

Parabens

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Parabens have been widely used as preservatives in the cosmetics, food, and pharmaceutical industries for more than 70 years. Monitoring for paraben allergy closely followed with studies reporting paraben testing in standard screening fashion as early as 1940. The frequency of sensitivity to this widely used biocide has remained low and remarkably stable for many decades despite extensive use and progressive expansion of utilization worldwide. The authors select paraben mix as the (non)allergen of the year. Paraben reactions are quite uncommon and generally relevant. Parabens remain one of the least allergenic preservatives available. The unsubstantiated public perception of paraben safety has led to its replacement in many products with preservatives having far greater allergenic potential. This report reviews the well-established safety of parabens from an allergologic standpoint.

The antimicrobial effect of parabens and their potential utility as preservatives were first reported in 1924 by Sabalitschka.¹ Their use has steadily increased; they are now among the most common biocides present in cosmetics, foods, and pharmaceuticals. This favored status has been achieved because of documented minimal toxicity, low cost, chemical inertness, and near worldwide acceptance (although that status is currently being challenged). Cosmetic

chemists use parabens in their formulations because they have no perceptible odor or taste, are effectively pH neutral, and do not discolor or harden.² Within this family, methylparaben, ethylparaben, propylparaben, and butylparaben are the most commonly used members, independently and in combination with each other or other biocides. Methylparaben and propylparaben are by far the most used, generally at concentrations of 0.4% or less and frequently much lower.^{3,4} Parabens are assessed as nonmutagenic.⁵

Without preservation, cosmetic products and pharmaceuticals rapidly become contaminated with mold, fungi, and bacteria, resulting in spoilage and increased infection risk. The cleaner the manufacturing process and site, the less preservation required. Particularly problematic microbes are the gram-positive *Staphylococcus aureus* and the gram-negative *Escherichia coli*. Product preservation is an absolute necessity. Despite the misguided apprehension about and public fear of preservatives being “bad for you” or “not natural,” parabens have been classified as generally regarded as safe by the US Food and Drug Administration (FDA).⁶

PHYSICOCHEMICAL PROPERTIES AND METABOLISM

Parabens are homologous esters of *p*-hydroxybenzoic acid and represent an aromatic carboxylic acid containing a carboxyl group bonded directly to a benzene ring; a hydroxy group is present on position 4 with varying alkyl radicals as side chain. Parabens in general are stable and nonvolatile; absorbed via the gastrointestinal tract and, to a degree, percutaneously; hydrolyzed to *p*-hydroxybenzoic acid; and conjugated with rapid urinary excretion. There is no solid evidence of accumulation within body tissues or organs, although detectable tissue and organ levels of indeterminate duration have been reported. One study has shown that parabens weakly interact

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TABLE 1. Biocide Potency as Measured by Minimal Inhibitory Concentration*

Preservative	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>	<i>Aspergillus niger</i>	<i>Candida albicans</i>
MCI/MI	4	3	4	5
MI	40	100	750	100
BIT	250	40	350	200
Methylparaben	2000	1500	1000	1000
BNPD	50	50	3200	400
MDGN	150	30	400	80
IPC	625	156	10	39
Phenoxyethanol	3200	6400	3200	3200

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*Minimal inhibitory concentration in µg/ml.

Abbreviations: BIT, benzisothiazolinone; BNPD, 2-bromo-2-nitropropane-1,3-diol; IPC, iodopropynyl butylcarbamate; MCI, methylchloroisothiazolinone; MDGN, methyl dibromoglutaronitrile; MI, methylisothiazolinone.

with human serum albumin, thus suggesting that they are present to some degree in free form in plasma and available to reach or, theoretically, even accumulate in internal organs and tissues.⁷ Notwithstanding, parabens have not been proven to be carcinogenic or cytotoxic. Parabens are white, odorless, and crystalline and exhibit adequate water solubility to achieve preservative activity. Increasing oil and organic solvent solubility is seen with increasing alkyl chain length (the same increase of chain length decreases water solubility and therefore the desired preservation activity). They are used in cosmetics, pharmaceuticals, and foods, but a strong, undesirable metallic taste occurs at concentrations of more than 0.08%, which (along with the understandable desire to minimize systemic exposure) results in limiting concentration used in foods.⁸ They are biodegradable by a number of nonspecific enzymes in nature, a fact that would suggest a potential environmental benefit in their use.⁹

ANTIMICROBIAL ACTIVITY

Paraben biocidal mechanism, in general, and propyl paraben, in particular, may be linked to mitochondrial failure dependent on induction of membrane permeability transition accompanied by the mitochondrial depolarization and depletion of cellular adenosine triphosphate through uncoupling of oxidative phosphorylation.¹⁰ At the root of antimicrobial activity is the disruption of membrane transport processes, although some investigators have identified the inhibition of DNA and RNA synthesis; action upon key enzymes such as adenosine triphosphatases and phosphotransferases may also play a role.^{11–13} On the macroscopic level, the mechanism of antibacterial action of parabens is linked to the membrane with disruption of the lipid bilayer, thereby interfering with bacterial membrane transport processes and perhaps causing the leakage of intracellular constituents.¹⁴

The paraben family has excellent coverage against fungi and gram-positive bacteria. They are more effective against fungi than bacteria, and antibacterial activity is most effective against gram-positive organisms.¹⁵ Evidence of antimicrobial activity for commonly used parabens shows broad inhibition of *E. coli*, *Pseudomonas aeruginosa*, *Aspergillus niger*, and *Candida albicans*, with higher inhibition of staphylococcal species, particularly *S. aureus*.¹⁶ The potency of cosmetic preservatives

has been studied, and minimal inhibitory concentration (MIC) determinations reveal parabens to be less powerful biocides in comparison to other common agents as evidenced by much higher MIC concentrations (Table 1).¹⁷ Antimicrobial activity also differs to a significant degree between parabens (Table 2).¹⁸ Within a bacterial genus, MIC levels may vary greatly; such is the case with *Salmonella* species.¹⁹

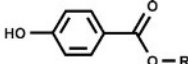
Combinations of parabens are often found in final formulations, depending on solubility differentials, desired shelf life, and spectrum of activity. Evidence exists for improved antimicrobial efficacy with the use of lower concentrations of multiple parabens. Methylparaben and ethylparaben are the 2 most frequently paired.²⁰ Paraben biocidal activity increases with the length of the hydrocarbon alkyl chain, while solubility simultaneously drastically decreases. This is another rationale behind using parabens in combination.^{10,21} The issue of solubility of individual parabens when used in combination is complex. Propylparaben exhibits a peculiar solubility behavior in aqueous solution, with approximately 50% decreased solubility in mixtures also containing ethylparaben, a finding substantiated by solubility experiments on tertiary and quaternary combinations of parabens.²²

TABLE 2. Inhibition of Bacteria and Fungi by Esters of *p*-Hydroxybenzoic Acid

Name	Methyl	Ethyl	Propyl	Butyl
<i>Salmonella typhi</i>	0.2	0.1	0.1	0.1
<i>Escherichia coli</i>	0.4	0.1	0.1	0.4
<i>Staphylococcus aureus</i>	0.4	0.1	0.05	0.0125
<i>Proteus vulgaris</i>	0.2	0.1	0.05	0.05
<i>Pseudomonas aeruginosa</i>	0.4	0.4	0.8	0.8
<i>Aspergillus niger</i>	0.1	0.04	0.02	0.02
<i>Chaetomium globosum</i>	0.05	0.025	0.00625	<0.003125
<i>Trichophyton interdigitale</i>	>0.008	0.008	0.004	0.002
<i>Candida albicans</i>	0.1	0.1	0.0125	0.0125

Values are percentages.

Adapted from Block.¹⁸

TABLE 3. Structure of Parabens[§]


R =	COMPOUND NAME	MOLECULAR FORMULA	CHEMICAL STRUCTURE
-H	HYDROXYBENZOIC ACID*	C ₇ H ₆ O ₃	
-CH ₃	METHYLPARABEN*	C ₈ H ₈ O ₃	
-CH ₂ (2)CH ₃	PROPYLPARABEN*	C ₁₀ H ₁₂ O ₃	
-CH ₂ CH ₃	ETHYLPARABEN*	C ₉ H ₁₀ O ₃	
-CH ₂ (3)CH ₃	BUTYLPARABEN*	C ₁₁ H ₁₄ O ₃	
-CH ₂ C ₆ H ₅	ISOPROPYLPARABEN*	C ₁₀ H ₁₂ O ₃	
-CH ₂ CHCH ₃ (2)	ISOBUTYLPARABEN*	C ₁₁ H ₁₄ O ₃	
-CH ₂ (2)CH ₃ + NaO ₃	SODIUM PROPYLPARABEN*	C ₁₀ H ₁₁ NaO ₃	
CH ₂ (3)CH ₃ + K ⁺	POTASSIUM BUTYLPARABEN*	C ₁₁ H ₁₃ KO ₃	
COMPLEX STRUCTURE	UNDECYLENOYL PEG 5 PARABEN*	C ₂₈ H ₄₄ O ₉	
-CH ₂ (6)CH ₃	HEPTYLPARABEN	C ₁₄ H ₂₀ O ₃	
-CH ₂ C ₆ H ₅	BENZYL PARABEN	C ₁₄ H ₁₂ O ₃	
-CH ₂ (4)CH ₃	PENTYLPARABEN	C ₁₂ H ₁₆ O ₃	
-CH ₂ (7)CH ₃	OCTYLPARABEN	C ₁₅ H ₂₂ O ₃	
-PHENYL	PHENYL PARABEN	C ₁₃ H ₁₀ O ₃	
-CH ₂ (11)CH ₃	ISODECYL OR DODECYL PARABEN	C ₁₉ H ₃₁ O ₃	
COMPLEX STRUCTURE	HEXAMIDINE DIPARABEN	C ₃₄ H ₃₈ N ₄ O ₈	
-K	POTASSIUM PARABEN	C ₇ H ₅ KO ₃	
-Na ⁺	SODIUM PARABEN	C ₇ H ₅ NaO ₃	
-CH ₂ (2)CH ₃ + Ca ⁺	CALCIUM PARABEN	C ₂₀ H ₂₂ CaO ₆	
-CH ₃ + K ⁺	POTASSIUM METHYL PARABEN	C ₈ H ₇ KO ₃	
-CH ₂ CH ₃ + K ⁺	POTASSIUM ETHYL PARABEN	C ₉ H ₉ KO ₃	
-CH ₂ (2)CH ₃ + K ⁺	POTASSIUM PROPYL PARABEN	C ₁₀ H ₁₁ KO ₃	

TABLE 3. (Continued)

-CH ₂ (1)CH ₃ + SO ₄	ETHYLPARABEN SULFATE	C ₉ H ₉ O ₆ S	
-CH ₂ (2)CH ₃ + SO ₄	PROPYL PARABEN SULFATE	C ₁₀ H ₁₂ O ₆ S	
-CD ₂ (2)CD ₃	PROPYL d7† PARABEN	C ₁₀ H ₁₂ O ₃	
-CD ₂ (2)CD ₃	BUTYL d9 PARABEN	C ₁₁ H ₁₄ O ₃	
-CD ₂ CD ₃ (2)	ISOBUTYL d9 PARABEN	C ₁₁ H ₁₄ O ₃	
-CD ₂ (4)CD ₃	PENTYL d11 PARABEN	C ₁₂ H ₁₆ O ₃	
-CD ₂ C ₆ D ₅	BENZYL d7 PARABEN	C ₁₄ H ₁₂ O ₃	
-CD ₂ C ₆ D ₅	ISOPROPYL d7 PARABEN	C ₁₀ H ₁₂ O ₃	
-CD ₂ CD ₃	ETHYL d5 PARABEN	C ₉ H ₁₀ O ₃	
-CD ₃	METHYL d3 PARABEN	C ₈ H ₈ O ₃	
-CH ₃ +D ₄	METHYL PARABEN d4	C ₈ H ₈ O ₃	
-CH ₃	METHYL PARABEN-13C ₆ ‡	C ₈ H ₈ O ₃	

* Currently used in cosmetics as identified in database search.

† Deuterium, the isotope of hydrogen that has a single neutron as well as a proton in the nucleus

‡ Carbon-13 (¹³C) is a natural, stable isotope of carbon with a nucleus containing six protons and seven neutrons.

§ Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, Han L, He J, He S, Shoemaker BA, Wang J, Yu B, Zhang J, Bryant SH. PubChem Substance and Compound databases. Nucleic Acids Res. 2016 Jan 4; 44(D1):D1202-13. Epub 2015 Sep 22 [PubMed PMID: 26400175] doi: 10.1093/nar/gkv951.

Because coverage against gram-negative bacteria is limited, a second nonparaben biocide is often added to final formulations. Phenoxyethanol is the most commonly found synergistic biocide, but formaldehyde-releasing biocides and isothiazolinones are also frequently used.²³ These combination biocides often allow effective preservation with lower concentrations of all preservative components.

STRUCTURAL CONSIDERATION

Thirty-five different parabens have been identified. Excluding *p*-hydroxybenzoic acid and structures with deuterium and carbon 13, and including complex structures, calcium, sodium, and potassium salts and sulfates, there are at least 24 different parabene moieties. Their relevant side chains, common names, chemical formulas, and structures may be compared (Table 3).²⁴ Up to 10 have been identified as present in a single cosmetic formulation, although use of 2 to 5 is not uncommon.^{25,26}

TABLE 4. Common Synonyms for Parabens

Methylparaben	Propylparaben	Ethylparaben	Butylparaben	Benzylparaben
Methyl paraben	Propyl paraben	Ethyl paraben	Butyl paraben	Benzyl paraben
Methyl <i>p</i> -hydroxybenzoate	Propyl <i>p</i> -hydroxybenzoate	Ethyl <i>p</i> -hydroxybenzoate	Butyl <i>p</i> -hydroxybenzoate	Benzyl <i>p</i> -hydroxybenzoate
Methyl 4-hydroxybenzoate	Propyl 4-hydroxybenzoate	Ethyl 4-hydroxybenzoate	Butyl 4-hydroxybenzoate	Benzyl 4-hydroxybenzoate
Methyl parahydroxybenzoate	Propyl parahydroxybenzoate	Ethyl parahydroxybenzoate	Butyl parahydroxybenzoate	Benzyl parahydroxybenzoate
<i>n</i> -Methyl- <i>p</i> -hydroxybenzoate	<i>n</i> -Propyl <i>p</i> -hydroxybenzoate	Ethyl <i>p</i> -hydroxybenzoate	<i>n</i> -Butyl- <i>p</i> -hydroxybenzoate	<i>n</i> -Benzyl- <i>p</i> -hydroxybenzoate
<i>p</i> -Hydroxybenzoic acid methyl ester	<i>p</i> -Hydroxybenzoic acid propyl ester	<i>p</i> -Hydroxybenzoic acid ethyl ester	<i>p</i> -Hydroxybenzoic acid butyl ester	<i>p</i> -Hydroxybenzoic acid benzyl ester
CAS 99-76-3	CAS 94-13-3	CAS 120-47-8	CAS 94-26-8	CAS 94-18-8
Nipagin <u>M</u>	Nipasol <u>M</u>	Nipagin A	Nipabutyl	Nipabenzyl
Tegosept M	Tegosept P	Tegosept E	Tegosept B	Benzyl Tegosept
Methyl parasept	Propyl parasept	Ethyl parasept	Butyl parasept	Benzyl parasept
Benzoic acid, 4-hydroxy-methyl ester	Benzoic acid, 4-hydroxy-propyl ester	Benzoic acid, 4-hydroxy-ethyl ester	Benzoic acid, <i>p</i> -hydroxy- butyl ester	Benzoic acid, <i>p</i> -OH-phenylmethyl est
Maseptol	Nipazol	Catalase	Butyl chemosept	Parosept
Preserval M	Propyl butex	Easeptol	Butoben	Nisapulvol (TN)
<i>p</i> -Oxybenzoesauremethylester	Betacide P	1 ethyl butex	Butyl tegosept	Solbrol Z
<i>p</i> -Carbomethoxyphenol	Parasept	HSDB 938	Butyl butex	Phenylmethyl 4-hydroxybenzoate
Methaben/methylben	Propagin	Mycocoten	Aseptoform butyl	W-100208
Metoxyde	Chemacide pk	Nipagin A	Preserval B	CAS-94-18-8
Preserval	Chemocide pk	Nipazin A	Butyl parasept	UNII-8Y41DYV4VG
Metaben	Propyl parasept	Solbrol A	Solbrol B	NSC 8080
Moldex	Aseptoform P	Solbrol A	UNII-3QPI1U3FV8	DSSTox_GSID_22526
<i>p</i> -Methoxycarbonylphenol	Propyl chemosept	<i>p</i> -Carbethoxyphenol	FEMA number 2203	ACMC-209raq
Paridol	Protaben P	UNII-14255EXE39	Caswell no. 130A	EINECS 202-311-9
Septos	Betacine P	Aseptoform E	4-(Butoxycarbonyl)phenol	8Y41DYV4VG
Solbrol	Propyl aseptoform	Mekkings E	Lexgard B	AI3-02955
FEMA no. 2710	Nipagin P	Aseptin A	<i>n</i> -Butyl-4-hydroxybenzoate	CHEBI: 34571
Methyl butex	Nipasol P	Bonomold OE	FEMA no. 2203	AC1L1O6S
Methyl Chemosept	Solbrol P	3NSC 23514	DSSTox RID_75434	SBB068798
Solbrol M	Bonomold OP	<i>p</i> -Oxybenzoesaureaethyl ester	Prestwick 0-3_000894	DSSTox RID_76613
Abiol	Preserval P	Caswell no. 447	EINECS 202-318-7	NGCC00164155-01
Aseptoform	Paseptol	Carbethoxyphenol	EPA Pest. Chemical Code 061205	DSSTox_CID_2526

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SYNONYMS FOR PARABEN

Marks et al²⁷ identified 14 synonyms for paraben preservatives. Similar synonym lists may be found in other references. PubChem, an online compendium of chemical substances, maintains a list of depositor-supplied synonyms for parabens in cosmetics and industrial products.²⁸ Thirty synonyms and trade names for the 5 most commonly used paraben derivatives are displayed (Table 4). Including all tabulated nomenclature from this list and similar names notwithstanding, there are many names by which paraben derivatives may be identified in occupational applications: methylparaben has 220 synonyms²⁹; propylparaben, 179 synonyms³⁰; ethylparaben, 175 synonyms³¹; butylparaben, 173 synonyms³²; and benzylparaben, 100 synonyms.³³ In cosmetic products, the International Nomenclature for Cosmetic Ingredients name, as listed in the column headers of Table 4, must be used.

SOURCES OF EXPOSURE TO PARABENS

Parabens are ubiquitous.^{34,35} They have been documented in house dust, pond water, and even trace amounts in mineral and treated water samples.³⁶ The 3 major sources of parabens are cosmetics, medications, and food stuffs, and these will be examined separately.^{35,36} Estimates in the United States suggest that the average total paraben exposure per individual is approximately 76 mg/d (up to 1.3 mg/kg per day for a person weighing 70 kg).¹⁰ Cosmetics and personal care products provide roughly two thirds of this at 50 mg/d, whereas pharmaceutical products supply 25 mg/d, and food contributes only 1 mg/d. The concentration of parabens in foods is usually less than 1%. However, given their poor percutaneous absorption, parabens applied to the skin may account for a significantly lower systemic burden than does exposure from foods or systemic medicaments.³⁷

Cosmetic Formulations

One European study found parabens in 99% of leave-on products and 77% of rinse-off products.³⁸ Zirwas and Moennich³⁹ found parabens as the seventh most common allergen in shampoos, behind the more frequently positive preservative isothiazolinone. Uter et al⁴⁰ in 2014 reported that, of 4680 German products, 39% contained between 1 and 5 parabens; most often, parabens were

found with phenoxyethanol. Our personal internet database searches have identified German products that contained up to 7 parabens.⁴¹

Gabb and Blake⁴² looked at 38,975 consumer products and found that 4435 contained methylparaben (11.4%), 1356 contained ethylparaben (3.5%), and 1008 contained butylparaben (2.6%) (Fig. 1). They found parabens to be rarely used in household products. Only methylparaben was identified in ingested products, whereas hair, oral, and personal care products enjoy relatively broad application at 10% to 30%. Bronzers, tanners, eye makeups, and foundations had methylparaben present more than 40% of the time.

In 1 comprehensive US series, Scheman et al^{43–46} and the American Contact Alternatives Group chronicled the frequency of paraben utilization in a widespread array of 5416 cosmetic products. Parabens were found in 66% to 87% of women's cosmetics, 30% of shampoos, 77% to 82% of lipsticks and lip liners, 30% of sunblocks, and 23% of wipes. Notably, none of the 195 deodorants and antiperspirants examined contained parabens.

The American Contact Dermatitis Society maintains a database of cosmetic and household products, known as the Contact Allergen Management Program (CAMP).⁴⁷ By using this interface, a search for products safe to use for the solely paraben-sensitive patient provides a wealth of information (Table 5).⁴⁸ As of May 28, 2018, the CAMP tabulates ingredients in 4612 products; overall, 874 contain parabens (19%). The CAMP database has 90 categories of products, so relevant information has been regrouped for highlighting purposes. Facial cosmetics and products average 30% paraben presence, with face makeup (other) (52.1%) and face powder (43.4%) having the highest percentages. One hundred thirty-three of 376 moisturizers (35.4%) contain parabens. Eye care products and makeups also average just more than 30%, with mascara and eyeliner as the most frequent products to contain parabens (53.3% and 42.9%, respectively). Less than 10% of hair care products, shampoos, and conditioners contain parabens. Lip and mouth care products average less than 15%, with a mere 1.3% of toothpastes containing parabens. Lip liner, however, contains it more than 30% of the time.

The CAMP household products, a total of 283 catalogued, contain parabens only 1.1% of the time. Topical medicaments frequently contain parabens (45.6% acne/rosacea, 37.5% topical antibiotics, and 35.5% of pain, first aid, and numbing products). Seborrhea therapies frequently contain parabens (66.7%), as do products for aging and wrinkling (39.3%). Products that are applied

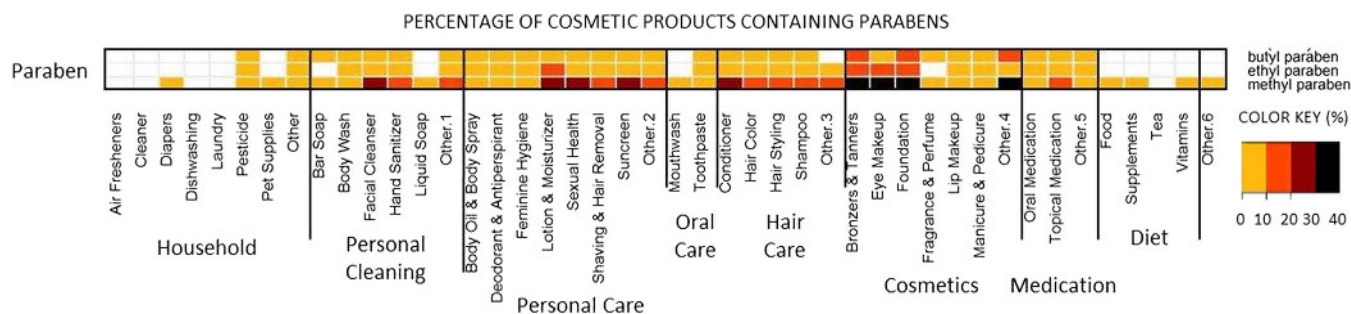


Figure 1. Parabens in consumer products.

TABLE 5. Contact Allergen Management Program Data

Product Type/Family	No. Containing Parabens	Total No. Products	% Containing Parabens
Eye care products			
Makeup: eyeliners	33	77	42.9
Makeup: mascara	64	120	53.3
Makeup: eye shadow	6	33	18.2
Other makeups and ophthalmic products	4	112	3.6
Total	107	342	31.3
Facial products			
Makeup: face, powder	20	46	43.4
Makeup: face, other	25	48	52.1
Foundation	19	68	27.9
Other facial products	43	175	24.6
Total	107	337	31.8
Hair care products			
Hair care: shampoos	13	270	7.6
Conditioners	18	194	9.3
Hair care: dyes and dye kits	10	78	12.8
Hair care: stylers and treatments	38	290	13.1
Total	79	832	9.5
Lip products			
Lip liner	4	13	30.8
Gloss	4	26	15.4
Lipstick	5	43	11.6
Other lip balms and makeups	8	71	11.3
Total	21	153	14
Oral care products			
Toothpaste	1	76	1.3
Mouthwash/rinse	6	38	15.8
Oral, lip misc, other	3	12	25
Total	13	138	9.4
Nail care products			
Cuticle	5	12	41.7
Polish	3	21	14.3
Polish remover	1	6	16.7
Nail med, top/base coat, strengthener	4	36	11.1
Total	13	75	17.3
Miscellaneous oral products			
Perianal	10	16	62.5
Chewing gum	0	38	0
Otic Rx	0	5	0
Oral breath drops/mints/strips	0	12	0
Denture products	1	15	6.7
Total	11	86	12.8

TABLE 5. (Continued)

Product Type/Family	No. Containing Parabens	Total No. Products	% Containing Parabens
Household products			
Household products (not laundry)	2	160	1.3
Laundry detergents	1	82	1.2
Fabric softeners	0	41	0
Total	3	283	1.1
Medications, topical			
Acne/rosacea Rx	36	79	45.6
Acne/rosacea OTC	14	103	13.6
Anesthetic/pain relief/first aid OTC	22	62	35.5
Corticosteroid OTC	9	12	75
Corticosteroid brand Rx	18	92	19.6
Corticosteroid, generic, Rx	17	155	11
Antibiotic, Rx	6	16	37.5
Antibiotic, generic, selected, Rx	5	16	31.2
Medications: seborrhea Rx	4	6	66.7
Barrier products Rx	6	13	46.2
All other topical medicaments	35	199	17.6
Total	172	753	22.8
Skin care products			
Moisturizers	133	376	35.4
Antiaging/antiwrinkle/skin firming	75	191	39.3
Shaving	12	70	17.1
Soaps/cleansers	50	408	12.3
Antiperspirants/deodorants	3	163	1.8
Personal lubricant/fresheners	12	25	48
Sunscreens	37	201	18.4
All other skin care products	26	179	14.5
Total skin care	348	1613	21.6
Total camp products	874	4612	19

to potentially inflamed skin regions for comfort or healing have parabens at frequencies which could be interpreted as worrisome (in light of the information about increased incidence of paraben sensitivity in patients with stasis dermatitis or skin integrity issues); these include barrier products (46.2%), perianal products (62.5%), and personal hygiene lubricants and fresheners (48%). This concern regarding allergic sensitization from anogenital paraben exposure has not been confirmed in a subsequent study.⁴⁹

Additional CAMP reports and alternative databases are available for product ingredient review; SkinSAFE and a database compiled by the Environmental Working Group (EWG) are 2 examples.^{26,50,51} The comparison of preservative use in these 3 databases provides useful information (although data set sources are not equivalent) (Table 6).

Parabens are frequently found in products in all 3 databases, at a rate between 17% and 21%. In the CAMP, parabens were the second

TABLE 6. Preservatives in Consumer Products Databases

Allergen/Database	CAMP,* No. Products	CAMP (n = 4737), %	EWG,† No. Products	EWG (n = 74,301), %	SkinSAFE,‡ No. Products	SkinSAFE (n = 30,722), %
Parabens						
All parabens	983	20.75	NR	NR	5392	17.6
Methylparaben	NR	NR	12,506	16.8	4866	15.8
Propylparaben	NR	NR	11,353	15.3	3735	12.2
Ethylparaben	NR	NR	4068	6.2	1391	4.5
Butylparaben	NR	NR	3420	4.6	916	3
Isobutylparaben	NR	NR	1885	2	486	1.6
Isopropyl paraben	NR	NR	368	0.5	87	0.3
4-Hydroxybenzoic acid	NR	NR	9	0.01	0	0
Other preservatives						
Phenoxyethanol	1132	23.9	5757	7.7	10,489	34.1
MI	611	12.9	1972	2.7	2840	8.1
Benzyl alcohol	602	12.7	2123	2.9	3429	11.2
Benzoic acid	545	11.5	612	0.8	NR	NR
MCI	416	8.8	1431	1.9	2076	6.8
Sorbic acid	391	8.3	671	0.9	997	3.2
DMDM hydantoin	278	5.9	979	1.3	1572	5.1
IPBC	192	4.1	582	0.8	1031	3.4
Diazolidinyl urea	139	2.9	618	0.8	1045	3.4
BAC	102	2.2	110	0.1	437	1.4
Quaternium 15	32	0.7	138	0.2	153	0.5
Imidazolidinyl urea	NR	NR	183	0.2	351	0.1
Methyldibromo glutaronitrile	NR	NR	10	0.01	315	0.05
Formaldehyde	NR	NR	8	0.01	21	0.07

*Contact Allergen Management Program. Available at: <http://www.contactderm.org>. With permission, A. Scheman M.D., CAMP Manager.

†Environmental Working Group. Available at: <https://www.ewg.org/skindeep/#.Wvi7DYgyUk>. Accessed April 2018.

‡SkinSAFE; Available at: <https://www.skisafeproducts.com>. Reprinted with permission from Yiannias,⁵¹ personal communication.

Abbreviations: BAC, benzalkonium chloride; DMDM, Dimethylol Idimethyl; IPBC, iodopropynyl butylcarbamate; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; NR, not recorded.

most frequently used preservative, present in a total of 983 products (20.75%). Only phenoxyethanol was more heavily represented at 23.9%, whereas methylisothiazolinone (MI) was present in 12.9% and the 2-part biocide methylchloroisothiazolinone/MI was present in 8.8%. The rare allergens benzyl alcohol and benzoic acid were also represented at more than 10%, whereas all other biocides were seen in less than 10% of products. The SkinSAFE database has similar proportions, with slightly lower paraben utilization by percentage compared with CAMP. The frequencies of the different parabens used in cosmetics as documented by the EWG and SkinSAFE are remarkably similar. Phenoxyethanol is seen in 20% more products than are parabens in CAMP and in nearly twice as many products in SkinSAFE; parabens are more commonly used than phenoxyethanol (16.8% vs 7.7%, respectively) in the EWG tabulation. These data are roughly equivalent to those in a published study from 2005.⁵²

Foods

The Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) established a total paraben (the sum of methylparaben, ethylparaben, and propylparaben) acceptable daily intake (ADI) of

0 to 10 mg/kg of body weight, although propylparaben and other parabens with yet longer alkyl side chains were later recommended for exclusion from the total paraben ADI because of endocrine disruptor activity potential.⁵³ There are no other defined regulations regarding the use of parabens in domestic foods, although recommended use parameters have been proposed at concentrations not to exceed 0.1% in medications.⁵⁴ In the United States, parabens are listed as such on the label of ingredients; in Europe, parabens are not generally identified but given E-numbers instead. The most commonly used parabens in food are methylparaben (food additive E218) and ethylparaben (E214), with the European Food Safety Authority setting an acceptable daily intake of 0 to 10 mg/kg of bodyweight per day for methylparaben and ethylparaben. Other less commonly found parabens preserving foods include propylparaben (E216), heptylparaben, butylparaben, and isobutylparaben.⁵⁵

Absolute amount and extent of paraben utilization in ingestibles are unknown but expected to vary greatly. For example, 50 fresh-cut vegetable samples from different farmer markets in Beijing, China, were collected to measure parabens, and only 1 sample tested positive to methylparaben with concentration at 81 µg/kg as determined by the QuEChERS technique (perhaps the optimal assay for detecting chemical residues in fruits and vegetables).⁵⁴ Conversely, a

TABLE 7. Foods and Beverages Reported to Contain Parabens

Alcoholic beverages	Fruit juices	Pickles/relish
Baked goods	Gelatin/pudding	Pie crusts
Beer	Icings	Salads
Cakes	Jams	Seafood
Cereal or potato snacks	Ketchup	Soft candy
Ciders	Liquid dietary food supplements	Spiced sauces
Coated nuts	Marinated and preserved fish products	Sugar substitutes
Confectionery (excluding chocolate)	Mayonnaise	Surface treatment of dried meats
Fats	Meats	Jelly coatings of meat products
Fillings	Milk products	Tomato pulp/puree
Flavoring syrups	Mustard	Toppings
Frozen dairy foods	Oils	Vegetables (processed/preserved/fresh)
Fruit and vegetable juices	Packaged meats/fish/poultry	

separate study in China found nearly all of the food sources to contain at least 1 kind of paraben (cereal products, meat, seafood, eggs, dairy products, bean products, vegetables, and fruits). Levels determined using high-performance liquid chromatography–tandem mass spectrometry detection revealed the total paraben sum of concentrations to range from undetectable to 2530 ng/g of fresh food weight (mean, 39 ng/g).⁵⁶ It seems predictable that fresh foods would have low-paraben content in comparison with processed foods.

Detailed lists of foods that contain parabens are frequently published, and the summary data are presented (Table 7). Not previously reported is the quantification of paraben content in different foods. Wang et al⁵⁷ examining foods from Albany, New York, found 90% of foods across all categories to contain a mean of 9.67-ng/g parabens; methylparaben, ethylparaben, and propylparaben predominated. They estimated the mean daily ingestion rates of food items to be 940, 879, 470, 273, and 307 ng/kg of body weight per day for infants, toddlers, children, teenagers, and adults, respectively; the daily ingestion for a 70-kg man calculates to 21 µg, well below the levels used in many in vivo and in vitro studies with no observed adverse effects.⁴ Foods with particularly high levels of methylparaben include pancake syrup, muffins, iced tea, pudding, and turkey roast; propylparaben and ethylparaben were highest in turkey breasts, turkey roast, yogurt, apple pie, and red wine. Chinese consumption may be yet higher, converting to approximately 27 mg/d in adults.⁴ Additional studies to look at paraben content in food are indicated. Although the margin of safety (MOS) has been estimated for multiple topical cosmetic product use at 3000 for infants and 840 for adults, an equivalent determination has not been made for the ingestion of parabens.⁴

Medications

A list of oral medications that contain parabens is maintained in a compendium generated by Drugs.com (Table 8).⁵⁸ Although not an exhaustive tabulation, methylparaben, propylparaben, and butylparaben are the 3 most common.^{59–61} Isobutylparaben, propylparaben sodium, and methylparaben sodium are found in a handful of products.^{62–64} Enteral and parenteral medications that tend to include these

preservatives include multidose vial antibiotics, local anesthetics, corticosteroids, enteral and parenteral vitamins, diuretics, insulin, heparin, antihypertensives, chemotherapeutic agents, haloperidol, and other syrups.^{15,48,65} Topical prescription agents include formulations of benzoyl peroxide, clindamycin, clocortolone, desonide, eflornithine, fluocinolone acetonide, fluorouracil, fluticasone, hydrocortisone, hydroquinone, imiquimod, metronidazole, salicylic acid, sertaconazole, sodium sulfacetamide, tretinoin, and urea.⁶⁶

Evaluation of the excretion of parabens resulting from their ingestion in pharmaceuticals has been undertaken. In 1 small study without control population and with a small sample size, paraben-containing medication ingestion on the same day as urine sampling (range, 0.75–7.0 hours) was associated with a nearly 14-fold increase in mean urinary methylparaben concentration. Dodge and colleagues⁶⁷ measured the temporal relationship between paraben-containing medication ingestion and levels of urinary excretion of parabens. Ingestion of a medication containing parabens within 7 hours was associated with 8.7- and 7.5-fold increases in mean methylparaben and propylparaben concentrations, respectively.

Individuals sensitized to parabens rarely, if ever, have to avoid foods or pharmaceuticals that contain parabens to control their dermatitis; flares of eczema are not reported with their ingestion. However, paraben-sensitive cooks and food handlers who prepare foods containing the preservative may develop hand dermatitis.^{15,65} Veien et al⁶⁸ performed peroral challenge with 100 mg of mixture 50/50 methylparaben and propylparaben in 14 paraben-allergic patients; dermatitis flared in 2, but neither improved with paraben avoidance in foods, suggesting that no direct cause and effect existed. Systemic contact dermatitis to parabens has been reported but is believed to be exceedingly rare.^{69,70}

SENSITIZATION POTENTIAL OF PARABENS

The sensitization potential of an antigen has traditionally been evaluated by the Buehler guinea pig and the guinea pig maximization tests (with injection of test material in Freund complete adjuvant). These techniques, bypassing the cutaneous barrier and antigen processing cell contact, have been reported to both overestimate the risk

TABLE 8. Common Medications Containing Parabens

Top Medications With Methylparaben*	Top Medications With Propylparaben†	Top Medications With Butylparaben‡
Acetaminophen 325 mg	Acetaminophen 325 mg	Benadryl Allergy Kapgels diphenhydramine 25 mg
Acetaminophen/diphenhydramine 500 mg/12.5 mg	Amantadine hydrochloride 100 mg	Chlordiazepoxide hydrochloride 10 mg
Benzonatate 100 mg	Anacin aspirin-free acetaminophen 500 mg	Diphenhist 25 mg
Chlorpheniramine maleate extended-release 12 mg	Anafranil 25 mg	Diphenhydramine hydrochloride 25 mg
Chlorpromazine hydrochloride 100 mg	Benzonatate 100 mg	Diphenhydramine hydrochloride 25 mg
Cyclobenzaprine hydrochloride 10 mg	Benzonatate 100 mg	Hydroxyurea 500 mg
Disopyramide phosphate 100 mg	Chlorpromazine hydrochloride 50 mg	Lescol 20 mg
Docusate sodium 100 mg	Cyclobenzaprine hydrochloride 10 mg	Loxapine succinate 25 mg
Ergocalciferol 1.25 mg	Dexbrom. maleate/ Pseudoeph. ER 6 mg/120 mg	Loxapine succinate 5 mg
Morphine sulfate SR 30 mg	Dipyridamole 75 mg	Oxazepam 10 mg
Morphine sulfate SR 15 mg	Disopyramide phosphate 100 mg	Phenytoin sodium extended 100 mg
Nifedipine 10 mg	Docusate sodium 100 mg	Phrenilin forte acetamin. 650 mg/butalbital 50 mg
Nortriptyline hydrochloride 25 mg	Ergocalciferol 1.25 mg	Seromycin 250 mg
Oxazepam 10 mg	Luoxetine hydrochloride 10 mg	Temazepam 30 mg
Tofranil-PM 75 mg	Methylergonovine maleate 0.2 mg	Temazepam 15 mg
Tofranil-PM 125 MG	Oxazepam 10 mg	Tetracycline hydrochloride 250 mg
Valproic acid 250 mg	Tetracycline hydrochloride 250 mg	Theophylline extended-release 200 mg
Verapamil hydrochloride SR 120 mg	Verapamil hydrochloride SR 120 mg	Theophylline extended-release 125 mg
Vimovo esomeprazole 20 mg/naproxen 500 mg	Verelan 180 mg	Theophylline extended-release 300 mg
Zenatane 10 mg	Vimovo esomeprazole 20 mg/naproxen 500	Tylenol extra strength 500 mg
Top medications with isobutylparaben§	Top medications with propylparaben sodium¶	Top medications with methylparaben sodium**
Surmontil 50 mg	Hydroxyurea 500 mg	Olanzapine (orally disintegrating) 5, 20, 15, 20 mg
	Olanzapine (orally disintegrating) 5, 10, 15, 20 mg	Zofran ODT 4 and 8 MG
	Zofran ODT 4 and 8 MG	Zyprexa Zydys 20 mg
	Zyprexa Zydys 5, 10, 15, 20 mg	

Data extracted from Drugs.com compendium.⁵⁸

*Available at: <https://www.drugs.com/inactive/methylparaben-290.html>.

†Available at: <https://www.drugs.com/inactive/propylparaben-87.html>.

‡Available at: <https://www.drugs.com/inactive/butylparaben-12.html>.

§Available at: <https://www.drugs.com/inactive/isobutylparaben-521.html>.

¶Available at: <https://www.drugs.com/inactive/propylparaben-sodium-240.html>.

**Available at: <https://www.drugs.com/inactive/methylparaben-sodium-406.html>.

Abbreviations: ER, extended release; SR, sustained release.

of weak antigens⁷¹ and underestimate the risk of strong antigens.⁷² For the past several decades, the murine local lymph node assay (LLNA) has been the criterion standard for testing materials for allergenicity in animals, because it not only uses fewer animals but also can be used to classify the potency of a given material.⁷³ In their excellent review of testing procedures with human skin sensitization test methodologies (including repeat insult patch testing, provocative use test, or extended product use test), Robinson et al⁷⁴ stressed the need for a comprehensive, balanced approach to all sensitization risk assays. Basketter⁷⁵ also reviewed skin sensitization methodology in detail and observed its essential nature to be that of comparative toxicology, because various substances are evaluated in a relative fashion.⁷⁶ Parabens have been classified as nonsensitizing in these 3 predictive assays.

The murine LLNA is based on measurement of the proliferative activity of draining lymph node cells on day 7 after 3 consecutive

days of index chemical application. Degree of activation is determined by incorporation of one of several different radiolabels, is seen to be an alternative from the methods hereinbefore, and is more animal friendly. Basketter et al,⁷⁷ using the LLNA, have ranked parabens as a human class 4 antigen with very weak or no sensitization risk. Comparatively, parabens are less sensitizing than class 2 and 3 antigens, dominated by fragrances, and class 1 with potent antigens such as dinitrochlorobenzene.

The European Union (EU) has banned animal testing for cosmetic ingredients, making alternative reliable testing methodology necessary. One approach that emulates the in vivo situation of human skin, known as the loose-fit coculture-based sensitization assay, cocultures primary human keratinocytes and allogenic dendritic cell-related cells.⁷⁸ Sensitization potency of parabens was assessed by flow cytometric analysis of the dendritic cell-related cell maturation

marker CD86 as indicators of dendritic cell activation. Parabens exhibited weak (methylparaben, ethylparaben, propylparaben, and isopropylparaben) or strong (butylparaben, isobutylparaben, pentylparaben, and benzylparaben) effects, with phenylparaben exhibiting an intermediate effect; as with cutaneous penetration capabilities, sensitization potencies of parabens correlate with side chain length. Parabens used in cosmetics showed no (methylparaben and ethylparaben) or weak (propylparaben, isopropylparaben, butylparaben, isobutylparaben, phenylparaben, and benzylparaben) irritative potencies; only pentylparaben was rated to be an irritant.

A novel modification of this technique adds lymphocyte surface marker determination, with antigens differentially affecting these markers based on potency: strong antigens raised interleukin-4 concentrations in coculture supernatants, whereas interferon gamma levels decreased, indicating T helper 2 (Th2) cell activation *in vitro*.⁷⁹

The Genomic Allergen Rapid Detection involves the assessment of transcriptional changes of selected genomic biomarkers (Genomic Allergen Rapid Detection predication signal) induced in a myeloid cell line in response to chemical stimulation.⁸⁰ Propylparaben was predicted as a sensitizer by this assay, whereas in the LLNA and human potency studies, it was not. Overall predictive performance of the test is estimated at 83% to 90%.⁸¹ Developments such as these are hoped to improve the evaluation of sensitization potential of new products and established allergens, including parabens.

These assays and similar *in vitro* methods are, like the LLNA, alleged to define hazard, rather than risk. Their predictive power (false negatives and false positives) remains in an early evaluation stage.⁸²

Schnuch and colleagues⁸³ of the Informationsverbund Dermatologischer Kliniken (IVDK or Information Network of Dermatology Clinics) identified the importance of relating the frequency of sensitization to the probable exposure to preservatives via leave-on cosmetics, which they quantified by the number of products containing the preservative in question ($n = 3566$, as documented by the Chemisches und Veterinaruntersuchungsamt Karlsruhe/Germany). By dividing the relative percentage of products containing a biocide (product share) by the percentage of "allergy share" of a product in screening (percent positive of all positive biocides), they were able to quantify exposure risk for preservatives in light of

allergen potency; they labeled this the sensitization exposure quotient (SEQ). Parabens ranked third lowest of 10 preservatives and biocide families studied (0.36). Only phenoxyethanol (significantly lower, 0.06) and benzoic acid (slightly lower, 0.30) have lower SEQ. Sorbates and benzoates were intermediate, whereas all of the biocides that contact dermatitis investigators examine in a standard screening fashion have SEQ values between 1.6 and 13. This evaluation would indicate that parabens are allergologically safer than all other preservatives evaluated except for phenoxyethanol and benzoic acid.

PATCH TEST PROCEDURE

A paraben mix is used to screen for contact allergy to parabens across the globe, using a combination of 4 or 5 different parabens at 3% to 4% concentration, depending on the testing system used (Table 9).⁶⁵ The North American Contact Dermatitis Group (NACDG) uses a 12% concentration with methylparaben, ethylparaben, propylparaben, and butylparaben, each at 3%; until 1996, the test concentration used was 15% and contained hexylparaben. In Europe and in many other parts of the world, parabens were tested in a 15% concentration (methyl, ethyl, propyl, butyl, and benzyl, each at 3%) until 1994; thereafter, test concentration was 16% (deletion of benzylparaben and other parabens raised to 4% concentration in petrolatum). This higher concentration is proposed by European investigators to be necessary to overcome the epidermal barrier and avoid false-negative results. The converse of the weak positive reaction must be interpreted with caution because this higher concentration approaches irritancy threshold. Patch testing with the paraben-allergic patient's own products is frequently negative because the concentration within the formulation is well below elicitation threshold. Repeated open application testing (also called provocative use testing) of the product on dermatitic or uninvolved skin may be positive and should be considered an important part of the evaluation.

Although the concentration of the paraben mix has varied for geographical area and time, mixes have been used since the earliest patch testing to parabens was undertaken. The recommendation that parabens be tested individually (as true-positive patch test reactions may be missed with the mix) has not been widely adopted by the contact dermatologic community.⁸⁴

TABLE 9. Testing Systems, Vehicles, and Strengths of Paraben Mix

Manufacturer		Concentrations, %			Delivery vehicle system	
T.R.U.E. Test SmartPractice (United States)		15			Methylcellulose pads	
Chemotechnique Diagnostics (Sweden)		12, 16			Petrolatum	
SmartPractice Allergeaze (Canada)		12, 15, 16			Petrolatum	
NACDG†		12			Petrolatum	
Percent concentration of parabens in testing systems						
Delivery system	Ethyl	Methyl	Propyl	Butyl	Benzyl	
T.R.U.E. Test	3	3	3	3	3	
12% petrolatum	3	3	3	3	X	
15% petrolatum	3	3	3	3	3	
16% petrolatum	4	4	4	4	X	

Abbreviation: NACDG, North American Contact Dermatitis Group; X, not present.

In a comprehensive study by the IVDK, patch test results were correlated to clinical causation and comparison of Reaction Index (relating the number of allergic reactions to the number of doubtful or irritant reactions) and the positivity ratio (relating the frequency of positive reactions to the total number of allergic reactions).⁸⁵ Problematic allergens included the paraben mix, which had a negative reaction index (−0.22) at a positivity ratio of 84.8%. This indicates a potential problem with the patch test material as irritating. Only 0.2% of their 121,247 patients tested had 2 to 3(+) strength reactions to paraben mix, with the remaining 1.1% having 1(+) reactions or weaker. Up to 50% of paraben mix reactions were false positives, which was verified as negative reactions when subsequently tested individually.

PARABENS AS CONTACT ALLERGENS

There are numerous excellent paraben contact dermatitis reviews.^{1,15,65,86–91} The gestalt among these studies is that, despite parabens being a ubiquitous group of preservatives with a remarkably high degree of exposure in the general public, the prevalence of positive patch tests is low. Despite being the most frequently used biocide, a general overall positivity rate in screening studies of 1% is frequently quoted, and the interpretation of the acceptance of this benchmark threshold varies by author and continent. Because we are discussing comparable sensitization risks to other available preservatives, paraben's performance as (non)allergenic is stellar.

North American Experience

The monitoring of paraben allergy has been ongoing for nearly as long as they have been used as biocides, with the first reported studies of paraben testing as an allergen and contact sensitivity dating to 1940.⁹² Schorr and Mohajerin⁹³ published the first case of contact dermatitis to parabens in the United States in 1966. Schorr also published one of the earliest reports of routine screening of parabens (tested at 5% in petrolatum) in 21 patients for 2 years and found 0.8% to be allergic.⁹⁴ Epstein⁹⁵ published his early experience 2 months earlier in 1968.

A report of 927 patients tested at 1 US institution showed a positivity rate of 2.9% for parabens for a 2-year period; they identified

an increased risk of co-sensitization to other preservatives, including formaldehyde and quaternium 15.⁹⁶ Nethercott⁹⁷ found parabens as rare sensitizers in 200 patients in Toronto (0.5%, 1 patient).

The Mayo Clinic Experience

The second largest body of data in North America comes from the Mayo Clinic. Testing at the higher “European” concentration of 16% paraben mix, the Mayo Clinic Contact Dermatitis Group reported paraben positivity in 1.6% of 1318 patients from 1998 to 2000,⁹⁸ 1.7% of 3841 patients from 2001 to 2005,⁹⁹ and 1.2% of 4439 patients from 2006 to 2010.¹⁰⁰ Irritant patch test frequency at this higher concentration was reported for the 2001 to 2005 data set at 0.7%, significantly higher than the NACDG irritancy rate during the overlapping period (0.2% from 2001 to 2002, $P = 0.0001$). A total of 98.5% of positives were relevant or of “questionable relevance.” By comparing the Mayo and NACDG data, 16% paraben mix is shown to have a higher frequency of irritant responses than the 12% concentration.

The North American Contact Dermatitis Group Experience

The NACDG, currently a consortium of 18 contact dermatitis specialists in the United States and Canada, periodically publishes the results of testing to its current standard screening tray, a set of chemicals that changes over time under the effects of emerging allergens and cumulative experience. The first report in this fashion was published by Rudner et al¹⁰¹ in 1973, with follow-up reports of subsequent data cycles by the same lead author in 1975 and 1977.^{102,103} The paraben positivity rate from 1971 to 1972 was 3.0% in 1200 patients, 3.5% from 1972 to 1974 in 2366 patients, 3.7% in 1900 patients from 1974 to 1975, and 2.7% in 1975 to 1976. The 1989 to 1990 data cycle showed paraben allergy in 1.3%,¹⁰⁴ whereas Storrs et al¹⁰⁵ reported paraben screening in a preservatives and vehicles series, positive in 7 of 661 patients (1.1%) tested from 1984 to 1985. Parabens were not reported in the summary of NACDG screening data from 1985 to 1989.¹⁰⁶

The NACDG has reported its experience with parabens routinely at 2-year cycles beginning in 1992.^{107–117} (Fig. 2, Table 10). What

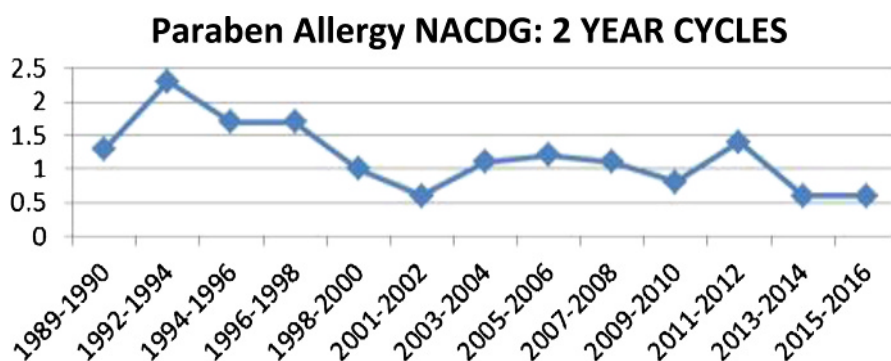


Figure 2. NACDG experience, 1989–2016.

TABLE 10. Paraben Allergy: NACDG 1992–2016

Years	% Allergic
1989–1990	1.3
1992–1994	2.3
1994–1996	1.7
1996–1998	1.7
1998–2000	1
2001–2002	0.6
2003–2004	1.1
2005–2006	1.2
2007–2008	1.1
2009–2010	0.8
2011–2012	1.4
2013–2014	0.6
2015–2016	0.6

Abbreviation: NACDG, North American Contact Dermatitis Group.

can be readily appreciated is that allergy to parabens is exceedingly uncommon.

Beginning in 1994, the NACDG began including relevancy data in its publications; this was reported in every 2-year data cycle except for 1996 to 1998 and 2003 to 2004 (Table 11). Definite relevance is uncommon because it necessitates positive testing to an actual product or item containing the allergen; probable relevance requires that the allergen be identified as an ingredient or component of an item used by the patient, and possible relevance is ascribed when the patient is exposed to circumstances where skin contact with the type of materials known to contain the allergen in question is possible. Confidence in the significance of the positive reaction is highest with definite relevance, high with probable relevance, and less certain with possible relevance.¹¹⁸

The highest reported positivity rate was the first data cycle between 1992 and 1994 at 2.3% (interestingly, the first 2 data cycles

from 1992 to 1996 had the highest rates reported, during which time the higher total concentration of paraben mix (15%) was used). Since that time, positivity rates have progressively fallen, with a positivity rate between 0.6% and 1.4% for the past 18 years. This would lead one to the assumption that this decrease may be due to the decrease in testing concentration. However, if one compares the 2 decades since 1996 (both sets containing five 2-year data cycles, 1996–2006 vs 2006–2016), the null hypothesis is still refuted at $P = 0.02$. The decline in positivity rates cannot be related solely to the decrease in testing concentration. The mean positivity rate for the entire period from 1992 to 2016 is 1.1% in a total of 55,013 patients. Relevancy data reveal that, when a positive nonirritant paraben reaction is identified, 67.5% to 100% of the time, it was interpreted as relevant (mean, 87.0%); in most patients, retesting to confirm true allergy was either not performed or not reported. Probable and possible relevance were the most common interpretations, with definite relevance ascribed for 0% to 16.7% of patients. The paraben mix is rarely irritating as tested by the NACDG, with the 1994 to 1996 data set showing 5.7% irritancy rate (using 15% paraben mix) and all subsequent reported rates for the 12% paraben mix being from 0.1% to 0.2% when reported, equivalent to that seen by European investigators.¹¹⁹

Another method of data assessment may be used by the selective weighting of definite/probable/possible relevance categories (the SPIN calculation or significance-prevalence index number).¹²⁰ This mathematic calculation allows one to incorporate the allergenicity and relevance of the allergen into 1 measure.¹²⁰ The SPIN indices for parabens for the past 10 years of the NACDG data period reports spanned 28 to 83, which ranks the paraben mix for that period 22nd to 52nd for all allergens tested. With parabens near the bottom of the list of antigen positivity in all study periods, their higher SPIN compared with their lower rate of positivity indicates higher-than-average certainty of relevancy (Table 12).

TABLE 11. Paraben Testing Data: NACDG 1992–2016

2-Year Data Cycle	No. Patients Tested	Positive, %	Number Positive	Irritant %	Definite REL, %	Probable REL, %	Possible REL, %	Total REL, %	Past REL, %
1992–1994	3476	2.3	80	NR	NR	NR	NR	67.5	3.8
1994–1996	3086	1.8	56	5.7	5.7	43.4	38.5	87.6	3.8
1996–1998	4096	1.7	70	NR	NR	NR	NR	NR	NR
1998–2000	5803	1	58	0	8.5	15.3	59.3	83.1	3.4
2001–2002	4898	0.6	29	0.2	10.3	17.2	51.7	79.2	3.4
2003–2004	5142	1.1	58	NR	NR	NR	NR	NR	NR
2005–2006	4439	1.2	53	NR	17	50.9	24.5	92.4	0
2007–2008	5082	1.1	56	NR	10.3	46.6	31	87.9	6.9
2009–2010	4308	0.8	35	NR	5.6	47.2	41.7	94.5	0
2011–2012	4231	1.4	59	NR	11.9	61	22	94.9	1.7
2013–2014	4859	0.6	30	NR	0	40	60	100	0
2015–2016	5593	0.6	34	0.1	11.8	32.4	38.2	82.6	0
Total	55,023		618						
Mean	4585	1.2	1.1	1.5	9	39.3	40.8	87	2.3

Abbreviation: NACDG, North American Contact Dermatitis Group; REL, relevance.

TABLE 12. The NACDG Spin Calculation 2007–2016

2-Year Data Cycle	Antigens Tested	Paraben Rank	Spin*	Spin Rank
2007–2008	65	42	56	34
2009–2010	70	50	40	40
2011–2012	70	38	83	22
2013–2014	70	59	28	52
2015–2016	70	58	28	48
Mean rank and spin	65–70	49	47	39

Calculation = (proportion of population allergic) $\times$ ($1 \times R_{\text{definite}} + 0.66 \times R_{\text{possible}} + 0.33 \times R_{\text{probable}}$) $\times$ 100.

*SPIN is a weighted calculation depending on degree of certainty ascribed to relevance.¹²⁰

Abbreviation: NACDG, North American Contact Dermatitis Group.

In interpretation of these data and those of other investigators, it behooves one to assess the burden of disease represented. In absolute numbers for the 24-year NACDG investigation in 55,023 patients, only 618 patients (1.0%) were identified with positive paraben mix reactions. This is in stark comparison with the data for all other biocides tested in the standard screening tray now and during the course of time. As an example, consider the 2 data sets between January 1, 2013, and December 31, 2016, when the NACDG evaluated a total of 10,452 patients for preservative allergy (Table 13). There were a total of 63 paraben reactions (0.6%). Conversely, MI was positive in 1249 patients (11.9%). Thus, positive reactions were nearly 20 times as common for MI in comparison with the paraben mix. The perspective of having more isothiazolinone allergic reactions in the last 2-year data cycle (749) as compared with paraben reactions for the entire 24 years that the NACDG has monitored for paraben allergy (618) is significant.

The SEQ as described by the IVDK can be roughly applied to the NACDG data by comparing paraben allergy in one 2-year data set

(2014–2016) to the relative proportion of products used in the United States as determined by the SkinSAFE experience (Table 14).⁵¹ The quotient again is calculated by dividing “product share” (the relative percentage of products containing a biocide) by the “allergy share” (the relative percentage of all biocide allergies). Using this formula, parabens account for 1.3% of the total “allergy share” and 19.6% of the “product share.” The SEQ for parabens is 0.04, up to a thousandfold less than that of methylchloro glutaronitrile (allowing for possible irritant responses) (80) and significantly less than that of quaternium 15 (7.45) and MI (1.56). Extending this interpretive line of study, by dividing the SEQ for an individual preservative by the sum of the quotients would provide an additional perspective not addressed by Schnuch¹¹⁹: that of relative share of each allergen to the quotient and that one might term “quotient load.” The quotient load for parabens with this calculation is 0.0001. If one were to remove products that might skew this formula, those being allergens contained in few products per se (formaldehyde) or decreasing in use because of industry reaction to reported past allergenicity and lasting sensitization issues (quaternium 15 and methylchloro glutaronitrile), the quotient load (although higher) remains low at 0.007. Parabens are both widely used and safe allergologically.

The actual prevalence of paraben sensitivity in the general population is unknown and is suspected to vary by geographic location because of genetic and exposure degree differences. Two studies from Denmark and Germany examining 1146 and 1141 patients reported 0.1% and 0.6% paraben positivity, respectively, in their nondermatitis cohorts.^{121,122} Mirshahpanah and Maibach¹²³ provided another estimate through pooled epidemiologic studies and computed model examination. Their novel approach suggests the incidence rate in patch test evaluation/prevalence in general public ratio to be a median of 5:1 across all allergens, with as high as 11.6 for formaldehyde ratios and as low as 1 for parabens when examining NACDG data.

TABLE 13. The NACDG Preservative Allergy (Percentage and Number) 2013–2016

Year	% positive	MI	FORM 2%	MCI/MI	FORM 1%	QUAT 15	IPBC
2013–2014	% positive	10.9	7	6.4	5.6	4.8	4.7
2015–2016	% positive	13.4	8.4	7.3	6.4	3.6	3.9
Year	No. positive	MI	FORM 2%	MCI/MCI	FORM 1%	Quat 15	IPBC
2013–2014	No. positive	500	340	311	272	233	228
2015–2016	No. positive	749	470	409	313	201	218
Total		1249	810	720	585	434	446

Year	% positive	MDGN	BNPD	DIAZ	IMID	DMDMH	Paraben	Total
2013–2014	% positive	3.7	2.1	1.6	1.6	1	0.6	0.6%–10.9%
2015–2016	% positive	3.5	1.3	1.2	1.1	0.8	0.6	0.6–5593
Year	No. positive	MDGN	BNPD	DIAZ	IMID	DMDMH	Paraben	Total
2013–2014	No. positive	180	102	78	78	49	29	7259
2015–2016	No. positive	198	73	67	62	45	34	8432
Total		378	185	145	140	94	63	15,701

Abbreviations: DIAZ, diazolidinyl urea; DMDMH, 3-dimethylol-5,5-dimethyl hydantoin; FORM, formaldehyde; IMID, imidazolidinyl urea; IPBC, iodopropynyl butylcarbamate; MCI, methylchloroisothiazolinone; MDGN, methylchloro glutaronitrile; MI, methylisothiazolinone; NACDG, North American Contact Dermatitis Group; QUAT 15, quaternium 15.

The corresponding International Contact Dermatitis Research Group ratio for parabens is 1.9, suggesting that the incidence of allergy in eczema patient evaluation is nearly twice that estimated for the general community. Limitations of this study include the exclusion of differences in antigen exposure in diverse population subsets and inherent genetic reactivity differences.

The International Experience

There are no domestic or international contact dermatitis groups other than the NACDG that routinely report screening series data at regular intervals. International reports published sporadically for the past 5 decades largely confirm the NACDG paraben experience. Smaller series outside the United States (<500 tested) are not included in these tables but are mentioned here for completeness and positivity rates, which ranged from 0.7% to 10.9%, in Eastern Europe (0.2% of 405),¹²⁴ Lithuania (0.3% of 297),¹²⁵ France (1.5% of 131),¹²⁶ Belgium (10.9% of 330),¹²⁷ Belgium (1.5% of 400),¹²⁸ United Kingdom (0.7% of 403),¹²⁹ India (8% of 63),¹³⁰ Brazil (20.9% of 134),¹³¹ United Arab Emirates (5.1% of 373),¹³² Japan (3.1% of 256),¹³³ and India (6% of 100).¹³⁴

Analysis of the data set reveals that, aside from the studies where the patient population is cosmetic in nature, the frequency of paraben allergy is low. In the 26 years between 1965 and 1991, 24 studies were performed on general populations of eczema patients (Table 15). A total of 89,402 patients were tested to a paraben mix at concentrations between 12% and 16%; 1499 reacted positively (1.7%), and paraben positivity in these studies for 26 years ranged from 0.2% (de Groot) to 3.8% (Fransway) (Table 15). The average positivity percentage of these older studies was 1.7%.^{1,102,135–157}

The data from outside the United States since 1992 affirm the North American experience of low reactivity (Table 16). A total of 300,544 patients have been tested, with 3020 patients reactive to

paraben mix at concentrations of 12% to 16% (1.0%); the mean percentage of reactivity among studies was 0.93%. The highest percentage of patients reacting came from Lithuania (3.4% of 680 tested, suspected because of a “highly selected patient population”), and the lowest came from Turkey (0% of 542 tested, speculated because of infrequent use of cosmetics by Turkish women at the time).^{119,158–174}

More than 40% of the population in Table 16 originated from 1 IVDK study, and 2 additional studies from this group were excluded because of data and year overlap; a positivity rate for parabens of 1.3% in all 3 studies is maintained.^{175,176} These authors confirmed the experience of the NACDG that, even at the higher concentration of 16% of 66,835 patients, paraben mix is not frequently reported to be irritating (0.2%), although negative repeat patch test results might suggest a higher value. No other studies in Tables 15 and 16 specifically addressed irritation frequency on patch testing. Relevance of the positive patch test was only addressed by the Australian study and reported to be 20.8%.¹⁷²

Several aspects of these international studies deserve specific mention. At least 3 studies, from the United Kingdom, Denmark, and the IVDK, observed reaction rates in men tested to be often higher than those of women by 15% to 30%.^{119,164,165} One of these groups relates this to a lower threshold for irritancy in men.¹¹⁹ Another Danish study found men nearly twice as likely to be allergic to parabens.¹⁶⁸

The multicenter experience authored by Jong et al¹⁶⁴ demonstrates significant variation of positivity rate by geographic location (0%–2.8%), presumably because of differences in exposure or, less likely, genetic differences in allergenic reactivity; reaction rates overall in the study decreased over time. Yin et al¹⁷⁰ and Helsing et al¹⁶⁹ report a similar multicenter variability experience (0.1%–3.4% and 0%–5.0%, respectively). Thyssen and colleagues¹⁶⁸ point out increasing incidence of paraben allergy with increasing age (0.3% younger than 18 years to 0.9% older than 60 years). In the

TABLE 14. Sensitization Exposure Quotient

Preservative, Vehicle, Concentration	Tested NACDG	% POS NACDG	Allergy Share	No. SkinSAFE Products	SkinSAFE Products Share	SEQ
	2014–2016	2014–2016				
Methylisothiazolinone, 0.2% aq.	5591	13.4	30.6	2840	19.6	1.56
Formaldehyde, 2.0% aq. (form)	5590	8.4	19.2	21	0.1	192
MCI/MI, 0.01% aq.	5593	7.3	16.7	2076	14.3	1.17
Iodopropynyl butylcarbamate, 0.5% pet.	5592	3.9	8.9	1031	7.1	1.25
Quaternium 15, 2.0% pet. (quat 15)	5592	3.6	8.2	153	1.1	7.45
MDGN/PE, 2% pet.	5592	3.5	8	15	0.1	80
Diazolidinyl urea (Germall II), 1.0% pet.	5593	1.2	2.7	1045	7.2	0.38
Imidazolidinyl urea, 2.0% pet.	5594	1.1	2.5	351	2.4	1.04
DMDM hydantoin (Germall 115), 1.0% pet.	5593	0.8	1.8	1572	10.8	0.17
Paraben mix, 12.0% pet.	5593	0.6	1.4	5392	37.2	0.04
Quotient total		43.8	100	14,496	99.9	285.06
Quotient load						0.0001
Quotient total without form, quat 15 or MDGN						5.61
Quotient load without form, quat 15 or MDGN						0.007

Abbreviations: aq, aqueous; DMDM, dimethylol dimethyl; MDGN/PE, methylidibromo glutaronitrile/phenoxyethanol; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; NACDG, North American Contact Dermatitis; pet, petrolatum.

TABLE 15. Screening Studies Reporting Paraben Allergy Through 1991

Investigator	Country	Data Years	Year Published	No. Tested	% Positive	No. Positive
Fregert	Europe	NR	1969	4825	1.9	92
Bandmann	Europe	NR	1972	4000	2	80
Burry	Australia	NR	1973	1000	1.7	17
Rudner	North America	1972–1974	1975	1900	3.7	70
Brun*	Switzerland	NR	1975	1000	1.7	17
Hannuksela	Finland	NR	1976	4097	0.3	14
Husain	Scotland	1970–1973	1977	1312	1.4	18
Camarasa	Spain	1977	1978	2806	1.5	42
Calas	France	NR	1978	500	1.8	9
Hammershøj	Denmark	1973–1977	1980	3225	1.1	34
Romaguera	Barcelona	1973–1977	1980	4600	1.24	57
Lynde	Vancouver	1972–1981	1982	4190	2.5	105
Edman	Sweden	NR	1982	8933	0.3	27
Angelini	Italy	1958–1983	1985	8230	2.6	212
de Groot	Netherlands	NR	1986	627	0.3	2
de Groot	Netherlands	1985	1986	501	0.2	1
Vestey	United Kingdom	1982–1985	1986	501	6.5	33
Broeckx	Belgium	NR	1987	5202	1.4	71
Menne	Denmark	1971–1986	1988	8020	0.9	72
Gollhausen	Germany	1997–1983	1988	11,962	2	239
Hogan	Canada	1983–1987	1988	542	4.2	23
Enders	Germany	1987	1989	1845	1.9	35
Seidenari	Italy	NR	1991	593	0.7	4
Shehade	United Kingdom	NR	1991	4721	1.3	63
Fransway	North America	1984–1991	1991	4270	3.8	162
25 studies		1968–1991	1969–1991	89402	46.94	1499
					Mean, 1.88	Total, 1.7%

*Tested at 3% concentration (1.5 × 2).

Abbreviation: NR, not reported.

Singapore study, more than 50% of patients tested had facial contact dermatitis, which might explain the higher-than-average positivity rate.¹⁷¹ The formidable database from the European Surveillance System on Contact Allergies network showed a low paraben positivity of 0.7% in 52,586 patients; the positivity rate in the T.R.U.E. Test assay in 2362 patients from this data set was half of that (0.35%).¹⁶⁹

Comparing the first 25 years of paraben sensitivity data (Table 15) with the second 25 years (Table 16), there has been a significant decrease in the frequency of paraben allergy for the 2 periods, indeed multiple powers greater than significance of less than 0.05% ($P = 0.0000015$).

Surveying the cumulative world experience (Tables 11, 15, and 16), beginning with the first studies screening for paraben allergy 50 years ago to the present, 444,969 patients have been evaluated. A total of 5137 patients exhibited positive reactions (1.2%); decreasing positivity rates are found over time. Allergologically, parabens are remarkably safe biocides.

There are a number of studies where the actual number of patients tested or the exact percentage of positivity was not listed (Table 17).^{95,103,133,147,157,177–183} Much like Tables 15 and 16, the studies before 1992 tend to have a higher rate of reactivity

overall (0%–2.7%; mean, 1.4%) than do the more recent studies after 1995 (<0.5%–1.0%).

Cosmetic Dermatitis Studies

Studies in which the patient population was suspected of having an allergic contact dermatitis to cosmetic products are tabulated in Table 18.^{151,162,184–194} In a total of 14 studies, 21,132 patients have been evaluated across the world, with 508 allergic to parabens (total, 2.3%; mean, 3.85%). Populations in Asian countries seem to have increased rates of sensitization because of the extensive use of cosmetics containing parabens at concentrations that may not be as closely monitored as in Europe or America; in 1 study from Thailand, parabens were identified in more than 80% of makeup and oral care items, with 20% to 65% of other cosmetic products containing 1 or more parabens.¹⁹⁵ The cosmetic nature of the patients in the 3 Asian studies reported the extensive use of parabens in cosmetics, and higher used concentrations in these products may account for this higher rate of reactivity.

Not all studies of cosmetic allergy indicated a high frequency of paraben sensitivity. Goossens¹⁹⁴ found only 1 of 597 patients to be paraben allergic and asserts that “the withdrawal of parabens from cosmetics is merely a consumer, publicity, and political issue.”

TABLE 16. Standard Series Screening Studies 1995–2017*

Investigator	Country	Data Years	Year Published	No. Patients Tested	% Paraben POS	No. POS Paraben
Perrenoud	Switzerland	1989–1990	1994	2295	1.7	39
Jacobs	London	1990–1993	1995	5167	0.46	23
Goossens	Belgium	1985–1997	1998	8521	0.8	71
Akasaya-Hillenbrand†	Turkey	1996–1999	2002	542	0	0
Hasan	Finland	1995–1997	2005	9267	0.3	28
Hasan	Finland	2000–2002	2005	6726	0.2	14
Boyvat	Turkey	2002–2004	2005	1038	0.2	2
Jong	United Kingdom	2004–2005	2007	6958	0.8	54
Carlsen	Denmark	1985–2005	2007	14,996	0.6	90
Dastychová	Czech Republic	2001–2006	2008	1927	1.1	21
Ertam	Turkey	2000–2005	2008	3017	1.3	39
Thyssen	Denmark	1985–2008	2010	18,178	0.5	91
Helsing	Norway	2007–2008	2010	2089	1.2	25
Schnuck	IVDK	1996–2009	2011	121,247	1.3	1752
Yin	Lithuania	2007–2008	2012	680	3.4	23
Yin	Austria	2007–2008	2012	678	2.2	15
Yin	Switzerland	2007–2008	2012	2402	1.2	29
Yin	Poland	2007–2008	2012	789	1.2	9
Yin	Germany	2007–2008	2012	2694	1	27
Yin	Spain	2007–2008	2012	1845	0.7	13
Yin	Italy	2007–2008	2012	2938	0.7	21
Yin	United Kingdom	2007–2008	2012	8909	0.6	53
Yin	The Netherlands	2007–2008	2012	2168	0.6	13
Yin	China	2004–2009	2011	2758	0.5	14
Yin	Finland	2007–2008	2012	760	0.4	3
Yin	Denmark	2007–2008	2012	1318	0.1	1
Cheng	Singapore	2006–2011	2014	3177	2.6	83
Chow	Australia	1993–2006	2015	6845	1.1	75
Giménez-Arnau	Europe	2009–2012	2017	52,586	0.7	368
Vogel	The Netherlands	1994–2013	2017	8029	0.3	24
Totals						
19 Studies	29 Study Centers	1985–2015	1995–2017	300,544	Mean, 0.93	3020
						1.0% positive

*500-patient threshold for inclusion.

†Tested paraben mix 12% concentration; all other studies used allergens screened in their geographic region or did not specify: (16%, 4 × 4%).

Abbreviation: IVDK, Informationsverbund Dermatologischer Kliniken.

TABLE 17. Paraben Studies Without Exact Numbers or Percentages

Investigator	Country	Data Years	Year Published	No. Patients Tested	% Paraben POS
Epstein	North America	UNK	1968	52–74	0
Agrup	Sweden	UNK	1969	130–547	0.5
Rudzki	Poland	UNK	1970	463–861	2
Meneghini	Italy	UNK	1971	340–1305	1.3
NACDG	North America	1975–1976	1977	900–2000	2.7
Hirano	Japan	1976–1979	1982	178–434	REQ
Angelini	Italy	UNK	1985	150–8230	2.6
Shehade	United Kingdom	UNK	1991	1753–4721	1.3
Wilkinson	Europe	1991–2000	2002	UNK	0.6–0.9
Zoller	Israel	1995–2004	2006	2285	Mostly <0.5
Svedman	Europe	2001–2008	2012	UNK	0.5–1.0

Abbreviations: NACDG, North American Contact Dermatitis Group; POS, positive; UNK, unknown.

CLINICAL PRESENTATIONS OF PARABEN ALLERGY

Cosmetics Allergy

Because of the dominance of paraben use in leave-on formulation exposure, it comes as no surprise that populations using cosmetics and presenting with facial dermatitis would have a higher reaction rate to such a common biocide than the general and contact dermatitis clinic populations as a whole. Numerous studies have all shown that makeups, moisturizers, hair care products, and eye cosmetics are the most common sources.^{196,197} The average woman uses 12 personal care products daily with 168 new unique ingredients (6 and 85 are corresponding figures for men).¹⁹⁸ With this level of exposure, it is not surprising that, in 7 pooled studies involving 30,207 contact dermatitis patients, 9.8% of positive reactions were due to cosmetic allergens.¹⁹⁹

Studies confirm that parabens rarely cause cosmetic allergy despite their extensive use in cosmetics.¹⁹⁴ In a Swedish compilation of complaints of cosmetic reactions to the Medical Products Agency for a 5-year period between 1989 and 1994, 191 reports concerning adverse effects of 253 cosmetics and toiletries were examined.²⁰⁰ Ninety percent of the reports concerned women, and the top-ranking product category was moisturizers, followed by hair care products and nail products. Fragrances, toluenesulfonamide formaldehyde resin, and preservatives were the causative agents in 79 patch-tested patients; 7 preservatives were implicated in 19 adverse effects, with none of them paraben based. The important NACDG study of causes of cosmetic allergy failed to show the paraben mix in the top 20 causes of dermatitis.²⁰¹ They did find it 19th in their list of causes of moisturizer-induced dermatitis, with the rate in men roughly half of that in women. Overall, parabens were implicated as causative in only 1% of all cosmetic allergic patients (slightly higher in men than women). This level is not statistically different than the NACDG results for

the population as a whole during the same 4-year period of 2001 to 2004 (0.9%). In an earlier 1985 report by the NACDG, 19 paraben-allergic patients were identified of 713 patients with cosmetic allergy (2.7%), a slightly higher rate than their noncosmetic dermatitis patients for the period.¹⁸⁶ Goossens and colleagues²⁰² examined 475 patients with cosmetic allergy and concur that preservatives and perfume components are the most common culprits; 16 were paraben allergic (3.4%).

In their excellent review of cosmetics and dermatitis, Alani and colleagues²⁰³ from the Mayo Clinic did not identify parabens as a common cause for allergic contact dermatitis and labeled them weak sensitizers. They did recommend its screening in a standard or cosmetics tray, if sensitivity to a cosmetic product is suspected, and included it in their list of antigens that can cause dermatitis in eye shadow products (but not eyeliners, concealers, mascaras, and nail or hair care series). The previously referenced CAMP database has a total of 342 ophthalmic medications, contact lens solutions, and eyelid makeups, with mascara (64/120, 53.3%) and eyeliner (33/77, 42.9%) more frequently containing parabens than do eye shadow products (6/33, 18.2%) (Table 5). Other reviews of cosmetic allergy mention parabens as rarely problematic in passing fashion only.²⁰⁴

The definitive study of patients identified as having cosmetics, sunscreens, and moisturizers as the only identified allergen sources was performed by the IVDK.²⁰⁵ Parabens were positive in 1.0% of 10,124 patients and 0.9% of 14,728 controls ($P = 0.73$); their evidence-based statement was that parabens are safe preservatives in cosmetics. These same authors cite one of their own studies asserting that up to half of these paraben reactions are believed to be irritant responses.²⁰⁶ Summarizing these cosmetic studies, it would seem that, generally, parabens do not cause cosmetic dermatitis at a significantly greater rate than the general eczema population, although

TABLE 18. Cosmetic Studies Reporting Paraben Allergy

Investigator	Study Location	Study Years	Year Published	No. Patients Tested	No. Positive	% Positive
Eiermann	North America	1977–1980	1982	487	15	3.1
Romaguera	Spain	NR	1983	460	37	8
Adams	North America	1977–1983	1985	713	19	2.7
de Groot	The Netherlands	REQ	1985	179	1	0.6
Emmons	North America	REQ	1985	31	0	0
Broeckx	Belgium	NR	1987	156	3	1.9
de Groot	The Netherlands	1981–1986	1987	75	1	1.3
de Groot	The Netherlands	NR	1988	254	0	0
Hasan	Finland	1995–1996	2005	9269	28	0.3
Hasan	Finland	2000–2002	2005	6726	13	0.2
Lee	Korea	2010–2011	2012	584	18	3.1
Boonchai	Thailand	1999–2003	2011	1247	102	7.2
Boonchai	Thailand	2004–2006	2011			9.2
Cheng	China	2001–2006	2011	1354	270	20
Goossens	Belgium	1990–2016	2016	597	1	0.2
12 studies		1977–2006	1982–2011	22,132	508	
					Total, 2.3%	Mean, 3.85%

differences in exposure load geographically may account for certain studies showing higher rates.

SPECIFIC EXPOSURES AND POPULATIONS

Moisturizers

As water-based leave-on formulations, the need for long-lasting broad-spectrum preservation of moisturizers is self-evident. Zirwas and Stechschulte,²⁰⁷ using a major pharmacy database, identified 276 moisturizers, 62% of which contained parabens (bested only by fragrance at 68%). The CAMP has 133 moisturizers of a total of 376 (35.4%) that contain parabens (Table 5).

Sunscreens

The NACDG examined a 10-year experience with sunscreen product testing and identified 3 of 124 patients with allergy to sunscreens to be paraben sensitive (2.4%).²⁰⁸ In the CAMP database, 37 of 201 products contained parabens (Table 5).

Diaper Products

In the Yu et al²⁰⁹ analysis in 2016, parabens (predominantly methylparaben) were found in 9.5% of diaper wipes and 24.4% of topical preparations. The authors noted a trend of substitution of parabens with ethylhexylglycerin in diaper products. There are isolated reports of diaper allergy in infants due to parabens.²¹⁰ The CAMP database has a high prevalence of parabens in products used in the perianal region (10/16 products, 62.5%) (Table 5).

Corticosteroid Formulations

In their examination of product inserts for corticosteroid formulations dispensed more than 20,000 times in 1 calendar year, Coloe and Zirwas²¹¹ found parabens to be present in 7 of 46 steroid formulations (15%); parabens were the most common preservative allergen identified in such formulations. The CAMP database showed an overall prevalence of 17% (44/259), with over-the-counter formulations more frequently containing parabens (9/12, 75%) than branded prescription products (18/92, 19.6%) and generic prescription corticosteroids (17/155, 11%) (Table 5). Perioperative use of corticosteroids may cause contact dermatitis; 1 group of authors suggests that preservatives and other inactive ingredients may be more frequently problematic than active ingredients.²¹² Ointments are less likely to contain parabens (or any preservatives because of the lack of aqueous phase) than are cream and lotion formulations.

Shampoos

Using a database from a major pharmacy chain, Zirwas and Moennich³⁹ found 43 of 179 shampoos to contain parabens, the eighth most common allergen identified. The CAMP database has 13 of 270 (7.6%). Hair dyes, stylers, and conditioners are all also low in frequency (7.6%–13.1%) (Table 5).

Imiquimod

As the major preservatives in imiquimod cream, parabens were found to be positive at no higher rate than in the general patch test population in patients who had been treated with imiquimod.²¹³

Facial Dermatitis

Aschenbeck and Warshaw^{214,215} compared the prevalence of parabens in facial wet wipes and in personal hygiene wet wipes and found no significant difference between the two (23.6% of 178 facial wipes and 20.4% of 132 personal hygiene wet wipes contained parabens, the 15th most common allergen in facial wipes). In the CAMP registry, facial products and cosmetics contain parabens 31.8% of the time, with powder makeup (20/46, 43.4%) and other facial makeup leading the way (25/48 products, 52.1%) (Table 5). Foundation concealers and blushers all have prevalence of roughly 30%.

Genital Dermatitis

A study from the Mayo Clinic, examining the most common causes of vulvar contact dermatitis, identified the top 5 allergens to be fragrances (3), benzocaine, and quaternium 15.²¹⁶ Only 1 of the 90 women reacted to paraben mix, which was deemed no higher incidence than baseline. A recent review of genital dermatitis tabulated the results from four investigations, with paraben positivity found in between 0.4% and 1.7% of patients.²¹⁷ As referenced previously, in the NACDG experience, parabens were not identified as a significant cause for anogenital dermatitis.⁴⁹

Leg Ulcers and Stasis Dermatitis

There is significant variation by geographic location with respect to paraben allergy prevalence in the leg ulcer and chronic venous insufficiency population. A Canadian study of 100 patients with chronic venous disease and leg ulceration failed to identify parabens as a relevant allergen, with 18 other allergens more often problematic at frequencies of more than 4%.²¹⁸ Another North American population showed a similar low frequency of positivity at 2%.²¹⁹ A Croatian study, on the other hand, found 17% of their patients with leg ulceration to be paraben allergic.²²⁰ Although many studies report that the incidence of contact dermatitis is increased in patients with venous disease, dermatitis, or leg ulceration, a recent German study found that patients with leg ulcer were less frequently sensitized than historical controls (16.9% of 5264 patients with stasis change; 25.9 of 4881 controls). Paraben sensitization was significantly elevated from control groups, however, at 2.6%.²²¹ Notwithstanding these mixed results, the overall perceived increased rate of sensitization in patients with leg ulceration, stasis dermatitis, and occluded skin (eg, Unna boot) may be an indication of the paraben paradox and the result of increased penetration of allergen and differential loss of hydrolysis of esters due to missing or dysfunctional cutaneous esterases.^{15,65}

Periorbital and Eyelid Dermatitis

Definitive studies have been performed on the subject of eyelid dermatitis. The NACDG reported its experience in 278 cases of isolated contact dermatitis of the eyelids examined in the 2003 to 2004 data cycle. Twenty-six allergens, including 4 preservatives, were identified as causative in between 1.1% and 8.2% of cases; parabens did not make this list of problematic antigens.²²² Similarly, Amin and Belsito²²³ did not identify parabens as an issue in 46 cases of eyelid dermatitis; 37 other antigens including 10 preservatives were found in 2.2% to 28% in this 10-year study. Herbst and colleagues,²²⁴ using the Information Network of the IVDK, did not list parabens as allergens in their top 30 causes of periorbital dermatitis in 1053 cases. In 204 patients with isolated allergic contact dermatitis of the eyelids, Herro and colleagues²²⁵ found 1 to 2 cases of paraben allergy. Indeed, in light of these data, parabens may be the preferred biocide for periocular products and instillation medicaments. A study from the ophthalmology literature demonstrated that, as opposed to benzalkonium chloride, parabens do not affect cell viability of keratinocytes.²²⁶ Landeck and colleagues,²²⁷ although finding 3% of their periorbital dermatitis patients to be paraben sensitive (8/266), noted that 3.2% of the control population for this period without periorbital dermatitis were paraben sensitive (not statistically significant). An isolated case has been reported of paraben allergy in an eyedrop.²²⁸

Dyshidrotic Eczema

A retrospective examination from 2008 to 2015 in Japan showed 2 of 21 patients (9.3%) to be allergic to paraben 15% in petrolatum.²²⁹

Pediatric Contact Dermatitis

Paraben reactions are rare in children. Hogeling and Pratt²³⁰ neither mentioned paraben mix nor listed it as a top 10 allergen in their study of 100 children. In an excellent review of pediatric contact dermatitis, parabens are not listed as a relevant allergen in any of the 16 studies reviewed. Unpublished data provided by the authors revealed 1 of 440 children (0.2%) positive to parabens in New Delhi.²³¹ Another review from 2011 detailed 9275 children tested in 20 series over 11 years.²³² Paraben mix was identified as a top 3 allergen in only 1 small series of 70 children in India (43%).²³³

Palmoplantar Pustulosis/Psoriasis

Noting abrogated barrier function as an issue for contact sensitization, a Kuwaiti study examined 103 patients with palmoplantar pustulosis and 100 regular psoriasis controls; no cases of paraben allergy were identified in either group.²³⁴

Photosensitivity

Although there is limited reference to parabens being photosensitizers, we could find no references reporting routine photopatch testing; parabens are not included on screening photopatch trays in North America or Europe. Methylparaben has been shown to

be photosensitizing in vitro, with dose-dependent decrease in cell viability in keratinocyte culture cell line HaCaT along with a 40% reduction in antimicrobial activity. Intracellular generation of reactive oxygen species and multiple organelle disruption were also identified. Oxidative stress led to DNA damage and apoptosis via mitochondrial and endoplasmic reticulum damage, leading the authors to call for parabens to be removed from products exposed to UV light.²³⁵ Another study failed to show photoreactivity (either photoallergy or phototoxicity), but the authors found that butylparaben products may induce hyperpigmentation and intensification of preexistent dermatitis upon exposure to sunlight.²³⁶

Excited Skin Syndrome

In a 2002 retrospective analysis of 39 patients with excited skin syndrome (of 630 total patients tested), 9 (23%) were positive to paraben mix on the first patch test experience; on retesting at further distance on the back from *p*-phenylenediamine (PPD), only 3 remained positive.²³⁷ The authors assumed that proximity of positive reactions on excited skin to each other and to cross-reacting antigens is an important consideration.

Systemic Contact Dermatitis

Five isolated cases of systemic contact dermatitis to parabens administered enterally or parenterally exist, clearly a rare phenomenon in light of the extensive use of parabens in medicaments and foods.^{15,69,70,238,239} Parabens were not included in Jacob and Zapolanski's²⁴⁰ 2008 review article on the subject.

Immediate Hypersensitivity to Parabens

Isolated cases of type 1 hypersensitivity to parabens have been reported.²⁴¹ Fisher²⁴² found 0.2% of patients with paraben allergy to react to scratch and intradermal testing of parabens. Pruritus, urticaria, localized angioedema, and bronchospasm have been rarely reported, with the cause often parenteral administration.^{15,65}

The Paraben Paradox

The paraben paradox, as classically proposed by Fisher,²⁴³ described parabens in topical therapeutic agents sensitizing roughly 1% of the population while rarely, if ever, inductive to those using paraben-containing cosmetics. He postulated that paraben-preserved therapeutic agents generally are used on inflamed, eczematous, excoriated skin, whereas other formulations such as cosmetics are used on normal skin; differential concentrations and penetration/barrier dysfunction are believed to explain this phenomenon. Schorr and Mohajerin⁹³ reiterated the paradox, postulating that the hydrolysis of the ester parent molecule to *p*-hydroxybenzoic acid in the skin by esterases was the cause of this phenomenon. The extension and corollary of this situation are where patch tests may be negative on uninvolved skin, yet parabens applied to involved skin can elicit dermatitis. The explanation of this paradoxical response is yet to be determined.

Hervella and colleagues,²⁴⁴ along with a case report, claim that the classic “paraben paradox” as described by Fisher is now rarely seen and that the most common picture of paraben allergy presently is sensitization through contact with cosmetics and subsequent intolerance of even minimal concentrations of parabens. They proposed that the predominance of weak positive patch test reactions to parabens is relevant when investigated adequately.²⁴⁴

Various other versions of the “paraben paradox” have been suggested:

- The (in)frequency of cross-reactions to *p*-aminobenzoic acid derivatives and other structurally related molecules;
- Lesser concentrations of 2 or more parabens are more effective than a larger concentration of a single paraben (this is postulated to be due to relative and complementary oil and water partitioning);
- Predictive patch testing with paraben-containing cosmetics has yielded no cases of allergic dermatitis, whereas there is a larger number (roughly 1%) among patients undergoing patch testing for suspected allergic contact dermatitis (the paradox questioned in this scenario is how, with the extensive testing performed, this could occur)²⁴⁵; and
- Patch testing with individual esters (at the same concentration as that present in the mix) may be positive despite paraben mix negativity.⁸⁴

CROSS-REACTIVITY OF PARABENS TO OTHER “PARA GROUP” ANTIGENS AND TO EACH OTHER

p-Phenylenediamine seems to be the allergen most frequently cited as at risk for cross-reaction in paraben-sensitive patients. Turchin and colleagues²⁴⁶ found that 2.37% of 253 PPD-sensitive patients also reacted to the paraben mix, whereas overall paraben sensitivity in 4115 PPD-negative patients was 0.68%. Patients allergic to PPD were 3.4 times more likely to be sensitive to parabens. Similarly, paraben-positive patients were 3.1 times more likely to have a positive reaction to PPD mix than those negative to the paraben mix. None of the 37 benzocaine-allergic patients reacted to parabens. These differences were statistically significant, but clinical relevance was indeterminate.²⁴⁶ Rudzki and Kleniewska¹⁷⁹ identified 20 paraben-allergic individuals (13.9%) among 144 PPD-sensitive patients; 20 of 63 benzocaine-sensitive individuals (31.7%) were allergic to parabens. In a much larger European series, 231 patients allergic to PPD were more frequently reactive to parabens (2.2%) than PPD-negative individuals (0.3%), $P < 0.001$.¹⁷⁴ Taking a conservative exposure approach, the CAMP database includes all hydroxybenzoates and PPD derivatives as cross-reactors to parabens. However, an analysis of 46 PPD- and 6 paraben-sensitive patients showed no cross-reactivity.²⁴⁷

p-Aminobenzoic acid derivatives, sulfonamides, and caine derivatives, other than benzocaine, may rarely cross-react with parabens, but these reports are exceedingly scarce because of the exclusion of these allergens from most standard screening series; isolated

reports of cross-reactions between parabens, PPD, and, specifically *p*-aminobenzoic acid are found in the literature.²⁴⁸

OCCUPATION AND PARABENS

In a cohort of 5112 occupational cases, Dickel and colleagues²⁴⁹ identified 69 allergic to parabens; only 6 of these (0.1%) were occupationally related or top 17 nonoccupationally related allergens in the NACDG study of 2732 production workers or as a relevant occupational allergen in 132 print machine operators.^{250,251} It was not among the 46 standard series allergens identified to be relevant in 691 mechanics and repair workers.²⁵² Kucenic and Belsito²⁵³ did not find paraben mix to be a notable allergen in their report of 135 occupational dermatitis cases. Jain et al²⁵⁴ tested 500 nurses in their northern India population and found the most common reactivity to be to their gloves (50%); 5% of this population was paraben sensitive.

REGULATIONS REGARDING PARABEN USE IN COSMETICS

United States Regulations

Cosmetics

In the United States, individual parabens have been interpreted as safe individually in cosmetics at a concentration of up to 0.4% and in mixtures of parabens of up to 0.8%; amounts of 0.3% or less are typically used in cosmetic formulations. The Cosmetic Ingredient Review (CIR) has identified a wide range of paraben concentrations in cosmetic products, but concentrations exceeding the 0.4% guideline in place at the time have been exceedingly infrequent. Cosmetic manufacturers with occasional exception seem to adhere to recommended guidelines and regulations, with CIR-Safety assessment of parabens³⁷ and Rastogi and colleagues³⁸ finding similar concentrations.

Recommendations for infant exposures are addressed separately from adult exposures in determining MOS; ranges from approximately 6000 MOS for single-paraben products to approximately 3000 MOS for multiple-paraben products in adults have been determined and are interpreted as conservative estimates.⁴

The question regarding CIR determination of safety levels deserves mention. The 2 most important laws pertaining to cosmetics marketed in the United States are the Federal Food, Drug, and Cosmetic Act and the Fair Packaging and Labeling Act; the FDA regulates cosmetics under the authority of these laws. The law does not require cosmetic products and ingredients, other than color additives, to have FDA approval before they go on the market.

Final CIR reports on a chemical substance are the result of literature search and review of government sources and databases. The CIR is a panel of 9 voting members with dermatological, veterinarian pathology, toxicologic, and pharmacologic expertise. In addition, there is 1 nonvoting member each from industry, the FDA, and the Consumer Federation of America. The expert panel of the CIR has examined parabens on 10 different occasions for the period spanning 1984 to June 2018. On each occasion, it has been the

opinion of the expert panel that parabens in cosmetics are safe for use, reiterating the guidelines for concentration, which have not changed over the 34-year period.³⁷

Foods

The most frequently used parabens, methyl and *n*-propyl, may be added (up to 0.1%) as antimicrobials to preserve food; these parabens, as well as ethylparaben, can also be used in food packaging.^{3,10,21} The FDA approved the use of parabens in foods in the specific Code of Federal Regulations (CFR); methylparaben (21 CFR 184.1490) and propylparaben (21 CFR 184.1670) are generally recognized as safe when used as chemical preservatives in foods, with use limits of 0.1% for each. The JECFA has placed the acceptable daily intake for methylparaben, ethylparaben, and propylparaben at 0 to 10 mg/kg per day. This was seconded by the European Food Safety Authority in 2004 for all, except propylparaben, “due to recent research demonstrating its effects on certain reproductive parameters in rats.” Specifically, the JECFA cited studies demonstrating propylparaben to have adverse effects in tissues of reproductive organs in male rats at dietary doses of as little as 10 mg/kg of body weight per day, which is within the range of the paraben allowable dietary intake at the time.²⁵⁵ Although noting that propylparaben exposure through diet is limited, the issue of adopted parameters was referred to the EU and propylparaben was removed from foodstuffs in Europe in the 2007 JECFA report.²⁵⁶

Pharmaceuticals

At maximum concentrations rarely exceeding 0.1%, parabens are allowed as preservatives in various pharmaceutical products. These are guidelines and recommendations and are not restrictions that are currently enforced in the United States. Outliers from the CIR report include oral solutions and syrups as well as rectal solutions at concentrations of 5% to 20%.²⁵⁷

European Union Regulations

When it comes to preservatives used in cosmetic formulations outside the United States, the EU has become the primary regulator. The organization determining preservative policy in the EU is the European Commission, which seeks the input of the Scientific Committee on Consumer Safety, as well as industry and other interested parties. Like the CIR, the Scientific Committee on Consumer Safety has reiterated its previous conclusion that the continued use of 4-methylparaben and ethylparaben as preservatives in cosmetics at the maximum authorized concentrations is considered safe for human health at 0.4% for 1 ester or 0.8% when used in combination; propylparaben and butylparaben as preservatives in cosmetic products are considered as safe to the consumer as long as the sum of their individual concentrations does not exceed 0.14%, because of “weak endocrine-modifying potential and quantitative risk assessment.” No additional restrictions were placed upon the use of parabens at that time for infants and children with or without active flexural dermatitis.²⁵⁸ The EU has a list of 59 allowable preservatives, known as Annex V, that not only governs preservative use

in the 28-nation alliance but also influences regulations in many other countries.²⁵⁹ Formulators find that often 2 or 3 options are appropriate for a particular formulation. Annex V was last updated on September 14, 2017. Entry 12 allows the use of 4-hydroxybenzoic acid, methylparaben and ethylparaben, and their potassium, calcium, and sodium salts at 0.4% for 1 ester or 0.8% when used in combination; butylparaben, propylparaben, and their sodium and potassium salts may not exceed the total sum of more than 0.14%. The Danish government, however, has subsequently banned the use of larger-molecule parabens (propylparaben, isopropylparaben, butylparaben, and isobutylparaben) in products for children up to 3 years old as a precautionary measure, because children might be especially vulnerable to these endocrine effects, particularly on broken skin.

In April 2014, the European Commission amended Annex II and V of the EU cosmetic regulation, adding the following 5 parabens to the list of substances prohibited in cosmetic products: isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben. They also banned the use of propylparaben and butylparaben in the nappy area in children younger than 3 years.²⁶⁰

There are those who would suggest that the European Commission is slow in reacting to scientific documentation involving trends in preservative allergy as evidenced by the perceived sluggish response to methyl dibromo glutaronitrile and methylisothiazolinone.²⁶¹ The decision to allow cosmetic preservatives to come to market and be listed on Annex V as safe until proven otherwise has been brought into question. Schwensen and colleagues²⁶² indicted the process as lacking. Their statement: “The introduction of new preservatives in Europe with inadequate premarket risk assessment has rapidly increased the overall burden of cutaneous disease caused by preservatives. We suggest that the cosmetic industry has a responsibility to react faster and replace troublesome preservatives when a preservative contact allergy epidemic is recognized, but the European Commission has the ultimate responsibility for failures in risk management after new, major sensitizing preservatives are introduced onto the market.”²⁶²

Asian Regulations

In 2014, after the EU decision on limits and bans on parabens, the Association of Southeast Asian Nations' Cosmetics Committee decided to ban the use of isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben as preservatives in cosmetics and had already adopted the guidelines recommended for paraben derivatives according to Europe's lead; their statutes are identical to those in place in Europe.

Canadian Regulations

The Canadians have not specifically placed restrictions or bans on any parabens but have weighed in stating that convincing hormonal mimicry and oncogenic potential data are lacking. In all other recommendations, Health Canada has agreed with the FDA position on parabens.^{263,264}

ALTERNATIVES TO PARABENS AND THE ISSUE OF HYPOALLERGENICITY

Parabens have been vilified by a number of consumer watchdog organizations and consumer product manufacturers. However, are there alternatives that are safer and as effective? A variety of approaches have been proposed, including but not limited to citrus extracts such as ascorbic acid, benzyl alcohol, synergistic blends of multifunctional natural ingredients including botanical extracts, honeysuckle extract, spice extracts, and fragrances. Pure essential oils, such as rosemary, lavender, clove, and plant extracts such as *Calendula*, exhibit variable microbistatic and microbicidal activities. The replacement of the aqueous component of creams with *Aloe vera* has been used, eliminating the need for the typical preservation required for the aqueous component. Natural antimicrobial enzyme systems and combinations with biocidal activity, such as the combination of benzoic acid with glycereth-2 cocoate and gluconolactone and sodium benzoate, are under study. Dissolvable film technology using single-dose separation and administration decreases preservative requirements, but it is expensive and currently rarely used. Other approaches include decreasing the pH of cosmetic formulations and using emollients with membrane-disrupting properties, chelating agents, or glycolics. A water-soluble mixture of citric acid with silver citrate with preservative activity has been developed, but the European Commission Scientific Committee on Consumer Products was unable to confirm safety without performance of an in vitro mammalian gene mutation assay. They also voiced concerns regarding the development of argyria.²⁶⁵

Airless packaging may also decrease the need for strong chemical biocides. Unfortunately, these systems are much more expensive to produce, obtain, and use than are the safe, effective, inexpensive, and formulation-friendly parabens. Stability and safety issues are also often associated with such systems, which makes large-scale production problematic. Refrigerated cosmetics are another consideration.⁵² Preservative-free, single-dose packaging is attractive albeit expensive.

For those unready to throw the biocide out of the cosmetic water, synergists added to aqueous formulations such as sorbitan caprylate serve to augment activity of established agents with preservative function such as phenoxyethanol, benzyl alcohol, and even parabens; this allows for lower concentrations of these synthetic biocides to act against microbial overgrowth effectively.²⁶⁶

Health and safety concerns and the natural origin of ingredients continue to rise in the public consumer conscience. Investigators looking at the consumer mindset failed to identify a relationship between attitudes toward chemical safety and purchasing. Fragrances generally do not elicit concern in the buyer, whereas there was a significant association regarding product concern and the presence of several potential or perceived toxicants including mercury, bisphenol A, and parabens.²⁶⁷ It would seem that the negative mantle in which parabens have been cloaked is having an impact on buyer selection. An additional issue, which arises in the alluring nature of the “natural” and “organic” claim, is that often fair trade organizations and manufacturers do not live up to their organic claims when

scrutinized. The degree of claim deviation is geographically dependent, with European companies generally scoring highest in fidelity to claim.²⁶⁸ In their excellent study of products claiming “dermatologist tested,” “hypoallergenic,” “fragrance free,” and “paraben free” (buzzwords in the hypoallergenic marketing package), Hamann and colleagues²⁶⁹ found that 79% to 89% of the 186 products they studied contained at least 1 proven contact allergen and more than 50% contained 2 or more. Five or more allergens were found in up to 12% of products made by manufacturers using such claims.²⁶⁹

From early on, the voice of restraint when evaluating the antiparaben bandwagon could be heard. Lorenzetti and Wernnet²⁷⁰ reviewed data available in 1977 and advised parabens as useful with minimal risks in light of the alternatives available. From another viewpoint with a similar perspective, certain manufacturers are staying with traditional preservative products that are, in their opinion, tried and proven in order not to disappoint their established consumer base. Reformulation inevitably requires the changing of successful product constitution, cost, and shelf life concerns that could upset the end user.^{271,272}

At the present time, there is not a definitive, clear understanding of the potential risks that parabens may possess to *Homo sapiens*; the toxicology of parabens is intensively being examined, and an overview of the safety aspects of parabens will be the subject of subsequent publication. Significant in vitro and laboratory animal data have indicated that there may be valid reasons for concern. However, sectors of the scientific community feel that the crusade against chemical preservation is unwarranted. In 2012, Castelain and Castelain⁹ reviewed the literature and concluded the assertions that parabens posed risks of endocrine disruption (minimal risk at approved use concentrations) and carcinogenesis (breast cancer causation lacking definitive evidence), and effects on fertility in men (under investigation) were unwarranted based on existing scientific information. They argue that elimination of proven, safe preservatives based on inadequate evidence opens the door to preservative misadventure via the unknown or substitution without adequate evidence of safety (such as in the case of isothiazolinones). Lundov and colleagues²⁷³ advise balance in the approach to product versus preservation, making the observation that the potential harm to consumers is not insignificant and that cosmetics and toiletries can be contaminated via 2 different means: direct from the manufacturer or after purchase by the consumer in (occasionally greatly prolonged) use. Numerous examples of such contamination have been catalogued, but truly, this represents the “tip of the iceberg” of the actual problem scope. It is also their opinion that many products are “overpreserved” by manufacturers and make the observation of differences of even a hundredfold for the concentration of preservatives in products of similar nature. Their call that additional studies be performed by manufacturers to evaluate the efficacy of preservation systems in products and to use realistic, scientifically and investigationally determined amounts rather than biocide overkill is well stated. Handwashing by consumer, maintaining products at appropriate temperature limits, and recognition by the consumer that toiletries and cosmetics are not eternal and

should be consumed before their expiration would also lift some of the burden from manufacturers.

SUMMARY AND CONCLUSIONS

Parabens have been used safely in cosmetic products, pharmaceuticals, and foods for more than 70 years and have admirably fulfilled their role as inexpensive, effective biocides. They are rarely problematic as contact allergens, and it is for this reason that parabens have been designated (non)allergen of the year (the second allergen designated); thimerosal was the first such allergen because of the converse experience of very frequent but typically irrelevant reactions. In the 20th century, it was the potential allergenicity of parabens that was at issue; the past 15 years have brought forth a large number of additional concerns to fuel the paraben controversy and provide new life to the “paraben-free” mantra for those who wish to embrace it. Concerns include endocrine disruption, carcinogenicity (specifically breast cancer), neonatal and perinatal exposure risks, fertility, spermatogenesis disturbance, emotional disorders, and environmental impact. These issues have been repeatedly addressed by industry and a number of regulatory authorities, most of whom have found parabens to be safe as cosmetic and food preservatives, as summarized by this article. Suffice to say that this nonallergen of the year's emerging potential pariah status, despite the well-documented scientific evidence to the contrary, may be the newest incarnation of the “paraben paradox.”

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