN: Right. And then, once I find the concentration, should I just add that in there?

DR. BELSITO: Yeah. I mean concentrations, I think, are more important to us than total amount of the material. But there are four studies there. The New Zealand white rabbit was the first one. The mesh, I don't know how to interpret, and then the New Zealand white Rabbit, again, at 0.5 grams in saline.

And then, under sensitization, you have Boric Acid and Sodium Borate in distilled water at 0.4 grams. But we don't know the concentration of those either. So, that would be nice to know as we look at this data.

MS. NGUYEN: Okay. I'll look for that because I believe those are ECHA studies, so it's going to be a little more harder to find.

DR. BELSITO: Right. Okay. Those were all my comments. In the end, I think we can probably -- and, again, I think the big issue is finding the concentrations in feminine care products and intimate wipes so we can do a margin of exposure based upon the DART NOAEL of 21.8. But Curt, Paul, Allan, what do you think?

DR. KLAASSEN: I think the margin of exposure might be limited by trying to figure out absorption or how much of this stuff is really absorbed. We don't have good data on that, I don't believe.

We need to know the systemic dose in humans, and we usually get that from absorption. I don't know, it seems to me we don't have that. So, I'm not convinced we can get margin of exposure.

DR. BELSITO: Well, we have a human in vitro dermal.

DR. KLAASSEN: Okay. Maybe we can if we really have that.

DR. BELSITO: I think we do.

DR. KLAASSEN: I think the main thing we had is that it's absorbed better when we have abraded skin.

DR. BELSITO: Yeah.

DR. KLAASSEN: But I didn't see it, but wouldn't be the first time I missed something.

DR. RETTIE: Yeah. So, as I said earlier, human minimal to none and also low dermal absorption in the earlier report, no figures -- no numbers.

MS. NGUYEN: I see Jinqiu has his hand up. He may be able to weigh in on this.

DR. RETTIE: Sure, please.

DR. BELSITO: Jinqiu?

DR. ZHU: Yeah. So, for the margin of safety calculation, we have the exposure type for mucous membrane. So, for mucous membrane exposure, the absorption rate, I

mean, what value the Panel wants us to use for the worst case scenario, 100 percent?

DR. KLAASSEN: I don't like the idea of using 100 percent.

DR. ZHU: Because it may be used in the vaginal -- cause the vaginal exposure, like an incubator.

DR. BELSITO: Yeah. Jinqiu is right, you know, Curt. If we're looking at absorption, we really want to know mucosal, not dermal.

DR. ZHU: Because it may be used in intimate wipes. So, we have -- you know, I found an exposure amount from a (inaudible) paper for the intimate wipes. But we need to assume the surface area for the intimate wipe use because there is no such information in the literature. And also, we need to assume the absorption rate for mucous membrane exposure.

DR. KLAASSEN: And we don't have that data, correct?

DR. ZHU: No. Worst case scenario is 100 percent for mucus membrane. That's basically as considered in the literature.

DR. KLAASSEN: But do you have surface area?

DR. ZHU: No, actually. But we may search on the website, like the sanitary pad. We may have the size -- the actual size, I mean, for those products. We may use that, the size data, to roughly estimate the surface area, if that works.

DR. BELSITO: I mean, the only mucous membrane study we have, a 14-day study, 40 women, vulvovaginal candidiasis, 5 percent Boric Acid and lanolin to areas with irritation in their vulvar area, and inserted 600 milligrams of Boric Acid two times a day vaginally. And, at the end of the study they didn't detect Boric Acid in their blood.

DR. RETTIE: Yep.

DR. BELSITO: But, of course, that makes little sense to me, given the dermal absorption that we see. One would have expected you would see something, right?

DR. RETTIE: Something.

DR. BELSITO: I mean, if you were to use oral as a surrogate for mucosal, basically it looks like 75 to 100 percent of what was ingested was eliminated in feces -- in

urine, rather. So, if we were to use that as default, Curt, would you be happy with that? But that gets you in high numbers.

DR. KLAASSEN: If it was up to me, I wouldn't try to calculate this. Yeah. We don't have to have -- I don't think we need to have a margin of exposure for every chemical that we do, and where there are so many unknowns here.

DR. BELSITO: But I think in this case we do since the EU has moved it to Category 2 -- or Annex 2, rather.

DR. KLAASSEN: But they did it not because of margin of exposure.

DR. BELSITO: Well, they did. They moved it to Annex 2 because of the reprotox.

DR. KLAASSEN: Right.

DR. BELSITO: And then, they allowed it in cosmetic products at varying concentrations, based upon their margin of exposure calculations.

DR. KLAASSEN: What did they come up with with margin of exposure?

DR. BELSITO: That's what I'm looking at now.

DR. KLAASSEN: I tried to find that, but I couldn't get it to click on for me.

DR. BELSITO: You're right, I'm not seeing --

DR. ZHU: It's PDF Page 23, SCCS opinion. But it's based on the Borate -- the (inaudible), not to the Boric Acid, but to -- you may do the conversion.

MS. FIUME: Right.

DR. ZHU: And yeah, they have that margin of safety value is 480.

DR. KLAASSEN: Well, so why don't we have this in our report? I mean, what they calculated? That's legal, isn't it, to give their number in our report?

DR. ZHU: So, we can calculate our own margin of safety -- our margin of exposure value, based on we have --

DR. KLAASSEN: I know we can. But my question is, if they have reported a margin of exposure, why don't we have that in our document? Is there a reason why we don't? Monice, are you around?

MS. FIUME: I am. I'm trying to see, Jinqiu, what PDF Page is that on?

DR. BELSITO: The FCC opinion that I had sent out on Boron compounds, PDF 23.

DR. KLAASSEN: Oh yes.

DR. BELSITO: But they have daily use in finished products, retention factors, Boric Acid percentages, Boron percentages, daily exposure calculated as Boron per milligram -- so they're assuming --

DR. ZHU: So, I'm working with Dr. Ross on calculating the margin of safety focused on the vaginal exposure, because we have the mucus membrane maximum exposure concentration is very, very low; it's about 0.00016 percent.

DR. BELSITO: It doesn't exactly give the number they used. It says, “the calculation for margin of safety given above is based on dermal absorption of healthy skin.” Then they point out that it may be higher in damaged skin. But it seems like it's relatively low because they're saying daily use of finished products powder is 18 grams, and the daily exposure in milligrams is 15.8.

So, the daily exposure is significantly lower than the daily use by a factor of 100, or a thousand grams to milligrams. At least that's how I'm reading it if you look at that table. It's in the page before – “dermal absorption of 0.5 percent has been used for calculations of systemic exposure.” So, they use 0.5 percent, Curt.

DR. KLAASSEN: Okay.

DR. BELSITO: But that's dermal. Mucosal will likely be higher.

DR. KLAASSEN: Right. But the surface area and the dose would be much less.

DR. BELSITO: Yeah.

DR. KLAASSEN: Well, if somebody wants to calculate this, we can calculate it. But we do need to know the concentration that's in these wipes. I don't know if we have that.

DR. BELSITO: No, we don't. And that was one of my insufficiencies.

DR. KLAASSEN: Right. And then, I don't know what data is available for surface area that one is going to use. So, those are a couple of reasons why I just thought about leaving it out. But if somebody wants to calculate it, go ahead.

DR. BELSITO: I'm not sure, again, that we can leave it out.

DR. KLAASSEN: Well, first of all we need to get those two pieces of data.

DR. BELSITO: Yeah. Concentration in feminine hygiene and intimate wipe products. And some idea, I guess, of systemic absorption from mucosal application, or how we want to deal with that, at least the 100 percent. I think we can --

DR. KLAASSEN: And the surface area.

DR. BELSITO: And surface area, discuss that with David Ross and the other team tomorrow.

DR. KLAASSEN: Right.

DR. BELSITO: This is really the first time that we're looking at this. So, just to go back to our comments from Women's Voice For The Earth, I think we've addressed most of them. We have accepted that it's in intimate wipes and feminine hygiene products, we're looking to concentration of use. We're going to be dealing with the repro and DART effects by our margin of exposure. And we've opened the review. I don't see anything else that they had raised in Wave 2 that we haven't addressed. So,

I think that's where we're at. Jinqiu and Tamima, we need concentration of use, and then we need to do a margin of exposure. But we need to determine mucosal absorption, surface area and how we're going to deal with that.

MS. NGUYEN: Okay. Sounds good.

DR. BELSITO: Anything else? Okay. If not, are we ready to move on?

MS. FIUME: I'm sorry.

DR. RETTIE: Monice, has her hand up.

MS. FIUME: Yeah. I muted myself. To clarify right now for the IDA, is mucosal absorption an IDA request or something the staff should be finding?

DR. BELSITO: I would make it a request. But, I mean, it doesn't hurt, we're going insufficient, right?

MS. FIUME: Yeah.

DR. BELSITO: So, yeah, absorption, some idea of the area of application to a feminine hygiene product -- well, I mean, they're used as a -- Summer's Eve is going to be a vaginal douche. So, that's going to be the entire

vaginal mucosa. So, we need some idea -- I mean, I'm sure that can be found -- of the surface area, an average vagina and labia. So, yeah, we would need that information to calculate our margin of exposure.

DR. RETTIE: So, going back to our report with regard to mucous membrane absorption, PDF 17, we've got those statements from the old report that there was no Boric Acid detected in the blood. Do we just leave that in there?

DR. BELSITO: I mean, it's there, so we can't remove it if that's in fact correct. But I find it hard to believe that there was no absorption through mucosa and there's absorption through the skin.

DR. RETTIE: So, that's what the request for extra information hopefully clarifies?

DR. BELSITO: Right.

DR. RETTIE: Okay.

DR. BELSITO: Paul, Curt, anything else before we move on to Fossil Waxes?

DR. SNYDER: Nothing for me. That was very thorough. Thank you.

Cohen Team – September 8, 2025

DR. DAVID COHEN: All right. This is a Draft Amended Report on the safety assessment of Sodium Borate and Boric Acid. We first published a review on the safety of Sodium Borate and Boric Acid in 1983. The Panel concluded that Sodium Borate and Boric Acid in concentrations less than or equal to 5 percent are safe as cosmetic ingredients when used as currently recommend. However, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant skin or injured skin.

In June 2024, the Panel determined to reopen this assessment due to changes in the reported use categories to

evaluate new data and to explore the reason why these ingredients have been banned by the E.U. The Panel previously considered re-review of this report in February 2003, and reaffirmed the 1983 conclusion as published in 2006. Although the data from the original 1983 report are summarized in the current amended report, due to time constraints the data from the original 2003 re-review are not included.

All right, so we have use data. In 2024, the RDL reported these ingredients of a higher frequency of use with Boric Acid and Sodium Borate being used in 40 and 144 formulations respectively. Concentration of use data by the Council in 2025 indicated a use decreasing to 0.00016 for Boric Acid in shampoos and rinse off, and bath soaps and body washes, and the highest concentration of use for sodium borate increased slightly to 3.7 percent in skin cleansers.

EU has an Annex II acknowledging repro tox. There's a lot here in my notes here, but I think I'll stop there for discussions.

DR. TILTON: I guess just a question; I heard Don comment that he sent some information out and I guess I didn't get that, but I didn't know if someone could just summarize it. Was it just on the Annex II designation?

DR. ROSS: I didn't get it, so I can't summarize it.

DR. DAVID COHEN: Hold on.

DR. BERGFELD: I got it, but I couldn't open it. I don't think it actually solved the problem, as I recall him stating this morning.

DR. DAVID COHEN: It was on boron compounds. It was reclassification of some boron compounds as mutagenic and/or toxic to reproduction according to condition regulation. It was a very pretty long document just on that, SCCS. And very a brief

document on Sodium Perborate and Perboric Acid. On the new classification of Sodium Perborate and Perboric Acid as toxic to reproduction, according to commission regulation. (Audio skip) repro tox.

DR. ROSS: Yeah, I think that comes out of the REACH classification of the 1B.

DR. DAVID COHEN: Didn't that come in the pre-meeting conversation?

DR. ROSS: Yeah. So that's a repro concern, so that's how it was classified. And that was mainly based on animal data rather than actual human data. Nevertheless, it was 1B, which is something to be discussed. Yeah.

DR. TILTON: Okay. So the conclusion is that it was Annex II as a ban, as opposed to a limitation on concentration. I think -- I just couldn't remember the -- or wasn't sure of the discussion this morning.

DR. HELDRETH: Yeah, I just forwarded a copy of Don's email to you, Susan, and Dave and Sam, you should all have --

DR. SAM COHEN: The problem will be, is that for the Europeans, is if there's repro tox or developmental tox at any concentration, it's going to get classified. And there is a clear NOAEL for the developmental tox at 21 milligrams per kilogram, and the repro tox, I think, was similar. And that was in the mouse and rat.

DR. ROSS: So, there were lots of different NOAELs. Yeah, lots of different NOAELs flying around and some we didn't quote, actually. Which we probably should have done, which are in the literature and used more extensively, but anyway.

DR. SAM COHEN: For the mouse it was 21 and for the rat it was 21.8 for NOAEL.

DR. ROSS: Oh, I see.

DR. EISENMANN: Also, there are normal dietary intake of boron which you could use as a comparison too.

DR. ROSS: I mean, EFSA used basically that and they used the Fail et al number of 9.6 migs per kig per day boron equivalents. And you can work with that because that's an overall for developmental tox, and has been used by other regulatory agencies, so that should probably be added. We do have reference to the EFSA in here --

DR. SAM COHEN: And they came up with an ADI 0.16 milligrams per kilogram.

DR. ROSS: Yeah, and they used that NOAEL in that calculation.

DR. SAM COHEN: How does Europe deal with it when REACH comes to one conclusion and bans it and EFSA comes to a conclusion and gives it an ADI?

DR. ROSS: Different agencies, I don't know. I don't know how they deal with it, Sam. But yeah, I mean, I

thought there's a lot in there, so I don't know where you want to start.

The WVE concerns? They had some great comments in here and I think we have to address them. And generally, I find their comments very helpful and these were along the same lines. And I think -- it all boils down to, obviously, with boric acid, we've got some fairly potent DART effects that we have to look at.

One of the discussion points in here was the use of cosmetic concentrations, which we have a max of boric acid of 0.00016 percent versus therapeutic concentrations, which I think was addressed in the response. Is it Jinqiu or was it Temima wrote that response -- anyway -- to WVE.

And you know the therapeutic concentrations were about 2 by 30 milligram vaginal tabs I think. And that was quoted in the two articles we're looking at.

The Acs et al. paper and the Mittelstaedt et al. paper, which WVE helpfully cited. The Acs said a weak teratogenic potential to vaginal boric acid during pregnancy couldn't be excluded. And Mittelstadt said despite the gaps, the available data suggests, intravaginal boric acid is safe as used, at least when used at doses commonly prescribed by clinicians.

And then we have the cosmetic uses. And WVE came up again with douches, Summer's Eve, vaginal wipes, et cetera. And incidentally, I did go to the website of Summer's Eve and I couldn't find the concentration of boric acid used in that product. But anyway, assuming -- and there may or may not be lower than the 0.0016 we already have. But anyway, that's kind of what we're dealing with and I'm just trying to sketch out the issue here.

DR. BERGFELD: Very similar to the octoxynols that we just dealt with.

DR. DAVID COHEN: So, are we clearing this with a lot of discussion comments?

DR. SAM COHEN: One of the concerns that was raised was the genotox but don't see any issue there. And one of the assays that was used was sister chromatid exchange, but that's not considered a valid measure of genotoxicity by OECD any longer.

DR. ROSS: I had some needs, David, if you wanted insufficiencies that I would say on this document if you

want it now, or you want more discussion first?

DR. DAVID COHEN: No, no. We can still spark discussion, and it helps get through the statutory things I have to put down.

DR. ROSS: Okay. All right. Well, I didn't see we had a lot of maximum concentrations for sodium borates in our document. We didn't have it for ocular, for mucous membrane exposure, or for baby products if used. That was for borate.

DR. DAVID COHEN: For sodium borate.

DR. ROSS: Yeah.

DR. DAVID COHEN: So, sodium borate --

DR. ROSS: Ocular, mucous membrane and baby products if used, maximum concentrations. We need maximum -- at least from my perspective, we need maximum concentrations of Boric Acid, ocular, and if used in baby products.

DR. TILTON: So, Dave, in Table 2.

DR. ROSS: Yeah.

DR. TILTON: Neither Boric Acid and odium Borate are listed as used in baby products.

DR. ROSS: Yeah.

DR. TILTON: Is that correct or am I --

DR. ROSS: No, there are --

DR. TILTON: -- misinterpreting the asterisks? I can't remember what the asterisks mean.

DR. ROSS: No, I think you're correct, actually. I think, got that from somewhere else in –

DR. DAVID COHEN: Non-reported.

DR. ROSS: Yeah.

DR. BERGFELD: It's a membrane.

DR. ROSS: Yeah, baby products was reported in the VRCP in 2023, but no baby products were reported in the -- oh, hang on.

DR. DAVID COHEN: Even in the VCRP of 2023, I don't see any baby products.

DR. ROSS: Yeah, I'm reading the wrong line there.

DR. HELDRETH: Dating back as far as 2002, wasn't in baby products, either one of them.

DR. DAVID COHEN: The eye area, yes, just not in the RLD.

DR. ROSS: Okay. Yeah, baby products no. So, you

think we're clear on baby products?

DR. TILTON: Mm-hmm. And we do have one reported use as a vaginal douche, but there is no concentration reported. So, we could request that.

DR. DAVID COHEN: Well, that's mucous membrane, but I guess we could specifically call out douche use, right?

DR. TILTON: I mean, it was one concern of the WVE, but we don't have a lot of information to go on.

DR. ROSS: Well, we have Boric Acid and mucous membranes at 0.00016, which is the maximum percentage. Yeah.

DR. TILTON: So, I guess it wouldn't be above that. Yeah. Oh, I guess it's the max concentration.

DR. ROSS: Yeah, it's the max. Sodium Borate we don't have a concentration there. We don't have a concentration in the eye on Sodium Borate -- around the eye, I should say.

DR. DAVID COHEN: I asked for that.

DR. ROSS: Yeah.

DR. DAVID COHEN: For Sodium Borate, too?

DR. ROSS: Yeah, we don't have it around the eye, at least in that top table that I can see. 2025, yeah, not reported.

DR. DAVID COHEN: What other data needs did you have, David?

DR. ROSS: The concentrations of use, I want your opinion on some of the dermal data. The old data, Sodium Borate was irritating at 3.2 percent. Our current max, I believe, is 3.7. We've got new data in Table 8, which is done according to an OECD method that's 406, which is good. Seems like quite a bit used in those studies. We were okay for irritation in rabbits, 0.5 grams and sensitization in guinea pigs, 0.4 grams.

But that was solid placed in the eye. I mean it seems okay to me. Let me go back to Table 8, so I'm quoting it properly. But I wanted your opinion on that.

DR. DAVID COHEN: You know, this is one of those situations -- I didn't have much on this. Boric Acid has been used a long time, it just doesn't come up much as a sensitizer.

DR. ROSS: I mean, it seems like quite a bit, 0.4

grams in guinea pigs, and then for irritation, 0.5 grams. This is for both compounds, Boric Acid and Sodium Borate. It seems like quite a bit of material and we're getting non-irritating and non-sensitizing.

DR. DAVID COHEN: I don't know if you noted it was 1.1 percent Sodium Borate was tested in a prophetic patch test.

DR. ROSS: I saw that.

DR. DAVID COHEN: What is that supposed to mean?

DR. ROSS: I had to -- please define in my returns. I'll take that out now we've discussed it. So that was another issue, and if we think that's okay, let's strike the fact we need that because the dermal is going to be all right. Ocular, we talked about. I think that emphasizing the absorption more likely with damaged or broken skin is very important, and I want to make sure we get that.

DR. BERGFELD: Big time.

DR. ROSS: Yeah. And then we have a couple of environmental epi studies, epidemiology studies, in the tables that aren't discussed in the text. And I think they probably would deserve a line in the text somewhere.

DR. DAVID COHEN: That sounds editorial, not a data need.

DR. ROSS: Yeah, it's an editorial; it can be changed. Just for Temima's benefit, in one of the environmental epi studies, the Hjelm et al. Argentina study, I'm probably engaging in some asymmetric analysis here, but it does have the potential confounder in the lithium content in the environmental samples. But anyway, we should certainly summarize those. But anyway, that's editorial, as David's pointed out.

So yeah, it's mainly concentrations of use if we ditch the dermal need. That's probably about it. Then we have to discuss, I guess, in more detail, the DART.

DR. DAVID COHEN: All right. So, before we hit that, were there any other data needs, Susan, that you have or Sam had before we go to DART because that's where all the action seems to be? All right. Okay. What do you want to talk about with the DART, David?

DR. ROSS: How do people feel about the DART? The cosmetic use versus the therapeutic use, and dangers per se.

DR. DAVID COHEN: Sam, you -- a comment?

DR. SAM COHEN: I didn't think that the new data that was provided really raised an alarm.

DR. ROSS: Susan?

DR. TILTON: I mean, I think we should just focus on the cosmetic use. I don't know if it's helpful to calculate an MOE for developmental tox with a NOAEL.

DR. BERGFELD: I'm sorry.

DR. TILTON: Go ahead.

DR. BERGFELD: This is the same problem that we had with the octoyxenols, I guess, how you pronounce that, in that we need to handle this in the Discussion, that we are dealing with the cosmetic, not the therapeutic. And I think that similar handling for these two entities, or ingredients, could be done, actually.

DR. ROSS: And, Susan, your MOE point was --

DR. BERGFELD: Discussion. Discuss this point of medication versus cosmetic use in the Discussion.

DR. ROSS: I agree, Wilma. I think that should be done. You had an MOE point as well or not, Susan?

DR. TILTON: Well, I think addressing it in the Discussion would work too. It would just be to distinguish the cosmetic use versus a drug use.

DR. ROSS: But I promised I wouldn't bring this up, but since I've heard it from someone else, what do you think, Bart, should I bring it up?

DR. DAVID COHEN: Now you have no choice.

DR. HELDRETH: Yeah, now you've got everybody in wonder.

DR. DAVID COHEN: No backing up.

DR. ROSS: It's the MOE, we've gone down the track. We're gone past the point of no return. The MOEs could be calculated, in fact we've done some initial MOE calculation on these things. And so, if we want to do that for the maximum use of Boric Acid at 0.00016 percent, using a developmental toxicology DART NOAEL, we can do that or we can just handle it in the Discussion.

I mean, it's actually quite a lot of work to do the MOEs, and Jinqiu and I did them -- actually, most of them yesterday. So, we do have those for tampons, for pads, for wipes and so forth, so we can do that. Or we could just

handle it in the discussion, and I think either way is fine, because you are looking at therapeutic versus cosmetic.

DR. SAM COHEN: And cosmetic uses I would anticipate there's quite a large margin.

DR. ROSS: That's what we were finding. I mean, we will have to double and triple check these things since we just bashed them off yesterday. But you have some pretty large MOE values.

DR. DAVID COHEN: I mean, if it makes you feel -- I was going to ask you about putting them in anyway because this is a really important issue.

DR. ROSS: It is.

DR. DAVID COHEN: It's not easy for people to distinguish a Boric Acid cosmetics versus therapeutic use because it's one of those things that's very easy to get.

DR. TILTON: Ingredients -- since the calculations have been done and we're in a draft report, I think it could be helpful to include them in the next draft to review.

DR. ROSS: Well, certainly with the initial calculations to be done. We'll have to refine those, but yes.

DR. TILTON: Yeah.

DR. DAVID COHEN: The difference when you talk about therapeutic products versus cosmetic products, there's often the gatekeeper of a prescription. But you can buy a drum of Boric Acid on the internet. You don't need a prescription for it. So, I think putting an Moe is important in this circumstance, different from when we have a pharmaceutical product that's prescription versus a cosmetic product.

DR. ROSS: Is Jinqiu on this call?

DR. HELDRETH: I think he's talking about hair dye epi in the other room.

DR. ROSS: Okay. What's your sense of this, Bart? Do we need to go down that MOE road like we're hearing?

DR. HELDRETH: So, as David pointed out, we're in early stages. So, what we could do is -- it sounds like this is going to go out as an IDA. And so, CIRs is not going to put out another version of this until we bring it back to you, the Panel, for a look at.

So, the IDA would go out, presumably it would be March before it comes back to the Panel to give people time to submit information. So, we could bring back a Draft Tentative Amended report in March, and we have all of that time for you and Jinqiu to feel comfortable about those calculations. And we could throw them in there at that point, and have them in that report that the Panel reviews.

And then if we look at it and we say, you know what the difference between these uses is absurd and we don't need this, it can come back up before it goes final.

DR. ROSS: Okay.

DR. SAM COHEN: I think that it really actually is pretty important to have the MOE calculations just to be able to demonstrate that at the cosmetic levels this is not a concern. And then a sentence in the Discussion about this is in comparison and contrast with the therapeutic use.

DR. ROSS: I agree with you. I mean, I had this as one of my insufficiencies but I thought I wasn't going to talk about it until someone else raised it.

DR. DAVID COHEN: No, we have (inaudible). We need to provide as much data as possible for people to feel safe that they could use it in cosmetics. On a multiplicity level, we need as much data, if we're going to clear it, to clear it.

DR. ROSS: I would agree with that, and I think this is why we start looking at it. I think Wilma's approach was also a good one. We can discuss it in the Discussion.

DR. BERGFELD: We can do both.

DR. ROSS: Yeah.

DR. BERGFELD: But what I'm hearing, though, also, we need to be helped by Courtney and get the word out, whatever we decide and what our recommendations are, because if it is true that Boric Acid is so available to the public, they're not going to read this document, they're going to have to hear from it from another source.

DR. ROSS: Good point.

DR. DAVID COHEN: Just -- I mean it's early. But what do we think about the old conclusion, which are usually very circuitous, but this whole conclusion had not for infant skin or injured skin. As I was going through it, I'm like, I generally don't like those old conclusions. I

kind of like these old conclusions.

DR. BERGFELD: As being part of the old conclusion, I said that was a good response at the end. That's a good conclusion still.

DR. ROSS: Yeah. I agree with that.

DR. DAVID COHEN: Yeah. And we often don't do that, but I kind of like it.

DR. BERGFELD: You like it?

DR. TILTON: Yeah, I think it's still necessary.

DR. ROSS: Absolutely.

DR. TILTON: Due to the difference in absorption.

DR. SAM COHEN: Agree.

DR. DAVID COHEN: Okay.

DR. HELDRETH: So, what I'm hearing is we're going to go out with an IDA, and that Jinqiu and Dave will work together to provide an MOE that will go into the Draft Tentative Amended report that will probably come out in March. And to help Temima out with writing that draft Discussion that will hit the Panel's table in March, we'll see some verbiage explaining these issues, hopefully, in your Panel returns. And then just to make sure to Temima has everything clear in front of her, since she's still coming up to speed on the whole CIR process, could we repeat the data needs real quick for her, for the IDA?

DR. DAVID COHEN: Yes. We need maximum concentration of Sodium Borate when used near the eye, mucous membranes and in douches. And for Boric Acid, maximum concentration of use near the eye.

MS. NGUYEN: All right, got it. Thanks.

DR. HELDRETH: Thank you.

DR. BERGFELD: Could I ask a question of Bart? Bart, we had two chemicals/ingredients discussed today that have some great public interest. Is there a way of engaging Courtney and her public awareness ability to get the message out about these two particular chemicals?

DR. HELDRETH: I'll leave that to Courtney. Besides putting out what you, the Panel, have told us to say, we don't do a lot of public engagement. But that may be something CFA is interested in, but I'll let Courtney speak.

DR. GRIFFIN: Yeah, I think it's a great idea. Let me speak to some folks at CFA and see what kind of

engagement we could get from CFA. But I think it would be really smart and meaningful to get this out in a more consumer-facing way. So let me dig into that and then I'll get some information to you all. And maybe, Bart, you and I can engage offline to talk about any practicality and any issues we might have.

DR. HELDRETH: I'd be happy to. Thank you.

Full Panel – September 9, 2025

DR. BELSITO: Yeah, okay, so this is a Draft Amended Report on the safety assessment of Sodium Borate and Boric Acid as used in cosmetics. We first published a safety assessment on these in '83, with a conclusion that in concentrations less than or equal to five percent they were safe as cosmetic ingredients. However, cosmetic formulations containing 3-Sodium Borate or Boric Acid at those concentrations should not be used on infants or injured skin.

Because it was 15 years since we last reviewed this, we looked at it again in 2003, and reaffirmed the 1983 conclusion. And again, because it's been another 15 years, we're being asked to look at this again. Not only because it's been 15 years, but based upon the fact that it's been banned in the European Union, and to those who weren't on the line earlier I just got confirmation from ESCCS, from the chair of the SCCS. that in fact it is banned in the European Union.

According to the 2023 VCRP survey data, Sodium Borate was used in 30 formulations and Boric Acid in eight. Those uses are down from prior use. Boric Acid is

currently being used at maximum concentration of 0.00016 percent in shampoos, rinse-off, and body washes. And Sodium Borate is at 3.7 percent in cleansing products. This is a decrease for Boric Acid and a slight increase for Sodium Borate from prior concentrations.

So, that's where we're at. That's the status. It is banned in Europe, so we know that. It is used potentially in feminine washes and wipes, and we know that. But we don't have a concentration of use for those. It clearly at some levels can be a reproductive toxicant. We have data on that.

And so, I think the question going forward is the data that we have, is it sufficient to assess the safety. And there are a lot of other issues that are needed in this report. We can go through that, but overall, okay, it was basically that we needed to do a margin of exposure. But in order to do that, we have to get a better sense of mucosum absorption, and the total area of the vaginal area that would be subject to absorption. And we don't have that, so insufficient for those endpoints.

DR. DAVID COHEN: Could you just -- so, I'm going to second your IDA. I just want to make sure we harmonize ours. So, maybe I can tell you what some of our needs were, but it looks like we're going out as an IDA.

We wanted maximum concentration of use of Sodium Borate near the eye, mucous membrane, and in douches maximum concentration of Boric Acid near the eye. There were currently no reported uses in baby products, right? And we wanted to do an MOE for cosmetic use as you mentioned. Yeah, did we add anything more in or leave anything out that you wanted in your IDA?

DR. BELSITO: No, you added a few things but I'm fine with that.

DR. DAVID COHEN: Okay.

DR. BELSITO: So, repeat your motion, David.

DR. DAVID COHEN: The IDA is for maximum concentration for Sodium Borate near the eye, mucous membrane, and in douches, maximum for boric acid near the eye, and the MOE as you outlined.

DR. BELSITO: Okay, I'll second that.

DR. BERGFELD: Second, well, it's your ingredient, so. It's seconded.

DR. BELSITO: I'll reiterate David's motion.

DR. DAVID COHEN: Yeah, I got it.

DR. BERGFELD: Okay and it's seconded. Okay, anything else we need to add? Did you need to speak about the Women's Voices For The Earth comment?

DR. BELSITO: I think we will have to address the Women's Voices For The Earth comments by our needs.

DR. BERGFELD: Okay.

DR. BELSITO: No, I think that we agreed that it has reproductive effects. The question is, is what's used in a cosmetic product, will that affect the reproductive effects? You know, it's very interesting that there were increases in (audio skip) the epididymis and the testes, but mating was normal for the male. I mean the effects really seemed to be more in male than female, so. But they will be addressed.

DR. BERGFELD: Okay.

DR. ROSS: The cosmetic versus therapeutic is the key issue here. Yeah.

DR. BERGFELD: And that will be taken up in the Discussion, just a given for us. All right, let me call the question. All those opposed? Abstaining? This ingredient is approved to go out as an IDA with the listed requests. Yes, David?

DR. DAVID COHEN: Don, did you need vaginal absorption data?

DR. BELSITO: Yes.

DR. DAVID COHEN: Okay, I just wanted to make sure that was clearly outlined on the IDA.

DR. BELSITO: Yeah.

DR. BERGFELD: Okay, let's make sure that's been added then. All right, we're moving down the list here to Other Items, the Fossil Waxes, Dr. Cohen.

DECEMBER 1982 MEETING – FIRST REVIEW/DRAFT REPORT

The Panel discussed whether they should set the maximum recommended concentration at 3 or 5 % and considered the EEC's 1979 directive authorizing a maximum concentration of 5% in talcs, excepting use on infants, and 3% in all other cosmetic products to justify their conclusion.

The following conclusion of the report was unanimously approved:

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

A sentence on absorption by damaged skin and testicular atrophy in experimental animals has been added to the Discussion section.

Subject to the other minor revisions, the document will be issued as a Tentative Report for a 90-day comment period.

FEBRUARY 2003 MEETING – SECOND REVIEW/FIRST RE-REVIEW

Dr. Belsito stated that a CIR Final Report with the following conclusion on Sodium Borate and Boric Acid was published in 1983: The Expert Panel concludes that Sodium Borate and Boric Acid, in concentrations less than or equal to 5%, are safe as cosmetic ingredients when used as currently recommended; however, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant skin or injured skin.

Dr. Belsito also stated that numerous reports on Sodium Borate and Boric Acid have entered the published literature since the Final Report was published in 1983, and that data relating to reproductive and developmental toxicity are of the most concern to his Team. Several publications on absorption were also identified. Dr. Belsito noted that these data are addressed to some extent in the published Final Report.

Additionally, in light of the new data, Dr. Belsito said that his Team determined that the Panel should begin the process of considering whether or not the Final Report on Sodium Borate and Boric Acid should be reopened. The initial step in the process would be for CIR to develop a report that includes the new data that have been identified in the published literature and subject these data to a critical review by the Panel.

The Panel voted unanimously in favor of beginning the process of considering whether or not the Final Report on Sodium Borate and Boric Acid should be reopened.

Dr. Bergfeld noted that a report including the new data on Sodium Borate and Boric Acid would be prepared.

JUNE 2003 MEETING – THIRD REVIEW/CONSIDERATION AND DECISION TO NOT RE-OPEN

Drs. Belsito and Marks stated that their Teams concluded that the CIR Final Report on Sodium Borate and Boric Acid that was published in 1983 should not be reopened. The published conclusion is stated as follows: The Expert Panel concludes that Sodium Borate and Boric Acid, in concentrations less than or equal to 5%, are safe as cosmetic ingredients when used as currently recommended; however, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant skin or injured skin.

Dr. Bergfeld wanted to know if there are any points that need to be made in the re-review discussion.

Dr. Belsito said that the concern in this re-review relates to male reproductive effects and how this relates to use concentrations and dermal absorption. With respect to information in the published Final Report, current use concentrations, and dermal absorption, Dr. Belsito noted that his Team concluded that absorption would not be an issue. He said that the issue of dermal absorption is addressed in the published conclusion, where a qualification relating to the use of free Sodium Borate or Boric Acid on damaged skin is stated.

Dr. Belsito said that in considering the Panel's old conclusion in light of the new data, there is no reason to reopen the Final Report, and that this should be stressed in the discussion section.

The Panel voted unanimously in favor of not reopening the Final safety assessment on Sodium Borate and Boric Acid.

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

Status: Draft Tentative Amended Report for Panel Review
Release Date: May 22, 2026
Panel Meeting Date: June 15-16, 2026

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	Adaptation to Technical and Scientific Progress
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
CMC	carboxymethyl cellulose
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary*
DMSO	dimethyl sulfoxide
DMBA	7,12-dimethylbenz(a)anthracene
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
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
VCRP	Voluntary Cosmetic Registration Program
XTT	2,3-bis-(2-methoxy-4-nitro-sulfopenyl)-2H-tetrazolium-5-carboxanilide

DRAFT 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…[to be determined].

INTRODUCTION

This assessment reviews the safety of Boric Acid and Sodium Borate (commonly known as borax) as used in cosmetic formulations. According to the web-based *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*. (This information is 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.

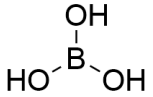

Figure 1. Boric Acid [CIR Staff]

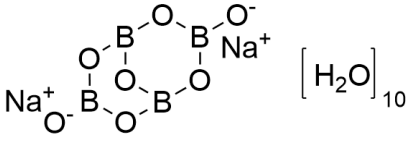

Figure 2. Sodium Borate (decahydrate) [CIR Staff]

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 uses 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.

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 (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 (ATP) 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 was 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, LH (lutenizing hormone) 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 made. 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 (estradiol), and AMH levels and an increase in FSH levels and ovarian apotosis. 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.

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.[5,33-35] Boric Acid and Sodium Borate (≤ 10,000 µg/l) were not genotoxic in a chromosomal aberration assay in human blood cultures.[35] 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).[36] In other genotoxicity studies, Boric Acid was not genotoxic in comet assays performed with Chinese hamster lung fibroblast (V79) cells (at ≤ 200 µM)[37] or with human Sertoli cells (at ≤ 1000 µM),[38]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.[39] 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). [40] 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 would 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.[41] 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.[42] 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.[43] 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).[44] Using cell counting kit-8 (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. [45] 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).[46] 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. [47] 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. A 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.[48]

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 bacteriocidal 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.[45] 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 the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 406.

Photosensitization/Phototoxicity

In 2 separate prophetic patch tests, two 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 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 from 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.

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

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 TLV for workroom environments for Sodium Borate set by the 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 American Conference of Governmental Industrial Hygienists (ACGIH) had a threshold limit value (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 average (TWA) TLV 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] The State of California's Division of Occupational Safety and Health set an 8h 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 0.000000328 to 0.000000075 mg 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.[58] 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 European Commission Scientific Committee on Consumer Safety (EC 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. 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 a NOAEL of 55 mg/kg bw/d,[62] derived from an oral developmental study in rats, 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 may also be associated with intimate-area exposure. However, concentration of use data were not available for these categories; therefore, quantitative SED and MOE calculations could not be performed. [61]

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/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. There were no signs of toxicity in any of the animals and the NOAEC for systemic toxicity in rats was 470 mg/m³, 175 mg/m³ for local effects in rats, and 57 mg/m³ 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 and 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, 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 apotosis. 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, rats (8 males/group and 16 females/group) were treated orally through feed 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. A 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.

Case reports involving a 2-yr-old girl and adults aged 56, 82, and 88 yr reported dermal exposure to 2% Boric Acid solution and oral ingestion of 6 - 300 g Boric Acid that resulted in both localized irritation and systemic toxicity. For dermal exposure, symptoms included erythema, lesions, crusting, edema, erosions, and exudation. Systemic toxicity was associated with headache, nausea, vomiting, thrombocytopenia, altered mental state, anemia, elevated transaminases, impaired renal clearance, diarrhea, 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 are 2 mg/m^3 (TLV- TWA) and 6 mg/m^3 (TLV-STEL). The State of California's Division of Occupational Safety and Health set an 8 h 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 0.000000328 to 0.000000075 mg 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.

DRAFT DISCUSSION

[Note: This Discussion is in the draft form, and changes will be made following the Panel meeting.]

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 European Union (EU).

The Panel issued an Insufficient Data Announcement following the September 2025 Panel meeting. In order to come to a conclusion of safety for these ingredients, the following additional data are needed:

- MOE calculations for cosmetic uses that result in mucosal and vaginal exposures.
- Mucosal absorption data
- Vaginal absorption and total application surface area data
- Maximum concentration for Sodium Borate in products applied near the eye area, that result in mucous membrane exposure, and in douches
- Maximum concentration for Boric Acid when used in products applied near the eye

These data were not received. However, CIR staff calculated an MOE for products that result in vaginal mucosal exposure.

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 was concerned that the potential exists for dermal irritation with the use of products formulated using Boric Acid and Sodium Borate. The Panel specified that products containing Boric Acid and Sodium Borate must be formulated to be non-irritating.

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. However, 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.

CONCLUSION

To be determined.

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	1.435	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
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

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]
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/m^3	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]
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]

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 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]
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]

Table 5. Developmental and reproductive toxicity studies from previous reviews

Test Article	*Vehicle*	*Animals/Test System*	*Dose/Concentration*	*Procedure*	*Results*	*Reference*
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]
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 250 and 125 mg/kg/d for rabbits (prenatal mortality and malformations)*	[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 an 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 LOAEL and NOAEL were 452 and 248 mg/kg/d for mice (fetal weight reduction), respectively.*	[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]

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Test System	Dose/Concentration	Procedure	Results	Reference
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]
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]

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Test System	Dose/Concentration	Procedure	Results	Reference
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 apotosis. 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
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	[33]
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.	[34]
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.	[35]
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.	[35]
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.	[36]
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.	[34]
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.	[35]
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.	[35]

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
				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.	[37]
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.	[38]
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.	[39]
				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.	[40]
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.	[40]

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.	[43]
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.	[47]
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.	[37]

Table 8. Cytotoxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
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	[45]
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	[45]
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.	[46]
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	[44]
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	[44]
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.	[35]
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.	[48]
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.	[45]
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.	[45]

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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6

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

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

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

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

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

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

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

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

INTRODUCTION

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

CHEMISTRY

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

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

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

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

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

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

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

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

USE

Cosmetic

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

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

TABLE 1. Product Formulation Data.

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

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

TABLE 1. (Continued.)

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

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

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

Data from Ref. 4.

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

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

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

Medical

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

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

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

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

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

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

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

Food

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

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

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

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

Pesticide

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

Other Uses

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

GENERAL BIOLOGY

Antibacterial/Antifungal Properties

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

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

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

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

Biochemical Effects

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

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

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

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

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

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

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

Tissue Effects

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

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

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

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

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

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

Absorption, Storage, and Excretion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Animal Toxicology

Acute Effects

Oral toxicity

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

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

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

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

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

Primary skin irritation

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

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

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

Tissue corrosiveness

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

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

Ocular irritation

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

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

Intravenous toxicity

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

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

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

Subcutaneous toxicity

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

Intraperitoneal toxicity

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

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

Subchronic Effects

*Oral toxicity**

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

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

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

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

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

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

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

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

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

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

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

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

Dermal toxicity

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

*Intravenous toxicity**

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

Subcutaneous toxicity

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

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

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

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

*See footnote under Subchronic Effects, Oral Toxicity section.

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

*Intraperitoneal toxicity**

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

Chronic Toxicity

*Oral toxicity**

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

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

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

*See footnote under Subchronic Effects, Oral Toxicity section.

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

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

Subcutaneous toxicity

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

Intramuscular toxicity

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

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

Special Studies

Mutagenesis

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

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

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

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

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

*Carcinogenesis**

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

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

Teratogenesis

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

Clinical Assessment of Safety

Skin Irritation and Sensitization

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

*See footnote under Subchronic Effects, Oral Toxicity section.

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

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

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

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

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

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

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

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

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

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

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

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

SIPT: 1 24 h Patch

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

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

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

Photosensitivity

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

Chronic Toxicity

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

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

Intravenous Studies

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

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

Other Clinical Experience

Product panel tests

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

Case reports

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

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

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

From Ref. 175.

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

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

Threshold Limit Values

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

CONCLUSION

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

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SAFFLOWER OIL

In 1985 the CIR Expert Panel concluded that this ingredient is safe as a cosmetic ingredient in the present practices of use (Elder 1985). Studies available since that safety assessment was completed, along with the updated information regarding uses and use concentrations were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004) has changed. Safflower Oil is currently Carthamus Tinctorius (Safflower) Seed Oil.

Carthamus Tinctorius (Safflower) Seed Oil was used in 94 products in 1981, based on voluntary reports provided to FDA by industry, and use concentrations ranged from less than 0.1% to greater than 50% (Elder 1985). In 2002 there were 142 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.00005% to 84% (CTFA 2004).

Table 20 presents the available use information. The most recent information is now considered to be the present practices of use and concentration.

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SODIUM BORATE AND BORIC ACID

In 1983, the CIR Expert Panel concluded that Sodium Borate and Boric Acid, at concentrations ≤5%, are safe as cosmetic ingredients when used as currently recommended, but that cosmetic formulations containing free Sodium Borate or Boric Acid should not be used on infant or injured skin (Elder 1983). Studies available since that safety assessment was completed, along

[21] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

with the updated information regarding uses and use concentrations were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Sodium Borate was used in 488 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0.1% to greater than 50% (Elder 1983). In 2002 there were 280 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.1% to 3% (CTFA 2002).

Boric Acid was used in 142 ingredients in 1981, based on voluntary reports provided to FDA by industry, and use concentrations ranged from less than 0.1% to greater than 50% (Elder 1985). In 2002 there were 77 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.1% to 2% (CTFA 2002).

Table 21 presents the available usage and use concentration information as a function of cosmetic product category for both ingredients.

Significant among the new studies considered by the CIR Expert Panel are those on the reproductive and developmental toxicity of Boric Acid. Under the auspices of the National Toxicology Program, Fail et al. (1991) reported results of a reproductive assessment by continuous breeding protocol in which Boric Acid administered to rats in their feed was determined to be a reproductive toxicant. The NOAEL was suggested to be 110 mg/kg day^{-1} and the LOAEL was 598 mg/kg day^{-1}. Price et al. (1997) reported results of another rat feeding study with a NOEAL of 10 mg/kg day^{-1} and a LOEAL of 13 mg/kg day^{-1} for decreased fetal body weight per litter. Yoshizaki et al. (1999) reported that an oral study using rats resulted in a NOAEL of 50 mg/kg day^{-1} and a LOAEL of 150 mg/kg day^{-1} for reduced sperm counts and the same NOAEL and LOAEL values for reduced implants and viable embryos.

The CIR Expert Panel considered that these findings do not suggest any reason for concern in the context of current use concentrations and the low dermal absorption through intact skin. These findings reinforce the Panel's prior determination that these ingredients should not be used on damaged skin, i.e., skin in which the barrier function has been compromised by disease or injury.

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TABLE 21
Historical and current uses and use concentrations for Sodium Borate and Boric Acid

Product category	1981 uses (Elder 1983)	2002 uses (FDA 2002)	1981 use concentrations (Elder 1983) %	2002 use concentrations (CTFA 2002) %
		Sodium Borate		
Baby care				
Lotions, oils, powders, creams	1	—	0.1–1	—
Bath				
Soaps and detergents	1	1	>0–0.1	20[a]
Bath oils, tablets, salts	3	—	1–50	—
Bubble baths	10	—	10–50	—
Eye makeup				
Eyeliner	14	1	0.1–5	—
Eye shadow	—	—	—	0.2
Eye lotion	2	—	0.1–1	—
Eye makeup remover	5	2	>0–5	—
Mascara	24	12	0.1–10	0.6
Other eye makeup	4	1	0.1–1	2
Fragrances				
Other fragrances	4	1	>0–1	—
Noncoloring Hair Care				
Conditioners	3	2	0.1–1	0.6
Sprays	1	—	1–5	—
Straighteners	2	—	1–5	—
Permanent waves	16	5	0.1–10	—
Shampoos	2	1	0.1–1	—
Tonics, dressings, etc.	13	7	>0–5	—
Wave sets	3	—	>0–1	—
Other hair care	3	1	0.1–10	—
Hair coloring				
Other hair coloring	3	—	0.1–1	—
Makeup				
Blushers	2	2	0.1–1	0.2
Face powders	—	1	—	—
Foundations	4	3	0.1–1	0.2–0.5
Lipstick	1	—	0.1–1	—
Makeup bases	19	15	0.1–5	—
Other makeup	1	—	0.1–1	1
Nail care				
Cuticle softeners	—	1	—	—
Nail creams and lotions	2	—	0.1–1	—
Oral hygiene				
Dentifrices	—	3	—	—
Mouthwashes and breath fresheners	—	1	—	—
Personal hygiene				
Underarm deodorants	2	—	>0–1	—
Other personal hygiene	8	6	5–>50	0.1
Shaving				
Aftershave lotions	2	—	>0–0.1	—
Shaving cream	4	8	0.1–5	—
Other shaving	1	1	0.1–1	—

TABLE 21
Historical and current uses and use concentrations for Sodium Borate and Boric Acid *(Continued)*

Product category	1981 uses (Elder 1983)	2002 uses (FDA 2002)	1981 use concentrations (Elder 1983) %	2002 use concentrations (CTFA 2002) %
Skin care				
Cleansing creams, lotions, etc.	144	68	>0–5	0.4–1
Depilatories	1	—	0.1–1	—
Face and neck skin care	71[b]	11	>0–5[b]	—
Body and hand skin care		32		0.4–0.8
Moisturizers	47	31	>0–5	0.3–1
Night skin care	37	22	>0–1	0.4–0.9
Paste masks/mud packs	3	6	1–5	0.2–3
Fresheners	12	4	>0–1	0.3
Other skin care	1	23	>0–>50	0.6–0.8
Skin lighteners[c]	1	NA[c]	0.1–1	NA[c]
Hormone products[c]	2	NA[c]	0.1–5	NA[c]
Wrinkle smoothing[c]	4	NA[c]	0.1–5	NA[c]
Suntan				
Suntan gels, creams, liquids	5	5	0.1–1	0.4
Other suntan	—	3	—	—
Total uses/ranges for Sodium Borate	**488**	**280**	**>0–>50**	**0.1–3**
		Boric Acid		
Baby Care				
Baby shampoos	1	—	0.1–1	—
Bath				
Soaps and detergents	1	—	1–5	
Oils, tablets, and salts	1	1	0.1–1	—
Bubble baths	—	1	—	—
Eye makeup				
Eye lotion	1	—	1–5	—
Eye makeup remover	3	4	0.1–5	—
Fragrances				
Powders	13	7	0.1–5	—
Other fragrances	1	—	0.1–1	—
Noncoloring hair care				
Conditioners	—	1	—	2
Permanent waves	13	5	0.1–5	—
Rinses	1	—	1–5	—
Shampoos	13	8	0.1–5	—
Tonics, dressings, etc.	3	1	>0–1	—
Wave sets	2	3	>0–5	—
Other hair care	3	—	0.1–5	—
Hair coloring				
Coloring rinses	14	—	1–10	—
Bleaches	—	3	—	—
Other hair coloring	3	—	0.1–5	—
Makeup				
Blushers	2	—	0.1–1	—
Face powders	1	1	0.1–1	—
Rouges	1	—	0.1–1	—
Makeup fixatives	2	2	1–5	—

(Continued on next page)

TABLE 21
Historical and current uses and use concentrations for Sodium Borate and Boric Acid *(Continued)*

Product category	1981 uses (Elder 1983)	2002 uses (FDA 2002)	1981 use concentrations (Elder 1983) %	2002 use concentrations (CTFA 2002) %
Oral hygiene				
Mouthwashes and breath fresheners	5	—	>0–5	—
Personal hygiene				
Underarm deodorants	5	2	1–10	—
Douches	5	1	>50	10[c]
Other personal hygiene	1	2	0.1–1	—
Shaving				
Aftershave lotions	5	5	>0–5	0.4
Preshave lotions	1	—	>0–0.1	—
Shaving cream	6	4	0.1–5	0.1–1
Other shaving	1	1	0.1–1	—
Skin care				
Cleansing creams, lotions, etc.	4	2	0.1–5	—
Face and neck skin care	5[b]	—	0.1–5[b]	—
Body and hand skin care		9		—
Foot powders and sprays	—	1	—	—
Moisturizers	4	2	0.1–5	0.5
Night skin care	1	1	0.1–1	—
Paste masks/mud packs	3	3	0.1–5	—
Skin fresheners	17	6	>0–5	—
Other skin care	—	1	—	—
Total uses/ranges of Boric Acid	**142**	**77**	**>0–>50**	**0.1–2**

[a]Diluted to about 0.3% Sodium Borate during use.
[b]These categories were combined in 1981 but are now separate.
[c]No longer considered as cosmetic product categories.
[d]Powder dissolved in water to produce a solution of about 0.1% Boric Acid before use.

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SODIUM DEHYDROACETATE AND DEHYDROACETIC ACID

A safety assessment of Sodium Dehydroacetate and Dehydroacetic Acid was published in 1985 with the conclusion that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration (Elder 1985). Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Sodium Dehydroacetate was used in 260 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0.1% to 1% (Elder 1985). In 2002 there were 325 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.00003% to 0.5% (CTFA 2002).

Dehydroacetic Acid was used in 139 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0.1% to 1% (Elder 1985). In 2002 there were 88 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0.007% to 0.7% (CTFA 2002).

Table 22 presents the available use and concentration information. The most recent information now constitutes the present practices of use.

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SODIUM LAURYL SULFOACETATE

A safety assessment on Sodium Lauryl Sulfoacetate was published in 1987 with the conclusion "On the basis of the available data presented in this report, the Expert Panel concludes that Sodium Lauryl Sulfoacetate is safe as a cosmetic ingredient in the present practices of use and concentration" (Elder 1987). Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. After reviewing the available data, the Panel determined to not reopen this safety assessment.

Sodium Lauryl Sulfoacetate was used in 93 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from >0.1% to >50% (Elder 1985). In 2002 there were 68 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 0.6% to 21% (CTFA 2004).

Table 23 presents the available use and concentration information. The most recent information now constitutes the present practices of use.

The CIR Expert Panel did note that Stepan Company had submitted robust summaries and test plans on Sodium Lauryl Sulfoacetate as part of EPA's high production volume chemical testing program. This submission argued that the only missing data were reproductive and developmental toxicity data. The company proposed conducting such a study. Though the Panel noted that there are no data in the published literature,

BUFF BOOK 1

COVER MEMO

AGENDA

MINUTES

DIOCTYL ADIPATE RE-REVIEW

SODIUM BORATE GROUP RE-REVIEW

PVP/VA COPOLYMER RE-REVIEW

PLANT WAXES RE-REVIEW

CIR Expert Panel Meeting
June 9-10, 2003

June 9 - 10, 2003

Memorandum

To: CIR Expert Panel

From: F. Alan Andersen, PhD
Melody A. Chen

Subject: Re-review of Sodium Borate and Boric Acid

The Panel looked at this re-review at the February, 2003 meeting. At that time, the Panel received a list of references from a review of the recent literature on Sodium Borate and Boric Acid uncovered many new studies in the literature, including reproductive and developmental toxicity studies conducted under the auspices of the National Toxicology Program. Because of a time limitation, only the reference list was available.

The Panel requested that CIR prepare a summary of these data. Melody and I have done that. The attached *review of new literature* is attached for the Panel's consideration.

Recall that, in the Panel's original safety assessment in 1983, CIR issued a Final Report which concluded that "Sodium Borate and Boric Acid, in concentrations ≤5%, are safe as cosmetic ingredients when used as currently recommended; however, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant or injured skin".

If the Panel decides to reopen this safety assessment, the *review of new literature* would be combined with a summary of the original report to constitute a Scientific Literature Review and the formal CIR safety assessment process would be initiated.

If the Panel concludes that there is no need to reopen the safety assessment, then that conclusion, a summary of the new data, and the Panel's rationale would be prepared and made available for public comment.

MAC: re-review references: 02/06/03
MAC/FAA: review of new literature: 06/09/03

Review of New Literature

on

Sodium Borate and Boric Acid

INTRODUCTION

In 1983, CIR issued a Final Report that "Sodium Borate and Boric Acid, in concentrations ≤5%, are safe as cosmetic ingredients when used as currently recommended; however, cosmetic formulations containing free Sodium Borate or Boric Acid at this concentration should not be used on infant or injured skin". A review of the recent literature on Sodium Borate and Boric Acid uncovered new published studies. Significant among these studies are those on the reproductive and developmental toxicity of Boric Acid. Many studies were carried out under the auspices of the National Toxicology Program.

In addition to these published studies, current use information on Sodium Borate and Boric Acid has been gathered and compared with the 1981 use data available when the earlier safety assessment was completed All available data are given in Tables 1 and 2. The use of both ingredients has decreased from 1981 to 2002, and the ranges of reported use concentrations have become more narrow.

Table 1 Product Formulation and Concentration of Use Data on Sodium Borate

Product Category [a] (FDA, 1981, 2002)	Number of Formulations Containing the Ingredient (FDA, 1981)	Concentration of Use (FDA 1981)	Number of Formulations Containing Ingredient (2002)	Maximum Concentration of Use (CTFA 2002)
Baby lotions, oils, powders, creams (60)	1	0.1 - 1%	-	-
Bath oils, tablets, salts (143)	3	1 - 50%	-	-
Bubble baths (215)	10	10 - 50%	-	-
Eyeliner (548)	30	0 1 - 5%	1	-
Eye shadow (576)	-	-	-	0.2%
Eye lotion (25)	2	0 1 - 1%	-	-
Eye makeup remover (100)	5	>0 - 5%	2	-
Mascara (195)	28	0.1 - 10%	12	0.6%
Other eye makeup prep (152)	4	0.1 - 1%	1	2%
Other fragrance prep (173)	4	>0 - 1%	1	-
Hair conditioners (651)	5	0 1 - 1%	2	0 6%
Hair sprays (aerosol fixatives) (275)	1	1 - 5%	-	-
Hair straighteners (63)	2	1 - 5%	-	-
Permanent waves (207)	16	0.1 - 10%	5	-
Shampoos (non-coloring) (884)	2	0 1 - 1%	1	-
Tonics, dressings, other hair groom (598)	14	>0 - 5%	7	-
Wave sets (53)	3	>0 - 1%	-	-
Other hair prep (277)	3	0.1 - 10%	1	-

Table 1 (continued). Product Formulation and Concentration of Use Data on Sodium Borate

Product Category [a] (FDA, 1981, 2002)	Number of Formulations Containing the Ingredient (FDA, 1981)	Concentration of Use (FDA 1981)	Number of Formulations Containing Ingredient (2002)	Maximum Concentration of Use (CTFA 2002)
Other hair coloring prep. (55)	3	0.1 - 1%		-
Blushers (all types) (245)	2	0 1 - 1%	2	0 2%
Face powders (305)	-	-	1	-
Foundations (324)	4	0 1 - 1%	3	0 2 - 0 5%
Lipstick (962)	1	0 1 - 1%		-
Makeup bases (141)	19	0.1 - 5%	15	-
Cuticle softeners (19)	-	-	1	-
Other makeup prep (201)	2	0.1 - 1%	-	1%
Nail creams, lotions (15)	2	0 1 - 1%	-	-
Dentifrices (40)	-	-	3	-
Mouthwashes, breath fresheners (46)	1	0 1 - 1%	1	-
Bath soaps, detergents (421)	1	>0 - 0 1%	1	20%
Deodorants (underarm) (247)	2	>0 - 1%	-	-
Douches (5)	1	25 - 50%	-	-
Other personal cleanliness products (308)	8	5 - >50%	6	0.1%
Aftershave lotions (231)	2	>0 - 0 1%	-	-
Shaving cream (134)	4	0 1 - 5%	8	-
Other shaving prep (63)	1	0 1 - 1%	1	-
Skin cleansing products (775)	168	>0 - 5%	68	0.4 - 1%
Depilatories (34)	1	0.1 - 1%	-	-
Face and neck (exc shaving) (310)	-	-	11	-
Face, body , hand*	74	>0 - 5%	-	-
Body and hand (exc shave) (840)	-	-	32	0 4 - 0.8%
Hormone products*	2	0 1 - 5%		-
Moisturizing products (905)	51	>0 - 5%	31	0.3 - 1%
Night prep (200)	38	>0 - 1%	22	0.4 - 0 9%
Paste masks (mud packs) (271)	3	1 - 5%	6	0 2 - 3%
Skin lighteners*	1	0 1 - 1%	-	-
Skin fresheners (184)	13	>0 - 1%	4	0 3%
Wrinkle smoothing products*	4	0.1 - 5%	-	-
Other skin care prep (725)	20	>0 - >50%	23	0 6 - 0 8%
Suntan gels, creams, liquids (131)	5	0.1 - 1%	5	0 4%
Other suntan prep.	-	-	3	-
Total Sodium Borate Uses and Concentration Ranges	488	>0 - >50%	279	0 1 - 20%

[a] Total Number of Formulations Reported to FDA in the Categroy in 2002

[b] Category used in 1981 but no longer in use

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Table 2. Product Formulation and Concentration of Use Data on Boric Acid

Product Category [a] (FDA, 1981, 2002)	Number of Formulations Containing the Ingredient (FDA, 1981)	Concentration of Use (FDA 1981)	Number of Formulations Containing Ingredient (2002)	Maximum Concentration of Use (CTFA 2002)
Baby shampoos (29)	1	0.1 - 1%	-	-
Bath oils, tablets, salts (143)	2	0 1 - 1%	1	-
Bubble baths (215)	-	-	1	-
Eye lotion (25)	1	1 - 5%	-	-
Eye makeup remover (100)	3	0.1 - 5%	4	-
Powders (273)	13	0 1 - 5%	7	10%
Other fragrance prep (173)	1	0.1 - 1%	-	-
Hair conditioners (651)	2	unknown	1	2%
Hair sprays (275)	1	>0 - 0 1%	-	-
Permanent waves (207)	13	0 1 - 5%	5	-
Rinses (non-coloring) (42)	2	1 - 5%	-	-
Shampoos (non-coloring) (884)	16	0 1 - 5%	8	-
Tonics, dressings, other hair groom (598)	4	>0 - 1%	1	-
Wave sets (53)	6	>0 - 5%	3	-
Other hair prep (277)	3	0 1 - 5%	-	-
Hair rinses (coloring) (20)	14	1 - 10%	-	-
Hair bleaches (120)	-	-	3	-
Other hair coloring prep. (55)	3	0 1 - 5%	-	-
Blushers (all types) (245)	2	0.1 - 1%	-	-
Face powders (305)	1	0 1 - 1%	1	-
Makeup bases (141)	1	unknown	-	-
Rouges (28)	1	0 1 - 1%	-	-
Makeup fixatives (20)	2	1 - 5%	2	-
Mouthwashes, breath fresheners (46)	5	>0 - 5%	-	-
Bath soaps, detergents (421)	1	1 - 5%	-	-
Deodorants (underarm) (247)	5	1 - 10%	2	-
Douches (5)	5	>50%	1	-
Other personal cleanliness products (308)	1	0 1 - 1%	2	-
Aftershave lotions (231)	6	>0 - 5%	5	0 4%
Preshave lotions (14)	2	>0 - 0 1%	-	-
Shaving cream (134)	6	0 1 - 5%	4	0 1 - 1%
Other shaving prep (63)	1	0 1 - 1%	1	-
Skin cleansing products (775)	4	0.1 - 5%	2	-
Face, body, hand (exc shaving prep)*	11	0 1 - 5%	-	-
Body and hand (exc shave) (310)	-	-	9	-
Foot powders and sprays (35)	-	-	1	-
Moisturizing products (905)	6	0.1 - 5%	2	0 5%

Table 2 (continued). Product Formulation and Concentration of Use Data on Boric Acid.

Product Category [a] (FDA, 1981, 2002)	Number of Formulations Containing the Ingredient (FDA, 1981)	Concentration of Use (FDA 1981)	Number of Formulations Containing Ingredient (2002)	Maximum Concentration of Use (CTFA 2002)
Night prep. (200)	1	0 1 - 1%	1	-
Paste masks (mud packs) (271)	3	0.1 - 5%	3	-
Skin fresheners (184)	17	>0 - 5%	6	-
Other skin care prep (725)	4	unknown	1	-
Total Boric Acid Uses and Concentration Ranges	142	>0 - >50%	77	0.1 - 10%

[a] Total Number of Formulations Reported to FDA in the Categroy in 2002

[b] Category used in 1981 but no longer in use

BIOLOGICAL EFFECTS

APOPTOSIS

Sylvain et al. (1998) reported that borax could induce apoptotic lesion in the thymus of male Wistar rats. Borax at 2000 ppm in the diet (2 mg/g) was fed to male rats (average weight of 200 g) for 16 days, followed by diet without borax from day 17 through day 28. A control rat was killed on the day 1 and two rats were killed on each of day 2, 5, 9, 12, 16, 19, 21, 26, and 28. Thymus samples from all rats were taken. The authors do not present quantifiable data. They note that altered cells are readily identifiable in treated cells and are not observed in the control tissue. The authors interpret these findings as characteristic of the apoptosis process They state that the number of cells altered in the thymus increases significantly according to the time elapsed after ingestion of borax, but no data are provided. The authors conclude that these data suggest that the genotoxicity of boron should be revisited.

BONE STRENGTH

Chapin et al. (1998) evaluated the effect of dietary boron on bone strength in male and female F344 rats. Animals were fed diet of powdered NIH-07 control feed to which Boric Acid was added to reach levels of 200, 1000, 3000, and 9000 ppm. These levels corresponded to <0 2 (control), 1 7, 8.5, 26, and 68 mg/kg day^{-1} of Boric Acid. At each dose level, 42 males and 6 females were used At the end of week 1, 2, 3, 4, 5, 8, and 12, 6 males at each dose level were weighed, killed, and necropsied. At the end of week 5, the 6 females were weighed, killed, and necropsied to provide a point of comparison between

genders. The femora and 4 lumbar vertebrae were removed and tested for strength. Femurs had a force applied to the middle of the long axis, yielding a breaking force measurement. Vertebrae were place between plates, yielding a crushing force measurement.

No effect on body weight gain was seen except that males consuming 9000 ppm had a slight reduction in weight gain. Serum Ca was reduced in a dose dependent manner to a maximum of 10% of control levels. Serum P was also reduced in a dose dependent fashion, but only to a maximum of 84% and serum Mg was reduced in a dose dependent fashion, but only to a maximum of 81% No alterations in bone microscopic structure were noted. No effect was seen on femur breaking strength A significant increase in crush resistance was seen at all levels of Boric Acid in the diet The same trend was seen in females at week 5, but the number was insufficient to demonstrate statistical significance (Chapin et al., 1998).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Stüttgen et al. (1982) reported that the absorption of boric acid through skin was dependent on the vehicle. An anhydrous water-emulsifying ointment containing the equivalent of 3% Boric Acid dissolved in glycerol and dispersed in an ointment base consisting mainly of soft paraffins was applied to the skin of 31 adult male patients. The total included 16 individuals with normal skin and 15 with diseased skin (not further characterized). Patients with normal skin received the emulsifying ointment in quantities ranging from 0 to 127.3 mg and those with diseased skin received from 5.2 - 87 5 mg of boron (1 g Boric Acid contains approximately 0.175 g boron). Absorption was based on one 24-hour urine samples collected before application and three 24-hour urine samples collected after application. No rise in average boron excretion in the urine was seen in patients with normal skin or patients with diseased skin.

The emulsifying ointment was also applied to the diapers of 3 infants (3.5 weeks to 2 months of age) with diaper rash in quantities ranging from 6.2 to 10.4 mg of boron A healthy 3.5 month old infant was the control. Blood and 24-hour urine samples were obtained. The blood level of boron was <0.05 µg/ml in all four infants. The boron concentration in the urine of the treated infants was actually less than in the control infant.

Another group of 6 patients with diseased skin (3 eczema, 2 psoriasis, and 1 urticaria) received a Boric Acid jelly containing the equivalent of 3% Boric Acid dissolved in water with 10% methyl cellulose added as a gelling agent. Quantities applied ranged from 42 - 89 mg of boron. Blood and 24-hour urine

samples were obtained. The mean ratio between boron excretion in urine on day 2 to day 1 ranged from 103.7% to 567.1% and the mean ratio of boron in blood ranged from 140.8% to 336.6%. The authors concluded that application of the aqueous jelly did result in absorption of boron.

The authors suggested that the type of vehicle in which Boric Acid is used influences the increase in blood levels of boron and boron excretion in the urine. Since they believe there is therapeutic value to use of an emulsifying ointment, the authors opined that Boric Acid acted by neutralizing biologic material from the superficial layer of the skin and suppressing microbial growth (Stüttgen et al., 1982).

Schou et al. (1984) assessed the in vitro pharmacokinetics of Boric Acid release into distilled water from either an water-emulsifying ointment, an hydrophobic ointment, or a water-methyl cellulose jelly. Over a 24 hour period, the release of Boric Acid from the water-emulsifying ointment and the hydrophobic ointment was flat. This contrasted with a rapid rise to 70% release of Boric Acid from the water-methyl cellulose jelly in the first hour, leveling off to 90% at 24 hours.

These authors also administered 750 mg Boric Acid dissolved in water orally or as much as possible of a 50 g tube of water-emulsifying ointment containing 3% Boric Acid. The cumulative 96 hour urinary excretion was not significantly different between the two vehicles, although a delay in the initial appearance of Boric Acid from the water-emulsifying ointment was seen at the 2 hour urine fraction.

These authors then administered an intravenous dose of 600 mg Boric Acid to seven young male volunteers (30 minute infusion). Plasma concentrations were followed for 120 hours. The half life of Boric Acid in blood was 21 ± 4.9 hours. They concluded that the half-life rules out any significant accumulation Schou et al., 1984).

Ku et al. (1991) examined the tissue disposition of boron in 30 adult male Fischer rats fed 9000 ppm Boric Acid (1575 ppm boron) in their normal feed for up to 7 days. Control animals (30) received only normal feed (less than 20 ppm boron) Six treatment and 6 contol animals were killed at 1, 2, 3, 4, and at 7 days after the start of the exposure. Plasma, tissue samples (liver, kidney, adipose, muscle, bone, large intestine, brain, hypothalamus, testis, epididymis, seminal vescicles,, adrenals, and prostate) and seminal vesicle fluid were analyzed for boron levels.

Boron in plasma rose rapidly through the first two days, but leveled off after day 2. All tissues except for bone, followed a similar pattern. Boron in bone reached a plateau at day 3, but then increased again on day 4 and was higher still on day 7, three times higher than plasma levels. The authors noted -

that deposition of boron in tissues of relevance to Boric Acid testicular toxicity or CNS hormonal effects was not selectively increased (Ku et al., 1991).

Murray (1998) reported a comparative review of the oral pharmacokinetics of Boric Acid in rodents and humans, concluding that the rodents and humans are remarkably similar. Citing developmental toxicity in rats as the most sensitive endpoint (NOAEL of 55 mg/kg day^{-1} and LOAEL of 75 mg/kg day^{-1}), the author compared the mean boron levels in the blood of rats in the relevant animal study (1.53 µg/g boron at the LOAEL) to boron blood levels in the most heavily exposed worker population at a borate mine (0.24 µg/ml boron). The author concluded that there was an ample margin of safety for humans.

Webster et al (1998a) reported the in vivo percutaneous absorption of ^{10}boron as a function of the form applied to human skin: ^{10}boron-enriched Boric Acid (5%), ^{10}boron-enriched borax (5%), and disodium octaborate tetrahydrate (10%) in aqueous solutons. Urinalysis of boron and ^{10}boron was used to determine percutaneous absorption. Unlike other studies in which the presence of dietary boron was a confounding factor, these authors measured ^{10}boron in samples using inductively coupled plasma mass spectrometry (ICPMS) in vitro, which eliminated dietary boron influences.

The dose given was 1.8 ml of each solution over a 900 cm^2 skin area (2 µl/cm^2). This was considered the maximum dose that would not run off the skin. A total of 24 male and female volunteers (22-50 years of age), with normal skin, participated in the study, 8 in each treatment group. Background urinalysis values were obtained for 4 days. On day 5, one dose was applied to an area on the back of each individual. Another dose was given to the same site on day 12 after application of a 2% sodium lauryl sulfate (SLS) solution on day 11 in an attempt to irritate the area. Each dose was allowed to air dry and each volunteer was instructed to wear a white T-shirt for 24 hours. Residual material was removed 24 hours after application. Volunteers were asked to avoid excessive dietary boron intake by avoiding a specific list of foods and to avoid use of products with Boric Acid or Sodium Borate on their ingredient labels.

The authors discriminated between ^{10}boron and ^{11}boron isotopes using ICPMS. The average daily dietary boron consumed by each subject was 1750 µg, of which 316 µg was ^{10}boron. The average ^{10}boron absorbed through the skin (only ^{10}boron was applied) was 4.75 µg. Treatment with SLS did not produce visible irritation, nor did it have any impact on the percutaneous absoption of boron. Overall, the authors concluded that the percutaneous absorption of boron, independent of the form, was low. The authors

expressed the view that percutaneous absorption in normal skin is sufficiently low that it is not necessary for borate workers to wear gloves, but cautioned that this view could not be extended to workers with abraded skin or in the presence of dermatitis (Webster et al., 1998a).

Webster et al. (1998b) followed the above study with a report on the in vitro percutaneous absorption of ^{10}boron as a function of the form applied· ^{10}boron-enriched Boric Acid, ^{10}boron-enriched borax, and disodium octaborate tetrahydrate Unlike other studies in which the presence of dietary boron was a confounding factor, this study was done in vitro, which eliminated dietary boron influences

Human skin was mounted on teflon diffusion cells to eliminate any contribution of boron from glass. The receptor solution was continuously perfused at a rate of 3ml/h Two dose volumes were applied. A volume of 1 ml/cm^2 provided material for absorption throughout the dosing period and was termed the "infinite dose." A volume of 2µl/cm^2 was chosen to mimic the residue that would remain on the skin as described in the previous in vivo study and was termed the "finite dose." Boric Acid was given in the 1 ml/cm^2 volume at 0.05, 0.5 and 5.0% and in the 2µl/cm^2 volume at 5%. Borax and disodium octaborate tetrahydrate were given in the 1 ml/cm^2 volume at 5.0% and 10%, respectively.

Calculated from the Boric Acid percutaneous absorption from the "infinite dose," the authors reported flux values of 0.25, 0.58, and 14.58 µg/cm^2 hour^{-1} for the 0 05, 0 5, and 5% solutions, respectively. The flux for borax and disodium octaborate tetrahydrate were comparable to the 5% solution value for Boric Acid. The flux value for Boric Acid from the "finite dose" (5% solution only) was 0.07 µg/cm^2 hour^{-1}, 200 times less than when the "infinite dose" was used.

Pahl et al (2001) studied the effect of pregnancy on renal clearance in 32 women. The volunteers were in good health and between the ages of 18 and 40; 16 of the women were pregnant and in their second trimester. Dietary boron was the only source of boron. A baseline blood sample was taken at the clinic on day 0 after each volunteer had emptied her bladder. At 2 hours, urine was collected and combined with any urine collected over the 2-hour period. A 2 hour blood sample was also taken. Urine was collected of the next 24 hours by each volunteer and a 24 hour blood sample was taken at the clinic

Boron excretion in the pregnant and non-pregnant women was 1.36 and 1.31 mg/day, respectively. Given this comparability, the authors calculated boron clearances in all subjects at 2 and 24 hours. The range was 43.85 to 68 30 ml/min/1.73 m^2 (Pahl et al , 2001).

This same laboratory, in a companion study (Vaziri et al., 2001), investigated the difference

hours. The range was 43.85 to 68.30 ml/min/1.73 m^2 (Pahl et al., 2001).

This same laboratory, in a companion study (Vaziri et al., 2001), investigated the difference between renal clearance of boron in pregnant and non-pregnant rats exposed to Boric Acid to determine if differential clearance may play a role in developmental abnormalities in the offspring of pregnant rats exposed to Boric Acid. They reported that the clearance actually was slightly higher in pregnant rats, but the difference was not statistically significant. In both pregnant and non-pregnant rats, the plasma half-life of boron was approximately 3 hours.

GENOTOXICITY

Benson et al. (1984) examined the genotoxicity of borax and Boric Acid in *S. typhimurium* strains TA98 (frameshift mutant) and TA100 (base pair substitution mutant) in the presence and absence of metabolic activation using a liquid preincubation technique. In addition, both borax and Boric Acid were used in combination with benzo[a]pyrene to treat both strains. And finally, the genotoxicity of borax or Boric Acid combined with sunlight exposure and benzo[a]pyrene combined with sunlight exposure was examined. Neither borax nor Boric Acid produced an increase in revertant colonies, independent of metabolic activation. Nor did boron or Boric Acid affect the concentration dependent increase in revertants produced by benzo[a]pyrene in the presence of metabolic activation. Exposure of the test material to sunlight (presumably in Lexington, Kentucky, but time of year not given) for 8 hours prior to preincubation with the *S. typhimurium* strains did not increase the revertants produced by borax or Sodium Borate, the levels remained at control levels. The same sunlight exposure to benzo[a]pyrene reduced the revertants produced in both strains with metabolic activation. Sunlight had no effect on the revertants produced by benzo[a]pyrene without metabolic activation, the levels remained at control levels.

Landolph (1985) reported the cytotoxicity and genotoxicity of refined borax and borax ores on V79 Chinese hamster cells, C3H/10T1/2 mouse embryo fibroblasts, and human foreskin fibroblasts. Dose dependent cytotoxicity was observed above a threshold that was both material and cell strain specific, but the threshold was in the range of 0.1 mg/ml for human fibroblasts for both materials. Mutation to ouabain resistance in C3H/10T1/2 mouse embryo fibroblasts and human foreskin fibroblasts was not seen with any material, but a weak mutagenic response was seen in the assay for 8-azaguanine resistance in V79 Chinese hamster cells. Refined borax did not induce neoplastic transformation in C3H/10T1/2 mouse embryo fibroblasts. Borax ores did produce a weak transformation that was not dose dependent and was

CARCINOGENICITY

Dieter (1994) reported on toxicity and carcinogenicity studies in mice exposed to Boric Acid under the auspices of the National Toxicology Program. In 2 week studies, male and female B6C3F$_1$ mice were fed Boric Acid at 0, 0.62, 1.25, 2.5, 5.0, and 10%. Body weights were reduced slightly as a function of increased percentage of Boric Acid in the diet. Death in males was noted at 2.5% (1/5), 5.0% (3/5), and 10% (5/5). In females, the only deaths were at 10% (4/5). In 13 week studies, the mice were fed Boric Acid at 0, 0.12, 0.25, 0.5, 1.0, and 2.0%. Death in male mice was seen at 1% (1/10) and 2% (8/10), while deaths in female mice were seen only at 2% (6/10). Similar body weight reductions were noted.

For the 2 year study, dose levels of 0, 0 25 and 0 5% were chosen. The most consistent finding from the prechronic through the chronic studies was testicular atrophy and interstitial cell hyperplasia in male mice, but the interpretation of the findings was not clear. For example, in the chronic study, atrophy of the seminiferous tubules was seen in >50% of the male mice dosed with 0.5%, but in none of those dosed with 0.25%. Similarly, in the chronic study, interstitial cell hyperplasia was noted in 7/47 male mice in the 0.5% group, but in none of the male mice in the 0.25% group. Slight increases in hepatocellular tumors and subcutaneous tissue tumors occurred in the 0.25% male group, but not in the 0.5% male group, and not at any dose in female mice. The authors noted several reasons why these tumor findings did not raise a concern. Neither of the tumors occurred in tissues that were considered target organs for reproductive effects, e.g., testes. The statistical significance of the increased tumor incidence was only demonstrated using a life table test not considered appropriate for tumors that are not fatal. The incidences of both tumor types are highly variable and yet each fell within the range of reported historical controls. Overall, Boric Acid was not considered carcinogenic in B6C3F$_1$ mice, confirming, according to the author, the previous finding that Boric Acid was not carcinogenic in Sprague-Dawley rats (Dieter, 1994)

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

SPERMATOTOXICITY

Linder et al. (1992) investigated spermatotoxicity in reproductive toxicants including Boric Acid by using male Sprague-Dawley rats. Six treatment rats were dosed by oral gavage twice (9 AM and 4 PM) for a total dosage of 2000 mg/kg. Animals were dosed on day 0 and killed on day 2 or 14. The testis, epididymis, seminal vesicles, and prostrate were excised. Tissues were prepared for light microscopy. On

day 2, no change was detected; however, on day 14 there were distorted enlarged residual bodies in Stage VIII, retention at lumen and base of Step 19 spermatids in Stages IX to XIII, and testicular debris in the proximal caput.

Luminal fluid samples from the distal cauda and proximal caput were aspirated into capillary tubes. Sperm motility analysis was performed using video analyses and sperm suspensions were used for studies on individual sperm cell morphology. Abnormalities that were noted included head separated from flagellum, misshapen head attached or separated from normal flagellum, misshapen head with abnormal flagellum, and normal head with degenerative flagellar defects At day 2, sperm counts were signficantly decreased, whereas by day 14, they were significantly increased from that of controls. Also, the caput sperm morphology was described as abnormal on day 14 (details not given) (Linder et al., 1992)

Yoshizaki et al. (1999) studied the effects of Boric Acid on sperm morphology and performed computer-assisted sperm analysis (CASA) for male Wistar rats. Each treatment group consisted of 20 males and 10 females. Boric Acid was dissolved in distilled water and administered orally for 3 weeks to male rats at dosages of 50, 150, and 500 mg/kg/day. Control rats received no Boric Acid. The dosage volume was 10 ml/kg. Some males were used in a breeding study to be described later The non-mated males were killed and necropsied after treatment for 3 weeks.

Sperm analysis was performed using the CASA system. Sperm suspensions from the right epididymis were examined microscopically, and the motion of the sperm was recorded on video tape. Two hundred or more sperm per each suspension were analyzed. Percent motile, curvilinear velocity, straight line velocity, linearity, beat cross frequency, and amplitude of lateral head displacement (ALH) were determined.

Morphological examination was performed for sperm in the caput, corpus, and cauda epididymis Four hundred sperm in each sample were examined microscopically for the following morphological abnormalities: 1) no head, 2) amorphous head, 3) flection in neck region, 4) flection in tail region, and 5) others.

In the 500 mg/kg group, one male died after the 27th dose, and another was killed in a moribund condition after the 10th dose. Body weight gain was suppressed during the first week of the treatment period in males in the 500 mg/kg group. The testis and epididymis weights in the 500 mg/kg group were lower than those in the control group, and the epididymis weight in the 150 mg/kg group tended to be low

The number of sperm were decreased dose-dependently in the 150 and 500 mg/kg groups. The percent motile was severely decreased in the 500 mg/kg group and moderately in the 150 mg/kg group (15.3%, 55.1%, and 78.3% in the 500 mg/kg, 150 mg/kg, and control groups, respectively) Curvilinear and straight line velocities in the 150 and 500 mg/kg groups were reduced, but not dose-dependent. The mean and max ALH values were decreased dose-dependently in the 150 and 500 mg/kg groups. Although the beat cross frequency of the head was decreased and linearity was slightly increased in the 500 mg/kg group, these values in the 150 mg/kg group were comparable to control values

The frequency of abnormalities in sperm from the caput region in the 500 and 150 mg/kg groups was higher than the control value (58.4% and 12.6%, respectively, vs 2 4%) In the 150 mg/kg group, mainly tail anomalies were observed, whereas head abnomalities were observed in the 500 mg/kg group. Sperm abnormalities were also observed at a high frequency in the corpus and caudal regions in the 150 and 500 mg/kg groups. In the caudal region in the 500 mg/kg group, the frequency of sperm with no head was higher than that of sperm with an amorphous head or flection in the neck region (25.4% vs. 2.3% and 1.2%, respectively). In the 150 mg/kg group, tail abnormalities were more frequently observed than head abnormalities in any of the three epididymal regions (Yoshizaki et al., 1999).

This same laboratory collaborated with several others to do a follow-up study (Ban et al., 2001) which reported that analysis of rat sperm motion using a semen analyzer also detected a decrease in the percentage of motile sperm in rats given Boric Acid orally.

TESTICULAR TOXICITY

Treinen and Chapin (1991) examined the development of Boric Acid induced testicular lesions as part of a National Toxicology Program evaluation. Fischer 344 rats (sex unspecified) were divided into control (n=30) and treated (n=36) groups. The rats in the treated group were given 9000 ppm (w/w) Boric Acid with their feed for the entire study, while control animals received untreated feed. At 4, 7, 10, 14, 21, and 28 days six treated and four controls per time point were killed and the right testis were removed. Tissues were then prepared for light and electron microscopy.

Using light microscopy, no abnormalities were detected after 4 days of dosing. By day 7 of Boric Acid treatment, half of the animals exhibited an inhibition in spermiation in approximatley 10-30% of stage IX tubules, whereas step 19 spermatids had been released from control animals. By day 10, all the treated animals showed inhibited spermiation in all stage IX and X tubules. By day 21, sloughed germ cells

occluded the lumina in approximately 20-50% of all tubules in treated animals. Also, the number of stage IX-XII tubules displaying abnormal residual bodies had increased. After 28 days, there was advanced epitheilial disorganization, cell exfoliation, luminal occlusion, and cell death. Using electron microscopy, the only detectable difference between Boric Acid treated and control rats was the presence of condensed spermatid nuclei undergoing degradation near the basement membrane on day 10.

In addition to histological studies, serum testosterone analysis was performed. For the hormone study, 10 control and 10 treated (9000 ppm Boric Acid in feed) animals per time group were bled for basal testosterone levels on 4, 7, 10, and 28 days after the initiation of dosing. Basal testosterone levels were significantly decreased by day 4 and at every time point thereafter (Treinen and Chapin, 1991)

Ku et al. (1993a), also part of the National Toxicology Program evaluation, reported on the relationship between Boric Acid dose and testicular lesion development in male Fischer 344 rats. Rats were assigned to control (6 rats per group per week for 9 weeks) and 4 treatment groups (6 per treatment per group per week). Treated rats were given 3000, 4500, 6000, and 9000 ppm Boric Acid in their feed Control rats received feed with no additives. At weekly intervals for 9 weeks, 6 rats from each group (control and 4 dose groups) were euthanatized. Testes were removed for histological examinations, testicular spermatid head count (TSHC), and epididymal sperm count (ESC). Rats in control and 4500, 6000, and 9000 ppm Boric Acid dose groups were given control feed after 9 weeks of exposure and recovery was assessed at 8 week intervals for up to 32 weeks post treatment. To assess testis lesion development over time for each dose group, lesions were assigned a numeric score between 0 and 6, depending on both the lesion characteristics and percentage of tubules affected.

Rats fed 3000 ppm Boric Acid showed only mildly inhibited spermiation (Grade 1) by week 5, which continued to week 9. Rats fed 4500 ppm Boric Acid showed severe and widespread inhibition of spermiation (Grade 2) by week 2 that was maintained to week 9, at which point germ cell exfoliation was observed. Rats fed 6000 ppm and 9000 ppm Boric Acid showed severe inhibition of spermiation by week 2, followed by progression to Grade 6 atrophy. The progression to atrophy was dose and time dependent with 6000 ppm reaching atrophy by week 9 and 9000 ppm by week 6.

For the 3000 ppm group, mildly inhibited spermiation was detected histologically, but with no consistent changes in any parameter. For the 4500 ppm group, severe and widespread inhibition of spermiation was reflected by variable increases in TSHC (24% to 62%, detected initially and most

significantly at week 2), with no significant changes in testes weight. This was followed by decreases in epididymis weight (10% to 29%) and profound decreases in ESC (72% to 97%) during weeks 4 to 9. Severely inhibited spermiation and progression to atrophy (6000 and 9000 ppm groups) were represented initially by increased TSHC (31% to 51%), reflecting the inhibited spermiation at week 2, followed by progressive and profound decreases in testis weight (12% to 68%), TSHC (16% to 99%), epididymis weight (12% to 57%), and ESC (78% to 99%), reflecting the progression to atrophy during weeks 3 to 9 (Ku et al., 1993a).

Ku et al. (1993b), again as part of a National Toxicology Program evaluation, examined possible direct effects of Boric Acid effects on testicular cells in vitro. Sertoli-germ cell cocultures were used to evaluate the effects of Boric Acid on 1) morphology/germ cell attachment, which might identify a target cell; 2) Sertoli cell energy metabolism, because lactate, secreted by Sertoli cells is a preferred energy source for germ cells; and 3) DNA/RNA synthesis, because germ cells synthesize DNA/RNA and Boric Acid impairs nucleic acid synthesis in the liver and may do so in the testis.

Cocultures of Sertoli cells and germ cells from Fischer 344 rats were isolated. Boric Acid, diluted to final concentrations ranging from 0.1 to 10.0 mM, was dissolved into the medium. Cocultures were continuously exposed up to 72 hours with daily replacement of control or Boric Acid containing medium. Control cocultures showed the characteristic confluent monolayer of enriched Sertoli cells with overlying germ cells. No overt morphologic changes or germ cell loss were observed in any of the treated cocultures.

For the second experiment, Sertoli-germ cell cocultures were treated with control or Boric Acid containing medium (0.1, 0.3, 1.0, 3.0, and 10 mM) for 72 hours. Lactate, pyruvate, and ATP levels were determined as described by Chapin et al. (1988) [GET REF]. Only the cocultures exposed to 3 and 10 mM Boric Acid showed significant decreases (about 30% to 60%) in 24 hour medium lactate and pyruvate levels compared to controls. A slight but significant decrease in cellular ATP levels (about 10% to 17%) was also observed at these test levels.

For the third experiment, cocultures were simultaneously labeled for 24 hours with both ^{3}H-TdR (4 µCi/1 mL/ well, specific activity: 50 to 80 Ci/mmol) and ^{14}C-UdR (0.4 µCi/1 mL/ well, specific activity: >350 mCi/mmol). Test concentrations of Boric Acid were (0, 0.1, 0.3, 1.0, 3.0, and 10 mM). Radioactivity was determined using a Beckman LS 3800 Series Liquid Scintillation System. There were significant dose-

related decreases in ^{3}H-TdR incorporation (from 25% to 70%) at 1 to 10 mM Boric Acid. Basal ^{14}C-UdR incorporation increased with time but showed no significant or consistent dose-related Boric Acid associated changes. While no data were given, the authors stated that no significant changes in DNA content were seen during Boric Acid exposure (Ku et al , 1993b).

Fukuda et al. (2000) assessed whether 2 weeks was a sufficient treatment period for the detection of testicular toxicity caused by Boric Acid. Boric Acid was given by oral gavage to male Wistar rats (6 per treatment group) at dosage levels of 300 and 500 mg/kg for 2 and 4 weeks. Control animals received distilled water for 4 weeks After 2 weeks, the 500 mg/kg group had significantly decreased testis weights (2.67±0.20 g compared to 3.08±0.18g for the control group). Histopathological effects included exfoliation of round spermatids, retention of step 19 spermatids, and increased numbers of residual body-like structures in the seminiferous tubules in the 300 and 500 mg/kg groups. After 4 weeks, testis and epididymis weights were significantly decreased in the 300 and 500 mg/kg groups (2.68±0.12 g and 1.08±0.15 g vs.3.08±0.18 g for testis; and 604±61 mg and 605±26 mg vs. 710±50 mg for epididymides) Histopathological changes in the 300 mg/kg group were similar to those found in the 300 and 500 mg/kg groups after a 2 week administration. Diffuse atrophy of the seminiferous tubules was additionally observed in the 500 mg/kg group. The authors concluded that 2 weeks was a sufficient treatment period for detection of Boric Acid testicular toxicity.

Kudo et al. (2000) confirmed that the detection of testicular toxicity of Boric Acid is possible in a 2-week study if dose selection is appropriate. Male Wistar rats (6 per treatment group) were given oral doses of Boric Acid (125, 250, 500) for 4 and 2 weeks while the control group received distilled water for 4 weeks. After the appropriate period of time, rats were killed and necropsied. The sperm number and motility rate were calculated, male reproductive organs weighed, and the testes and epididymides examined under light microscopy.

There were no effects on reproductive organ weights in any groups in either the 2 or 4 week studies. The sperm number and motility rate were not decreased in any group after 2 weeks. Sperm number was significantly decreased for the 500 mg/kg group after 4 weeks (10.9±2.2x10^{4}/l mg of caudal epididymis vs 48.6±4.2x10^{4}/l mg of caudal epididymis for control). Motility also decreased in the 250 and 500 mg/kg groups after 4 weeks (25.5±18.1% and 4.5±5.2% vs. 54.8±13.4 for control). Retention of step 19 spermatids of stages IX-XI was observed in the testes of almost all rats treated with 500 mg/kg after

both 2 and 4 weeks (Kudo et al., 2000).

REPRODUCTIVE TOXICITY

Linder et al. (1990) studied the effect of Boric Acid on the male reproductive system of the rat. Twenty-four male Sprague-Dawley rats were given oral doses (gavage) of either water or Boric Acid. The Boric Acid solutions were administered in a dose volume of 20 ml/kg to obtain a total dosage of 0 (control) or 2000 mg/kg of Boric Acid. Groups of 6 control and 6 treated rats were killed at day 2, 14, 28 and 57.

Histologic study of the testis and epididymis revealed no changes at 2 days posttreatment. At day 14, however, distinct abnormalities were apparent in the Boric Acid treatmed rats. Atypical structures that appeared to be enlarged distorted cytoplasmic lobes of Step 19 spermatids were observed in Stage VIII seminiferous tubules. At 28 days, 4 out of 6 animals still exhibited retention of Step 9 spermatids at the lumen of the seminiferous epithelium, but only through Stage X. At 57 days posttreatment, no changes were detected in the testis of 4 out of 6 rats, while 2 animals still had some retention of Step 19 spermatids into Stage X

In another experiment, 8 male Sprague-Dawley rats per dosage group were given 0 (control), 250, 500, 1000, or 2000 mg/kg Boric Acid via gavage and killed on day 14. The reproductive organ weights of rats given 250-2000 mg/kg of Boric Acid did not differ from control values at 14 days posttreatment. No definite histologic changes were detected in animals dosed with 250 or 500 mg/kg of Boric Acid In animals dosed with 1000 mg/kg, varying degrees of retention of Step 19 spermatids at the lumen of Stage IX-XII tubules was observed. Atypical cytoplasmic lobes of Step 19 spermatids were observed in Stage VIII Similar effects occurred more frequently at 2000 mg/kg, and one animal also had reduced numbers of Step 15-19 spermatids (Linder et al., 1990).

Noting that data were not available regarding reproductive toxicity in females, in juveniles, or in mice, Fail et al. (1991) studied reproductive toxicity of Boric Acid using the National Toxicology Program's reproductive assessment by continuous breeding (RACB) protocol using male and female CD-1 mice (11 weeks of age at the start of the breeding phase). Boric Acid was administered in the feed at concentrations of 0, 1000, 4500, and 9000 ppm. These doses were predicted to provide 110 mg/kg for males and 182 mg/kg for females at 1000 ppm, 598 and 846 mg/kg at 4500 ppm, and 1260 and 1660 mg/kg at 9000 ppm.

During Task 2, the cohabitation phase, exposure to Boric Acid significantly reduced fertility in a

dose dependent manner. None of the pairs treated with 9000 ppm were fertile. Severe seminiferous tubular atrophy in the high dose males suggested that the testis is the major target of Boric Acid. Significant decreases in the 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. The number of females producing litters decreased from 19/20 for the 1st litter, to 17/20 for the 2nd litter, to 6/20 for the 3rd litter, and to 1/20 for the 4th and 5th litters. The 1000 ppm group had fertility rates that were statistically similar to that of the controls.

During Task 3, the crossover mating to determine the affected sex, the infertility in the 9000 ppm group required the assignment of the control and mid-dose animals in an effort to ensure detectable fertility. As if the seminiferous tubular atrophy noted above was not reason enough to identify male mice as the affected sex, males from the 4500 ppm group mated with control females demonstrated reduced fertility compared to males from the control group mated with females from the 4500 ppm group Treated females in the 4500 ppm group mated to control males did demonstrated a slight reproductive effect: the average number of litters per pair was the same as control matings, but the live pup weight adjusted for litter size was significantly decreased and the average dam weight on postnatal day 0 was significantly lower for those females that produced litters.

For Task 4, the fertility trial of the F_1 animals, the fertility reductions noted above complicated the matter. F_1 animals from the 1000 ppm and the control groups were chosen. All parameters were indistinguishable, except that F_1 females from the 1000 ppm group had estrous cycles significantly shorter than those of the controls (4.19 ± 0.15 versus 4.70 ± 0.14) and fewer ambiguous vaginal smears (3% versus 13%).

The authors concluded that the RACB protocol indicated that Boric Acid is a reproductive toxicant in male mice, and to a much lesser extent in female mice. The NOAEL for the parenteral generation approached 1000 ppm, but the authors were not certain that 1000 ppm represented a NOAEL for the second generation (Fail et al., 1991).

Chapin and Ku (1994) continued the National Toxicology Program evaluation by conducting another RACB study to further evaluate male fertility and to correlate levels of boron in the testes to lesion development. Female fertility was not addressed. Male and female Swiss CD-1 mice were fed 1000, 4500, and 9000 ppm Boric Acid in their diet. Animals were cohabited for 14 weeks and pups were

evaluated as the litters were born, then euthanatized. The cohabitation period was followed by a 6-week separation period to allow for the delivery of the last litter. After weaning this litter, a test to determine the most affected sex was performed by mating animals from the middle-dose group with controls. After the delivery of the resulting litters, the F_0 mice were killed and necropsied. The F_1 mice were reared to sexual maturity while being fed the same diet given to their parents, and mated to nonsiblings within the same dose level. The resulting litter was evaluated and the F_1 mice were killed and necropsied.

To address the pathogenesis of Boric Acid, several small pilot studies were performed to determine that boric acid would affect rats (yet the Linder et al., 1990 study was in the reference list!) For the definitive study, treated animals received 9000 ppm Boric Acid in their feed, and 6 treated and 4 control animals were killed on each of days 4, 7, 10, 14, 21, and 28 and reproductive parameters evaluated. Because the testicular lesions seen in the pilot studies resembled those caused by androgen insufficiency, this hormone was evaluated on days 4, 7, and 10.

To address the relationship between lesions and testicular boron concentration, young adult male rats were fed a diet containing 0, 3000, 4500, 6000, and 9000 ppm Boric Acid. Six rats from each group were killed at weekly intervals for up to 9 weeks Body and organ weights, sperm parameters, histologic exams, clinical chemistries, and boron measurements were performed.

The 9000 ppm dose group had no litters at all, while the controls averaged 4.7 litters per cohabiting pair. Mean litter size was decreased in the 4500 ppm group as was adjusted live pup weight The 1000 ppm group was not different from controls in their fertility at any time. Other patterns of reproductive toxicity were comparable to that described by Fail et al., 1991. (*It is difficult to determine just why this arm of the study was done, the impact of 9000 ppm was so dramatic in the first study!*)

In the male rat pathogenesis study, the first lesion appeared in some animals at day 7, and consisted of an inhibition of sperm release. This progressed in severity, and was soon accompanied by a disorganization of the epithelium and the release of immature germ cells. By day 28, there were some atrophic tubules that contained only residual spermatogonia and somatic Sertoli cells.

In the study linking boron dose to the testes to lesions, the authors determined that 1) spermiation was inhibited in the 3000 and 4500 ppm groups with no atrophy (germ cell death and loss); 2) initially normal testis weight, with a significant decrease in numbers of epididymal sperm in these two dose groups; 3) a rise in bone boron until week 5, after which it plateaued, and no accumulation of boron in the

testes (compared to blood); 4) a correlation of dose rate with lesions, but not total dose, since no accumulation occurred in the testes; 5) testes that became atrophic did not recover for up to 4 full spermatogenic cycles

The authors expressed the view that rats are more sensitive to Boric Acid than mice They noted that the 9000 ppm dose level in mice and rats would correspond to 214 and 68 mg/kg day^{-1}; doses which are comparable to the well-known testicular toxicant, ethylene glycol monomethyl ether. They concluded that the target for male effects is the spermiation process, but could not distinguish between Sertoli cells and elongated spermatids as the target cell. They concluded that dose rate was related to the spermiation effect. They went on to describe the import of this finding to the overall risk assessment of Boric Acid. They argued that the pattern of testicular toxicity is such that there is only a mild effect with administration of a few high doses, while lower doses given more frequently produces a significant effect. Once the dose falls below a certain point, however, even increased frequency of administration does not produce an effect. All of this supports a threshold effect for reproductive toxicity, they suggested (Chapin and Ku, 1994).

The Yoshizaki et al. (1999) report mentioned earlier also included a breeding arm to the study. As noted earlier, each treatment group consisted of 20 males and 10 females. Boric Acid was dissolved in distilled water and administered orally for 3 weeks to male rats at dosages of 50, 150, and 500 mg/kg/day. Control rats received no Boric Acid. The dosage volume was 10 ml/kg. After treatment for 3 weeks, 10 males in each group were mated with 10 untreated females and dosing was continued until the presence of a copulation plug was confirmed. This was designated GD 0. On GD 13, all females were killed and necropsied. The numbers of corpora lutea, implants, dead embryos, and live embryos were counted. When treated males were mated with females after 3 weeks of treatment, no males in the 500 mg/kg group impregnated the females they cohabited with. Numbers of implants and live embryos in females mated with males in the 150 mg/kg group were lower and the pre-implantation loss rate was higher than the control values.

DEVELOPMENTAL TOXICITY

Heindel et al. (1992) reported the results of National Toxicology Program studies on the developmental toxicity of Boric Acid in rodents and rabbits. Timed-mated rats were given Boric Acid (0, 0.1, 0.2, or 0.4%) in the feed continuously from the morning of GD 0 to the morning of GD 20, or Boric

Acid at 0.8% in the feed from GD 6 to GD 15. Time-mated mice were given Boric Acid (0, 0.1, 0.2, or 0.4%) in the feed from GD 0 to GD 17. Rabbits were artificially inseminated and given Boric Acid by gavage (62.5, 125, or 250 mg/kg day^{-1}) on GD 6 - 19 Endpoints for maternal toxicity were food and water consumption, body weight, liver and kidney weights, kidney histology, uterine weight, and any signs of toxicity from daily observation. On GD 17 (mice), GD 20 (rats), or GD 30 (rabbits), animals were killed End points for developmental toxicity were embryonal/fetal weight and structural malformations and variations.

Rats

For the rats given Boric Acid on GD 0-20, there was a statistically significant decrease in maternal weight gain for the 0.4% group (143.6±3 9 g versus 160.6±3.8 g for the control). When considering all litters, the percentage of adversely affected implants/litter was significantly increased for the 0.2 and 0.4% groups compared to the controls (11.17±2.16% and 53 58±5.63% versus 5.46±1.35%). All the treatment groups had a significantly higher percentage of litters with one or more adversely affected implants. 75, 85, and 100% for the 0.1, 0.2, and 0.4% groups respectively, compared to 50% for controls.

There was also a statistically significant decrease in maternal weight gain for the 0 8% rats which were given Boric Acid on GD 6-15 (102.5±5.3 g versus 143.6±3.9 g). Likewise, there was a significant increase in the percentage of resorptions/litter for the treated group (36 2±8.7% versus 4.4±1.9%) There was also an increase in the percentage of adversely affected implants/litter and the percentage of litters with one or more adversely affected implants (77.71±6.77% versus 7.06±2.41% and 100% versus 50%, respectively).

Mice

For the mice, which were exposed to Boric Acid on GD 0-17, maternal weight gain was significantly decreased for the 0.4% group (16.0±1.1 g versus 21.4±0.8 g). Similarly there was a significant increase in the percentage of litters with one or more resorptions (19 3±4.5% versus 6.1±1.6%), litters with one or more adversely affected implants (27.4%±4.9% versus 9.5±1.8%), and fetuses malformed/litter (9.1±2.4% versus 2.7±1.2%) for the 0.4% group compared to the controls, but not for any other groups

Rabbits

In rabbits, maternal effects at 250 mg/kg day^{-1} included decreased feed consumption, decreased body weight, and decreased uterine weight, although the corrected maternal weight change was increased

at both 125 and 250 mg/kg day^{-1}. No definitive developmental toxicity was observed at 62.5 or 125 mg/kg day^{-1}. At the high dose, the rate of resorption was high (90% versus 6% for controls) and there was a high proportion of does with complete prenatal loss (73% of litters lost versus 0% for controls). The overall incidence of malformed fetuses was increased at the high dose only. There was no distinctive pattern of individual malformations, however.

The authors summarized the developmental toxicity findings across these three species as occurring in the range of 80 - 400 mg/kg day^{-1}. They contrasted this range with the level of human exposure in occupational settings. Dietary plus occupational exposure to boron were said to be 0.38 mg/kg day^{-1}, equivalent to 1.9 mg/kg day^{-1} of Boric Acid, 40 to 200 times less than the range at which developmental effects were seen in animals. (Heindel et al., 1994).

Price et al. (1996a) undertook another rat developmental toxicity study to confirm fetal body weight reductions and fetal skeletal anomalies at 0 1 and 0.2% Boric Acid in the diet, to determine the fetal weight reduction and skeletal effects NOAEL, to determine postnatal recovery, and to determine if the incidence of skeletal anomalies changed among groups postnatally. Timed-mated female Sprague-Dawley rats (numbers not given) were fed control or treated feed containing 0.025, 0.05, 0.075, 0.1, or 0.2% Boric Acid from GD 0 to GD 20. To assess prenatal develpment, pregnant females were killed on GD 20 and the body, liver, right kidney, and uterus were weighed. The numbers of ovarian corpora lutea, uterine implantation sites, resoprtions, dead fetuses, and live fetuses were recorded. Individual fetuses were weighed and live fetuses examined for external malformations. All fetal carcasses were evaluated for skeletal malformations

To assess postnatal development, pregnant females were allowed to deliver litters naturally and rear them to weaning age (PND 21). On PND 0, 4, 7, 14, and 21, the number of live or dead pups/litter was recorded, pups were weighed, and examined externally. Females which delivered a litter were killed on PND 21. Maternal liver and right kidney were weighted, and the uterine implantation sites were counted. Pups were killed on PND 21 and were examined internally for morphological abnormalities and gross pathology of the viscera. Heads from these pups were decapitated and examined for soft-tissue malformations. All pup carcasses were processed for evaluation of skeletal malformations.

No maternal deaths occurred in this study. Maternal body weight did not differ among groups during gestation or lactation, and weight gain was similarly unaffected. The maternal corrected weight -

gain and postpartum body weight were not affected. Absolute or relative maternal liver weight did not differ among groups on GD 20 or PND 21. Relative, but not absolute maternal right kidney weight was elevated in the 0.200% Boric Acid group on GD 20, but no effect was observed on PND 21.

On GD 20, the number of ovarian corpora lutea/dam, number of implantation sites/litter, percentage preimplantation loss/litter, and live litter size were equivalent among groups. Also, the percentages of resorptions or late fetal deaths were not affected. There was no definitive evidence for an adverse effect on offspring viability from conception through weaning. On GD 20, fetal body weight was significantly decreased by 6 and 12% for the 0.1 and 0.2% groups, respectively. Fetal body weight deficits on GD 20 did not persist into the postnatal period.

On GD 20 and PND 21, external malformations occurred with low incidences (≤0.5% fetuses or pups/group) which showed no apparent dose-response relationship. Visceral malformations also failed to show dose-related increases following Boric Acid exposure. On GD 20, the percentage of fetuses with skeletal malformations/litter showed a significant increasing trend, but the overall incidence of skeletal variations was not affected. Short rib XIII occurred in 0, 0, 0 2, 0.7, 1.5, and 3.4% of fetuses from the control through high dose groups respectively. On PND 21, the incidence of short rib was 0, 1.3, 0.5, 0.2, 0.9, and 3 9% of pups examined in the control through high dose groups, respectively. Based upon the absence of a dose-response relationship for short rib XIII across the nearly 10-fold concentration range between the low and high dose, findings of short rib XIII at concentrations below 0.2% Boric Acid in the diet did not appear to be treatment related.

The authors concluded that the fetal weight reduction was comparable to that in the previous report. They stated that the NOAEL for fetal weight reduction was 0.075% Boric Acid in the diet (55 mg/kg day^{-1}) and the LOAEL was 0.1% (76 mg/kg day^{-1}). The NOAEL and LOAEL for skeletal effects, based on an increased incidence of short rib XIII and wavy rib was the same as for fetal weight reduction. When evaluated postnatally, the NOAEL and LOAEL for skeletal effects, based on an increased incidence of short rib XII because wavy ribs were a repairable defect, was higher - the NOAEL was 0.1% Boric Acid (76 mg/kg day^{-1}) and the LOAEL was 0.2% (145 mg/kg day^{-1}). The authors state that recent risk assessments (see for example, Moore et al. (1997), discussed later) of toxicity to humans at current dietary or drinking water levels, based in part on the data from this study, indicated no significant risk to humans (Price et al., 1996a).

Although results had been reported in part in Heindel et al. (1994), Price et al. (1996b) again reported the results of this rabbit developmental toxicity study. The results did not change. The low dose of 62.5 mg/kg day^{-1} was nontoxic to both the dam and the fetus. No developmental toxicity was observed at 125 mg/kg day^{-1}. Increased prenatal mortality and malformations at 250 mg/kg day^{-1} constituted the LOAEL for rabbits. The authors again assigned a maternal and developmental NOAEL for rabbits at 125 mg/kg day^{-1} for Boric Acid (Price et al. 1996b).

In another study by Price et al. (1997) where the focus was on blood boron concentrations, 180 female Sprague-Dawley rats were assigned to a teratology study. These animals, 23 to 32 per group, were fed control chow or chow containing 0.025%, 0.050%, 0.075%, 0.100%, or 0.200% Boric Acid from GD 0 to GD 20. Of the180 rats, 169 were confirmed pregnant by uterine examination at necropsy on GD 20.

Average concentrations of boron in the blood increased with increasing dietary concentrations: 0.229 ± 0.143 (0), 0.564 ± 0.211 (0.025%), 0.975 ± 0.261 (0.05%), 1.27 ± 0.298 (0.075%), 1.53 ± 0.546 (0.1%), and 2.82 ± 0.987 (0.2%) µg/g. Maternal boron concentrations in the blood were correlated with indices of maternal dietary intake and embryo/fetal toxicity. Average fetal body weight per litter on GD 20 (both sexes) were significantly reduced following exposure to 0.1% or 0.2% Boric Acid. The 0.075% group with a blood concentration of 1.27 ± 0.298 µg/g (5.5x the control boron levels) corresponds to the developmental NOAEL of 10 mg/kg day^{-1}. The 0.1% group with a blood concentration of 1.53 ± 0.546 µg/g (6.7x the control boron levels) corresponds to the developmental LOAEL of 13 mg/kg day^{-1} (Price et al., 1997).

Narotsky et al. (1998) sought to more fully characterize the morphological changes in the axial skeleton of rats following prenatal exposure to Boric Acid. There are five experiments described in this study: multiple-day dosing, 1x per day; multiple-day dosing, 2x per day; single-day dosing, 2x per day; a pilot study on postnatal viability of exposed pups; and whole-embryo culture. In the first experiment, 3-5 dams per group received Boric Acid by gavage once daily on GD 6-9 at 0, 100, 200, 400, or 800 mg/kg. Distilled, deionized water was used as the vehicle. Maternal body weights were measured on GD 6-10, 13, 16, and 21. On GD 21, dams were killed and liver, kidney, and gravid uterine weights were obtained. Live fetuses were weighed individually, fixed, and stained for skeletal examination. In the second experiment methods were similar to those in Experiment 1 except 11-14 dams/group were used, and

Boric Acid was administered at 500 mg/kg twice daily on GD 5-9, 6-9, or 6-10. Controls received similar volumes (10 ml/kg) of vehicle on GD 5-10. Experiment 3 used methods similar to Experiment 2, except that Boric Acid, dosed at 500 mg/kg, was administered on single days during gestation. In the first block, 11-13 animals per group were treated on GD 6, 7, 8, or 9, and controls received vehicle on GD 6-9. In the second block, rats were dosed on GD 9, 10, or 11, and controls received vehicle on GD 9-11. In Experiment 4, dams (3-5 per group) were allowed to deliver. PND 1 was defined as GD 22 independent of actual time of parturition. Pups in each litter were individually examined and weighed on PND 1, 7, 14, 21, and 28. Litters were weaned on PND 21. On PND 28, pups were killed, their skin and viscera removed, and stained. In Experiment 5, embryos harvested at GD 9.5 were exposed in vitro to 0, 28.6, 57.2, or 85.8 µg/ml of Boric Acid for 48 hours, or Boric Acid for 24 hours followed with control serum for 24 hours.

In Experiment 1, the highest dose levels (800 mg/kg) caused no clinical signs of toxicity to the dams. Changes in maternal body weights were comparable for all dose levels. In Experiment 2, groups receiving 500 mg/kg on GD 5-9, 6-9, and 6-10 had one, one, and three maternal deaths, respectively. No clinical findings attributable to treatment were noted among surviving dams. Maternal body weights, however, showed significant decreases during GD 6-7 and 9-10 in all three treated groups and during GD 7-8 in the groups starting treatment on GD 6. In Experiment 3, no mortality or clinical signs of toxicity were noted following single-day dosing of 500 mg/kg. Significant losses in body weight were noted in all but the GD 10 group, which showed a nonsignificant reduction in weight gain.

As for developmental effects, in Experiment 1, none of the doses given on GD 6-9 had any significant effects of fetal viability; however, 800 mg/kg, the highest dose tested, was associated with a significant reduction (23%) in fetal weight. Increased incidences of cervical ribs were noted at 400 and 800 mg/kg, with the incidence at 400 mg/kg reaching statistical significance. All fetuses in this experiment had at least 13 pairs of ribs (the normal number in rats), though some were observed to have shortened 13^{th} ribs. Furthermore, the incidence of a 14^{th} thoracic rib was significantly increased at 800 mg/kg.

In Experiment 2, Boric Acid was clearly teratogenic. Resorption rates were significantly increased, and fetal weights were markedly reduced in all three treatment groups. Morphologically, progeny from all three groups receiving Boric Acid were affected. The group receiving Boric Acid on GD 5-9 was affected most severely with micro- or anophthalmia, agnathia, brachygnathia, cleft lip or palate, exencephaly, encephalocele, domed head, sternoschisis, rachischisis, craniorachischisis, scoliosis, and a variety of

abnormal bone fusions. Shortening or absence of the 13th rib was seen following all three treatment regimens, and reached significance in the groups exposed on GD 5-9 and 6-10.

In Experiment 3, single day exposures caused no significant effects on prenatal mortality; however, a slight increase in postimplantation loss was associated with progressively later treatments Fetal malformations were relatively rare following single day treatments, compared to the multiple day treatments. Both the GD 8 and GD 9 groups had low, but significant incidences of cervical ribs. The most notable effects induced by single day Boric Acid administration were alterations in the number of vertebrae, ribs, and sternebrae. In the GD 9 group, about 90% of the fetuses had only six cervical vertebrae. Progeny exposed on GD 10 also had increased incidences of <6 sternebrae. Unlike other groups, however, the GD 10 group had nearly 60% incidence of fetuses with <13 ribs.

In Experiment 4, the small sample sizes precluded a comprehensive statistical evaluation of postnatal growth and survival; however, there were several significant findings. Most notably, in the GD 9 exposed group, the six cervical vertebrae phenotype had 100% penetrance among the PND 28 survivors, though there was no significant effects on mortality or pup weight in this group. In the GD 10 exposed group, postnatal mortality was significantly increased during the PND 1-7 period. On PND 28, the survivors had significant incidences of cervical ribs and fused or small vertebrae. For the progeny exposed on GD 8, pup weights were significantly reduced on PND 21 and PND 28

In Experiment 5, exposure of embryos in vitro to Boric Acid resulted in decreases in head length (57.2 and 85.8 µg/ml groups), and in crown-rump length, somite number and developmental score (85.8 µg/ml group). Morphological analysis of somites 3-13 demonstrated a decreased width in the high dose group. Embryos exposed to Boric Acid for 24 hours and then grown in control serum for 24 hours had somites comparable to control embryos (Narotsky et al., 1998).

In order to study the vertebral column sensitivity to Boric Acid in developing CD-1 mice in utero, Cherrington and Chernoff (2002) conducted 4 experiments. In the first, 26 timed pregnant mice (10 per dose and 6 control) were given 0, 500, and 750 mg/kg Boric Acid by oral gavage once daily. Controls were given distilled water. On GD 17, all animals were killed and the fetuses removed and examined. Thirteenth rib length was significantly decreased for both treatment groups (2 59±0.03 mm and 2 46±0 04 mm for the 500 and 750 mg/kg dose groups vs. 2.82±0.02 mm for control).

For the second experiment, 160 timed pregnant females were assigned to10 groups: controls

treated on each of GDs 6-8, or only on a ingle GD 6, 7, or 8, and groups treated with Boric Acid on each of GDs 6-8, or only on a single GD 6, 7, 8, 9, or 10 Each dam in the Boric Acid groups was dosed with 400 mg/kg twice a day. GD 9 and 10 were not included in the statistical analysis because of the lack of concurrent controls Average fetal weight was decreased significantly for all treatment groups. Agenesis of the 13th rib was noted only on GD 8 and GDs 6-8. Also, reduced rib length and fused and/or branched ribs were observed in the thoracic region in the group treated on GDs 6-8.

For the third experiment, doses of 750 mg/kg Boric Acid were given twice daily on GD 8. Gross fetal examinations and skeletal evaluations were conducted as above Among the observations that were significantly different from the control at the $p \leq 0.05$ level were exencephaly, misshapen vertebrae, rudimentary ribs (defined as any free rib that was reduced in length), and unilateral lumbar vertebrae Among the malformations that were significant at the $p \leq 0.01$ level were fused arches, fused ribs, agenesis of ribs, and agenesis of a lumbar vertebra.

For the last experiment, mice received one dose of 750 mg/kg Boric Acid on GD 8. Gross fetal examinations and skeletal evaluations were conducted as above except no measurements were taken on ribs. Only the variables unilateral thoracic vertebrae and cervical ossifications differed significantly from the control An increase in fused ribs, arches, and hemivertebra were also observed (Cherrington and Chernoff, 2002).

Table 3 presents the available reproductive and developmental toxicity data in terms of the LOAEL or the NOAEL as reported by the authors or as gleaned from the report

CLINICAL ASSESSMENT

CASE REPORTS

Schillinger et al. (1982) reported the skin manifestations of Boric Acid poisoning in a 44 year old black woman. Half a can of Boric Acid had been ingested 3 days prior to presenting at an emergency room with a widespread exfoliative dermatitis. The patient also exhibited a persistent sensation of nausea with multiple episodes of vomiting. Blood samples taken at admission were lost. Renal function improved after one course of hemodialysis Over the course of a few days, skin lesions increased in severity and

Table 3. Boric Acid LOAELs and NOAELs for reproductive and developmental toxicity endpoints.

Animal/Delivery	Sex	Endpoint	LOAEL	NOAEL	Reference
rat/oral	male	sperm count reduction	150 mg/kg day^{-1}	50 mg/kg day^{-1}	Yoshizaki et al., 1999
rat/feeding	male	mildly inhibited spermiation	3000 ppm		Ku et al., 1993a
rat/cell culture	testicular cells in culture	decrease in ^{3}H-TdR incorporation	1 mM	0.3 mM	Ku et al., 1993b
rat/gavage	male	retention of step 19 spermatids	1000 mg/kg	500 mg/kg	Linder et al , 1990
rat/feeding	male and female	reduced male fertility	4500 ppm (598 mg/kg in males and 846 mg/kg in females)	1000 ppm (110 mg/kg in males and 182 mg/kg in females)	Fail et al., 1991
rat/feeding	male and female	reduced male fertility	4500 ppm	1000 ppm	Chapin and Ku, 1994
rat/oral	male	reduced number of implants and live embryos	150 mg/kg day^{-1}	50 mg/kg day^{-1}	Yoshizaki et al., 1999
mice/feeding	male and female	increase in % litters with one or more resorptions and malformations per litter	0.4%	0.2%	Heindel et al., 1992
rats/feeding	male and female	prenatal skeletal abnormalities	0.1%	0 75%	Price et al., 1996a
rats/feeding	male and female	postnatal skeletal abnormalities	0.2%	0.1%	Price et al., 1996a
rabbits/gavage	male and female	increase in prenatal mortality and malformations	250 mg/kg day^{-1}	125 mg/kg day^{-1}	Price et al., 1996b
rats/feeding	male and female	decreased fetal body weight per litter	13 mg/kg (0.1% in diet) with blood levels of 1.53 ± 0.546 µg/g	10 mg/kg (0.75% in diet) with blood levels of 1.27 ± 0.298 µg/g	Price et al., 1997

degree of involvement and a fever of 39.0 °C developed. Skin lesions were responsive to topical gentian violet at denuded areas with daily soaks in $KMnO_4$ diluted 1 : 80000. One week after admission, hematocrit levels dropped to 19%, with a hemoglobin of 6.5 g. A bone marrow aspirate was consistent with bone marrow toxicity secondary to Boric Acid poisoning. The patient responded well to transfusion with 3 units of packed red blood cells.

O'Sullivan and Taylor (1983) reported on 7 infants with seizures induced by chronic Boric Acid ingestion. The infants were each regularly given pacifiers dipped in a proprietary mix of borax and honey available over the counter. Initial identification of the link with Boric Acid was made in 4 infants who presented with a seizure disorder with vomiting, loose stools, and iritability *(no kidding)*. A further 3 infants were identified with a seizure disorder in which borax and honey were implicated. Blood boron was measured in three infants and found to be 2.6, 8.5, and 8.4 µg/ml. Blood boron levels measured in 15 infants had a mean level of 0.21 µg/ml. The authors added a postscript noting that since 1 April 1983, Boric Acid preparations in the Republic of Ireland have been available only by prescription.

Linden et al. (1986) described 4 patients with elevated serum Boric Acid levels after single ingestions of 10 to 297 g of Boric Acid.

- A 14 month old male ingested 20 g of 50% Boric Acid mixed with sugar. No symptoms developed, but the blood Boric Acid level at 4 hours after ingestion was reported as 8 mg/dL (13 µg/ml boron).
- A 2 year old male ingested 10 g of Boric Acid mixed with flour. Intermittent vomiting was noted for 3 hours following ingestion. No further symptoms developed. Blood boron levels were reported as 53 mg/dL *(90 µg/ml boron)* at 1 hour after ingestion and 58 mg/dL at 7 hours.
- A 28 year old female ingested an estimated 297 g of a 99% Boric Acid insecticide. Spontaneous vomiting developed within 1 hour after ingestion. The patient underwent gastric lavage followed by activated charcoal and a cathartic. No further symptoms developed. The blood boron level was reported at 2 hours post ingestion to be 4.9 mg/dL *(8.1 µg/ml boron)*.
- A 35 year old woman ingested 80 g of boric acid in a fungicidal preparation. Spontaneous vomiting developed within ½ hour, accompanied by facial flushing. Syrup of ipecac was administered, followed by activated charcoal and a cathartic. No further symptoms developed. Blood boron levels were reported as 232 mg/dL *(390 µg/ml boron)* at 1 hour after ingestion and 136 mg/dL *(226 µg/ml boron)* at 13 hours.

Astier et al. (1988) described an acute boron poisoning following accidental oral ingestion of Boric Acid. A 72 year old woman ingested 2 doses of Boric Acid totaling 45 g as a result of a dispensing error.

The first dose was taken in the morning of day 0 and produced vomiting and diarrhea. The second dose was taken in the evening of day 0 and again resulted in vomiting. She was seen at a hospital in the early morning hours of day 1 post-ingestion. She underwent a gastric enema and was hospitalized in the intensive care unit. The patient had a non-pruriginous erythema predominant in the upper half of the thorax and face. Her blood pressure was 160/100 mm Hg, pulse was 90/minute, and body temperature was 37.2°C. Total parenteral feeding was maintained for 9 days. A fever of 38.8°C persisted for 7 days. At 12 days, the patient had recovered.

The initial concentration of boron in the plasma was 64 mg/L (day 1, 4 am - time 0) Plasma levels decreased to around 37 mg/L, 10 hours later. A slow linear decrease to around 2 mg/L over the next 5 days. The urinary excretion at time 0 was approximately 250 mg/L. Urinary excretion increased to around 1000 mg/L 24 hours later, then leveled off to 1400 - 1450 m/L at 3 to 6 days (Astier et al., 1988).

Miyazaki et al. (1992) described the case of an 82 year old woman who accidentally ingested insecticide containing Boric Acid. The insecticide was homemade, using ½ tablespoon milk, 1 tablespoon sugar, 200 g of chopped onion, 250 g of Boric Acid, and 70 - 100 g flour. Vomiting and diarrhea occurred within 3 hours of ingestion. At around 24 hours after ingestion, the woman was semi-conscious. Three days post-ingestion the patient was comatose, with a blood pressure of 70 mm Hg, pulse rate of 150/minute and a fever (38.5°C). Support therapy for low blood pressure and sinus bradycardia were performed initially. Inflammation of the skin and mucous membranes developed. Blood pressure continued to fall, however, and the patient died on the 8th day after ingesting the Boric Acid insecticide.

Restuccio et al. (1992) reported the case of a 45 year old male who ingested two cups of Boric Acid crystals dissolved in water. Nausea, vomiting, diarrhea, and dehydration occurred shortly thereafter. Two days after ingestion, he presented to the emergency room with hypotension, metabolic acidosis, renal failure, a generalized erythematous rash, and several superficial skin abrasions. Intravenous fluids and vasopressors failed to improve his condition Atrial fibrillation developed, but attempts at conversion were unsuccessful and the rhythm deteriorated to electromechanical dissociation. The patient died 17 hours after admission. The blood Boric Acid level 52 hours after ingestion was 42 mg/dL *(70 µg/ml boron)*.

Ishii et al. (1993) described the case of a 77 year old male who ingested an estimated 30 g of Boric Acid as a single oral dose (to stop hiccups!). On admission he exhibited vomitting, diarrhea, and still had the hiccups. The skin of the face and trunk was markedly erythematous. Acute renal failure was

treated with hemodialysis and charcoal hemoperfusion in series. Prior to dialysis, the blood Boric Acid level was 37.7 µg/ml (*6.3 µg/ml boron).* Therapy reduced blood levels of Boric Acid to 25.3 µg/ml , but the patient died of cardiac insufficiency.

OCCUPATIONAL EXPOSURES

Garabrant et al. (1984) evaluated workers exposed to boron oxide and Boric Acid in a plant in which Boric Acid was manufactured from borax and boron oxide manufactured from Boric Acid. Both boron oxide and Boric Acid were described as fine, crystalline powders. Airborne dust measurements had been recorded at different plant locations and were used to relate respiratory and ocular irritation symptoms to exposure. Workers were placed in the exposed group if they had held at least one job in an area with exposure to boron oxide or Boric Acid (113 workers) Workers were placed in the non-exposed group if they had never worked in an area with exposure (214 workers). There were no demographic differences between the two groups The mean total particulates measured in exposure areas was 4 1 mg/m^3, with a range from 1.2 to 8 5 mg/m^3. The authors noted that it was possible for levels to occasionally exceed the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of 10 mg/m^3. A statistically significant increase in eye irritation, dryness of the mouth, nose or throat, sore throat, and productive cough were seen. The authors noted that the ACGIH TLV was based on ocular and dermal effects of boron oxide and Boric Acid and suggested that this was the first report of respiratory toxicity at levels below the ACGIH TLV.

Garabrant et al. (1985) reported a study of workers at a borax mining and refining plant in which borax ore is recovered from an open pit mine, crushed, and dissolved with steam. Borax is crystallized from the solution, washed, and kiln dried, to produce a hydrated borax material. Anhydrous borax is produced by heating the hydrated borax to a molten glass, followed by cooling and pulverization to a fine powder. Mean dust exposures were measured in different plant areas and combined with each worker's occupational history from their personnel file to establish three groups: low exposure (0.9 mg/m^3); medium (4.5 mg/m^3); and high (14.6 mg/m^3). Each worker was administered a standard questionairre to obtain information on respiratory symptoms and smoking history. Pulmonary function tests were performed and a chest radiograph was taken. Pulmonary function and chest radiographs did not show a clear pattern of abnormalities, but chronic bronchitis and productive cough were related to exposures above 4.4 mg/m^3 (the medium and high exposure groups).

Hu et al. (1992) related acute respiratory and ocular irritant responses to occupational exposures to Sodium Borate dusts. Symptom assessment in 79 exposed and 27 unexposed workers was done in interviews before their shift began and then hourly for the next 6 hours of the shift, four days in a row. At each interview, peak respiratory flow was measured (the best of three efforts was recorded). Exposure assessments were done using personal direct reading aerosol monitors from which were recorded continuous measurements of particulate matter. Because of the study design, the authors reported both daily exposures and short-term peak exposures. Both exposures were linearly related to acute respiratory and ocular irritation, but the authors suggested that the short-term peak exposures are likely responsible for the excess of irritant symptoms

Hu et al. (1993) refined the above study by providing each worker with an electronic recording device with which the worker could mark the onset of an irritant response with precision; an event monitor The time course of symptom response was then correlated with the continuous particulate monitoring in an attempt to link symptoms with changes in exposure level in a field setting. Hourly surveys were done as in the previous study described above. There was not a complete match between survey findings and the event monitor. Some surveys indicated an irritant response at the end of an hour in which no event monitor entries were made by the worker. There was also a high rate of false positives recorded on the event monitor, when the survey failed to elicit any report of irritant response.

RISK ASSESSMENT

Moore et al. (1997) described an assessment of Boric Acid and borax using the IEHR evaluative process for assessing human developmental and reproductive toxicity of agents The process included an exposure assessment, a general review of an agent's toxicology profile, a review of specific reproductive and developmental toxicity data, a comparison of these latter data for consistency, and a conclusion about the agent's potential risk for humans, including additional studies that might be needed All doses were converted to millimoles (mmol) of boron per kg body weight using the conversion that 1 g of Boric Acid corresponded to 16.2 mmol boron and that 1 g of borax corresponded to 10.5 mmol boron.

Because of its natural occurrence, boron is widely distributed in surface and ground water. Boron levels are not currently regulated in municipal drinking water. Most drinking water boron concentrations can be expected to be below 1 mg/L. Consumer exposures mentioned included cosmetics. *[According to this report, in 1981 the Food and Drug Administration limited Boric Acid concentrations to 5% in consumer*

goods. On more close scrutiny, this appears to be the CIR Safety Assessment!!!] Food intake comes primarily from boron in fruits, vegetables, nuts, legumes, and grains. Daily dietary intake was estimated to be on the order of 1.5 mg boron in the U.S. Boron is used in some pesticides. Occupational exposure of some 450,000 workers was estimated. Exposure estimates did not include any contribution from cosmetics

No toxicologic findings were described that were not considered by CIR in its initial assessment or in the studies summarized in this review. A threshold in the IEHR process appears to be the sufficiency and relevance of the information. For both reproductive and development toxicity, there were sufficient animal data to permit judgment regarding safety. For reproductive toxicity, a boron NOAEL of 1.6 mmol/kg (inhibited spermiation) was the lowest given (98 mg/kg Boric Acid). For developmental toxicity, a boron NOAEL of 0.9 mmol/kg (in rats) was the lowest given (55 mg/kg Boric Acid).

A margin of exposure (MOE) is the magnitude of difference between human exposure levels and either or both the NOAEL values or subsequently calculated benchmark doses (BMDs). The BMD is the lower confidence limit on a model-derived estimate of a dose corresponding to a particular adverse effect seen at a frequency higher than background. The MOE for reproductive toxicity for a male exposed to boron in food, drinking water, body-building supplements, and the workplace would be 72. The MOE for developmental toxicity in individuals exposed to boron in diet and drinking water was 200. The author further went on to determine an unlikely effect level (UEL), an estimate of the daily exposure of the human population that is without appreciable risk of reproductive or developmental effects. For reproductive toxicity, the boron UEL was 0.07 - 0 13 mmol/kg day^{-1} (4.3mg/kg day^{-1} Boric Acid). For developmental toxicity, the boron UEL was 0.03 mmol/kg day^{-1} (1.9 mg/kg day^{-1}). In both cases, typical human exposures were below those "without appreciable risk" levels (Moore, et al , 1997)

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