Safety Assessment of Sodium Benzotriazolyl Butylphenol Sulfonate as Used in Cosmetics

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ABSTRACT

This is a safety assessment of sodium benzotriazolyl butylphenol sulfonate as used in cosmetics. This ingredient is reported to function as a light stabilizer in cosmetics. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed relevant data related to the ingredient. The Panel concluded that sodium benzotriazolyl butylphenol sulfonate is safe in cosmetics in the present practices of use and concentration.

INTRODUCTION

This report presents the CIR Panel's safety assessment of sodium benzotriazolyl butylphenol sulfonate as used in cosmetics. This ingredient is reported to function as a light stabilizer (ie, protecting the product from chemical or physical deterioration induced by light) in cosmetics.[1]

A comprehensive search of the literature identified little published data relevant to this safety assessment. No toxicity data have been submitted by industry. However, pertinent data were discovered in the European Chemicals Agency (ECHA) database.[2] Data from robust summaries located on the ECHA database are presented below.

CHEMISTRY

Definition and Structure

Sodium benzotriazolyl butylphenol sulfonate (CAS No. 92484-48-5) is an organic compound (Figure 1).[1] It is also referred to by its International Union of Pure and Applied Chemistry (IUPAC) name, as sodium 3-(2*H*-benzotriazol-2-yl)-5-*sec*-butyl-4-hydroxybenzenesulfonate, in the literature.

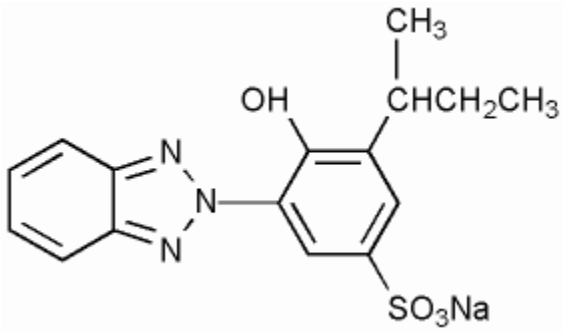

Figure 1. Sodium benzotriazolyl butylphenol sulfonate.

Physical and Chemical Properties

Sodium benzotriazolyl butylphenol sulfonate is a light-beige to white powder with a trace characteristic odor (Table 1). It is an ultraviolet (UV) absorber, which converts the energy of absorbed UV light to heat through a mechanism analogous to keto-enol tautomerization.[3]

The UV absorption spectrum of sodium benzotriazolyl butylphenol sulfonate shows 2 peaks at wavelengths of approximately 290 and 335 nm, and no significant absorption above approximately 390 nm.[4]

Sodium benzotriazolyl butylphenol sulfonate is a sodium sulfonate salt and is reported to be soluble in water and alcohol.[4] It is hydrolytically stable at 50°C.[2,4]

Method of Manufacture

Sodium benzotriazolyl butylphenol sulfonate is prepared by warming 2-(2'*H*-benzotriazol-2'-yl)phenol containing *t*-alkyl substituents in a toluene solution with an aluminum chloride/nitro-methane catalyst, resulting in the release of the *t*-alkyl groups to the solvent, leaving 2-[2'*H*-benzotriazol-2-yl]phenol.[5] The 2-[2'*H*-benzotriazol-2-yl]phenol is then treated with chlorosulfonic acid to give sodium benzotriazolyl butylphenol sulfonate.

A patent for the manufacture of sodium benzotriazolyl butylphenol sulfonate describes the following procedure.[6] 2-(2'-Hydroxy-3'-*sec*-butyl-5'-*tert*-butylphenyl)benzotriazole is combined with oleum at cool temperatures. This solution is stirred at room temperature, and then poured into ice water. The precipitate is heated, cooled, and filtered. The acid is well pressed, then suspended in water. The pH is adjusted to 7 with sodium hydroxide. The resulting crystal slurry is heated, cooled, and then filtered. The product is heat-dried under vacuum.

Impurities

A supplier reported that the purity of sodium benzotriazolyl butylphenol sulfonate was 98.6%-99.4%.[2] The impurities were not specified.

USE

Cosmetic

The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP).[7] In 2015, sodium benzotriazolyl butylphenol sulfonate was reported to be used in a total of 477 cosmetic formulations, consisting of 68 leave-on products, 380 rinse-off products, and 29 products for the bath (Table 2). These products include one baby product, hair products (coloring and non-coloring), perfumes, and other dermal products; 310 products have the potential for mucus membrane exposures.

A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for this ingredient.[8] Sodium benzotriazolyl butylphenol sulfonate was reported to be used up to a highest maximum concentration of 0.17% in leave-on products (nail polish and enamels) and up to 0.1% in perfumes. It is used in rinse-off products at up to 0.1%, which is the highest maximum concentration in skin cleansing products. It is also used at up to 0.033% in bubble baths.

Sodium benzotriazolyl butylphenol sulfonate was reported to be used in perfumes and body and hand aerosol/spray products, and these products could possibly be inhaled. This ingredient is reportedly used in sprays at concentrations up to 0.1%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.[9-12] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[9,12]

Sodium benzotriazolyl butylphenol sulfonate is not restricted from use in any way under the rules governing cosmetic products in the European Union.[13]

Non-Cosmetic

Sodium benzotriazolyl butylphenol sulfonate is a UV absorber used to protect coatings, plastics, paint, wood, wool and other items that degrade when exposed to UV light.[3,14]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Dermal/Percutaneous

Two formulations of sodium benzotriazolyl butylphenol sulfonate (composition of the formulations not provided) showed minimal penetration into cadaver skin using Franz cells (n=3) and the finite dose approach.[2] Most of the test substance remained on the surface of the skin; there was no evidence of accumulation in the skin. Total absorption was 0.037, 0.029, 0.016 µg, respectively, for the 3 groups of Franz cells. The skin for these experiments was collected from 3 donors within 24 h of death; 6 replicate experiments per donor were used. In the first group of cells, the test substance (0.1%; 0.8 mg/0.8 cm^2; formulation not specified) was placed on the skin for 30 min; then the surface of the skin was washed with deionized water. In the second group (0.5%; 0.8 mg/0.8 cm^2; same unspecified formulation as for the first group) and third group (0.5%; 1.6 mg/0.8 cm^2 in an emulsion; formulation not specified) of Franz cells, the test substance was placed on the cadaver skin, and the phosphate-buffered saline was replaced in the receptor cells at 2, 4, 8, 12, 24, 32, and 48 h. Receptor cell fluids were analyzed by diode-array ultraviolet detection. Following the last receptor solution collection, the skin samples were surface-washed with deionized water. The skin was then removed from each chamber, tape-stripped 20 times to collect the stratum corneum (10 strips/vial), separated into epidermis and dermis, and extracted with a solvent (solvent not specified) for no less than 24 h.

In another study, sodium benzotriazolyl butylphenol sulfonate was not detected in the receptors of Franz cells (n=10; 3 donors) after 24 h; the permeation rate of the test substance through the skin was <5 ng/cm^2 (ie, the limit of detection) or approximately 0.08 % of the administered dose.[2] The total amount of the test substance recovered from the deeper layers of the skin was 0.026 µg/cm^2 (<0.4 % of the administered dose). The experimental protocol of this study included administering an oxidative hair dye containing sodium benzotriazolyl butylphenol sulfonate (0.67% mixed with developer for a final concentration of 0.33%; 2 mg/cm^2) to the epidermal membranes with a glass rod. The doses ranged from 1.6-2.6 mg/cm^2 (mean 2.1 ± 0.1 mg/cm^2; 6.9 ± 0.3 µg/cm^2 of the test substance). The receptor cells were sampled at 2, 4, 6, 12 and 24 h and the samples tested by HPLC. The diffusion cells were dismantled, any formulation remaining on the skin surface was removed by gentle wiping with a cotton bud, and the epidermal membrane was tape stripped (tape-strip fractions collected: 1-3, 4-6, 7-12 and 13-20 times).

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Dermal – Non-Human

The dermal LD_{50} of sodium benzotriazolyl butylphenol sulfonate was shown to be >2000 mg/kg when administered to the shaved backs of KFM-Han Wistar rats (n=5/sex) in carboxymethyl cellulose (4 mL) under occlusion for 24 h.[2] The

test was conducted in accordance with Organization for Economic Co-operation and Development (OECD) Guideline 402. The test material was administered to 10% of the body surface. The rats were observed for 15 days and then killed and necropsied. The necropsies were unremarkable.

When sodium benzotriazolyl butylphenol sulfonate (100%; 0.5 g moistened with distilled water) was dermally administered to the shaved skin (3 cm x 3 cm) of New Zealand White rabbits (n=1 male, 2 females) under semi-occlusion for 4 h, no discoloration or toxic signs were observed.[2] The test site was then washed with lukewarm tap water. The rabbits were observed for 72 h.

Oral – Non-Human

The oral LD_{50} of sodium benzotriazolyl butylphenol sulfonate was found to be >5000 mg/kg when administered to KFM-Han Wistar rats (n=5/sex) by gavage in carboxymethyl cellulose (20 mL).[2] The test was conducted in accordance with OECD guideline 401. The rats were observed for 15 days after exposure and then necropsied. One female rat died on day 2 of observation. Clinical signs were sedation, dyspnea, hunched posture, diarrhea, and ruffled fur, all of which were resolved by day 8. At necropsy, the lungs of the rat that died had reddish discoloration and dark-red foci. The rest of the necropsies were unremarkable.

Repeated Dose Toxicity

Oral – Non-Human

Sodium benzotriazolyl butylphenol sulfonate (0, 200, or 1000 mg/kg in 4% carboxymethyl cellulose; 10 mL/kg) was administered by gavage to Wistar rats (n=3/sex) for 5 days, and there were no clinical signs that could be attributed to the test material in any group in this range-finding study.[2] At necropsy, there was an increase in absolute liver weights in male rats and in liver-to-body weight ratios in male and female rats in the high-dose group when compared to controls and to the low-dose group. The absolute and relative adrenal weights of the female rats of the high-dose group were decreased compared to those of the rats of other groups. Compared to male rats in the control and low-dose group, the males of the high-dose group had decreased feed consumption during the first 3 days of treatment. Feed consumption was comparable to that of the other groups at termination of treatment. The feed consumption of the females was similar among the groups. No differences in body weight gains were observed between rats in the control and treatment groups. The ophthalmoscopic examinations at termination were unremarkable.

The oral no-observed-adverse-effects level (NOAEL) for sodium benzotriazolyl butylphenol sulfonate was 200 mg/kg/d for rats in a 28-day gavage study.[2] The test was conducted in accordance with OECD Guideline 407. In this study, benzotriazolyl butylphenol sulfonate (0, 20, 50, 200, 800 mg/kg/d in carboxymethyl cellulose 4% in distilled water; 10 mL/kg) was administered by gavage to Wistar rats (n=5/sex; controls=10/sex) for 28 days. The rats were then killed and necropsied. A second high-dose group was allowed a recovery period (time not specified) before they were killed and necropsied. There was 1 death of a female in the high-dose group due to intubation error. There were no reported changes in clinical condition, body weights, or feed consumption. There were increases in absolute and relative liver weights in male and female rats at termination of the treatment period in the 200 mg/kg group. These findings were considered to be adaptive and not adverse because no histopathological lesions were observed in the livers. No other effects were observed at 200 mg/kg/d. In the high-dose groups, the absolute weights of the adrenal glands were decreased in males at the termination of treatment and following the recovery period. There was no evidence of abnormal histopathological findings resulting from treatment with the test material. No effects were observed in clinical laboratory investigations (hematology, clinical biochemistry, and urinalysis). There were no ophthalmoscopic effects.[2]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

One study reported the oral NOAEL for reproductive and developmental toxicity for Wistar rats as 800 mg/kg/d sodium benzotriazolyl butylphenol sulfonate when administered by gavage throughout gestation (starting at pairing).[2] The NOAEL for parental toxicity was 200 mg/kg/d because salivation and increased water consumption were noted for animals in the 800 mg/kg/d group. Wistar rats (n=10/sex) were dosed by gavage with sodium benzotriazolyl butylphenol sulfonate (0, 50, 200 and 800 mg/kg/d in 1% carboxymethyl cellulose) in accordance with OECD Guideline 421. The males were treated for a total of 29 days and the dams for a total of 43-55 days. Parents and pups were killed and necropsied. No further details on the methods were provided.

During this experiment, there were no mortalities in the parental groups. There were no changes in body weights or body weight gain. There were no changes in feed consumption. In the high-dose group, water consumption was increased for males and females during the entire experiment, which may be a behavioral adaption in response to increased salivation observed in all rats in this group. Mating, fertility and conception indices, precoital time, and number of corpora lutea and implantation sites were similar in all groups. No macroscopic treatment-related findings were observed at necropsy, and there were no treatment-related microscopic findings. There were no toxicologically relevant effects on the gestation index and duration, parturition, maternal care or early postnatal pup development (mortality, clinical signs, body weight and macroscopic findings).[2]

GENOTOXICITY

In Vitro

In a bacterial reverse mutation assay using *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537), sodium benzotriazolyl butylphenol sulfonate (10, 33.3, 100, 333.3, 1000, and 5000 µg/plate; vehicle not provided) was not mutagenic with or without metabolic activation.[2] Results of the positive control were as expected. The test was conducted in accordance with OECD guideline 471 and Guideline EU Method B.13/14.

In a mammalian chromosomal aberration assay using Chinese hamster lung fibroblasts (V79), sodium benzotriazolyl butylphenol sulfonate (8, 80, and 110 µg/plate without metabolic activation; 10, 50, 120, 130 µg/plate with metabolic activation; in dimethyl sulfoxide [DMSO]) was genotoxic with and without metabolic activation at the highest test concentrations.[2] There were increased numbers of cells with structural aberrations after treatment with the test material with metabolic activation. Without metabolic activation, an increase of the aberration rate was observed only at the incubation time of 18 h. Treatment of the cells with 110 µg/mL without metabolic activation and 130 µg/mL with metabolic activation reduced the plating efficiency of the V79 cells. The highest concentrations yielded 18% survival (110 µg/mL; without metabolic activation) and 67.1 % survival (130 µg/mL; with metabolic activation). Results of the positive control were as expected. The test was conducted in accordance with OECD Guideline 473 and Guideline EU Method B.10.

In a mammalian cell gene mutation assay using V79 fibroblasts targeting the hypoxanthine-guanine phosphoribosyl transferase gene, sodium benzotriazolyl butylphenol sulfonate (10, 30, 45, 60, 70, 80, and 100 µg/plate in saline, with and without metabolic activation) was not genotoxic up to 80 µg/plate.[2] The highest concentration was cytotoxic; 100 µg/plate reduced the survival rate of the cells by 13.2 % without metabolic activation and 22.7 % with metabolic activation. Results of the positive control were as expected. The test was conducted according to OECD Guideline 476.

In Vivo

In a mammalian erythrocyte micronucleus assay, a single dose of sodium benzotriazolyl butylphenol sulfonate (3000 mg/kg in 0.5% methocel; 20 mL/kg) was not genotoxic to NMRI mice (n=6/sex) when administered by gavage.[2] The test was conducted in accordance with OECD Guideline 474 and Guideline EU Method B.12. The mice were killed 24, 48 and 72 h after administration of the test material, and the bone marrow was collected. The positive control was cyclophosphamide (30 mg/kg). When examining the marrow, 1000 polychromatic erythrocytes (PCE) were analyzed per animal for micronuclei.

In an unscheduled DNA synthesis assay, a single dose of sodium benzotriazolyl butylphenol sulfonate (100, 330, 1000 mg/kg in 1% carboxymethylcellulose suspension; 10 mL/kg) was not genotoxic to male Wistar rats (n=5) when administered by gavage.[2] In the high-dose group, the viability of the isolated hepatocytes of 2 rats was slightly decreased. The in-vitro attachment of the hepatocytes was not affected by the in-vivo pre-treatment with the test article. The test was conducted in accordance with OECD Guideline 486 and Guideline EU Method B.39. The rats were killed 12-14 h after administration of the test material. The positive control was 2-acetylaminofluorene (100 mg/kg).

CARCINOGENICITY

No published carcinogenicity studies were discovered in the literature and no unpublished data were submitted.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

No irritation, erythema, or edema was observed when sodium benzotriazolyl butylphenol sulfonate (100%; 0.5 g moistened with distilled water) was administered to the shaved skin (3 cm x 3 cm) of New Zealand White rabbits (n=1 male, 2 females) under semi-occlusion for 4 h.[2] After exposure, the test site was washed with lukewarm tap water. The rabbits were observed for 72 h. The test was conducted in accordance with OECD Guideline 404 and EU method B.4.

When sodium benzotriazolyl butylphenol sulfonate (2000 mg/kg) was administered to the shaved backs of KFM-Han Wistar rats (n=5/sex) in carboxymethyl cellulose (4%; 4 mL) under occlusion for 24 h, all rats had erythema that resolved by day 8.[2] The test material was administered to 10% of the body surface.

Ocular

Sodium benzotriazolyl butylphenol sulfonate (0.1 g; 100%) was an ocular irritant causing irreversible corneal damage in one of the rabbits tested in a study in which this substance was instilled into the conjunctival sac of the left eye of New Zealand White rabbits (n=1 female, 2 males).[2] The test was conducted in accordance with OECD Guideline 405. The damage to the cornea was irreversible over 21 days of observation. The primary irritation score was 4.3 out of 5. The ocular irritation/corrosion was observed at 24, 48, and 72 h. The untreated eyes served as the control.

Sodium benzotriazolyl butylphenol sulfonate (30%; composition of the remaining 70% of the test substance was not specified; 0.01 mL) caused irreversible ocular damage in a New Zealand White rabbit.[2] The test was conducted in accordance with OECD Guideline 405 and EU Method B.5. At administration, no signs of initial pain (class 1 on a 0-5 scale) were observed. Slight or mild corneal opacity, involving the whole cornea, was observed on day 1 and remained after 21

days. There were no iridial effects. Conjunctival effects consisted of slight or moderate redness for up to 4 days, slight or mild chemosis for up to 4 days, and a slight or moderate discharge for up to 7 days. Additional signs of irritation consisted of lachrymatory, mucoid and Harderian discharge, irregular corneal surface and raised corneal opacity, erythema, edema, thickening and convolution of the eyelids, dried secretion around the periorbital skin, and neovascularization. Irritation was still apparent 21 days after instillation and there was little evidence of recovery. No further rabbits were tested because of the severity of these results.

Sensitization

Dermal – Non-Human

Sodium benzotriazolyl butylphenol sulfonate (0, 3%, 10%, or 30% w/v; 25 µL in propylene glycol) was not found to be a potential dermal sensitizer in a mouse local lymph node assay (LLNA) using male CBA/Ca/Ola/Hsd mice (n=4).[2] The test was conducted in accordance with OECD Guideline 429. The Stimulation Indices were 0.78, 0.57, and 2.06 for the concentrations of 3%, 10%, and 30%, respectively. Hexyl cinnamic aldehyde (1%, 3%, and 10%) was the positive control and gave the expected results.

Sodium benzotriazolyl butylphenol sulfonate (5% intradermal induction followed by 25% dermal induction) was not a dermal sensitizer in a guinea pig maximization test using Dunkin-Hartley guinea pigs (n=10/sex; control=5/sex) when challenged and re-challenged at 25%.[2] The test was conducted in accordance with OECD Guideline 406. Edema, erythema, and necrosis were similar in both the control and test groups. Edema, erythema, and necrosis were observed after the first challenge in 3 and 2 guinea pigs at 24 and 48 h, respectively. When challenged the second time, positive reactions were observed in 2 and 1 guinea pigs at 24 and 48 h, respectively. The intradermal induction was performed at 5% in physiological saline and in an emulsion of Freund's Complete Adjuvant (FCA)/physiological saline. The dermal induction patch was conducted under occlusion with the test substance at 25% in physiological saline. Two weeks after induction, the challenge was conducted by dermal administration of the test material at 25% in physiological saline under occlusive dressing for approximately 24 h. A second challenge was performed 2 weeks after the first challenge. The guinea pigs were observed at 24 and 48 h after each dermal administration.

Sodium benzotriazolyl butylphenol sulfonate (5% intradermal induction followed by 50% dermal induction) was not a dermal sensitizer in a guinea pig maximization test using female Ibm: GOHI, SPF-quality guinea pigs (n=20; control=10) when challenged at 10%.[2] The test was conducted in accordance with OECD Guideline 406. There was no erythema or edema formation observed at 24 and 48 h after removal of the induction patch in either the control or test group. The intradermal induction was performed with a 5% dilution of the test article in distilled water and in an emulsion of FCA/physiological saline. The dermal induction was conducted under occlusion with the test article at 50% in distilled water for approximately 24 h. Two weeks after induction, the challenge was completed by dermal administration of the test material at a concentration of 10% in distilled water under occlusion. The control group was exposed to distilled water and FCA/physiological saline during the induction phase and challenged in the same manner as that of the test group.

Photosensitization and Phototoxicity

Sodium benzotriazolyl butylphenol sulfonate (0, 10%, 15%, 25%, or 30% in distilled water; 0.025 mL/2 cm^2) was not phototoxic when the test article was administered dermally to the shaved skin of anesthetized Dunkin-Hartley guinea pigs (n=10; control=5) for 30 min and the test site then exposed to UVA (20 J/cm^2; exposure time not specified).[2] On the irradiated flanks, 1 guinea pig in each of the 30% and the 25% groups exhibited erythema at 24 h, which was resolved at 48 h. On the non-irradiated flank, 2 guinea pigs in the 30% group and 1 in the 25% group exhibited erythema, which was resolved at 48 h. All concentrations of the test substance were administered to both flanks of the guinea pigs, and the irradiation was administered only to the left flank. The test sites were pretreated with DMSO (2% in ethanol; 0.025 mL/2 cm^2) to enhance the dermal penetration of the test substance. The test was conducted 30 min later. The guinea pigs were observed for 72 h.

In an acute dermal phototoxicity dose-response test using female albino Dunkin-Hartley guinea pigs (n=20; control=10), sodium benzotriazolyl butylphenol sulfonate (30%; 0.1 mL in double-distilled water) was not a photosensitizer. The challenge concentrations were 1%, 5%, 10% and 15% (0.025 mL/2 cm^2).[2] No signs of toxicity were evident in the guinea pigs of the control or test group. Induction was accomplished through epicutaneous injections of sodium benzotriazolyl butylphenol sulfonate (30%) to an 8 cm^2 area of shaved skin (marked previously with 4 intradermal injections of FCA/physiological saline). The test sites were then exposed to 1.8 J/cm^2 UVB and 10 J/cm^2 UVA irradiation 4 times over the 2 weeks of the induction phase. Control animals were intradermally injected with FCA/physiological saline only. The challenge was performed 3 weeks after the beginning of the induction period. The test sites on both flanks were treated epicutaneously with the test material at concentrations of 1%, 5%, 10%, and 15%. The treated sites were then either exposed to 10 J/cm^2 UVA irradiation (left flank) or remained unirradiated (right flank). Erythema and edema formation were evaluated at 24, 48 and 72 h after the challenge exposure.

SUMMARY

This is a safety assessment of sodium benzotriazolyl butylphenol sulfonate as used in cosmetics. This ingredient is reported to function as a light stabilizer in cosmetics.

Sodium benzotriazolyl butylphenol sulfonate was reported to be used in a total of 473 cosmetic formulations, consisting of 67 leave-on cosmetic products, 377 rinse-off products, and 29 products diluted for the bath. This ingredient is used at concentrations up to 0.17% in leave-on products (nail polish and enamels), 0.1% in rinse-off products, and 0.033% in bubble baths.

Minimal dermal penetration by sodium benzotriazolyl butylphenol sulfonate was observed in in vitro assays using human skin.

In rats, the dermal LD_{50} of sodium benzotriazolyl butylphenol sulfonate was >2000 mg/kg and the oral LD_{50} was >5000 mg/kg. The oral NOAEL for sodium benzotriazolyl butylphenol sulfonate was 200 mg/kg/d for rats when administered over 28 days.

The oral NOAEL for reproduction and development for rats was 800 mg/kg/d sodium benzotriazolyl butylphenol sulfonate. The oral NOAEL for parental toxicity was 200 mg/kg.

In a bacterial reverse mutation assay using *S. typhimurium*, sodium benzotriazolyl butylphenol sulfonate was not mutagenic up to 5000 µg/plate with or without metabolic activation. In a mammalian chromosomal aberration assay using V79 fibroblasts, sodium benzotriazolyl butylphenol sulfonate was mutagenic with metabolic activation at 130 (but not at 120 µg/plate) and at 110 µg/plate (but not at 80 µg/plate) without metabolic activation. In a mammalian cell gene mutation assay using V79 fibroblasts, sodium benzotriazolyl butylphenol sulfonate was not mutagenic up to 80 µg/plate with or without metabolic activation; it was cytotoxic at 100 µg/plate. In a mammalian erythrocyte micronucleus assay, sodium benzotriazolyl butylphenol sulfonate at 3000 mg/kg was not genotoxic to mice when administered by gavage. In an unscheduled DNA synthesis assay, up to 1000 mg/kg sodium benzotriazolyl butylphenol sulfonate was not genotoxic to rats when administered by gavage.

Sodium benzotriazolyl butylphenol sulfonate at 100% was not dermally irritating to rabbit skin. In a study in rats, erythema was observed at 4%, which resolved by day 8.

Sodium benzotriazolyl butylphenol sulfonate, at concentrations up to 30% w/v, was not a potential dermal sensitizer in an LLNA.

Sodium benzotriazolyl butylphenol sulfonate (5% intradermal induction followed by 25% dermal induction) was not found to be a dermal sensitizer in a guinea pig maximization test when challenged and re-challenged at 25%. Edema, erythema, and necrosis were observed after the first challenge in 3 and 2 guinea pigs at 24 and 48 h, respectively. When challenged the second time, positive reactions were observed in 2 and 1 guinea pigs at 24 and 48 h, respectively. These results were similar to the control group. In another test, sodium benzotriazolyl butylphenol sulfonate (5% intradermal induction followed by 50% dermal induction) was not a dermal sensitizer in a guinea pig maximization test when challenged at 10%.

Sodium benzotriazolyl butylphenol sulfonate at 30% and 100% was an ocular irritant and caused irreversible eye damage to the cornea in 1 of 3 rabbits and the single rabbit tested, respectively, when administered to the conjunctival sac of rabbits.

Sodium benzotriazolyl butylphenol sulfonate at 30% was not phototoxic or photosensitizing when dermally administered to the shaved skin of guinea pigs for 30 min, and the test site was then exposed to UVA.

DISCUSSION

The majority of the data in this safety assessment were from robust summaries found in the ECHA database. The Panel determined that data from these summaries was applicable for use in reviewing the ingredient in this report.

The Panel expressed concern about studies that indicated the potential for ocular irritation; however, the Panel noted that the test concentrations that resulted in ocular damage were much greater than the concentrations reported to be used in cosmetics including those that are used on the face, thus possibly near the eyes.

Studies showed no evidence of systemic toxicity, and negative sensitization studies were at concentrations well above the reported concentrations of use. Although there were no carcinogenicity studies available for this ingredient, the Panel determined that the lack of systemic toxicity, the negative in-vivo genotoxicity data, and lack of dermal penetration indicated that carcinogenicity was not a concern.

The limited impurity data was noted. The Panel concluded that the manufacturing process would minimize any impurities in the source material, assuming that available information is representative, but also noted that it is incumbent on industry to suitably confirm consistent sufficiency of purity. Also, the low concentration of use and the lack of genotoxicity at high concentrations further assured the Panel that impurities were not a concern.

The Panel discussed the issue of incidental inhalation exposure from sodium benzotriazolyl butylphenol sulfonate in fragrance preparations up to 0.1% and spray body and hand product(s) up to 0.05%. There were no inhalation toxicity data available. The Panel noted that 95%-99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel noted the lack of systemic toxicity in single- and repeated-dose oral exposure studies, little or no irritation or sensitization in tests of dermal exposure, the absence of genotoxicity in Ames tests, a mammalian cell gene mutation assay, as well as in mammalian erythrocyte micronucleus assay, and an unscheduled DNA synthesis assays. This ingredient did not

appreciably penetrate cadaver skin. In addition, this ingredient has a low estimated vapor pressure value of 6.06×10^{-18} Pa, physiochemical characteristics inconsistent with diffusion into the systemic circulation, and these facts, in conjunction with the very low concentrations of use, supports the view that this substance is unlikely to be absorbed or to cause local effects in the respiratory tract. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The Panel concluded that sodium benzotriazolyl butylphenol sulfonate is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Chemical and Physical Properties of Sodium Benzotriazolyl Butylphenol Sulfonate.

Property	Value	Reference
Physical Form	Solid; powder fine powder	2 15
Color	Light-beige light-beige/white	2 15
Odor	Trace characteristic odor	15
Molecular Weight	369.37	16
Density/Specific Gravity @ 22°C	1.39	2
Vapor pressure (mmHg) @ 25°C	< 0.000000001	2
Melting Point (°C)	Decomposes before melting at >170 138-141	2 4
Water Solubility (g/L) @ 20°C & pH 6 @ 20°C	9.8 1.0	2 4
Other solubility (g/L) @ 20°C		
PEG-7 glyceryl cocoate	4.10	4
propylene glycol	2.20	4
sodium laureth sulfate	0.90	4
cocamido propyl betaine	0.80	4
ethanol	0.40	4
2-propanol	0.30	4
$logK_{ow}$*	-0.55 est.	16
$logP_{ow}$ @ 25°C	2.370 est.	**
Acid dissociation constants (pKa) @ 25°C		
Sulfonic	-0.84 est	**
Phenolic	7.93	2
UV Absorption (λ) nm	290, 335	4

* Benzenesulfonate form as exists in the sodium salt

** Predicted using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2015 ACD/Labs)

Table 2. Frequency of Use According to Duration and Exposure of Sodium Benzotriazolyl Butylphenol sulfonate.[7,8]

Use type	Uses	Maximum Concentration (%)
Total/range	**477**	**0.0033-0.17**
Duration of use		
Leave-on	68	0.033-0.17
Rinse-off	380	0.0033-0.1
Diluted for (bath) use	29	0.033
Exposure type[a]		
Eye area	NR	NR
Incidental ingestion	NR	NR
Incidental Inhalation-sprays	36; 20[b]; 7[d]	0.05-0.1; 0.035[b]
Incidental inhalation-powders	1[c];7[d]	0.033-0.09[c]
Dermal contact	392	0.0033-0.1
Deodorant (underarm)	NR	NR
Hair-noncoloring	22	NR
Hair-coloring	62	NR
Nail	1	0.17
Mucous Membrane	310	0.033-0.035
Baby	1	NR

NR=Not Reported; Totals=Rinse-off + Leave-on + Diluted Product Uses.

[a] Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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

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

[d] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

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