Safety Assessment of Benzyl Salicylate As Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of Benzyl Salicylate, which is reported to function in cosmetics as a fragrance ingredient and light stabilizer. The Panel reviewed the available data to determine the safety of this ingredient. The Panel concluded that Benzyl Salicylate is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

INTRODUCTION

This is a safety assessment of Benzyl Salicylate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), this ingredient is reported to function in cosmetics as a fragrance ingredient and light stabilizer.[1]

CIR Procedures state that fragrance ingredients may be excluded from evaluation by the Panel if their safety is being determined by the Research Institute for Fragrance Materials (RIFM), and a fragrance ingredient is defined therein as an ingredient that is only known to function as a fragrance in cosmetic formulations. Accordingly, as an ingredient assessed by the RIFM for its fragrance use, but not as a light stabilizer, Benzyl Salicylate does not qualify for such exclusion. An earlier safety assessment by the Panel addressed the safety of benzyl alcohol, benzoic acid, and its salts (i.e. benzyl benzoate, calcium benzoate, magnesium benzoate, and potassium benzoate).[2] The Panel concluded that these ingredients were "safe as used in cosmetic products." The Panel reviewed the safety of salicylic acid and 18 salicylates, and at the April 2019 meeting, issued a Final Amended Report with the conclusion that salicylic acid and salicylate ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment."[3] Both reports are available on the CIR website (https://www.cir-safety.org/ingredients).

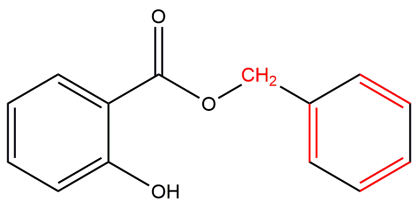
This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this assessment were obtained from a RIFM Expert Panel review.[4,5] Additionally, some chemical and toxicological data on Benzyl Salicylate included in this safety assessment were obtained from data submitted to the European Chemical Agency (ECHA) by companies as part of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH).[6] To address some toxicological endpoints of Benzyl Salicylate as part of the REACH registration, cyclohexyl salicylate was proposed to share structural similarities and 'mechanistic action' similarities, which are both general and endpoint specific, such that read-across is justified. Accordingly, toxicological data on cyclohexyl salicylate (not a cosmetic ingredient) is included herein for the purposes of read-across, as proposed in the ECHA dossier. As appropriate, information from these summary documents has been included in this report and is cited to these sources. Toxicology data from an earlier CIR safety assessment on benzyl alcohol are also included in this safety assessment for read-across.[7]

CHEMISTRY

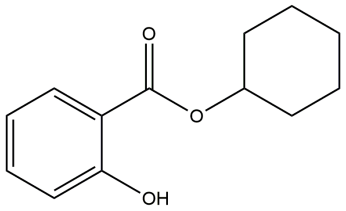
Definition and Structure

Benzyl Salicylate (CAS No. 118-58-1) is the ester of benzyl alcohol and salicylic acid.[1] It conforms to the formula that is depicted in Figure 1. As some of the data obtained from ECHA for Benzyl Salicylate (Figure 1) have been read-across from cyclohexyl salicylate,[6] the inference source structure is also included below (Figure 2).



Benzyl Salicylate

Figure 1. Benzyl Salicylate



cyclohexyl salicylate

Figure 2. cyclohexyl salicylate

Physical and Chemical Properties

Benzyl Salicylate is a colorless to pale yellow liquid.[6] The freezing point of Benzyl Salicylate was determined to be less than -50 °C. The solubility of Benzyl Salicylate in water at 20°C is 8.8 mg/L. Other pertinent physical and chemical properties of Benzyl Salicylate are presented in Table 1.

Method of Manufacture

A synthetic methodology for manufacturing Benzyl Salicylate reported that Benzyl Salicylate can be synthesized by homogeneous reaction of sodium salicylate with benzyl chloride, with a stoichiometric ratio of 2.5:1, in dimethylformamide (DMF) at 100°C, for 2.5 h.[8]

Impurities

Impurity data were not discovered in the published literature, and unpublished data were not submitted. However, according to the United States Pharmacopeial (USP) Convention's Food Ingredients Expert Committee, Benzyl Salicylate must not be less than 98% of $C_{14}H_{12}O_3$ in food. [9]

Natural Occurrence

Benzyl Salicylate can be found in ylang-ylang oil (5.2%), carnation oil (3.9%), and tuberose absolute (2.6%).[10]

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to information supplied to the FDA in 2019 by industry as part of the VCRP, Benzyl Salicylate is reported to be used in 3079 formulations, 2419 of which are leave-on products (Table 2).[11] Additionally, 949 of those uses are in fragrance-type formulations. However, the VCRP does not indicate the function of ingredients in cosmetic formulations, so it is not known what the intended function of Benzyl Salicylate is in any of the reported ingredient categories.

In 2016, the Council conducted a survey of the maximum use concentrations of Benzyl Salicylate, but only for the function of light stabilizer.[12] According to the survey, the greatest concentration of use of Benzyl Salicylate as a light stabilizer is up to 0.5% in skin cleansing preparations, and the greatest leave-on use concentration for this function is up to 0.15% Benzyl Salicylate in "other" makeup preparations.

According to VCRP data, Benzyl Salicylate is used in formulations that are applied near the eye, that can be incidentally ingested, and that come in contact with mucous membranes; no concentration of use data were provided for these use-types.[11] Additionally, in the VCRP, Benzyl Salicylate is reported to be used in spray formulations (56 hair sprays, for example; concentration of use not provided) and could possibly be inhaled. 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 < 10 μm compared with pump sprays.[13] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Benzyl Salicylate is also reported in the VCRP to be used in powder formulations, such as face powders (34 reported uses); concentration of use data were not provided for any powder formulations. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[14-16]

The International Fragrance Association (IFRA) has recommended restriction limits for the use of Benzyl Salicylate based on the weight of evidence evaluation of the sensitization data and therefore classified Benzyl Salicylate as a weak sensitizer.[17] The IFRA Standard limits range from a maximum of 0.5% Benzyl Salicylate in lip products to a maximum of 12.8% in oral care products; additional finished product use categories and standard limits are listed in Table 3.

According to the European Union, Benzyl Salicylate may be used in cosmetics and personal care products, but its presence must be indicated when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.[18]

Non-Cosmetic

In the US, Benzyl Salicylate has been approved as a direct food additive for use as a synthetic flavoring substance by the FDA [21 CFR 172.515]. It should be used in the minimum quantity required to produce the intended effect, and otherwise in accordance with all the principles of good manufacturing practice. In addition, Benzyl Salicylate has been granted generally recognized as safe (GRAS) status as a flavoring ingredient by the Flavor and Extract Manufacturers Association.[19]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

The penetration of Benzyl Salicylate through human epidermis was studied using a glass chamber.[20] Benzyl Salicylate (0.2 mL) was applied to a sample of human lower abdominal cadaver skin for 72 hours. The chamber was kept at 21°C and 55% relative humidity. The upper surface of the skin was fixed to a glass tube and then placed inside one arm of a U-shaped glass chamber. The experiment was repeated six times. Benzyl Salicylate penetrated the epidermis very slightly. It was reported that 0.031% ± 0.004% of the chemical traversed the skin.

In an in vitro percutaneous absorption study, [^{14}C]-Benzyl Salicylate at 1%, 3%, and 10% in ethanol was applied to excised intact skin of a naked rat for 30 seconds at a dose of 120 µg, 360 µg or 1200 µg active substance/cm^2.[5] Unabsorbed Benzyl Salicylate was removed from the skin surface at 1, 6, 16, and 24 hours after application and absorption was measured at intervals, i.e. after 6, 16, 24, hours. An estimated 62.7, 58.8, and 40.3% of 1, 3, and 10% of Benzyl Salicylate migrated into the receptor fluid and was recovered in the chamber liquid, respectively. When the same test was conducted using guinea pig skin, after 16 hours, 3.5, 1.7, and 0.9% of the solution migrated through the skin into the receptor fluid for the 1, 3, and 10% concentrations, respectively.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

In an acute dermal toxicity study, Benzyl Salicylate was applied (neat) to the clipped area of three albino rabbits at doses of 5, 10, or 20 g/kg and held in close contact with the skin under a plastic wrap and bandages for an exposure period of 24 hours.[5] Animals were observed for seven days. No effects were observed at 5 g/kg. One of three rabbits at the 10 g/kg level and two of the three at the 20 g/kg level died. No significant gross pathology was noted in animals that died during the study; however, a low hemoglobin value was noted for the animal treated at the 20 g/kg level. The acute dermal LD_{50} of Benzyl Salicylate was calculated to be 14.15 g/kg.

Oral

Three groups of 6 rats were dosed by gavage with 1.25, 2.5, or 5.0 g/kg Benzyl Salicylate.[5] The LD_{50} was reported to be 2.23 g/kg. Rats were observed for a 7-day period. At 1.25 g/kg, no deaths (0/6) were observed; 4/6 deaths were observed at 2.5 g/kg and all (6/6) animals died at 5.0 g/kg. The principal toxic effect observed before death was depression.

Short-Term Toxicity Studies

Oral

In a combined repeated-dose reproductive/developmental screening toxicity test, Benzyl Salicylate was administered to 9-week old male and female Sprague-Dawley rats (5 per sex) via gavage at 0 (corn oil), 250, 500, or 1000 mg/kg/day for 14 days.[21] All animals died in the 1000 mg/kg/day treatment group and one female died in the 500 mg/kg/day treatment group. Significant decreases in the body and thymus weights and significant increases in the liver weights and aspartate aminotransferase (AST) were observed in both sexes in the 500 mg/kg/day treatment group. Slight decreases in glucose and thymus absolute weights were also observed in males in the 250 mg/kg/day treatment group. The considered tolerable dose was 250 mg/kg/day. Based on the results of the 14-day dose-range finding study (described earlier), it was determined that

the doses used in the DART study are 30, 100, and 300 mg/kg/day, respectively. Reproductive and developmental toxicity data are summarized in the DART section.

Subchronic Toxicity Studies

Oral

Cyclohexyl Salicylate (read-across for Benzyl Salicylate)

Repeated-dose toxicity data were not available for Benzyl Salicylate. However, ECHA identified a read-across source material. In a 90-day study conducted using cyclohexyl salicylate, 10 females and 10 male rats were administered the test substance via gavage at doses of 0 (vehicle control), 40, 120, and 360 mg/kg bw/day in arachis oil.[6] The total volume administered was 5 mL/kg in all dose groups. An additional five male and female rats served as the recovery animals in the control and the high-dose group during a 29-day recovery period without oral treatment. The no-observable-adverse-effect-level (NOAEL) in this oral repeated dose toxicity study was 360 mg/kg bw/day. There were no adverse systemic effects on rats in this study.

Benzyl alcohol (read-across for Benzyl Salicylate)

Benzyl alcohol was administered in corn oil to groups of 10 male and 10 female B6C3F1 mice at doses of 0, 50, 100, 200, 400, and 800 mg/kg bw by gavage, five days a week for 13 weeks.[7] Animals were observed twice daily for signs of toxicity and mortality. Deaths of five mice were attributed to rupture caused by the gavage procedure. The final mean body weight of males at 800 mg/kg bw was 5% lower than that of controls; the final mean body weight of female mice at this dose was 5% lower than that of controls. Both male and female mice at the high dose showed staggering during the first and second weeks of the study. No treatment-related histopathological effects were observed.

When benzyl alcohol was administered in corn oil to groups of 10 male and 10 female Fischer 344 rats by gavage at doses of 0, 50, 100, 200, 400, and 800 mg/kg bw, five days per week for 13 weeks, eight males and two females at 800 mg/kg bw, one female at 400 mg/kg bw, one male at 200 mg/kg bw and one female in the control group died after treatment.[7] The deaths of fives rats were attributed to gavage error. Aside from these, 4/10 male rats and one female of the 800 mg/kg group, as well as one female of the 400 mg/kg group and one male of the 200 mg/kg group died on study. At 800 mg/kg bw, signs of neurotoxicity were observed, and animals had blood around the mouth and nose. After 13 weeks, the body weights of males and females at the high dose were 7 and 5 % lower than those of the controls, and histopathological examination showed some treatment-related histopathological effects including necrosis of the dentate gyrus of the hippocampus, skeletal muscle necrosis, nephrosis of the kidney, thymic congestion, hemorrhage, and atrophy. Lesions were not observed at lower doses; therefore, treatment-related effects (mortality and neurotoxicity) were only observed at the high dose (800 mg/kg-day).

Chronic Toxicity Studies

Benzyl alcohol (read-across for Benzyl Salicylate)

Groups of 100 F344/N rats (50 per sex) were dosed with 200 or 400 mg/kg benzyl alcohol in corn oil, 5 days per week for 103 weeks.[7] Mean body weights were comparable among dosed and vehicle control rats throughout the study. A number of accidental deaths were due to gavage errors in female rats of both dose groups (17 deaths, low-dose; 13 deaths, high-dose) and in males of the 400 mg/kg group (14 deaths). At the end of the study, 17 female rats survived from each of the dose groups compared to 35 female vehicle control; 27 low-dose males and 24 high dose males survived, compared to 28 male vehicle controls. Clinical signs of sialo dacryoadenitis virus (cervical swelling, pink eyes, and red exudate around eyes) were observed in dosed and vehicle-control rats.

Groups of 100 B6C3F1 mice were dosed with 100 or 200 mg/kg benzyl alcohol following the same schedule as the previous study.[7] Mice were unintentionally given α-methylbenzyl alcohol for 4 days during week 80 with no observed toxicological syndromes. Animals were observed twice daily for signs of toxicity. Mean body weight was compared among dosed and vehicle control mice throughout the study. Survival of female vehicle controls was significantly lower than that of the high-dose group after week 74 (female; vehicle control, 26/50; low dose, 32/50; high dose, 36/50). Corpora amylacea (foci of mineralization in the thalamus) was observed at an increased incidence in high-dose mice (male: vehicle control, 15/49; low dose, 21/48; high dose, 22/05; female 14/50; 15/48; 25/50), but was noted to be a common and spontaneously occurring lesion.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

Following a short term screening assessment described above, Sprague–Dawley rats were administered Benzyl Salicylate dissolved in corn oil once daily via gavage at levels of 0 (control), 30, 100, or 300 mg/kg/day using a dosing volume of 5 mL/kg.[21] Males (n = 12 per group) were dosed for 14 days prior to mating and a further 28 days during mating, giving a total of 42 dosing days. Females in the mating group (n = 12 per treatment group) were dosed for 14 days prior to

mating and then through mating and gestation until postpartum day 4, giving a total of 41 to 46 days of dosing, while females in the non-mating group (n = 10 per treatment group) were dosed for 42 days. In total, 5 males and 5 non-mated females in the control and high-dose groups were left untreated for 14 days as a recovery period.

In terms of reproductive/developmental toxicity, Benzyl Salicylate was not found to have any effects on fertility or implantation or to cause severe maternal toxicity. However, at the end of the recovery period, males in the 300 mg/kg/day treatment group had significantly greater relative weights of the kidney and seminal vesicle, as well as a greater relative thymus weight. By contrast, non-mated females in the 300 mg/kg/day treatment group exhibited a significantly lower absolute brain weight than the control group. Also, marked embryotoxicity was observed in the form of early embryonic resorption in 6/12 females in the 300 mg/kg/day treatment group, and dead offspring exhibited neural tube defects. Offspring of rats that had been administered 30 or 100 mg/kg/day exhibited lower body weights on PND 0 or 4. Based on the developmental toxicity, the lowest-observable-adverse-effect-level (LOAEL) of Benzyl Salicylate was 30 mg/kg/day.

GENOTOXICITY

In Vitro

The genotoxicity of Benzyl Salicylate was evaluated in an Ames test, in the presence and absence of exogenous metabolic activation, using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, and TA1537, and/or TA97.[22] Benzyl Salicylate, at doses of 3.3 to 333 µg/plate in dimethyl sulfoxide (DMSO), did not produce any mutagenic effects with or without metabolic activation.

Chinese hamster lung fibroblastic cells (CHL), at doses of 0 - 170 µg/mL, were used to evaluate the cytogenetic toxicity of Benzyl Salicylate.[21] Using the 6-hour direct method, 50 µL of the test chemical solution was added to the 60 mm dishes on day 3 after seeding and left for 6 hours; cells were then washed and cultured for 18 hours. With 24 hours of continuous treatment, 50 µL of negative control (DMSO) or test article solution was added on day 3 after seeding. In the metabolic activation method, 833 µL of S9 mix and 50 µL of test article solution were added on day 3 after seeding and were treated similarly as the 6-hour direct method. Appropriate positive controls were used. All of the Benzyl Salicylate treatment groups had ≤ 1.0% structural aberrations and ≤ 1.3% polyploidy and exhibited no significant differences in the frequencies of chromosomal aberrations from the negative controls or dose-dependency. No significant increases in chromosomal aberrations were seen at these doses.

In Vivo

In vivo genotoxic studies of Benzyl Salicylate were not found in the published literature, and unpublished data were not provided.

CARCINOGENICITY STUDIES

Carcinogenicity studies of Benzyl Salicylate were not found in the published literature, and unpublished data were not provided.

OTHER RELEVANT STUDIES

Estrogen Activity

Benzyl Salicylate was tested in assays using the estrogen-responsive MCF-7 human breast cancer cell line to determine its estrogenic effects on breast cancer cells in vitro.[23] Benzyl Salicylate (98% purity) in ethanol and diluted 1 in 10,000 (v/v) into culture medium increased the growth of estrogen-dependent MCF-7 human breast cancer cells at 10^{-4} M, an effect which could be inhibited by the anti-estrogen fulvestrant, suggesting involvement in an ER-mediated mechanism; however, concentrations are not detrimental to proliferation of MCF-7 cells.

In order to examine the estrogenic activities of plasticizers used in tissue conditioners, plasticizers, including Benzyl Salicylate, were evaluated by the E-screen test using MCF-7 cells.[24] Seven plasticizers and two metabolites, including Benzyl Salicylate (97% purity), were diluted with DMSO and a medium containing 5% bovine serum at concentrations ranging from 10^{-9} to 10^{-4} M. The samples included 0.1% DMSO. The estrogenic activities and liquid compositions of the four commercial tissue conditioners were examined by high-performance liquid chromatography. The negative control was the cell culture medium including 0.1% DMSO. Benzyl Salicylate increased proliferation of MCF-7 breast cancer cells at 10^{-5} M (22.8 mg/L), however, it had the opposite effect at 10^{-4} M (22.8 mg/L). At a concentration of 10^{-5} M, Benzyl Salicylate significantly increased proliferation of MCF-7 cells ($p < 0.05$).

The estrogenic potential of Benzyl Salicylate was evaluated using an in vitro human estrogen receptor hERα-coactivator recruiting assay and in an in vivo immature rodent uterotrophic bioassay.[25] The estrogen receptor agonist activity of the salicylate esters (SEs) was measured using a ligand-dependent coactivator recruiting assay with glutathione *S*-transferase (GST)-tagged hERα – ligand binding domain (LBD). Stock solutions of test chemicals were subjected to a 10-fold serial dilution with DMSO to prepare eight concentrations in the range of 10^{-3} to 10^{-10} M. The binding affinities of the tested chemicals for hERα were expressed as the absorbance at 405 nm (bone alkaline phosphatase (BAP) activity). The

wells with only DMSO added were used as background values for this assay. Benzyl Salicylate exhibited obvious dose-dependent increases with a maximal acceptable daily exposure of 0.0294 ppm. The immature rodent uterotrophic assay showed that the uterine weights were significantly increased in mice that received 11.1, 33.3, 100, and 300 mg/kg/day. Benzyl Salicylate was intragastrically administered for 3 days, beginning on postnatal day (PND) 21; the corresponding uterine weights were 114%, 118%, 138%, and 119% of vehicle control, respectively. The uterine weights were also significantly increased at a dose-dependent manner in rats who were given 11.1, 33.3, and 100 mg/kg/day Benzyl Salicylate by intragastric administration for 3 days, beginning on PND 21. The mean uterine weights in rats given 11.1, 33.3, and 100 mg/kg/day Benzyl Salicylate were higher than the uterine weights of rats given 1 µg/kg/day 7β-estradiol (E2) but lower than the uterine weights of rats given 5 µg/kg/day E2.

DERMAL IRRITATION AND SENSITIZATION

The skin irritation and sensitization studies summarized below are presented in greater detail in Table 4.

Irritation

In a preliminary test, 0.025 mL of Benzyl Salicylate (concentration not specified) was applied with a pipette to the clipped flank of groups of 6 to 8 male and female outbred Himalayan white-spotted guinea pigs.[26] The concentration of 0.1% was the lowest concentration to produce mild erythema in at least 25% of the animals, and this dose was selected as the minimal irritating concentration after one application. The skin irritation potential of Benzyl Salicylate was then evaluated in the induction phase of an Open Epicutaneous Test (OET). Benzyl Salicylate (0.1 mL) was applied to the clipped flank of 6 to 8 male and female outbred Himalayan white spotted guinea pigs. The minimal irritating concentration after 21 applications was 0.1% (vehicle not specified). A preliminary irritation screen was conducted to determine the Injection Challenge Concentration (ICC) of Benzyl Salicylate using four inbred Hartley albino guinea pigs.[27] Benzyl Salicylate (0.1 mL) was administered via intradermal injection (unspecified vehicle) at a range of concentrations. The concentration giving slight but perceptible irritation with no edema was 0.5% and it was selected as the ICC. In a modified Draize sensitization study, the irritation potential of Benzyl Salicylate (0.1 mL) was evaluated in four inbred Hartley albino guinea pigs to determine the Application Challenge Concentration (ACC).[27] The highest concentration causing no irritation was 2%, and it was selected as the ACC. A 4-hour semi-occlusive patch test was conducted on four female New Zealand white albino rabbits.[28] No irritation was observed when Benzyl Salicylate (0.5 mL neat) was applied to intact dorsal skin. No irritation was observed in a 24-hour closed patch test conducted using three albino rabbits.[4] As a part of an acute dermal LD_{50} study, irritation was not observed with neat Benzyl Salicylate at 5, 10, or 20 g/kg when applied to a clipped area and held in contact with the skin for 24 hours under occlusion.[5] No irritation was observed in a maximization pre-test when 30% Benzyl Salicylate in petrolatum was administered in a closed patch test on the volar forearms of five subjects for 48 hours.[5] Two irritant reactions were observed in a maximization pre-test study when 30% Benzyl Salicylate in petrolatum was applied under occlusion to the backs of 22 male subjects. No irritation was observed in a patch test conducted on 30 subjects when administered 0.2 mL Benzyl Salicylate (neat) to the upper outer arm for up to 4 hours.[28] Benzyl Salicylate at 5% in petrolatum caused no irritation when applied to the upper arms of 12 male and 13 female subjects.[5] Five positive reactions were observed when 0.2% Benzyl Salicylate in 99% ethanol was applied under occlusion for 24 to 48 hours to the upper inside of the arm of 313 subjects.[29] Irritation was not observed when a 24 to 72-hour closed patch with 2% Benzyl Salicylate in unguentum simplex (a simple ointment containing 5 parts olive oil and 2 parts white wax) was applied to the upper inside arm of 30 subjects. In a 48-hour closed patch test conducted in five subjects, 20% Benzyl Salicylate in petrolatum applied to the back of each subject produced no irritation.

Sensitization

In a local lymph node assay (LLNA) performed to assess the sensitization capacity of Benzyl Salicylate, 4 female CBA/JN mice were administered 25 µl of Benzyl Salicylate topically at 10% in 4:1 acetone/olive oil vehicle to the left and right ear lobe for three days.[5] The estimated concentration required to produce a three-fold increase in lymphocyte proliferation (EC3) was determined to be 1.5% (375 µg/cm^2) therefore, Benzyl Salicylate was categorized as a weak sensitizer. Benzyl Salicylate was considered to have the potential to be a sensitizer in an LLNA in which 4 female CBA/Ca mice were treated with 25 µl of the chemical at 2.5, 5, 10, 25, or 50% w/v in 3:1 DEP:EtOH (diethyl phthalate:ethanol) vehicle.[5] The EC3 value was calculated to be 2.9% (725 µg/cm^2). Sensitization was observed at all concentration in a maximization test conducted in 8 test and 8 control female albino Dunkin-Hartley guinea pigs.[5] Sensitization was observed in a guinea pig maximization test (number of animal not specified) conducted using 10% Benzyl Salicylate for both induction and challenge phase.[5] A maximization test on 10 Hartley guinea pigs per dose using 1% Benzyl Salicylate in ethanol and 100% dermally administered revealed no sensitization reactions.[30] Five of 20 animals revealed sensitization reactions in a study in which 10% Benzyl Salicylate in liquid paraffin and Freund's Complete Adjuvant (FCA) was intradermally injected in the shoulder of 4-week old female Hartley strain guinea pigs (20 per group).[31] Twenty-four hours later, 50% Benzyl Salicylate in white petrolatum was applied for 48 hours with adhesive bandage. Two weeks after the topical application, Benzyl Salicylate at 5%, 10%, and 20% in white petrolatum was applied. Two reactions were observed at 20%. "Questionable" reactions were observed in three (3/20) animals at 5%, five (5/20) animals at 10%, and four (4/20) animals at

20%. Results were negative in a maximization test conducted using outbred Himalayan white-spotted guinea pigs.[26] In another maximization test, 10% Benzyl Salicylate in liquid paraffin and 30% Benzyl Salicylate in ethanol were administered to 10 female Hartley albino guinea pigs.[32] During the first challenge, positive reactions were observed at 48 and 72 hours for all doses. At the second challenge, positive reactions were observed with 0.03% at 24 hours and all concentrations at 48 and 72 hours. No sensitization was produced in a guinea pig open epicutaneous test (OET) using Benzyl Salicylate at 30% for both induction and challenge (vehicle not specified).[5] In an OET conducted in guinea pigs, there was no reaction to 10% Benzyl Salicylate in a 21 daily open application study. In a closed epicutaneous test (CET) in guinea pigs, 30% Benzyl Salicylate (vehicle not provided) was not a sensitizer.[5] Sensitization was observed in a cumulative contact enhancement test (CCET) conducted in 10 female Hartley albino guinea pigs when induced for 24 hours with an occlusive patch containing 30% Benzyl Salicylate in ethanol.[32] Sensitization was evaluated in groups of ten Pirbright guinea pigs using a modified FCA method.[33] Benzyl Salicylate at 10% was a moderate sensitizer.

In a quantitative risk assessment (QRA) for dermal sensitization, the RIFM Expert Panel reviewed the critical effect data for Benzyl Salicylate via a weight of evidence (WoE) approach.[34] IFRA reported a no expected sensitization induction level (NESIL) of 17,700 µg/cm^2 based on a human maximization test, and therefore classified the chemical as a weak sensitizer. No sensitization was observed in a human repeated insult patch test (HRIPT) when 0.3 mL of 15% Benzyl Salicylate in 3:1 DEP:EtOH was applied to the left side of the back of 29 male and 72 female subjects via an adhesive patch for 24 hours.[5] No sensitization was observed in 17 male and 18 female volunteers when patch tested with a 0.5 mL aliquot of 10% Benzyl Salicylate in alcohol SDA 39 C for 24 hours. No sensitization was observed when 0.5 mL of 5% Benzyl Salicylate in dimethyl phthalate was applied to absorbent patches and administered to the inner surface of the left deltoid area of eight male and female volunteers for 48 hours. Another HRIPT was performed in 101 volunteers (29 males and 72 females) induced with 0.3 mL of Benzyl Salicylate for 2 weeks. Under the conditions of the study, 15% Benzyl Salicylate in 3:1 DEP:EtOH did not induce dermal sensitization. No sensitization was observed when 35 subjects (17 males and 18 females) completed an HRIPT with 10% Benzyl Salicylate (0.5mL) in alcohol SDA 39C under semi-occlusion for 24 hours. No sensitization was observed when 52 volunteers using a modified Draize method were patch tested with an aliquot of 5 mL of 5% Benzyl Salicylate in dimethyl phthalate for 48 hours (ten induction patches). In five maximization tests each using 25 human subjects, Benzyl Salicylate was administered at 20 to 30% in petrolatum. Reactions were observed in two of the five studies, affecting 2/25 and 1/25 subjects at 20%. No positive reactions were reported at 30%.

Cross-Reactivity

To evaluate the potential for cross-reactivity, an HRIPT was conducted on 103 subjects (29 male and 74 females).[5] Subjects were administered 30% hexyl salicylate in DEP:EtOH (3:1), and challenged with 15% Benzyl Salicylate in DEP:EtOH (3:1). No cross-reactions were observed.

Phototoxicity/Photosensitization

Phototoxicity and photoallergy studies summarized below are presented in Table 5.

No phototoxic effects were observed in a study conducted on groups of hairless mice (6/group) following application of 20 µl of 100% Benzyl Salicylate and 25% Benzyl Salicylate in methanol.[5] The first group was exposed to a florescent black light (a bank of 6 Sylvania F40T12BL psoralen ultraviolet A (PUVA) lamps with a broadband output of 350 nm) for one hour and at a distance of 0.65 m. The second group was irradiated one meter from simulated sunlight (6.5 kw xenon light source) for one hour. No phototoxic responses were observed in an open application of 5%, 10%, and 30% Benzyl Salicylate in acetone tested on five female albino Dunkin-Hartley guinea pigs. The application sites were irradiated with 13 J/cm^2 ultraviolet (UV) light (UV-A black light 300 – 400 nm, max 360 nm) at 10 cm for 60 minutes. Mixed results were found in another study conducted on Himalayan white spotted guinea pigs (10 per dose) when 0.025 mL of Benzyl Salicylate at 1% or 3% in ethanol was applied, with 2% DMSO added to enhance penetration. Sites on the left flank were irradiated with 20 J/cm^2 UV light (320–400 nm, energy 1 x 10^4 ergs/cm^2), at 10 cm from the animal. No reactions were observed with 1% Benzyl Salicylate however, with 3%, phototoxic reactions were observed in 10/10 animals. No phototoxic effects were observed when 20 (10 per sex) adult albino Dunkin Hartley guinea pigs were administered a single application of 0.5 mL of 10% Benzyl Salicylate in absolute ethanol under an occlusive patch. Irradiation was carried out using lamps in the UV-A range (wavelength from 4000 to 315 nm) and in the UVB range (wavelength from 315 to 290 nm). No photoallergic reactions were observed in a photoallergy study conducted on 25 adult albino Dunkin–Hartley guinea pigs when administered 0.5 mL of Benzyl Salicylate at 10% in absolute ethanol.

In human studies, no phototoxic reactions were observed in six female subjects administered 0.025 mL/2 cm^2 of 3% and 10% Benzyl Salicylate in 1:1 ethanol/acetone. The test sites were exposed to non-erythrogenic UV-A radiation at 1, 2.5, 5, 10, and 20 J/cm^2.

OCULAR IRRITATION STUDIES

In Vitro

In a bovine corneal opacity permeability (BCOP) study conducted according to Organization for Economic Co-operation and Development test guideline (OECD TG) 437, 0.75 mL undiluted Benzyl Salicylate was applied to isolated bovine corneas for 10 minutes, followed by rinsing and further 120-minute incubation. An irritancy score of 0/5 was reported and it was concluded that the Benzyl Salicylate is not predicted to be an ocular corrosive or severe irritant.[35]

Animal

The potential for Benzyl Salicylate to induce ocular irritation was evaluated following the instillation of 0.1 mL of 10% Benzyl Salicylate in SD alcohol 39-C into the right eye of three albino rabbits; the left eye of each animal served as an untreated control.[5] The animals were observed for 10 days. Mild conjunctival irritation was observed in all three rabbits and corneal opacity was observed in one rabbit. All effects were reversed within seven days. Benzyl Salicylate was determined to be irritating.

CLINICAL STUDIES

Retrospective and Multicenter Studies

Incidence of sensitivity to Benzyl Salicylate was evaluated in a perfume screening series in 241 consecutive patients (180 females and 61 males) from October 1981 to June 1983.[36] Patients were patch-tested for sensitivity to fragrances in a perfume screening series using the Finn Chamber technique. Reactions to 2% Benzyl Salicylate in paraffin were observed in 6 patients (2.5% incidence) and were characterized by erythema and edema.

To identify the specific fragrance chemicals responsible for allergic reactions to perfumes, patch tests to several screening sets of fragrance materials were performed on 20 perfume-sensitive patients during a one-year period (1975).[37] Patches were applied to the back of each patient for 48 hours. Readings were made at the time of removal or 24 hours after removal. Patients were instructed to return if an additional delayed reaction occurred. Benzyl Salicylate at 2% gave a positive reaction in 2/20 patients. All the fragrance allergens were tested on 50 control patients, with negative results.

In an assessment of the hypersensitization potential of Benzyl Salicylate initiated in 1979, data from 10,538 patch tests utilizing a wide range of Benzyl Salicylate concentrations in 8430 different subjects were evaluated.[38] Results were reported from a total of 6291 patch tests on personal care and household products in which the applied concentrations of Benzyl Salicylate ranged from 2×10^{-10} to 1×10^{-6} %. Vehicles used in the test included water, ethanol petroleum, dimethylphthalate, and mineral oil. Exposure to these products did not induce sensitization or identify pre-existing Benzyl Salicylate reactivity in any of the subjects. No elicited or induced sensitization reaction was observed in 3164 tests on personal products containing a mixture of 3×10^{-6} to 0.2% Benzyl Salicylate. No sensitization reaction was observed in 3127 tests in household products containing 1×10^{-6} to 0.2% Benzyl Salicylate. No sensitization was observed in 3217 HRIPTs evaluated in fragrances containing a mixture of 0.008 to 1.0% Benzyl Salicylate. No sensitization was observed in 20 occluded patch tests in product blends containing 0.006 to 0.008% Benzyl Salicylate. In another blend containing 5×10^{-6} to 0.005% Benzyl Salicylate, no sensitization was observed in 975 tests. The study authors indicated that Benzyl Salicylate has a very low potential to induce hypersensitivity or to elicit reactions attributable to preexisting sensitization (prior induction).

To determine the prevalence and risk factors of responses to selected fragrance materials in patients with suspected fragrance allergy, 167 patients were patch tested with selected fragrance substances in 7 centers worldwide.[39] Benzyl Salicylate was applied to Finn chambers and placed on the upper back. Fifteen to 45 minutes were allowed between the initial patch test removal and the first reading. The patch test sites were evaluated using the North American Contact Dermatitis Research Group modification. The patients were tested with Benzyl Salicylate at 2 and 5%. Benzyl Salicylate, at 2% in petrolatum, produced irritant reactions in 5 patients and allergic reactions in 3% of the patients. At 5%, irritant reactions were observed in 8 of the patients and allergic reactions were observed in 4.8% of the patients. Benzyl Salicylate was a more common cause of positive patch test reactions in Japan than in Europe or the US.

Over a 64-month period (September 1977 to August 1983), twelve dermatologists from various sections of the US studied a total of 713 out of an estimated total of 13,216 patients with contact dermatitis.[40] The patients were evaluated using standard patch tests with numerous cosmetic products and specific ingredients, including Benzyl Salicylate. When such data were not available for an ingredient, the dermatologists performed the patch tests at an empirically determined concentration utilizing controls to exclude irritancy where possible. Patch tests were done on some products and ingredients without dilution; others were suspended in petrolatum or another appropriate, inert material. Shampoos were generally tested at 1% to 4% in water. Patch tests were applied to the upper back for 48 hours. The result of the study identified 713 patients with cutaneous reactions to cosmetic products. In 578 cases, allergic reactions were observed. In one subject Benzyl Salicylate was one of the causative ingredients as judged by patch testing.

To study the frequency of sensitization to 26 fragrance compounds qualified as allergens by the European Union, a total of 21,325 dermatitis patients were patch tested with Benzyl Salicylate (0.1%), from January 2003 to December 2004.[41]

Benzyl Salicylate at 1% showed a positive reaction in 2/2041 patients. The calculated frequency of allergic reactions, standardized for age and sex was also 0.1% with the 95% confidence interval (95% CI). The authors classified Benzyl Salicylate as a "very rare allergen."

In a trial intended to evaluate the delayed hypersensitivity to Benzyl Salicylate brought out by UV exposure, fifteen patients, age 9 to 62 years, applied a trade name mixture (containing 1% Oxsoralen with acetone, 71% alcohol, and propylene glycol (concentration not specified)) to vitiliginous areas of the right forearm and hand, and a trade name mixture in a vehicle containing more than 5% Benzyl Salicylate to the left forearm and hand.[42] The patients used the medications from 2 to 20 months. Control patients applied a 6% Benzyl Salicylate solution to make it similar to the test article. The control test article contained Benzyl Salicylate (6%), chloroform (20%), hexadecyl alcohol (1%), liquid petrolatum (20%), and isopropyl alcohol (53%). Fourteen subjects applied the solution containing 6% Benzyl Salicylate to their left volar forearms twice daily for six weeks. To test the stability of Benzyl Salicylate to UV, 1% solution in xylene was irradiated for six hours with a fluorescent sunlamp. The absorption spectra of the irradiated and non-irradiated Benzyl Salicylate solutions were compared on a spectrophotometer. All 15 subjects developed the expected moderate erythema, while six developed severe erythema and itching on the side treated with trade name mixture and Benzyl Salicylate. In patch tests on 14 controls, Benzyl Salicylate produced only one positive reaction. Delayed hypersensitivity to Benzyl Salicylate was enhanced by the phototoxic effects of the test product.

Photoallergy

Summary data from four clinical reports demonstrated no photoallergic reactions.[5] No photoallergic reactions were observed when a photopatch test that was conducted in 482 patients with 2% Benzyl Salicylate in petrolatum. Photopatch testing was conducted on 386 patients with suspected contact dermatitis from cosmetic and toiletry products. A photopatch test was conducted in two subjects with 10% Benzyl Salicylate in dimethylphthalate. No photoallergic reactions were observed. Benzyl Salicylate at 2% in petrolatum was photopatch tested in 706 patients with contact dermatitis. No photoallergic reactions were observed.

Case Reports

A case report described the incidence of a 74-year-old woman who presented with a two-month history of worsening non-pruritic pigmented patches over the face.[43] Patch tests were performed with standard series, cosmetic series, and the patient's own products using the inert quadrate (IQ) chamber. Patches were removed from the back after day 2 and readings were performed on day 3. The patch tests showed positive reactions to colophonium, nickel sulfate, potassium dichromate 0.5 %, fragrance mix I, and Benzyl Salicylate. The patient also showed a positive reaction to her own face wash, which contained Benzyl Salicylate. In addition, the positive reactions to Benzyl Salicylate and the face wash showed a similar appearance of brownish hyperpigmentation.

A 60-year old woman presented with an 11-month history of chronic eyelid erythema and swelling with slight pruritus.[44] On examination, weak edema and erythema were observed in the upper and lower eyelids, with a bilateral and symmetrical distribution. The patient was patch tested with an exposure time of two days, using two different allergen series (Spanish Standard Patch Test Series supplemented with further allergens and another cosmetics and fragrance series), and readings were performed on days 2 and 4. On Day 4, a weak positive reaction to Benzyl Salicylate in 10% petrolatum was observed in both series.

A 70-year old woman was presented with a history of facial dermatitis with scaly erythematous plaques affecting the upper and lower eyelids and extending to both infraorbital regions. The patient had come into contact with several hair products that contained Benzyl Salicylate.[45] The patient was patch tested with the Spanish Contact Dermatitis Research Group (GEIDAC) baseline series. The patch tests were applied on the upper back for 2 days. Readings were performed on day 3 and day 7. Patch test results were positive on day 3 and day 7 for 10% Benzyl Salicylate in petrolatum.

SUMMARY

This is a review of the safety of Benzyl Salicylate as used in cosmetics. According to the *Dictionary*, this ingredient is an ester of benzyl alcohol and salicylic acid, and is reported to function in cosmetics as a fragrance ingredient and light stabilizer. According to 2019 VCRP data, Benzyl Salicylate is used in a total of 3079 cosmetic formulations, 433 of which are in are in perfumes (spray). The results of a concentration of use survey provided in 2016 indicate that Benzyl Salicylate, as a light stabilizer, is used at concentrations up to 0.15 % in leave-on products and up to 0.5% in rinse-off products.

For fragrance use, IFRA has a suggested use concentration of Benzyl Salicylate dependent on product type. Limitations include 12.8% for oral care products and a limit of 0.5% for lip products. According to the European Union, Benzyl Salicylate may be used in cosmetics and personal care products, but its presence must be indicated when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

Benzyl Salicylate has been approved as a direct food additive for use as a synthetic flavoring substance by the US FDA. Benzyl Salicylate has been granted GRAS status as a flavoring ingredient by the Flavor and Extract Manufacturers Association.

In a skin penetration study, 0.2 mL of Benzyl Salicylate was administered to the human epidermis using a glass chamber; it was reported that 0.031% ± 0.004% of the chemical traversed the skin. In an in vitro absorption study in which 1, 3, and 10% Benzyl Salicylate in ethanol was applied to naked rat skin, the amount that migrated into receptor fluid was measured to be 62.7, 58.8, and 40.3%, respectively. When the same test was conducted in guinea pig, 3.5, 1.7, and 0.9% of the solution migrated through the skin into the receptor fluid for the 1, 3, and 10% concentrations, respectively.

Studies involving acute dermal and oral toxicity of Benzyl Salicylate reported low toxicity levels. The acute dermal LD_{50} of Benzyl Salicylate was calculated to be 14.15 g/kg in rabbits. The LD_{50} for Benzyl Salicylate was reported to be 2230 mg/kg bw when three groups of 6 rats were dosed with 1.25, 2.5, or 5.0 g/kg Benzyl Salicylate by gavage and observed for a 7-day period. At 1.25 g/kg, no deaths (0/6) were observed; 4/6 deaths were observed at 2.5 g/kg and all (6/6) animals died at 5.0 g/kg.

In a combined repeated dose and reproductive/developmental screening toxicity test, male and female rats (5 per sex) were administered Benzyl Salicylate by gavage at 0 (corn oil), 250, 500, or 1000 mg/kg/day for 14 days. All animals died in the 1000 mg/kg/day treatment group and one female died in the 500 mg/kg/day treatment group. Significant decreases in the body and thymus weights and significant increases in the liver weights and AST were observed in both sexes in the 500 mg/kg/day treatment group. Slight decreases in glucose and thymus absolute weights were also observed in males in the 250 mg/kg/day treatment group. The considered tolerable dose was 250 mg/kg/day.

In a 90-day oral repeated dose toxicity study, rats were administered cyclohexyl salicylate (used for read-across to Benzyl Salicylate) at doses of 0 (vehicle control), 40, 120, and 360 mg/kg bw/day; the total volume of administered formulation was 5 mL/kg in all dose groups. No adverse systemic effects were observed, and the NOAEL was 360 mg/kg bw/day.

Following a short-term screening assessment described above, Sprague–Dawley rats were administered Benzyl Salicylate dissolved in corn oil once daily via gavage at doses of 0 (control), 30, 100, or 300 mg/kg/day, using a dosing volume of 5 mL/kg. Females in the mating group (n = 12 per treatment group) were dosed for 14 days prior to mating and then through mating and gestation until postpartum day 4, giving a total of 41 to 46 days of dosing, while females in the non-mating group (n=10 per treatment group) were dosed for 42 days. Based on reproductive/developmental toxicity study, Benzyl Salicylate was not found to have any effects on fertility or implantation or to cause severe maternal toxicity. However, males in the 300 mg/kg/day treatment group had significantly greater relative weights of the kidney and non-mated females in the 300 mg/kg/day treatment group exhibited a significantly lower brain weight. Also, marked embryotoxicity was observed in the form of early embryonic resorption in the 300 mg/kg/day treatment group, and dead offspring exhibited neural tube defects. Offspring of rats that had been administered 30 or 100 mg/kg/day exhibited lower body weights on PND 0 or 4. The LOAEL of Benzyl Salicylate was 30 mg/kg/day.

An Ames test of Benzyl Salicylate, in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and/or TA97 did not produce any mutagenic effects, with or without metabolic activation. Benzyl Salicylate was found to be non-genotoxic in vitro based on the chromosomal aberration test using Chinese hamster lung cells.

Benzyl Salicylate, tested in an assay using an estrogen responsive MCF-7 human breast cancer cell line, produced estrogenic responses and increased the proliferation of MCF-7 cells at 10^{-4} M. In order to examine the estrogenic activities of plasticizers used in tissue conditioners, plasticizers including Benzyl Salicylate were evaluated in vitro and evaluated by the E-screen test using MCF-7 cells. Benzyl Salicylate increased proliferation of MCF-7 breast cancer cells at 10^{-5} M (22.8 mg/L). In an in vivo study evaluating the estrogenic potential of Benzyl Salicylate, estrogenic activities were observed in rat and mouse uterotrophic assays almost in all concentrations tested. The immature rodent uterotrophic assay showed that the uterine weights were significantly increased in mice who received 1.1, 33.3, 100, and 300 mg/kg/day.

In a preliminary test, 0.025 mL of Benzyl Salicylate was applied with a pipette to the clipped skin on the flank of 6 to 8 male and female outbred Himalayan white-spotted guinea pigs. The concentration of 0.1% was the lowest concentration to produce mild erythema in at least 25% of the animals and this dose was selected as the minimal irritating concentration after one application. The skin irritation potential of Benzyl Salicylate was evaluated in the induction phase of an OET. Benzyl Salicylate (0.1 mL) was applied to the clipped flank of 6 to 8 male and female outbred Himalayan white spotted guinea pigs. The minimal irritating concentration after 21 applications was 0.1% (vehicle not specified). In a preliminary irritation screen conducted to determine the ICC of Benzyl Salicylate using four inbred Hartley albino guinea pigs, Benzyl Salicylate (0.1 mL) administered at a range of concentration gave slight but perceptible irritation with no edema tested at

0.5% and it was selected as the ICC. In a modified Draize sensitization study, the irritation potential of Benzyl Salicylate was evaluated in four inbred Hartley albino guinea pigs to determine the ACC. The highest concentration causing no irritation was 2% and it was selected as the ACC. No irritation was observed in a 4-hour semi-occlusive patch test was conducted on four female New Zealand white albino rabbits. No irritation was observed in a 24-hour closed patch test conducted using three Albino rabbits. As a part of an acute dermal LD_{50} study, irritation was not observed with neat Benzyl Salicylate at 5, 10, or 20 g/kg when applied to a clipped area and held in contact with the skin for 24 hours under occlusion. No irritation was observed in maximization pre-test when 30% Benzyl Salicylate in petrolatum was administered in a closed patch test on the volar forearms of 5 subjects for 48 hours. Two irritant reactions were observed in a maximization pre-test study conducted when 30% Benzyl Salicylate in petrolatum was applied under occlusion to the backs of 22 male subjects. No irritation was observed in a patch test conducted on 30 subjects administered 0.2 mL Benzyl Salicylate (neat) to the upper outer arm for up to 4 hours. Benzyl Salicylate at 5% in petrolatum caused no irritation when applied to the upper arms of 12 male and 13 female subjects.[5] Reactions were scored after 1 and 24 hours. Five positive reactions were observed when 0.2% Benzyl Salicylate in 99% ethanol was applied under occlusion for 24 to 48 h to the upper inside of the arm of 313 subjects. Irritation was not observed when a 24- to 72-hour closed patch with 2% Benzyl Salicylate in unguentum simplex (a simple ointment containing 5 parts olive oil and 2 parts white wax) was applied to the upper inside of the arm of 30 male and female subjects. In a 48-hour closed patch test conducted in five male and female subjects, 20% Benzyl Salicylate in petrolatum applied to the back of each subject produced no irritation.

In an LLNA performed to assess the sensitization capacity of Benzyl Salicylate, 4 female CBA/JN mice were administered 25 µl of Benzyl Salicylate topically at 10% in 4:1 acetone/olive oil vehicle to the left and right ear lobe for three days. The EC3 value was calculated to be 1.5% (375 µg/cm^2) therefore, Benzyl Salicylate was categorized as a weak sensitizer. Benzyl Salicylate was considered to have the potential to be a sensitizer in another LLNA in which 4 female CBA/Ca mice were treated with 25 µl of the chemical at 2.5, 5, 10, 25, or 50% w/v in 3:1 DEP:EtOH vehicle. The EC3 value was calculated to be 2.9% (725 µg/cm^2). Sensitization was observed at all concentrations in a maximization test on Benzyl Salicylate was conducted in Dunkin-Hartley guinea pigs. Sensitization was observed in a guinea pig maximization test conducted using 10% Benzyl Salicylate for both induction and challenge phase. A maximization test on 10 Hartley guinea pigs per dose using 1% Benzyl Salicylate in ethanol and 100% dermally administered revealed no sensitization reactions. Five of 20 animals revealed sensitization reactions in a study in which 10% Benzyl Salicylate in liquid paraffin and FCA was intradermally injected in the shoulder of 4-week old female Hartley strain guinea pigs (20 per group). 'Questionable' reactions were observed in three (3/20) animals at 5%, five (5/20) animals at 10%, and four (4/20) animals at 20%.

Results were negative in a maximization test conducted using outbred Himalayan white-spotted guinea pigs. In another maximization test, 10% Benzyl Salicylate in liquid paraffin and 30% Benzyl Salicylate in ethanol were administered to 10 female Hartley albino guinea pigs. At first challenge, no reactions were observed at 24 h, but positive reactions were observed at 48 and 72 hours for all doses. At the second challenge, positive reactions were observed with 0.03% at 24 h and all concentrations at 48 and 72 hours. No sensitization was produced in a guinea pig open epicutaneous test (OET) using Benzyl Salicylate at 30% for both induction and challenge (vehicle not specified). An OET conducted in guinea pigs exhibited no reaction to 10% Benzyl Salicylate in a 21 daily open application study. In a CET in guinea pigs, 30% Benzyl Salicylate (vehicle not provided) was not a sensitizer. Sensitization was observed in a CCET conducted in 10 female Hartley albino guinea pigs when induced for 24 hours with an occlusive patch containing 30% Benzyl Salicylate in ethanol. Sensitization was evaluated in groups of ten Pirbright guinea pigs using a modified FCA method. Benzyl Salicylate at 10% was a moderate sensitizer. In a QRA for dermal sensitization, the RIFM Expert Panel reviewed the critical effect data for Benzyl Salicylate via a WoE approach. IFRA reported a NESIL of 17,700 µg/cm^2 based on a human maximization test, and therefore classified the chemical as a weak sensitizer.

In five maximization tests using 25 human subjects, Benzyl Salicylate was administered at 20 to 30 % in petrolatum. Reactions were observed in two of the five studies, affecting 2/25 and 1/25 subjects at 20%. No positive reactions were reported at 30%. In another study, 15% Benzyl Salicylate in 3:1 DEP:EtOH did not induce dermal sensitization in an HRIPT conducted on 101 subjects (29 males and 72 females). No sensitization reactions were observed when 35 subjects completed an HRIPT with 10% benzyl salicylate in alcohol SDA 39C. No sensitization reactions were observed when 52 volunteers were administered an aliquot of 5 ml of 5% benzyl salicylate in dimethyl phthalate. No sensitization was observed in an associated HRIPT study involving 8 male and female subjects when administered 0.5 mL of 5% Benzyl Salicylate in dimethyl phthalate. To evaluate the potential for cross-reactivity, an HRIPT was conducted on 103 subjects (29 male and 74 females). No cross-reactions were observed in subjects administered 30% hexyl salicylate in DEP:EtOH (3:1), and cross-challenged with 15% Benzyl Salicylate in DEP:EtOH (3:1).

Undiluted Benzyl Salicylate and 25% Benzyl Salicylate in methanol produced no phototoxic effects when applied to 6 groups of hairless mice. The first group was exposed to a florescent black light (a bank of 6 Sylvania F40T12BL PUVA lamps with a broadband output of 350 nm) for one hour and at a distance of 0.65 m. The second group was irradiated one meter from simulated sunlight (6.5 kw xenon light source) for one hour. In another study, 5%, 10%, and 30% Benzyl Salicylate in acetone administered to five female albino Hartley-Dunkin guinea pigs caused no phototoxic effects. The

application sites were irradiated with 13 J/cm^2 UV light (UV-A black light 300 – 400 nm, max 360 nm) at 10 cm for 60 minutes. No irritation was observed with 5% Benzyl Salicylate; however, irritation was observed at 10% and 30% in 5 female albino Hartley-Dunkin guinea pigs. Benzyl Salicylate (0.025 mL) at 1%, with 2% DMSO, revealed no evidence of phototoxicity; however phototoxic reactions were observed in 10/10 animals administered 0.025 mL of Benzyl Salicylate at 1% or 3% in ethanol with 2% DMSO added to enhance penetration. Sites on the left flank were irradiated with 20 J/cm^2 UV light (320–400 nm, energy 1 x 10^4 ergs/cm^2), at 10 cm from the animal. No phototoxic effects were observed when 20 (10/sex) adult albino Dunkin Hartley guinea pigs were administered 0.5 mL of 10% Benzyl Salicylate in absolute ethanol. Irradiation was carried out using lamps in the UVA range and in the UVB range. No photosensitization reactions were observed when Dunkin–Hartley guinea pigs (25/group) were administered 10% Benzyl Salicylate in ethanol.

No phototoxic reactions were observed in a test conducted on 6 female subjects when administered 0.025 mL/2 cm^2 of 3% and 10% Benzyl Salicylate in 1:1 ethanol/acetone. The test sites were exposed to non-erythrogenic UVA radiation at 1, 2.5, 5, 10, and 20 J/cm^2.

The ocular irritation potential of 0.75 mL undiluted Benzyl Salicylate was evaluated using a BCOP study according to OECD TG 437. An irritancy score of 0/5 was reported and it was concluded that the Benzyl Salicylate is not an ocular corrosive or severe irritant. Irritation was evaluated following the instillation of 0.1 mL of 10% Benzyl Salicylate in SD alcohol 39-C into the right eye of three albino rabbits. Mild conjunctival irritation was observed in all three rabbits and corneal opacity was observed in one rabbit

In a patch test conducted in 241 patients from October 1981 to June 1983, sensitivity to 2% Benzyl Salicylate in paraffin was observed in 6 patients (2.5% incidence) and was characterized by erythema and edema. Benzyl Salicylate at 2% gave a positive reaction in 2/20 patients when patch tested with several fragrance materials during a one-year period (1975). In 10,503 patch tests of consumer products containing < 2% Benzyl Salicylate, no reactions were directly attributed to Benzyl Salicylate. In a worldwide multicenter study to investigate fragrance sensitization in 167 patients with suspected fragrance allergies, allergic reaction were observed in eight and 5 patients tested with 2% and 5% Benzyl Salicylate, respectively. Over a 64-month period (September 15, 1977 to August 31, 1983), twelve dermatologists from various sections of the US studied a total of 713 out of an estimated total of 13,216 patients with contact dermatitis. Of 713 cosmetic dermatitis patients, one (0.14%) reacted to Benzyl Salicylate (concentration not reported). In 578 cases of eczema patients known to be sensitized to cosmetics, one (0.17%) tested positive to Benzyl Salicylate. To study the frequency of sensitization to 26 fragrances including Benzyl Salicylate, patch tests were conducted during 4 periods of 6 months, from 1 January 2003 to 31 December 2004, in a total of 21 325 patients. The study reported 2 positive reactions to 1% Benzyl Salicylate in 2041 (0.1%) patients. In a study to evaluate the delayed hypersensitivity to Benzyl Salicylate, Benzyl Salicylate caused severe pruritus in six of 15 patients who applied a trade name mixture (containing 1% Oxsoralen with acetone, 71% alcohol, and propylene glycol (concentration not specified)) in a vehicle containing more than 5% Benzyl Salicylate. Delayed hypersensitivity to Benzyl Salicylate was enhanced by the phototoxic effects of the same lotion. Only one of 14 control patients reacted to Benzyl Salicylate.

No photoallergic reactions were observed when several photopatch tests were conducted in 482 patients with 2% Benzyl Salicylate in petrolatum. Another photopatch test in two subjects with 10% Benzyl Salicylate in dimethylphthalate showed no photoallergic reactions. Benzyl Salicylate at 2% in petrolatum tested in 706 patients with contact dermatitis resulted in no photoallergic reactions. No photoallergic reactions were observed when 386 subjects with suspected contact dermatitis were administered Benzyl Salicylate at 2% in petrolatum.

DISCUSSION

This report reviews the safety of Benzyl Salicylate, which is reported to function in cosmetics as a fragrance ingredient and light stabilizer. Use concentration survey data provided by the Council on Benzyl Salicylate were only reported for its use as a light stabilizer. However, the VCRP does not indicate the function of ingredients in cosmetic formulations, so it is not known what the intended function of Benzyl Salicylate is in any of the ingredient categories reported in the VCRP.

The Panel noted the potential for Benzyl Salicylate to bind to and interact with estrogen receptors of the skin. However, it was considered irrelevant to cosmetic safety taking into consideration that the low concentrations of use and low dermal absorption would prevent effective systemic exposure and potential estrogenic effects.

The Panel recognized several positive sensitization studies as well as the outcome of a QRA for dermal sensitization. Consequently, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including site and duration of exposure, formulation, and frequency of use. The Panel noted that the induction of skin sensitization is not dependent on function in cosmetic products, but it does vary depending on the area and location of product application and should be assessed using a QRA or other accepted methodologies. The Panel was also

concerned that the potential exists for dermal irritation with the use of products formulated using Benzyl Salicylate, and thus specified that products containing Benzyl Salicylate must be formulated to be non-irritating.

CONCLUSION

The CIR Expert Panel concluded that Benzyl Salicylate is safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

TABLES

Table 1. Physical and Chemical Properties

Property	Value	Reference
Physical Form	Liquid	[6]
Color	Colorless to pale yellow	[6]
Odor	Floral, Jasmine-like, Balsamic, mushroom-like	[6]
Molecular Weight (g/mol)	228.5	[46]
Density/Specific Gravity	1.181 ± 0.001	[6]
Viscosity (mm^2/s at 20 ± 0.5 °C) (mm^2/s at 40 ± 0.5 °C)	17.0 ± 0.5 7.1 ± 0.5	[6]
Vapor pressure (@ 25 ºC)	0.01	[6]
Melting Point (ºC)	122.1 ± 0.2	[6]
Boiling Point (ºC)	322	[6]
Water Solubility (mg/L)	8.8	[6]
log K_{ow}	4.0	[6]
Disassociation constants (pKa @ 25 °C)	9.82	[6]
UV Absorption (λ) (nm)	200 - 340	[4]

Table 2. Frequency (2019) and concentration of use (2016**) for Benzyl Salicylate[11,12]

	# of Uses[11]	*Max Conc of Use (%)[12]* **
Totals*	**3079**	**0.0036-0.5**
Duration of Use		
Leave-On	*2419*	*0.019-0.15*
Rinse-Off	*628*	*0.0036-0.5*
Diluted for (Bath) Use	*32*	*NR*
Exposure Type		
Eye Area	25	NR
Incidental Ingestion	28	NR
Incidental Inhalation-Spray	976;562[a];492[b]	NR
Incidental Inhalation-Powder	62;492[b]	NR
Dermal Contact	2525	0.0036-0.5
Deodorant (underarm)	77[a]	NR
Hair - Non-Coloring	490	0.0065
Hair-Coloring	19	NR
Nail	16	NR
Mucous Membrane	324	NR
Baby Products	2	NR

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

** The Council concentration of use survey was only for the light stabilizer function

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

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.

NR – no reported use

Table 3. IFRA Standard: Benzyl Salicylate in finished products[47]

Category	Standard limits
Category 1	0.5% in lip products
Category 2	0.7% in deodorants / antiperspirants
Category 3	2.7% in hydroalcoholics for shaved skin; baby lotion; eye area products
Category 4	8% in hydroalcholics for unshaved skin; body products; hair sprays
Category 5	4.2% in baby powder; face products; hair treatments
Category 6	12.8% in oral care products
Category 7	1.3% in wipes; feminine hygiene
Category 8	2% in eye makeup removers; powders; hair grooming; hair dyes; nail products
Category 9	5% in rinse-off products; shampoos; conditioners; bath products; shaving products
Category 10	2.5% in hard surface cleaners
Category 11	Includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products, there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

IFRA - International Fragrance Association

*42nd Amendment to the IFRA QRA Category (2007)

*The RIFM Expert Panel reviewed the critical effect data for Benzyl Salicylate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 17,700 µg/cm².

*The Category Consumer Exposure Level (mg/cm^2/day) is driven by the product type in that category with the combined highest consumer exposure level and highest Sensitization Assessment Factor (SAF)

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
		Irritation Animal		
0.03 – 100% Benzyl Salicylate	6 to 8 male and female outbred Himalayan white-spotted guinea pigs	Pre-test for OET; a single application of Benzyl Salicylate (vehicle not specified) was administered for 24 hours.	At 0.03%, no irritation was observed. The concentration of 0.1% was the lowest concentration to produce mild erythema in at least 25% of the animals and this dose was selected as the minimal irritating concentration after one application	[26]
0.03 –100% Benzyl Salicylate	6 to 8 male and female outbred Himalayan white spotted guinea pigs	Induction phase of OET; Benzyl Salicylate was applied daily for 21 days (vehicle not specified)	0.03%: no irritation. Minimal irritating concentration was observed after 21 applications at 0.1%.	[26]
0.1 mL of Benzyl Salicylate in an unspecified vehicle at a range of concentrations	4 inbred Hartley strain albino guinea pigs (same sex)	As a part of a modified Draize sensitization study, a preliminary irritation screen was conducted to determine the ICC and ACC. Animals were administered intradermal injections of 0.1 mL aliquots of Benzyl Salicylate on shaved flanks in an unspecified vehicle. Reactions were read 24 hours after injection.	The concentration giving slight but perceptible irritation with no edema was 0.5% and it was selected as the Challenge Concentration (ICC). The highest concentration causing no irritation was 2% and it was selected as the Application Challenge Concentration (ACC)	[27]
0.5 mL of Benzyl Salicylate (neat)	4 New Zealand white albino rabbits	4-hour semi-occlusive patch test	No irritation was observed	[28]
0.5 mL aliquot of 10% Benzyl Salicylate in SD alcohol 39-C	3 Albino Rabbits; Sex not reported	24-h closed patch test	No irritation was observed	[4]
Benzyl Salicylate at 5, 10 or 20 g/kg (neat)	Rabbit	LD_{50} study for 24 hours under occlusion	No irritation was observed	[4]
		Irritation- Human		
0.2 mL of Benzyl Salicylate (neat)	30 subjects	4 hour closed patch test	No irritation was observed	[28]
0.2% Benzyl Salicylate in 99% ethanol	313 subjects	24 - 48 hour closed patch test	Five (5/313) positive reactions were observed	[29]
2% Benzyl Salicylate in unguentum simplex (A simple ointment containing 5 parts olive oil and 2 parts white wax)	30 male and female subjects	24 - 72 hour closed patch	No irritation observed	[5]
5% in petrolatum	12 male and 13 female subjects	24 hour closed patch test	No irritation was observed	[5]
20% Benzyl Salicylate in petrolatum	5 male and female subjects	48 hour closed patch test	No irritation observed	[29]
30% Benzyl Salicylate in petrolatum	5 subjects	maximization pre-test study	No irritation was observed	[5]
30% Benzyl Salicylate in petrolatum	22 male subjects	maximization pre-test	Two irritant reaction (2/22)	[5]

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
		Sensitization- Animal		
10% Benzyl Salicylate in FCA for induction; 5%, 10%, and 20% in acetone for challenge	8 test and 8 control female albino Hartley-Dunkin guinea pigs	GPMT Induction consisted of a two-stage procedure. In the first stage, three intradermal injections (0.1 mL each) were administered to the clipped shoulder region of each animal. The injections consisted of Freunds Complete Adjuvant (FCA) plus distilled water (1:1); 10% Benzyl Salicylate in FCA; and 10% Benzyl Salicylate in FCA with distilled water (1:1). The second stage was a 48-hour topical application made seven days later to the same area on the shoulder. The shoulder was treated with 10% sodium lauryl sulfate (SLS) in petrolatum. Challenge test was performed by applying 0.02 mL of 5%, 10% and 20% Benzyl Salicylate in acetone to each site.	Sensitization was observed at all concentrations	[5]
10% Benzyl Salicylate for induction and challenge	Guinea pigs (sex and number not specified)	GPMT	Sensitization was observed	[5]
1% Benzyl Salicylate in ethanol intradermally and 100% dermally	10 Hartley guinea pigs/dose	Magnusson–Kligman GPMT Induction: a patch containing 0.2 mL of the test solution was applied for 24 hours under closed conditions and repeated every other day over a period of 2 weeks. An untreated group acted as a control. In combination with this procedure, 0.1ml FCA was administered intradermally on each side of the application unit on day 3 and 7 before the initial patch and before the initial 2nd, 3rd, and 4th patch application. Challenge: was performed with 0.01 mL to the lateral part of the animal on the 11th day.	No sensitization reactions were observed	[30]
Benzyl Salicylate at 10% in liquid paraffin for intradermal induction; 50% in white petrolatum for topical induction; 5%, 10% and 20% in white petrolatum for challenge	4- week old female Hartley strain guinea pigs (20/group)	GPMT Benzyl Salicylate at 10% in liquid paraffin and FCA was intradermally injected in the shoulder region of each animal. Five days after the intradermal injections 10% SLS in petrolatum was topically applied to the same region. Twenty-four hours later, 50% Benzyl Salicylate in white petrolatum was applied for 48 hours with impermeable tape and an adhesive bandage. Two weeks after the topical application, Benzyl Salicylate at 5%, 10% and 20% in white petrolatum was applied on the backs of the animals.	No sensitization at 5% and 10%; Sensitization were observed in 2/20 at 20%	[5]
Intradermal induction: 5% Benzyl Salicylate in FCA Topical induction: 25% Benzyl Salicylate in petrolatum Topical Challenge: sub-irritant concentration (< 0.1%) in petrolatum	Himalayan white-spotted male and female guinea pigs (numbers not specified)	GPMT Induction: was via two intradermal injections on day 0. On day 8, 25% Benzyl Salicylate in petrolatum was applied to a clipped area on the neck for 48 hours under occlusion. Challenge: conducted on day 21 1 with a 24-hour occluded patch	No sensitization reactions were observed	[26]

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
Intradermal induction: 10% in liquid paraffin Topical induction: 30% in ethanol Topical Challenge: 0.003%, 0.01%, or 0.03% in ethanol	10 female Hartley albino guinea pigs	GPMT Induction was via intradermal injection of 10% Benzyl Salicylate in liquid paraffin and a 48-hour occlusive patch with 30% Benzyl Salicylate in ethanol. The animals were challenged twice with Benzyl Salicylate at 0.003%, 0.01%, and 0.03% in ethanol. The second challenge was conducted three weeks after the first challenge.	At first challenge, no reactions were observed at 24 hours, but positive reactions were observed at 48 and 72 hours at all doses. At the second challenge, positive reactions were observed with 0.03% at 24 hours and all concentrations at 48 and 72 hours.	[32]
Induction and challenge: 30% Benzyl Salicylate (vehicle not specified)	6 to 8 male and female guinea pigs	A guinea pig OET; Daily applications of 0.1 mL Benzyl Salicylate (undiluted or progressively diluted solutions) were made for 3 weeks to a clipped 8.0 cm2 area on the flank of each guinea pig. Ten control animals were either left untreated or treated with 0.1 mL of the vehicle for 21 days. Challenge: Both the test and control animals were treated on days 21 and 35 on the opposite flank with 30% Benzyl Salicylate.	No sensitization reactions were observed	[5]
Induction and challenge: 10% Benzyl Salicylate (vehicle not specified)	Guinea pigs (6 to 8 males and females)	A guinea pig OET consisted of 21 daily open applications to the shaved flank of 6–8 guinea pigs per group. Open challenge applications were made on days 21 and 35	No sensitization reactions were observed	[5]
Induction and challenge: 0.03 - 100% Benzyl Salicylate (vehicle not specified)	Himalayan white spotted guinea pigs (6 to 8 males and females)	In an OET, test animals received 21 daily open applications of 0.1 mL of undiluted and progressively diluted solutions of Benzyl Salicylate applied to clipped flank. Guinea pigs were challenged by an open application of 0.025 mL Benzyl Salicylate to a skin area measuring 2 cm^2 on the contralateral flank on days 21 and 35.	0.03%: minimum eliciting concentration 30%: minimum sensitizing concentration	[26]
Induction: 30% (vehicle not specified) Challenge: 1% (vehicle not specified)	Guinea pigs (20, sex not specified)	In a CET Induction: 30% Benzyl Salicylate (vehicle not provided) under occlusion for 48 hours on the shaved nape. The same procedure was repeated three times per week for two weeks. Following a 2-week rest period and challenge with 1% Benzyl Salicylate for 48 hours.	Sensitization observed in 3/20	[5]
30% Benzyl Salicylate in ethanol for induction; 1%, 3%, and 10% in ethanol for challenge	10 female Hartley albino guinea pigs	In a CCET, guinea pigs were administered 30% Benzyl Salicylate in ethanol applied to each test animal in 24-hour occlusive patch. The animals were challenged twice (2nd challenge was conducted 3 weeks after the 1st challenge) with 1%, 3% and 10% Benzyl Salicylate in ethanol.	At 1% concentration, one positive (1/10) reaction was observed at 24 hours, while no reactions were observed at 48 or 72 hours in both challenges. At 3%, positive reactions (3/10) were observed at 24 hours of the first challenge and (2/10) were observed at 24 and 48 hours in both challenges. At 10%, positive reactions were observed at 24, 48 and 72 hours in both challenges.	[32]
Induction: 3%, 10%, 30%, and 100% topically Challenge: concentration not specified topically	Pirbright and Hartley albino guinea pigs (6 – 10/group)	In a CCET the application of test article was repeated every other day over a period of 2 weeks. Eleven days after the final induction patch, a challenge was performed.	10%: no reactions 30%: sensitization in 3/6 Pirbright guinea pigs 100%: sensitization in 1/10 Hartley guinea pigs	[30]

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
Induction: 100% Challenge: 50% topically	30 tortoise shell guinea pigs	In a CCET, animals were shaved and 24 hours occluded patch with Benzyl Salicylate (neat) was applied. Patches were applied every third day for 2 weeks (maximum, 4 applications). An injection of FCA was intradermally administered before the third patch. An untreated group of five animals was used as a control. Challenge: After 11 days, 0.01 mL aliquot of 50% Benzyl Salicylate in ethanol was applied to a previously untreated site once daily for 1 to 3 days.	Sensitization reactions were observed in 13/30 animals	[48]
10% Benzyl Salicylate in FCA for intradermal induction; 10% in acetone for challenge	10 Pirbright guinea pigs	In a modified FCAT, a total of 4.5 mg of Benzyl Salicylate (10%) was administered and challenged by applying 0.05 mL of 10% Benzyl Salicylate in acetone onto the clipped, shaved right flank.	Benzyl Salicylate at 10% was a moderate sensitizer	[33]
50% Benzyl Salicylate in FCA for induction application; 0.1% for challenge application	Himalayan white spotted guinea pigs (6 to 8 males and females)	FCAT was conducted using induction via five intradermal injections of 0.1 mL of a 50:50 mixture of Benzyl Salicylate and FCA into the neck Challenge: A 24 hour closed patch challenge application was conducted on days 21 and 35 <0.1% (vehicle not specified)	No reactions were observed	[26]
Intradermal induction: 1% in saline Intradermal challenge: 0.1% in saline Topical challenge: 10% in petrolatum	20 Pirbright White Strain guinea pigs (10/sex).	Optimization test; test population received one intracutaneous injection of 0.1% Benzyl Salicylate in saline. Benzyl Salicylate was incorporated at the same concentration in a mixture of FCA and physiological saline (adjuvant/saline, 1:1 v/v). The animals were challenged with 0.1% Benzyl Salicylate in saline at week 6 (intradermally) and at week 8 (epidermal challenge)	One (1/20) reaction was observed after the intradermal challenge, and seven (7/20) reactions were observed after the epidermal challenge	[49]
Induction: 30% Benzyl Salicylate in ethanol Challenge: 1%, 3%, or 10% in ethanol	10 Female Hartley guinea pigs	Delayed contact hypersensitivity assay using the AP2 test method; Two induction applications were administered via intradermal injection with FCA and an occluded patch with 30% Benzyl Salicylate in ethanol. Two open challenge applications were administered with 1%, 3% and 10% Benzyl Salicylate in ethanol. A third challenge application was made with 0.003%, 0.01% and 0.03% Benzyl Salicylate in ethanol.	Sensitization was observed at all three challenges	[5]
25 µl of 10% Benzyl Salicylate in 4:1 acetone: olive oil	4 Female CBA/JN mice/group	In an LLNA, test article was applied to the dorsal surface of ear. The procedure was repeated daily for three consecutive days. Three days after the third application, all test subjects were injected via the tail vein with 250 µl of phosphate buffered saline (PBS) containing 20 µCi of 2.0 Ci/mmol specific activity ^{3}H-methyl thymidine.	Benzyl Salicylate was categorized as a weak sensitizer. The EC3 value was calculated to be 1.5% (375 µg /cm^2)	[5]
25 µl of 2.5%, 5.0%, 10%, 25%, and 50% Benzyl Salicylate in DEP:EtOH (3:1)	4 Female CBA/Ca mice/group	Evaluated in an LLNA; Test article was applied to the dorsal surface of each ear and three days after the third application, all animals were injected via the tail vein with 250µl of phosphate buffered saline (PBS) containing 20 µCi of 2.0 Ci/mmol specific activity ^{3}H-methyl thymidine.	Overall, Benzyl Salicylate was found to have the potential to be a skin sensitizer. The EC3 value was calculated to be 2.9% (725 µg /cm^2)	[5]

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
0.5% Benzyl Salicylate for intradermal induction; 0.5% for intradermal challenge and 2% for dermal challenge (vehicle not specified)	Hartley albino guinea pigs (4 or 6 of each sex, 10 total)	In a Draize (Modified) test, a 0.1 ml aliquot of 1.25% Benzyl Salicylate, at 2.5 times the ICC (injection challenge concentration: 0.5%), was injected intradermally at four sites. The animals were challenged 14 days later by intradermal injection of 0.1 ml Benzyl Salicylate into one flank and a topical open application of Benzyl Salicylate on the other flank at the respective ICC of 0.5% and ACC at 2% (vehicle not provided).	No sensitization	[27]
0.1% in isotonic saline for intradermal induction; 0.1% in isotonic saline for challenge	Himalayan white spotted guinea pigs (6–8 males and females)	Draize (Modified); Induction consisted of ten intradermal injections on alternate days with a dose of 0.05 mL of 0.1% Benzyl Salicylate in isotonic saline. Test subjects were challenged on days 35 and 49 with an intradermal injection of 0.05 mL of 0.1% Benzyl Salicylate in saline. Control test subjects were also challenged intradermally on days 35 and 49 with Benzyl Salicylate	No sensitization	[26]
		Sensitization- Human		
0.3mL of 15% Benzyl Salicylate DEP:EtOH (3.1)	29 male and 72 female subjects	HRIPT; adhesive patch (25mm) was applied to the left side of the back of each subject. Patches remained in place for 24 hours. Nine induction patches were completed over a period of approximately three weeks. After a 2-week rest period, challenge patches were applied to a virgin site on the back and kept in place for 24 h.	No sensitization was observed	[5]
0.5mL of Benzyl Salicylate in SD alcohol 39-C	17 male and 18 female subjects	HRIPT; test article was applied on a test patch and administered to the upper arms of the subjects for 24 hours. Nine applications were made during the induction phase and reactions were scored 48 hours after application. After a 2-week rest period, a 24-hour challenge application was made to the same site and to a virgin site in the same manner as the induction applications	No sensitization was observed	[5]
0.5 mL of 5% Benzyl Salicylate in dimethyl phthalate.	8 male and female subjects	HRIPT; 0.5mL of 5% Benzyl Salicylate in dimethyl phthalate was applied to absorbent patches and applied to the inner surface of the left deltoid area for 48 hours. Reactions were read at 24 and 48 hours.	No sensitization was observed	[5]
10% Benzyl Salicylate in SD alcohol 39-C	35 subjects	HRIPT; Patches remained in place for approximately 24 hours. Nine induction patches were completed over a 3-week period. After a 2-week rest period, a 24-hour challenge application was made to the same site and to a virgin site in the same manner as the induction applications.	No sensitization reactions	[5]
5% Benzyl Salicylate in dimethyl phthalate	52 subjects	HRIPT using a modified Draize method. Patch was then applied to the inner surface of the right deltoid area of each. The patches remained in place for 48 hours. A series of ten induction patches were applied. The challenge patches were applied after a 2-week rest period in the same manner as the induction patches except they were applied in duplicate, one set to the inner surface of each deltoid area. Patches remained in place for 48 hours.	No sensitization reactions	[5]

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
20% Benzyl Salicylate in petrolatum	25 male and female subjects	MAX; application was under occlusion to the same site on the volar forearms of all subjects for five alternate day, 48 hours. After a 14-day rest period, a challenge patch was applied under occlusion and reactions were read at 48and 96 hours.	Sensitization was observed in two (2/25) subjects	[5]
20% Benzyl Salicylate in petrolatum	25 subjects	MAX; application was under occlusion to the volar forearms of all subjects for five alternate day, 48-hour periods. The patch site was pre-treated for 24 hours with 5% aqueous SLS under occlusion. Following a 10 to 14-day rest period, a challenge patch of Benzyl Salicylate was applied to fresh sites for 48 hours under occlusion.	One (1/25) sensitization reaction was observed	[5]
30% Benzyl Salicylate in petrolatum	25 male and female subjects	MAX; application was under occlusion to the same site on the volar forearms of each subject for five alternate days, 48-hour periods. Patch sites were pre-treated for 24 hours with 5% aqueous sodium lauryl sulfate (SLS) under occlusion. After a rest period, a challenge patch was applied under occlusion and challenge sites were read 24 hours later.	No sensitization reactions	[5]
30% Benzyl Salicylate in petrolatum	25 male subjects	MAX; application was under occlusion for five alternate days, 48 hours. Each application was preceded by 24-hour occlusive applications of 5% aqueous SLS. Following a 10-day rest period, challenge patches of Benzyl Salicylate were applied to fresh sites on the backs of each subject under occlusion for 48 hours.	No sensitization reactions	[5]
30% Benzyl Salicylate in petrolatum	22 male subjects	MAX; application under occlusion to the same site on the forearms of all subjects for five alternate days, 48-hour periods. Following a 10 to 14-day rest period, a challenge patch was applied to a fresh site for 48 hours under occlusion.	No sensitization reactions	[5]

Abbreviations: ACC= application challenge concentration; CCET = cumulative contact enhancement test; CET = closed epicutaneous test; DEP:EtOH = diethyl phthalate:ethanol; FCA = Freund's Complete Adjuvant; FCAT = Freund's complete adjuvant test; GPMT = guinea pig maximization test; HRIPT = human repeat insult patch test; ICC = injection challenge concentration; LLNA = Local lymph node assay; MAX = human maximization test; OET = open epicutaneous test; PBS = phosphate buffered saline; SLS = sodium lauryl sulfate.

Table 5. Phototoxicity studies on Benzyl Salicylate

Concentration/Dose	Test Population	Procedure	Results	Reference
		ANIMAL		
20 µl aliquot of 100% Benzyl Salicylate and 25% Benzyl Salicylate in methanol	Skh:hairless mice (6/group)	The test material was applied to 5 cm^2 site on the back of each animal. Thirty minutes later, the first group was exposed to a florescent black light (a bank of 6 Sylvania F40T12BL PUVA lamps with a broadband output of 350 nm) for one hour and at a distance of 0.65m to provide a measure dose of 200 RB units. (One RB unit corresponds to ~0.068 mJ/cm^2.[50]) The second group was irradiated one meter from a simulated sunlight (6.5 kw xenon light source) for one hour providing a dose of 200 RB units. The areas were examined at 4, 24, 48, 72, and 96 hours.	No phototoxic effects were observed.	[5]
0.02 mL of Benzyl Salicylate at 5%, 10%, or 30% in acetone	Five female albino Dunkin Hartley guinea pigs	Test material was applied to clipped skin sites and irradiated with 13 J/cm^2 UV light (UVA black light 300 – 400 nm, max 360 nm) at 10 cm for 60 minutes. Reactions were graded according to Draize at 24 and 48 hours after application.	No phototoxic effects were observed	[5]
0.025mL aliquot of Benzyl Salicylate as 1% or 3% in ethanol, with 2% DMSO	Himalayan white spotted guinea pigs (10/dose)	The test material was applied to 2 cm^2 skin on the left flank of the animals. Thirty minutes after the application, the sites on the left flank were irradiated with 20 J/cm^2 UV light (320 – 400 nm, energy 1 x 10^4 $ergs/cm^2$), at 10 cm from the animal. Sites on the right side were not irradiated and served as controls.	No reactions were observed with 1% Benzyl Salicylate. However, phototoxic reaction were observed in 10/10 animals administered 3% Benzyl Salicylate	[5]
0.5mL of 10% Benzyl Salicylate in absolute ethanol	Twenty (10/sex) adult albino Dunkin Hartley guinea pigs weighing 300 to 400g.	A single application of the test material was applied under an occlusive patch for 90 minutes on the anterior part of the back. Irradiation was carried out using a system of fluorescent lamps with continuous spectrum emission. Radiation emitted by these lamps was principally in the UVA range (wavelength from 315 to 400 nm) and in the UVB range (wavelength from 290 to 315 nm). The two lamps used were placed 10 cm from the back of each animal and irradiated for 5 min. The total radiation dose was 12.5 J/cm^2 and 1% of the radiation was in the UVB range.	No phototoxic effects were observed	[5]
10% Benzyl Salicylate in ethanol	Dunkin Hartley guinea pigs (25/group)	Photosensitization test; 4 topical application of 0.5 mL of Benzyl Salicylate in absolute ethanol was applied and challenged with 0.5 mL of 10% Benzyl Salicylate in absolute ethanol	No photosensitization reactions were observed	[5]
		HUMAN		
0.025 mL/2cm2 aliquot of 3% and 10% Benzyl Salicylate in 1:1 ethanol/acetone	Six female subjects	Test article was applied to the left and right side on the back of each subject. The right test side served as control. The test sites were exposed to non-erythrogenic UVA radiation at 1, 2.5, 5, 10, and 20 J/cm^2. The light source was a bank of four blacklight fluorescent tubes with an emission spectrum of 320 – 400 nm housed in a reflector unit.	No phototoxic responses were observed.	[5]

Abbreviations: PUVA = psoralen ultraviolet A; RB = Robertson-Berger; UV A = ultraviolet A; UVB = ultraviolet B

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