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Final Report on the Safety Assessment of Benzylparaben

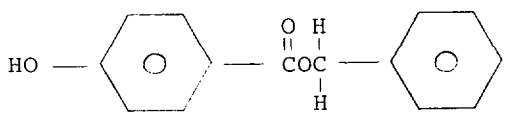
The safety of this ingredient has not been documented and substantiated. The Cosmetic Ingredient Review Expert Panel cannot conclude that Benzylparaben is safe for use in cosmetic products until such time that the appropriate safety data have been obtained and evaluated. The data that were available are documented in the report as well as the types of data that are required before a safety evaluation may be undertaken.

INTRODUCTION

Benzylparaben was originally included in the CIR group review of Methylparaben, Ethylparaben, Propylparaben, and Butylparaben.[1] The CIR Expert Panel noted the difference in chemical structure and the lack of safety test data on Benzylparaben and deleted that ingredient from the group review. CIR issued a public announcement that Benzylparaben would be reviewed as a separate cosmetic ingredient.

CHEMISTRY

Benzylparaben (CAS No. 94-18-9) is an ester of benzyl alcohol and *p*-hydroxybenzoic acid and conforms to the following structure[2]:



The properties of Benzylparaben are shown in Table 1.

Reactivity

Benzylparaben can form salts with strong alkalies. The compound is subject to hydrolysis by both acids and alkalies.[3]

TABLE 1. Physical Properties[2,3]

Molecular weight		228.25
Description		White, crystalline, odorless powder
Solubility	Water	0.01 g/100 ml
	Ethanol	72.0 g/100 ml
	Propylene glycol	13 g/100 ml
Assay		99–100%
Acidity		<0.01 mEq/200 mg
Melting range °C		110–112
Sulfated ash		0.1% maximum

Method of Manufacture

Benzylparaben can be prepared by esterification of *p*-hydroxybenzoic acid with benzyl alcohol.[3] It can also be prepared by conversion of benzyl chloride with sodium *p*-hydroxybenzoic acid.[4]

PURPOSE AND USE IN COSMETICS

Benzylparaben is used in cosmetic products as a preservative.[5] In general use since 1943, it is more commonly used in Europe than in the United States.

The Food and Drug Administration (FDA), in its computer tabulation of voluntary filing of product formulations, reported six uses of Benzylparaben in deodorant and moisturizing skin care preparations. One deodorant contained concentrations in the 0.1–1.0% range, and the remaining five uses were reported as below 0.1%.[6] The EEC reports Benzylparaben to be in general and widespread use as a preservative in conjunction with other paraben esters. Maximum concentration in use is 0.1% as the acid.[2]

The advantage of Benzylparaben use as a preservative is its effectiveness over a wide pH range. It is more effective against fungi and gram-positive bacteria than against gram-negative bacteria. Its disadvantages are low water solubility, partition in favor of the oily phase, and inactivation by ions and proteins.[5]

BIOLOGY

Antimycotic and Antibacterial Effects

A comparative study on the bactericidal effects of Benzylparaben has been published.[7]

Benzylparaben was effective in prevention of growth of *Epidermophyton interdigitale* and *Microsporum audouni* in a substrate concentration of 1:10,000.[8]

The use of 0.025 mg of Benzylparaben/ml in agar medium was effective in inhibiting the growth of *Cryptococcus neoformans*.[9]

Pseudomonas species of bacteria are inhibited by 0.002–0.008% Benzylparaben. The development of aerobic sporogenic agents, such as *Bacillus subtilis*, can be inhibited with 0.002–0.008% Benzylparaben.[10]

Metabolism

Two grams of Benzylparaben were consumed by each of two human volunteers per day for 5 days. Their urine was analyzed for metabolic products. Approximately 6% of the administered compound was eliminated unchanged, and approximately 87% was eliminated as the sulfate conjugate of the ester. Small quantities of the ester were also hydrolyzed to *p*-hydroxybenzoic acid and benzyl alcohol, the latter being oxidized to benzoic acid. The latter two were excreted either unchanged or as their glycine conjugates, *p*-hydroxyhippuric acid and hippuric acid. The investigators reported these percentages as approximations due to the isolation and analytical procedures used in the study.[11]

ANIMAL TOXICOLOGY

Acute Studies

Oral Toxicity

No deaths or toxic signs were reported when up to 10 g/kg of Benzylparaben was given by oral intubation to groups of slc-ddy mice.[12] No deaths occurred when 5 g/kg of Benzylparaben was given to groups of Charles River CD rats.[13]

Two guinea pigs were fed 2 g of Benzylparaben per day; no injurious effects to the animals were noted. The duration and method of dosing were unspecified.[11]

Guinea pigs fed 1 g of Benzylparaben per day for 19 days had no signs of toxicity.[7] See also reference 12.

Spasmolytic action was observed in cerebral vessels of cats after intravertebral injection of 5 mg/kg of Benzylparaben.[14] Intravenous injection of Benzylparaben to dogs and cats caused no variation in blood sugar concentration of the animals.[15] Intravenous injection of 0.7 g/kg of Benzylparaben to dogs produced no ill effects.[16]

Skin Irritation

The Primary Irritation Index (PII) of 500 mg of Benzylparaben when applied under occlusive patches to intact and abraded skin of six female New Zealand rabbits was 0.11 ± 0.08 (control: 0.09 ± 0.09).[2] In another study, Benzylparaben was neither an irritant nor a corrosive agent when 0.5 g of the pure ingredient was applied under semiocclusive conditions to the abraded skin of rabbits.[13]

Ocular Irritation

No adverse ocular responses were observed at 1, 24, 48, or 72 h after the instillation of 0.1 g of Benzylparaben into the conjunctival sac of three New Zealand rabbits.[13]

CLINICAL ASSESSMENT OF SKIN SENSITIZATION

The principal patch tests of the North American Contact Dermatitis Group from 1970–1976 were performed using a 15% paraben mixture containing 3% each of methyl, ethyl, propyl, butyl, and benzyl esters. Positive results were noted in 3% of 1200 patients, 3.5% of 3000, 3.7% of 1900, and 2% of 900–2000 patients, respectively.[17]

Cronin[18] reported irritation in 10 of 1000 eczematous patients patch tested with a 15% paraben mixture similar to the Rudner (1978) study.[17] Scoring was performed at 2 and 4 days after application of the mixture using A1 test patches and zinc oxide strapping.[18]

Four thousand eczematous patients in five European clinics were tested with a series of medicaments including the 15% mixed paraben ester solution previously described.[17] Positive reactions for parabens were 1.3% of males, 2.3% of females, and 2% total.[19]

Nine of 465 patients with dermatitis were sensitized to a mixed paraben ointment. The reactive patients were sensitized as well to a number of other products.[20]

Romaguera and Grimalt reported 57 of 4600 (1.24%) positive reactions to a 15% mixed paraben ointment containing 3% of each of the esters.[21] The above studies are summarized in Table 2.

TABLE 2. Patient Sensitivity to Mixed Paraben Esters

Allergen	*Total patients tested*	*Percent positive*	*Reference*
Paraben mixture	1200	3	17
(3% each of methylparaben,	3000	3.5	17
ethylparaben, propylparaben,	1900	3.7	17
butylparaben, and Benzyl-	900–2000	2.7	17
paraben)	1000	1	18
	4000	2	19
	465	1.5	20

Hjorth and Trolle-Lassen[22] reported on the sensitivity and cross-sensitivity of eczematous patients to paraben esters. Preliminary tests were conducted using routine patch tests with a mixture comprised of 10% methylparaben, 2% ethylparaben, and 2% propylparaben in equal parts Aquaphor and water. Fifteen cases positive to this mixture were assayed for Benzylparaben sensitivity, and 7/15 were sensitive to both 1 and 5% Benzylparaben solutions (Table 3). About two thirds of the patients sensitive to one of the paraben esters also reacted to one or several other esters (Table 4).

Allergic contact dermatitis to Benzylparaben and cross-sensitizations with other parabens is possible but is considered to be rare.[2]

TABLE 3. Sensitivity to Benzylparaben in 15 Paraben-sensitive Persons[22]

Benzylparaben[a] (%)	No. of cases	
	Positive	Negative
5	7	8
1	7	8
0.5	4	11
0.1	2	13

[a]In equal parts Aquaphor and water.

TABLE 4. Cross-sensitivity between Paraben Esters[a][22]

			Methylparaben		Ethylparaben		Propylparaben	
			Positive	Negative	Positive	Negative	Positive	Negative
		No. of cases	21	11	27	5	22	9
Ethyl-paraben	Positive	27	18	9				
	Negative	5	3	2				
Propyl-paraben	Positive	22	15	7	20	2		
	Negative	9	5	4	7	2		
Benzyl-paraben	Positive	14	10	4	12	2	13	1
	Negative	17	16	7	15	2	9	8

Note: One case was not tested with propyl paraben or benzyl paraben.
[a]Thirty-two cases tested with 5% paraben esters in petrolatum or in equal parts Eucerin and water.

SUMMARY

Benzylparaben is an ester of benzyl alcohol and *p*-hydroxybenzoic acid used in cosmetics as a preservative. It is often used in conjunction with other paraben esters.

Metabolism of Benzylparaben is by sulfate conjugation of the parent compound. Excretion is in the urine. Small amounts of the ester are excreted unmetabolized or hydrolyzed to the benzyl alcohol and *p*-hydroxybenzoic acid.

Benzylparaben was not considered an acute toxic agent to mice or rats and was neither an eye nor skin irritant when tested in rabbits. Intravenous injections of Benzylparaben to dogs and cats caused no variation in blood sugar, circulation, and respiration.

Sensitization to Benzylparaben has been observed in eczematous patients. A 3% mixture of Benzylparaben, methylparaben, ethylparaben, propylparaben, and butylparaben produced positive reactions ranging from 1 to 3.7%. The cross-sensitization potential of paraben esters was demonstrated in patients previously sensitized to a paraben mixture. Two thirds of the patients sensitive to one paraben ester also reacted to one or more of the other esters.

DISCUSSION

Section 1 paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the CIR Procedures, the Expert Panel informed the public of its decision that the data on Benzylparaben are insufficient to determine that this ingredient, under the relevant condition of use, is either safe or not safe. The Panel released a "Notice of Insufficient Data Announcement" on October 10, 1984, outlining the data needed to assess the safety of Benzylparaben. The types of data required included:

1. UV absorption spectrum. If absorption occurs between 280 and 360 nm, a photosensitization study is required (in animals only, not in clinical assays).
2. Data detailing the possible presence of impurities.
3. Subchronic feeding study—90-day in rats.
4. Mutagenicity studies and/or in vitro assays for genotoxicity.
5. Eye irritation study at concentration of use.
6. Metabolism and associated pharmacokinetic studies are not requested at this time. If significant toxicity is shown in the above tests, the Expert Panel may request this additional type of testing.

Acute animal oral toxicity and animal eye and skin irritation data were received in response to the above requests and are included in this report. The eye test data included in this report cannot be interpreted without an adequate description of the methodology used. The Expert Panel again concurred with the decision made during its earlier review that similar data on methylparaben, ethylparaben, propylparaben, or butylparaben were not necessarily applicable to the safety evaluation of Benzylparaben.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of Benzylparaben as used in cosmetics.

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*Available upon request: Director, Cosmetic Ingredient Review, 1110 Vermont Ave., NW, Suite 810, Washington, DC 20005.

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