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Final Report on the Safety Assessment of Isobutylparaben and Isopropylparaben[1]

Abstract: Isobutylparaben and Isopropylparaben are esters with a phenol ring structure intended for use as preservatives in cosmetics. In 1993, only Isobutylparaben was reported to be in use. When administered to rabbits via a stomach tube, Isobutylparaben was metabolized primarily to *p*-hydroxybenzoic acid; <1% was recovered unchanged. Spleen, thymus, hepatic parenchyma, and lymph node atrophy was observed in short-term feeding studies in mice with Isobutylparaben at a concentration of 1.25%. All mice died at concentrations of 5 and 10%. Isobutylparaben at a concentration of 0.6% produced no adverse effects. Mutagenesis was not observed with either ingredient in Ames tests, but both positive and negative results were seen in chromosome abberation assays of Chinese hamster ovary cells in culture. In chronic mouse-feeding studies, 0.15, 0.3, and 0.6% Isobutylparaben caused no increase in neoplasias or decrease in time to neoplasm development. Data on Methylparaben, Ethylparaben, Propylparaben, and Butylparaben considered relevant to the assessment of Isobutylparaben and Isopropylparaben were summarized. Subchronic and chronic studies indicate that these other parabens are practically nontoxic, nonmutagenic, and noncarcinogenic. They also do not irritate or sensitize normal skin. Tests of patients with damaged skin, however, do show that a few of these individuals can be sensitized. These data support the recommendation that all six of these parabens should not be used on damaged skin. Given the absence of any adverse effects, including irritation and sensitization, in persons with normal skin, the conclusion that Methylparaben, Ethylparaben, Propylparaben, and Butylparaben are safe as cosmetic ingredients was reaffirmed. By extension, because of their similarities, the conclusion was reached that Isobutylparaben and Isopropylparaben are safe as cosmetic ingredients in the present practices of use. **Key Words:** Isobutylparaben—Isopropylparaben—Cosmetic use—Rabbits—Mice—Toxicity—Mutagenicity—Carcinogenicity.

Isobutylparaben and Isopropylparaben are used in cosmetic formulations as preservatives. This report is a summary of data available to the Cosmetic Ingredient Review (CIR) concerning the chemistry, cosmetic use, toxicity, mutagenicity, and carcinogenicity of these compounds. The CIR Expert Panel has reviewed the safety of Methylparaben, Ethylparaben, Propylparaben, and Butylparaben. The summary from that report is also included herein. Abstracts published in the 10 years since publication of the Final Report on Parabens have described additional case reports of allergic reactions to Parabens or to products containing

[1] Reviewed by the Cosmetic Ingredient Review Expert Panel.

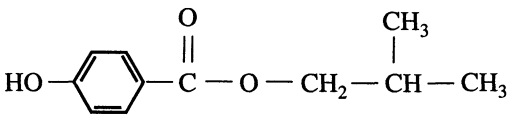
Address correspondence and reprint requests to Dr. F. A. Andersen at Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, D.C. 20036, U.S.A.

Parabens: contact dermatitis to bandages containing Propylparaben (Lindner et al., 1989); allergic reactions to Parabens, particularly Methylparaben, found in medical supplies such as anesthetics, barium enemas, and mandibular block injections (Ivy, 1983; Wahl, 1983; Javors et al., 1984; Schwartz et al., 1984; Fine and Dingman, 1988); and one report of facial contact urticaria to Methylparaben in cosmetics (Kojima, 1992). In addition, there has been a report that Methylparaben is mildly ciliotoxic to male Wistar rats at an inhaled concentration of 1.18 m*M* (Jain and Po, 1993) and a report of intercellular vacuolization and thickening of the endothelial layer in rabbit corneal endothelium 1 day following subconjunctival administration of solutions containing Methylparaben and Propylparaben (Weinreb et al., 1986). The four parabens, especially Butylparaben, have been shown to exhibit spermicidal activity, possibly through impairment of sperm membrane function (Song et al., 1989).

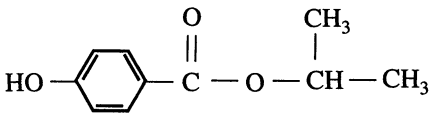
CHEMISTRY

Definition and Structure

Isobutylparaben (CAS No. 4247-02-3) and Isopropylparaben (CAS No. 4191-73-5) are esters of *p*-hydroxybenzoate that conform to the following formulas (Nikitakis et al., 1991):



Isobutylparaben



Isopropylparaben

Other names for Isobutylparaben are benzoic acid, 4-hydroxy-, 2-methylpropyl ester; 4-hydroxybenzoic acid, 2-methylpropyl ester; isobutyl *p*-hydroxybenzoate; isobutyl parahydroxybenzoate. Other names for Isopropylparaben are benzoic acid, 4-hydroxy-, 1-methylethyl ester; 4-hydroxybenzoic acid, 1-methylethyl ester; 1-methylethyl-4-hydroxybenzoate (Nikitakis et al., 1991).

Chemical and Physical Properties

Isobutylparaben has a molecular weight of 194.25. Isopropylparaben has a molecular weight of 180.22 (Registry of Toxic Effects of Chemical Substances, 1993).

Analytic Methods

Detection of Isopropylparaben and Isobutylparaben can be made by high-performance liquid chromatography (Kitada et al., 1980; Terada and Sakabe, 1985; Shiroma and Oshiro, 1986; Maeda et al., 1987).

USE

Cosmetic

Isobutylparaben and Isopropylparaben are used in cosmetic formulations as preservatives (Nikitakis, 1988). The product formulation data submitted to the Food and Drug Administration (FDA) in 1993 reported that Isobutylparaben was used in a total of 83 cosmetic product formulations (Table 1) and that no formulations contained Isopropylparaben (FDA, 1993). Cosmetic products containing either Isobutylparaben or Isopropylparaben may be applied to or come in contact with skin, eyes, hair, nails, and mucous membranes. Product formulations containing either Isobutylparaben or Isopropylparaben may be applied as many as several times a day and may remain in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

International

Isobutylparaben (as isobutyl parahydro benzoate, isobutyl paraben, or isobutyl *p*-hydroxybenzoate) and Isopropylparaben (as isopropyl *p*-hydroxybenzoate) are approved for use in Japan in cosmetic formulations (Rempe and Santucci, 1992). Isobutylparaben and Isopropylparaben are included in the list of allowed preservatives in cosmetic products by the European Economic Commission under the category of 4-hydroxybenzoic acid and its salts and esters. Maximum concentra-

TABLE 1. *Cosmetic product formulation data for Isobutylparaben*

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Mascara	247	3
Bath capsules	7	1
Eyebrow pencil	113	2
Eyeliner	253	1
Other eye makeup preparations	160	1
Other hair preparations	418	1
Lipstick	937	1
Other makeup preparations	418	1
Other shaving preparations	157	1
Face and neck (except shaving preps)	148	12
Paste masks (mud packs)	293	4
Skin fresheners	246	1
Suntan gels, creams, and liquids	290	5
Indoor tanning preparations	53	1
Other suntan preparations	65	3
Other fragrance preparations	177	3
Face powders	313	2
Foundations	398	5
Cleansing	854	7
Body and hand (except shaving)	1,229	4
Moisturizing	933	12
Night	263	2
Other skin care preparations	848	10
1993 Totals	—	83

tions set were 0.4% for any single ester and 0.8% for mixtures of esters (European Economic Community, 1990).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

Four male rabbits weighing between 2.25 and 3.50 kg were given a 12% solution in the form of Na salt of either 800 mg/kg or 400 mg/kg of Isobutylparaben via a stomach tube. A 24-h urine sample was collected and analyzed via paper chromatography. Between 25 and 33% of the Isobutylparaben dose was metabolized to free *p*-hydroxybenzoic acid, 16–31% became *p*-hydroxybenzoic acid conjugated with glycine, and 7–17% was recovered as *p*-hydroxybenzoic acid conjugated with one of the following three acids: ester-type glucuronic acid, ether-type glucuronic acid, or sulfuric acid. In total, between 77 and 85% of the Isobutylparaben was recovered as one of the above-mentioned forms of *p*-hydroxybenzoic acid. Only between 0.2 and 0.9% of Isobutylparaben was detected in the urine as the unchanged alkyl ester. No explanation was offered as to why ~20% of the initial dose was not recovered (Tsukamoto and Terada, 1964).

ANIMAL TOXICOLOGY

Acute Toxicity

The subcutaneous LD_{50} of Isobutylparaben in mice was 2,600 mg/kg (details not available) (Registry of Toxic Effects of Chemical Substances, 1993).

Short-term Toxicity

Groups of 10 male and 10 female ICR/Jcl mice were administered 0.6, 1.25, 2.5, 5, and 10% Isobutylparaben in the feed for 6 weeks (Inai et al., 1985). A group of 20 males and 20 females served as a control. All mice of the 5 and 10% Isobutylparaben dose groups died during the first 2 weeks of the study. Body weight gain percentages for mice of the 1.25 and 2.5% Isobutylparaben groups were ~10% of the control group. Body weight gain for mice of the 0.6% dose group was about the same as control. Upon microscopic examination, atrophy of the spleen, thymus, and lymph nodes was observed in groups dosed with ≥1.25% Isobutylparaben. Multifocal degeneration and necrosis of the hepatic parenchyma was also noted in these groups. No significant lesions were found in mice dosed with 0.6% Isobutylparaben.

Chronic Toxicity

Groups of 50 male and 50 female 8-week-old ICR/Jcl mice were administered 0.15, 0.3, and 0.6% Isobutylparaben in the feed for 102 weeks (Inai et al., 1985). A group of 50 males and 50 females served as a control and were fed the basal diet. Body weights were measured once a week for the first 6 weeks, once every other week for the next 24 weeks, and once every 4 weeks for the remainder of the study. Feed consumption was measured once a week for the first 30 weeks, once

every other week for the next 20 weeks, and once every 4 weeks for the remainder of the study. Animals found moribund during the study were killed and necropsied. Animals surviving to the end of the study (nine females in the test group) were killed and necropsied. There was no significant difference between groups in the amount of feed consumed; the intake of Isobutylparaben was four times greater by mice in the 0.6% dosing group than in the 0.15% group.

Data were compiled from animals surviving the study for ≥78 weeks (30% of males and 57% of females in the dosing group and 24% of males and 44% of females in the control group). There were no significant differences in the incidence of neoplasms between the treated mice and the controls or between groups given different doses of Isobutylparaben. Among treated male mice, the most frequently observed neoplasms were lung adenomas and adenocarcinomas. A high incidence of hematopoietic neoplasms was found in males in the 0.6% group and in treated females. There was a low incidence of neoplasms at other sites in females. Amyloidosis was noted in 58% of dosed males and 33% of dosed females compared with 25% of control males and 10% of control females. While no information is available concerning the incidence of amyloidosis in historical controls, it is known that spontaneous amyloidosis is common in mice, particularly in some inbred strains and in older mice (Rigdon and Schadewald, 1972; Soret et al., 1977; Conner et al., 1983).

GENOTOXICITY

A chromosomal abberation assay was performed using a Chinese hamster fibroblast cell line. Cells treated with 0.03% Isobutylparaben in ethanol (dose volume equal to 1.0% of total volume) had no chromosomal aberrations after 48 h (Ishidate and Odashima, 1977). At a concentration of 1 mg/plate in Dimethyl Sulfoxide, Isopropylparaben and Isobutylparaben were negative in Ames tests using *Salmonella typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98. A chromosomal aberration assay was also performed using a Chinese hamster fibroblast cell line. After 48 h, cells treated with 0.125 mg/ml Isopropylparaben or 0.6 mg/ml Isobutylparaben in ethanol had 2.0% and 3.0% polyploid cells, respectively, and both had a 1% incidence of structural chromosomal aberrations (Ishidate et al., 1984). Kawachi (1976) (in Odashima, 1980) reported that Isobutylparaben was positive in a chromosomal aberration assay but negative in an Ames test and a *rec* assay (details not available).

CARCINOGENICITY

Groups of 50 male and 50 female ICR/Jcl mice were administered 0.15, 0.3, and 0.6% Isobutylparaben in the feed for 102 weeks (Inai et al., 1985). A group of 50 males and 50 females served as a control. Animals found moribund during the study were killed and necropsied. A microscopic examination was performed on all neoplasms. No changes in either neoplasm incidence or time to neoplasm development were observed in dosed mice compared with controls.

SUMMARY OF ISOBUTYLPARABEN/ISOPROPYLPARABEN

Isobutylparaben and Isopropylparaben are esters of *p*-hydroxybenzoate and are used as preservatives. In 1993, Isobutylparaben was reported to be used in 83 cosmetic formulations (at unknown concentrations), and Isopropylparaben was not in use. When male rabbits were administered either 800 mg/kg or 400 mg/kg of Isobutylparaben via a stomach tube, 77–85% of the ingredient was recovered as a form of *p*-hydroxybenzoic acid; 20% was not recovered. Isobutylparaben had a subcutaneous LD_{50} of 2,600 mg/kg in mice.

No significant histological changes were observed in mice dosed with 0.6% Isobutylparaben in the feed for 6 weeks. Mice dosed with 1.25% had atrophy of the spleen, thymus, and lymph nodes as well as multifocal degeneration and necrosis of the hepatic parenchyma. Mice dosed with 5% and 10% Isobutylparaben died within the first 2 weeks of the study. Mice were orally dosed with 0.15, 0.3, and 0.6% Isobutylparaben in the feed for 102 weeks. Upon necropsy, the only effect noted was amyloidosis in 58% of dosed males and 33% of dosed females surviving past 78 weeks, as compared with 25% of control males and 10% of control females. Chinese hamster fibroblast cell lines treated with 0.03% Isobutylparaben had no chromosomal aberrations after 48 h.

At a concentration of 1 mg/plate Isobutylparaben and Isopropylparaben had negative Ames tests in *S. typhimurium*. After 48 h, cells treated with 0.125 mg/ml Isopropylparaben or 0.6 mg/ml Isobutylparaben in ethanol had 2.0% and 3.0% polyploid cells, respectively. Both had a 1% incidence of structural chromosomal aberrations. No changes in either neoplasm incidence or time to neoplasm development were observed in mice dosed with 0.15, 0.3, or 0.6% Isobutylparaben in the feed for 102 weeks as compared with controls.

SUMMARY OF METHYLPARABEN, ETHYLPARABEN, PROPYLPARABEN, AND BUTYLPARABEN

The CIR review of Methylparaben, Ethylparaben, Propylparaben, and Butylparaben (Elder, 1984) concluded that the parabens are esters of *p*-hydroxybenzoic acid (PHBA). They are prepared by esterification of PHBA with the corresponding alcohol in the presence of a catalyst. Parabens are generally oil soluble and poorly soluble in water. Water solubility decreases as the ester chain length increases. These compounds are stable in air and resist hydrolysis in acid solutions and under conditions of sterilization. In alkaline solutions, Parabens hydrolyze to PHBA and the corresponding alcohol. Paraben interactions with gelatin, sodium lauryl sulfate, polysorbates, polyethylene glycols, cellulase esters, and polyvinylpyrrolidone have been reported. Micellar interactions bind Parabens to such nonionic surfactants as sodium lauryl sulfate.

Parabens are used as preservatives in >13,200 cosmetic formulations at concentrations almost exclusively <5%. They are most commonly used at concentrations <1%. Parabens preserve fats, proteins, oils, and gums in cosmetics. Products containing Parabens contact all surfaces of the body as well as ocular, oral, and vaginal mucosae. Duration of application may be continuous and may extend over a period of years. Certain Parabens are also used as preservatives in

foods (≤0.1% as GRAS ingredient), pharmaceuticals (as inactive or safe and effective OTC ingredients), and other products.

Parabens are quickly absorbed from the blood and gastrointestinal tract, hydrolyzed to *p*-hydroxybenzoic acid, and conjugated; the conjugate is excreted in the urine. Data obtained from chronic administration studies indicate that Parabens do not accumulate in the body. Serum concentrations of Parabens, even after intravenous administration, quickly decline and remain low. Varying amounts of Parabens are passed in the feces depending upon which Paraben is administered and the size of the dose. Little or no unchanged Paraben is excreted in the urine. Most of an administered dose can be recovered within 5–72 h as *p*-hydroxybenzoic acid or its conjugates. Parabens appear to be rapidly absorbed through intact skin.

The antimicrobial activity of the Parabens increases with increasing ester chain length. They are more active against fungi than bacteria and more active against gram-positive than gram-negative bacteria. Their effect is more microbiostatic than microbicidal. Parabens are effective within a pH range of 4–8. Parabens act as microbiostatic agents by increasing cell wall permeability and thereby disrupting transport. Parabens also alter cellular respiration, electron transport, and oxidative enzyme systems of microbes. Both the ester linkage and the parahydroxy group of the Paraben molecule have been implicated as active sites.

The Parabens inhibit and potentiate many enzyme systems. They also compete with bilirubin for binding sites on serum albumin. These substances inhibit growth of cultures of animal and human cells and reduce biosynthesis of RNA and DNA in cultures of fibroblasts. Parabens have varying anticonvulsive, vasodilating, analgesic, and anesthetic effects in animals.

Acute toxicity studies in animals indicate that Parabens are practically nontoxic by various routes of administration. Methylparaben (10 and 100%), Propylparaben (10%), and Ethylparaben (10 and 100%) were, at most, mildly irritating when applied to rabbit skin. Methylparaben and Ethylparaben at 100% concentration were slightly irritating when instilled into the eyes of rabbits. Subchronic and chronic oral studies indicate that Parabens are practically nontoxic. Almost all animal sensitization tests indicate that the Parabens are nonsensitizing.

Numerous mutagenicity studies, including the Ames test, dominant lethal assay, host-mediated assay, and cytogenic assays, indicate that the Parabens are nonmutagenic. Methylparaben was noncarcinogenic when injected subcutaneously in mice or rats or when administered intravaginally in rats. It was not cocarcinogenic when injected subcutaneously in mice. Propylparaben was noncarcinogenic in a study of transplacental carcinogenesis. Methylparaben was nonteratogenic in rabbits, rats, mice, and hamsters. Ethylparaben was nonteratogenic in rats.

Parabens are practically nonirritating and nonsensitizing in a population with normal skin. Paraben sensitization has occurred, especially when Paraben-containing medicaments have been applied to damaged or broken skin. Even when applied to patients with chronic dermatitis, Parabens generally induce sensitization in <3% of such individuals. Of 27,230 patients with chronic skin problems, 2.2% were sensitized by preparations of Parabens at concentrations of

1–30%. Many patients sensitized to Paraben-containing medications can wear cosmetics containing these ingredients with no adverse effects. Skin irritation and sensitization tests on product formulations containing from 0.1 to 0.8% of one or two of the Parabens showed no evidence of significant irritation or sensitization potential for these ingredients. A subchronic oral toxicity study in humans indicated that Methylparaben was practically nontoxic at doses ≤2 g/kg/day. A primary eye irritation study in humans showed Methylparaben to be nonirritating at concentrations ≤0.3%. Photocontact sensitization and phototoxicity tests on product formulations containing 0.1–0.8% Methyl-, Propyl-, and/or Butylparaben gave no evidence of significant photoreactivity. Industry complaint experience data showed low to moderate numbers of safety-related complaints, with the incidence depending on the product.

DISCUSSION

The Expert Panel recognizes that the actions and effects of Isobutylparaben and Isopropylparaben closely resemble those of Butylparaben, Ethylparaben, Methylparaben, and Propylparaben. In the evaluation of those parabens (Elder, 1984), the Panel issued a "safe as used" conclusion. The Panel acknowledges that since publication of that report there have been additional isolated cases of Paraben sensitivity. However, the fact that Parabens may be sensitizing was addressed in the discussion of Parabens in 1984, and the Expert Panel feels that the new case reports do not warrant a reevaluation of that conclusion. Furthermore, the body of evidence concerning Isobutylparaben and Isopropylparaben supports the conclusions drawn in 1984 concerning Parabens.

CONCLUSION

From the available information, the Panel concludes that Isobutylparaben and Isopropylparaben are safe as cosmetic ingredients in the present practices of use.

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