Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics

Status: Tentative Amended Report for Public Comment
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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, and Jinqiu Zhu, Ph.D., Toxicologist.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of Salicylic Acid and Salicylates. Some of the possible functions in cosmetics that are reported for this ingredient group are hair and skin conditioning agents, and, less frequently, preservatives and fragrance ingredients. The Panel reviewed relevant data relating to the safety of these ingredients under the intended conditions of use in cosmetic formulations and concluded that Salicylic Acid and 18 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.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of Salicylic Acid and 16 salicylates in 2003.[1] Based on the available data, the Panel issued the following conclusion: Salicylic Acid, the salts Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate; the esters Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate; and Tridecyl Salicylate, and the compounds Butyloctyl Salicylate and Hexyldodecyl Salicylate are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection. The complete report is available on the CIR website (https://www.cir-safety.org/ingredients). In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years; therefore this re-review document has been prepared. MEA-Salicylate was recently re-reviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts; thus it is not included in this re-review.

Also, according to the CIR Procedures, if the Panel concludes that a re-review is warranted, the Panel may consider adding ingredients during the re-review process. Furthermore, if the Panel concludes that the data in the original Final Report substantially address the safety of the expanded list of ingredients, a Tentative Amended Report shall be issued that includes a summary of the data in the original Final Report plus all available new published and unpublished data for the expanded list of ingredients. The following ingredients, in addition to those included in the original Final Report, are included in this safety assessment: Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate. These 3 ingredients are esters of Salicylic Acid, and are structurally similar to the ingredients that were reviewed in the original report. The expanded list of 19 ingredients (16 from the original Final Report + 3 additions) appears below:

Butyloctyl Salicylate
Calcium Salicylate
C12-15 Alkyl Salicylate
Capryloyl Salicylic Acid
Ethylhexyl Salicylate
Hexyldodecyl Salicylate
Isocetyl Salicylate
Isodecyl Salicylate
Magnesium Salicylate
Methyl Salicylate
Myristyl Salicylate
Potassium Salicylate
Salicylic Acid
Sodium Salicylate
TEA-Salicylate
Tridecyl Salicylate

Amyl Salicylate
Hexyl Salicylate
Isotridecyl Salicylate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), some of the functions that are associated with this group of salicylates include hair and skin conditioning agents, and, less frequently, preservatives and fragrance ingredients.[2] The complete list of functions is presented in Table 1.

The published data in this re-review document were identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data may be provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summaries of the 2003 report are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information, except for chemical and physical properties, is not included in the tables or the Summary section.)

CHEMISTRY

Definition and General Characterization

Salicylic Acid, an aromatic monohydroxybenzoic acid (specifically, 2-hydroxybenzoic acid) is a colorless, crystalline organic acid that can be derived from salicin (a β-glucoside in willow bark; similar to aspirin (acetylsalicylic acid); Figure 1). The rest of the ingredients in this report (salicylates) are esters or salts of Salicylic Acid (Figure 2). However, there is one exception, Capryloyl Salicylic Acid (Figure 3), wherein the ester is actually the product of caprylic acid and *the phenolic hydroxyl group* of Salicylic Acid. As such, this compound is chemically more akin to aspirin (acetylsalicylic acid) than to the salicylate carboxyl esters. The definitions of the salicylates that are being reviewed in this safety assessment are included in Table 1.

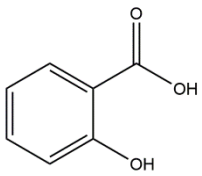


Figure 1. Salicylic Acid

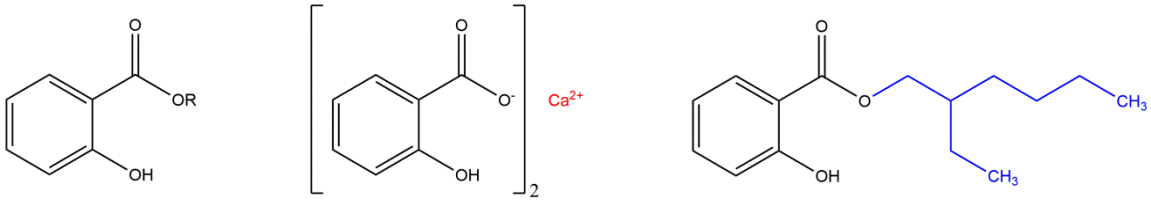


Figure 2. Salicylates generic structure (wherein R is a salt cation or an alcohol residue), and examples: Calcium Salicylate and Ethylhexyl Salicylate

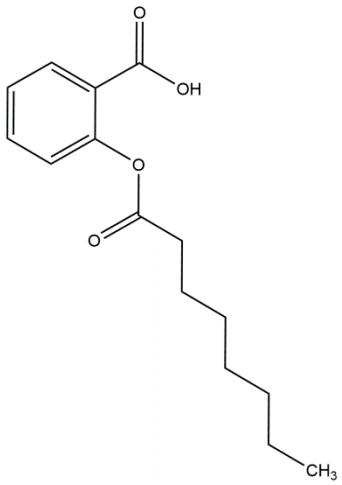


Figure 3. Capryloyl Salicylic Acid

Chemical and Physical Properties

Chemical and physical properties of Salicylic Acid and salicylates (salts and esters) are presented in **Error! Reference source not found.**.[3,4,5,6]

Method of Manufacture

Amyl Salicylate

Amyl Salicylate can be synthesized by heating a mixture of Salicylic Acid, *n*-amyl alcohol, and concentrated sulfuric acid under a reflux condenser for approximately 4 h.[7] After the unreacted alcohol had been removed by distillation at atmospheric pressure, the residue is washed with 10% aqueous potassium carbonate and dissolved in ether, and the ether solution is dried over anhydrous sodium sulfate. The high-boiling material that remains after removal of the ether is fractionated under reduced pressure. The Amyl Salicylate fraction boils at 116 to 121ºC and 1.4 mmHg. According to another source, Amyl Salicylate can be synthesized from Salicylic Acid and *n*-pentanol, using sodium hydrogen sulfate as a catalyst.[8]

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated based on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics.[9] Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2018 VCRP data, the following salicylates in this safety assessment are being used in cosmetic products: Butyloctyl Salicylate, Capryloyl Salicylic Acid, Ethylhexyl Salicylate, Isodecyl Salicylate, Magnesium Salicylate, Methyl Salicylate, Salicylic Acid, Sodium Salicylate, TEA-Salicylate, Tridecyl Salicylate, Amyl Salicylate, and Hexyl Salicylate.[9] The greatest use frequency of 3474 uses is reported for Ethylhexyl Salicylate, followed by 1300 reported uses for Salicylic Acid. (Reported use frequencies for the remaining ingredients are ≤ 165.) The frequency of use for both of these ingredients increased greatly when 2018 VCRP data are compared to the VCRP data from the original report; in 1998, Ethylhexyl Salicylate was reported to have 83 uses and Salicylic Acid was reported to have 107 uses. Furthermore, in 1998, there were no reported uses of Magnesium Salicylate, but 10 uses are being reported in 2018.

The results of a concentration of use survey conducted in 2018 indicate that Butyloctyl Salicylate is being used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest maximum use concentration for leave-on formulations that is being reported for the salicylates that are being reviewed in this safety assessment.[10] Salicylic Acid is being used at concentrations up to 30% in rinse-off products (peels); this is the highest maximum ingredient use concentration that is being reported for rinse-off products. In the published CIR final report on salicylates, the highest ingredient use concentrations in rinse-off and leave-on products were 3% (Salicylic Acid) and 8% (Ethylhexyl Salicylate), respectively.[1] Further use frequency and concentration of use data are presented in Table 3.

Collectively, the 2018 VCRP data and results from a 2018 Personal Care Products Council use concentration survey (i.e., data reported as maximum ingredient use concentrations per product category) indicate that the following salicylates are not reported to be in use in cosmetic products in the US:

Calcium Salicylate
C12-15 Alkyl Salicylate
Hexyldodecyl Salicylate
Isocetyl Salicylate
Myristyl Salicylate
Potassium Salicylate
Isotridecyl Salicylate

Cosmetic products containing salicylates may be applied to the skin or, incidentally, may come in contact with the eyes. These ingredients are also applied to mucous membranes, and could be incidentally ingested. Products containing salicylates may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

The highest maximum ingredient use concentration in a spray product is being reported for Ethylhexyl Salicylate, which is used in suntan aerosol and pump sprays at concentrations up to 5%. The use concentration data on Ethylhexyl Salicylate in spray products relate to cosmetic ingredient functions other than that of a sunscreen. Salicylic Acid is being used in suntan product pump sprays at concentrations up to 0.5%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[11,12,13,14] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they

would not enter the lungs) to any appreciable amount.[11,12] The highest maximum ingredient use concentration in a powder is being reported for Butyloctyl Salicylate, which is being used at concentrations up to 3.6% in face powders. 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.[15,16,17]

Non-Cosmetic

Ethylhexyl Salicylate

Ethylhexyl Salicylate (a.k.a. octyl salicylate) is an active ingredient, at the specified concentration of up to 5%, in over-the-counter (OTC) sunscreen drug products, whereby the finished product provides a minimum SPF value of not less than 2. [21 CFR 352.50]

Methyl Salicylate

Non-aspirin salicylates (i.e., not acetyl salicylic acid), such as methyl salicylate, are found in many OTC brands of creams, ointments, lotions, liniments and medicated oils intended for topical application to relieve musculoskeletal aches and pains.[18]

Salicylic Acid

Salicylic Acid is a non-steroidal anti-inflammatory drug (NSAID), of which aspirin is a simple phenolic acetate derivative.[19] The FDA has issued a final rule for OTC drug products that permits the use of Salicylic Acid, at concentrations of 0.5 to 2%, as an active ingredient in topical acne drug products. [21 CFR 333.310]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Salicylates

In vitro data on pig, mouse, and rat skin indicate that salicylates are percutaneously absorbed.[1]

Ethylhexyl Salicylate

The skin penetration of a sunscreen formulation containing Ethylhexyl Salicylate was evaluated using human full-thickness skin (from 3 women) that was mounted in a Franz diffusion cell with a receptor volume of 12.4 ml.[20] The sunscreen formulation tested was either in an oil-in-water emulsion gel or in petrolatum jelly. The receptor compartment was filled with an aqueous solution containing sodium chloride (0.9%) and bovine serum albumin (1.5%). The cell allowed skin (1.76 cm^2) to be exposed to the sunscreen formulation (in the oil-in-water emulsion or in petrolatum jelly), and the formulation (3.0 ± 0.4 $\mu g/cm^2$) was applied to the skin for either 30 min or 6 h. Each value for skin penetration is reported as the mean value ($n = 4$). After either duration, Ethylhexyl Salicylate was not detected in the dermis. Skin penetration and the amount of Ethylhexyl Salicylate found in the epidermis were the same following the 30-min application using both vehicles and the 6-h application using the oil-in-water emulsion gel; skin penetration was 0.4 $\mu g/cm^2$, and 0.2% of the applied dose was detected in the epidermis. The 6-h value for skin penetration of Ethylhexyl Salicylate (in petrolatum jelly) into the epidermis was 0.6 $\mu g/cm^2$, and 0.3% of the applied dose was detected in the epidermis.

A mathematical method was used to estimate the total body absorption of some salicylate esters, including Ethylhexyl Salicylate.[21] Rate constants were calculated from the relevant physicochemical properties. The applied dose of the active ingredient used in the simulation was 40 $\mu g/cm^2$ based on the FDA recommendation (200 mg of product per 100 cm^2 of skin) and a value of 2%. The release rate from the formulation was fixed at 1 $\mu m/cm^2/h$. The simulations were conducted on a 12-h time scale. The estimated total body absorption of Ethylhexyl Salicylate was 0.022 $\mu g/1.4$ m^2 at 2 h, 0.5 $\mu g/1.4$ m^2 at 6 h, and 3.3 $\mu g/1.4$ m^2 at 12 h.

Methyl Salicylate

The skin penetration of Methyl Salicylate was evaluated using rat full-thickness skin (cleared of excess subcutaneous tissue) from male Wistar rats.[22] The skin was cut into 15 x 15 mm pieces and mounted in Franz-type glass diffusion cells (surface area = 1.3 cm^2). The receptor fluid consisted of degassed, 20% ethanol:80% distilled water. A formulation containing 20% Methyl Salicylate (1 g) was placed on the skin and receptor fluid was removed and replaced over a 28-h period. Approximately 25% of the Methyl Salicylate that was absorbed through the skin was hydrolyzed to salicylate. At 24 h, the total amount of salicylate that penetrated through the skin was within 20%.

In vitro skin penetration tests on Methyl Salicylate were performed using fresh dermatomed (0.3 to 0.4 mm thick) female breast skin and leg skin in Bronaugh flow-through polytetrafluoroethylene diffusion cells.[23] Each dose of the test substance was applied to a 0.38 cm^2 skin area in each cell. Skin samples were exposed to Methyl Salicylate for 30-min, and there was a 6.5-h reservoir collection period. The skin penetration of Methyl Salicylate was described as rapid. There was 32% absorption at the low dose (2 mM Methyl Salicylate), 17% absorption at the medium dose (20 mM Methyl Salicylate), and 11% absorption at the high dose (200 mM Methyl Salicylate). Regarding these results, the authors noted that the percent absorption from a high concentration of test chemical may be lower than that observed from a lower dose level, but may still give rise to higher calculated µg/cm^2/h amounts absorbed.

Percutaneous absorption of Methyl Salicylate was evaluated in the isolated perfused porcine skin flap (IPPSF).[24,25] A dose of 400 µg/cm^2 of radiolabeled [^{14}C]-Methyl Salicylate was applied non-occluded to a 7.5 cm^2 Stomadhesive® dosing template on the IPPSF. Skin flaps were allowed to equilibrate for 1 h prior to chemical application. A total of 16 flaps were dosed and terminated at 2, 4, or 8 h. Percutaneous absorption into IPPSF was 2.39% of the applied dose at 8 h. With the amount in skin and fat added, the penetration was 3.04% of the applied dose. The rate of absorption was also evaluated. Radiolabeled Methyl Salicylate showed a rapid absorptive flux profile that peaked at approximately 30 min at 0.016% dose/min.

The ester cleavage of Methyl Salicylate to Salicylic Acid in hairless mouse skin, in vitro, following topical application of 1% Methyl Salicylate in acetate buffer to the skin was evaluated.[26] Less than 5% of the applied dose was metabolized to Salicylic Acid.

Animal

Salicylates

In vivo percutaneous absorption data on rabbits, guinea pigs, rats, mice (including hairless mice), dogs, and monkeys are available.[1] These data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol > water); absorption varies as a function of pH; and absorption is greater through damaged skin when compared to normal skin. Approximately 10% of applied salicylates can remain in the skin.

Methyl Salicylate

Twenty-seven 10-week-old Yorkshire-Landrace cross barrow pigs were used in a skin absorption study.[27] A circular plastic cup with two holes pierced through it to accept an 18-gauge needle was positioned over a piece of gauze cloth that was cut to a diameter slightly smaller than the cup and that was placed over the skin. Four sites were challenged including ear, epigastrium, perineum, and inguinal crease with total area of exposure of 49.3, 132.4, 49.3 and 88.2 cm^2, respectively. Neat Methyl Salicylate was introduced into the cup through one of the holes at volumes of 848 µl for the ear, 2544 µl for the epigastrium, 848 µl for the perineum and 1696 µl for the inguinal crease. Arterial blood samples were taken every 10 min for the first 60 min and then every 15 min up to 360 min. The average dose absorbed through the skin at the ear region after 6 h was 11 µg/cm^2; at the perineum regions, the average dose absorbed was 8 µg/cm^2, and, through the epigastrium and inguinal crease regions, the average dose absorbed was 3 µg/cm^2. The initial flux (permeation rate) of Salicylic Acid through the skin after application of neat Methyl Salicylate was 0.063 µg/cm^2/ min at the ear region, 0.025 µg/cm^2/ min at the epigastrium region, 0.044µg/cm^2/ min at the perineum region and 0.012 µg/ cm^2/ min at the inguinal crease region.

Human

Ethylhexyl Salicylate

The skin penetration of two Ethylhexyl Salicylate sunscreen formulations was evaluated in a study involving 6 subjects.[20] Penetration was determined by tape-stripping. Each sunscreen formulation was applied to 2 x 2 cm areas on the

volar side of the forearm. At 30 minutes post-application, the remaining product formulation was removed from the skin using cotton swabs and the skin was tape-stripped 16 times. The mean value for penetration of Ethylhexyl Salicylate in oil-in-water emulsion gel (n = 6) into the stratum corneum was 28.4 ± 6.6 µg/cm^2, and 25.6% of the applied dose penetrated into the stratum corneum. The mean value for Ethylhexyl Salicylate in petrolatum jelly (n = 6) was 10.1 ± 3.5 µg/cm^2, and 11% of the applied dose penetrated into the stratum corneum. The authors noted that the concentration of Ethylhexyl Salicylate in the upper part of the stratum corneum was significantly higher (p value not stated) after application of the emulsion gel formulation than after application of the petrolatum jelly formulation. In the deeper parts of the stratum corneum, the concentration of Ethylhexyl Salicylate delivered form the emulsion gel formulation was significantly lower (p value not stated), but still greater than that achieved with the petrolatum jelly formulation.

The systemic absorption of a sunscreen lotion, with the following composition, after dermal application was evaluated using 9 healthy volunteers: Ethylhexyl Salicylate (5% w/v), oxybenzone (6% w/v), octocrylene (7% w/v), and octyl methoxycinnamate (7.5% w/v).[28] All of these chemicals were identified as sun screening agents. The subjects were instructed to apply the product to the entire surface of their forearms generously in accordance with their normal sun protection behavior. In practice, "13.0 (1.0) g" of sunscreen product was applied to a surface area of "1051 (60.8) cm^2". The application density of the product was 12.4 mg/cm^2. The formulation remained unoccluded for 12 h prior to removal with soap and water. Urine samples were collected before product application and at 48 h post-application. Over the period of application, only 1 to 2% of the sunscreen in the applied product was absorbed. Data comparing the absorption of each ingredient were not provided.

Hexyl Salicylate

A mathematical method was used to estimate total body absorption of some salicylate esters including Hexyl Salicylate. Rate constants were calculated from the relevant physicochemical properties.[21] The applied dose of active ingredient used in the simulation was 40 µg/cm^2 based on the FDA recommendation (200 mg of product per 100 cm^2 of skin) and a value of 2%. The release rate from the formulation was fixed at 1 µm/cm^2/h. The simulations were conducted on a 12-h time scale. The estimated total body absorption of Hexyl Salicylate per µg over 1.4 m^2 was 0.18 at 2 h, 4.1 at 6 h and 27 at 12 h.

Methyl Salicylate

The systemic exposure to Methyl Salicylate following the application of a number of adhesive patches (each containing 74.88 mg Methyl Salicylate) to the skin of 8 human subjects was evaluated.[29] The patches remained in place for 8 h. Blood samples were obtained for up to 12 h after placement of the patches. Exposure was quantified by determining the plasma concentration time profiles of the substance as a function of exposure to 2, 4, or 8 patches (or to very high doses). Data were presented as a plot of the average plasma concentration-time data as a function of dose. For the 2-patch application, the average maximum plasma concentration (C_{max}) value for Methyl Salicylate was 8.6 ± 3.8 ng/mL (range: 4.0-12.7 ng/mL). For the 4-patch application, the average C_{max} for Methyl Salicylate was 16.8 ± 6.8 ng/mL (range: 8.9-25.7 ng/mL). For the 8-patch application, the average C_{max} was 29.5 ± 10.5 ng/mL (range: 15.8-45.9 ng/mL). The authors noted that although it was not possible to determine the absolute dermal bioavailability of Methyl Salicylate, there appeared to be relatively low systemic exposure, even when an unrealistically large number of patches were applied for an unusually long time.

Salicylates

Data describing the penetration of salicylates through human skin are available.[1] These data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol > water); absorption varies as a function of pH; and absorption is greater through damaged skin when compared to normal skin. Approximately 10% of applied salicylates can remain in the skin.

Penetration Enhancement

Salicylic Acid

Salicylic Acid is reported to enhance percutaneous penetration of vitamin A, ammoniated mercury, and triamcinolone acetonide, but not methyl nicotinate, (which itself rapidly penetrates the skin), hydrocortisone, diflucortolone-21-valerate, or cyclosporine.[1]

Absorption, Distribution, Metabolism, and Excretion

Animal

Dermal

Methyl Salicylate

The in vivo absorption of a formulation containing 20% Methyl Salicylate was studied using groups of 3 male Wistar rats.[22] The formulation (1 g) was applied to a 9.6 cm^2 area of abdominal skin, and a blood sample was removed from the tail vein at 0.5, 1, 2, 4, and 6 h thereafter. After 6 h, the animals were killed, the formulation was removed from the skin, and tissue samples (skin, subcutaneous tissue, superficial muscle, deep muscle, and fat) were excised. The levels of unhydrolyzed Methyl Salicylate in tissues below the treated site were low, i.e., only 2 to 3 µg/ml throughout the study period. The highest concentrations were observed in the dermal and subcutaneous sites in the first hour of application. At 0.5 to 1 h after application of the formulation, there was a significant increase in the concentration of total salicylate in contralateral dermal tissue, corresponding to 4 to 5 times above the circulating systemic plasma levels. At 2 h, the dermal levels were below the observed plasma salicylate concentration. The presence of unhydrolyzed Methyl Salicylate was only observed at the 0.5 h time point. The fraction of Methyl Salicylate observed in the tissues as a proportion of total salicylate varied from 0 to 0.26. The results of this study indicate that tissue and plasma concentrations of salicylate after the application of Methyl Salicylate increased rapidly within the first hour of application.

Oral

Salicylates

Extensive data from oral delivery studies in animals are available.[1] Metabolism by hepatic microsomal enzyme systems conjugates salicylates to glycine, forms glucuronides, or oxidizes them to hydroxybenzoic acids.

Human

Oral

Methyl Salicylate

Reportedly, after oral ingestion, Methyl Salicylate is readily metabolized to Salicylic Acid.[18] No further details were provided.

Four (1 male/3 female) adult human volunteers participated in a study that was conducted as an open label, 4-way crossover design with randomized treatment order.[30] The subjects ingested 6.7 and 20 g of a Methyl Salicylate-containing cream (commercial 15% cream containing 900 or 2700 mg salicylate). Plasma was collected at 0, 20, 40, 60, 120, 240, 480, 720, and 1440 min for the determination of salicylate concentrations by TDx immunoassay. The time to reach maximum salicylate concentration (T_{max}) and the peak plasma salicylate concentration (Cp_{max}) were determined. The T_{max} for the low-dose cream (900 mg salicylate) was 2.4 h (1.5 - 4 h), and the Cp_{max} was 42 mg/l (36–51 mg/l). The T_{max} for the high-dose cream was 7 h (4 - 12 h), and the Cp_{max} was 145 mg/l (120 - 201 mg/l). As a part of the same experiment, four fasting adults ingested 1 ml of wintergreen oil (which is primarily Methyl Salicylate; 14.2 mg/kg mean). Plasma was collected for salicylate determination at 0, 20, 40, 60, 120, 240, 480, 720 and 1440 min. Time to reach maximum concentration was 2.4 h with the maximum concentration of 70 mg/l. The 4 subjects were also instructed to hold 5 g of the cream in the buccal cavity for 1 minute and then expectorate. No plasma salicylate was detected after the buccal treatment phase.

Salicylates

Extensive data from oral delivery human studies are available.[1] Metabolism by hepatic microsomal enzyme systems conjugates salicylates to glycine, forms glucuronides, or oxidizes them to hydroxybenzoic acids.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Ethylhexyl Salicylate

Undiluted Ethylhexyl Salicylate was applied (under occlusion) to intact or abraded skin of 4 rabbits for 24 h.[3] The animals were observed for mortality and/or clinical signs for a 14-day period. No clinical signs were observed. The dermal LD_{50} in rabbits exceeded 5.0 g/kg.

Hexyl Salicylate

Ten rabbits received a single dermal application of neat Hexyl Salicylate at 5.0 g/kg.[4] The rabbits were observed for mortality and clinical symptoms. No clinical signs were observed. The acute dermal LD_{50} in rabbits exceeded 5.0 g/kg based on 0/10 deaths at that dose. In another study involving rabbits (number and strain not stated), the acute dermal LD_{50} for Hexyl Salicylate (concentration not stated) was > 5 g/kg.[31]

Methyl Salicylate

A single dermal application of neat Methyl Salicylate at 5 g/kg was applied to 4 rabbits (strain not stated) for 24 h under occlusion.[3] Animals were observed for a 14-day period. None of the animals died, and no clinical signs were observed. The dermal LD_{50} in rabbits exceeded 5 g/kg.

**Butyloctyl Salicylate, Methyl Salicylate,
Salicylic Acid, and Tridecyl Salicylate**

Little acute toxicity (LD_{50} in rats; > 2 g/kg) via a dermal exposure route is seen for Butyloctyl Salicylate, Methyl Salicylate, Salicylic Acid, and Tridecyl Salicylate.[1]

Oral

**Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate,
Methyl Salicylate, Salicylic Acid, Sodium Salicylate, and Tridecyl Salicylate**

The following acute oral toxicity data for Salicylic Acid and salicylates have been reported in studies involving rats: Butyloctyl Salicylate (LD_{50} > 5 g/kg), Ethylhexyl Salicylate (LD_{50} > 2 g/kg), Isodecyl Salicylate (no toxicity at levels as high as 4.83 g/kg), Methyl Salicylate (LD_{50} between 0.887 g/kg and 1.25 g/kg), Salicylic Acid (LD_{50} ranging from 0.891 g/kg to 1.58 g/kg), Sodium Salicylate (LD_{50} between 0.9 g/kg and 1.7 g/kg); and Tridecyl Salicylate (LD_{50} > 1.98 g/kg).[1] *Values for acute oral toxicity in other species are consistent with these values*.

Ethylhexyl Salicylate

In an acute oral toxicity study involving 10 rats (strain not stated) dosed with Ethylhexyl Salicylate, the animals were observed for mortalities and/or clinical signs for 14 days post-dosing.[3] It was concluded that the acute oral LD_{50} exceeded 5.0 g/kg, based on one animal death at that dose on day 6 of the study. No clinical reactions were observed.

Hexyl Salicylate

The acute oral toxicity of Hexyl Salicylate was evaluated in a study involving 10 rats.[4] The rats were observed for mortalities and/or systemic effects for 14 day after dosing. Urinary incontinence was observed at 24 h. It was concluded that the LD_{50} exceeded 5.0 g/kg, based on one animal death at that dose on day 4 of the study.

Methyl Salicylate

The acute oral toxicity of Methyl Salicylate was determined in ddY male mice (10/dose).[32,5] Methyl Salicylate was administered at dose levels of 1.0, 1.2, 1.3, 1.5, or 1.7 g/kg. Mice were observed for a 7-day period. One animal died at 1.0 g/kg; 2/10 died at 1.2 g/kg; 4/10 died at 1.3 and 1.5 g/kg; and 9/10 died at 1.7 g/kg. Most animal deaths occurred on day 1. The LD_{50} was calculated to be 1.39 g/kg (95% CI 1.25 - 1.54 g/kg).

Methyl Salicylate was evaluated as a part of a study investigating the development of acute myocardopathy in dogs.[33] Healthy mongrel dogs were lightly anesthetized with pentobarbital sodium. Methyl Salicylate was intragastrically administered at a dose of 0.7 g/kg. After 4 - 5 h, animals either died or were sacrificed. Increases in arterial concentrations of plasma salicylate, potassium and lactate were seen and a period of respiratory alkalosis was initially observed followed by metabolic acidosis after three hours. Microscopy studies revealed abnormalities in the mitochondria, swelling of cardiac muscles with separation of myofibrils and bulging of sarcolemma.

Inhalation

Methyl Salicylate

Methyl Salicylate administered by inhalation exposure is not lethal in rats and mice.[1]

Short-Term Toxicity Studies

Oral

Methyl Salicylate

Groups of 2 dogs (breed not stated) were dosed orally with Methyl Salicylate (in capsule form) at doses up to 1200 mg/kg daily (6 days per week) for up to 59 days.[1] *Marked fatty changes in the liver were observed in both animals at the highest dose. No adverse effects were observed at doses of 50 to 250 mg/kg. Groups of 12 male and female rats (strain not stated) were fed diets containing methyl Salicylate at concentrations up to 12,000 ppm (i.e., 12,000 mg/kg) for 7 weeks. Bone lesions were observed at the highest dietary concentration only. In a shorter-duration study, that involved the feeding of 10 male rats with 12,000 ppm Methyl Salicylate in the diet for up to 5 days, bone lesions were not observed. However, when groups of 10 male and 10 female rats (strain not stated) were fed 12,000 ppm or 20,000 ppm Methyl Salicylate for 8 weeks, bone lesions were observed in all animals of both groups. Also, when groups of 5 male rats were fed 20,000 ppm Methyl Salicylate and a protein diet (75% basic feed and 25% casein) with water for 7 weeks, an increase in cancellous bone was reported. This finding was not reported in the group that was fed the same concentration of Methyl Salicylate plus the protein diet and 40% dextrose (dextrose, but no water). In a study that was longer in duration than the preceding 4 studies, groups of 10 male and 10 female Sprague-Dawley rats were fed a fat-enriched diet containing up to 2% Methyl Salicylate for 11 weeks. At the highest dietary concentration and the 1.2% concentration, but not at lower concentrations, positive bone lesions were observed at week 2; microscopic changes were observed at weeks 2 and 8 in these 2 groups, respectively. In another 11-week study, 5 male and 5 female rats were fed 12,000 ppm Methyl Salicylate and bone lesions were observed at 4 weeks (earliest time at which x-rays were taken). Decreased body weight was also observed in these studies.*

The oral toxicity of Methyl Salicylate was determined in male and female CD-1 mice (8/sex/dose).[34] Methyl Salicylate was administered in corn oil by gavage once daily for 14 days at dose levels of 0.05, 0.1, 0.25, 0.50, and 1.00 g/kg. Two females died at 0.05 g/kg; 2 females and 3 males died at 0.10 g/kg; and 1 female and 1 male died at 1.00. Clinical signs observed prior to death were piloerection and dehydration. According to the authors, the LD_{50} was calculated to be 1.44 g/kg/day.

As a part of an associated reproductive toxicity study, a 2-week acute study was conducted using CD-1 mice (8/sex/dose).[35] Methyl Salicylate was administered by gavage at 0.05, 0.1, 0.25, 0.5, and 1 g/kg once a day for 14 days. The animals were observed for survival, body weights, and clinical signs. The maximum tolerated dose (MTD) was determined for the associated study. No effects were observed at 0.05, 0.1, 0.25, and 0.5 g/kg. Two (2/8) animals died at 0.05 g/kg but the deaths were diagnosed as possible gavage trauma. Three (3/8) animals died at 1 g/kg; one death was diagnosed as possible gavage trauma and the cause of death for the 2 remaining animals was diagnosed as pulmonary congestion or cardiac myodegeneration and tubular nephrosis. The dose of 0.5 g/kg was selected as the MTD.

Salicylic Acid

Salicylic Acid short-term oral delivery produces liver and plasma enzyme changes.[1]

Sodium Salicylate

Sodium Salicylate short-term oral exposures are linked with reduced growth and feed consumption, clear kidney damage, and some liver damage.[1] *In these studies, rats received up to 21,020 ppm (i.e., 21,020 mg/kg) Sodium Salicylate in the diet for 11 weeks or up to 600 mg/kg of 10% aqueous Sodium Salicylate for 4 to 21 days. In the 21,020 ppm study, a positive increase in cancellous bone was observed. In one of the studies, in which groups of Fischer 344 rats were dosed*

orally with aqueous Sodium Salicylate for 4 weeks, the 28-day LD_{50} was 646.5 mg/kg. Dogs received 300 mg/kg of 10% aqueous Sodium Salicylate for 2 weeks. A group of 6 male and 6 female Sprague-Dawley rats was fed a 5% hydrogenated fat-enriched diet containing 2.1% Sodium Salicylate for 12 weeks. Mortality was 100% at week 11, and bone lesions were observed. Groups of 5 male Sprague-Dawley rats were fed a 5% fat enriched diet containing 0.7% or 2.1% Sodium Salicylate for 12 weeks. Mortality was 100% in the low-dose group at week 7 and in the high-dose group at week 2. Bone lesions were observed with 2.1% Sodium Salicylate.

Inhalation

Amyl Salicylate

The short-term inhalation toxicity of a fragrance mixture containing 5.8% Amyl Salicylate was evaluated using groups of female CD rats or female Syrian hamsters.[36] The animals were exposed (whole body inhalation, in chamber) to the mixtures at 5 mg/m^3 (20 rats) or 9 mg/m^3 (12 rats and 12 hamsters), five days per week (4 h per day) for 6 weeks (26 exposures total). The doses used generally represented a 10- to 100-fold exaggeration of levels expected to be achieved during typical use by consumers. Particle sizes ranged from 0.5 to 7.5 µm. There were no exposure-related, toxicologically significant effects on the following: animal survival, behavior, body weights or weight gains, organ weights, or in hematology, clinical chemistry, or urinalysis parameters. Additionally, no test substance-related gross pathological or histopathological findings were observed.

Methyl Salicylate

In a study involving 4 female Alderley Park rats, no toxicity was observed after inhalation of Methyl Salicylate in a series of 20 exposures of 7 h each at 0.7 g/m^3.[1] The organs appeared normal at necropsy.

Subchronic Toxicity Studies

Dermal

Methyl Salicylate

Subchronic dermal exposures to Methyl Salicylate were associated with kidney damage.[1] *Groups of 3 rabbits were dosed dermally with synthetic Methyl Salicylate (doses up to 4 ml/kg) five days per week for up to 96 days*.

Oral

Isodecyl Salicylate

No toxicity is seen with subchronic oral exposure to Isodecyl Salicylate.[1] *Ten male and 10 female Wistar albino rats were fed 0.5% (~ 500 mg/kg/day) Isodecyl Salicylate in a basal diet for 15 weeks*.

Methyl Salicylate

Subchronic oral exposure to Methyl Salicylate results in reduced weight gain and bone lesions, which disappear when Methyl Salicylate is co-administered with calcium carbonate.[1] *All of the feeding studies involved rats, and the longest duration study involved groups of 20 Osborne-Mendel rats fed up to 1% synthetic Methyl Salicylate in the diet for 17 weeks.*

Sodium Salicylate

The neurotoxic potential of 138 to 550 mg/kg Sodium Salicylate was determined using groups of 9 to 10 Fischer 344 rats dosed 5 days per week for 15 weeks.[1] *The LD_{50} during 15 weeks of dosing was estimated to be 366.5 mg/kg; a dose-related decrease in hindlimb grip strength was noted.*

Tridecyl Salicylate

Ten male and 10 female Wistar rats were fed ~500 mg/kg/day Tridecyl Salicylate in a basal diet for 15 weeks.[1] *A control group of 10 males and 10 females was given untreated feed. No treatment-related observations were observed. Oral administration of ~ 500 mg/kg/day Tridecyl Salicylate did not produce a significant toxic effect.*

Inhalation

Amyl Salicylate

The subchronic inhalation toxicity of a fragrance mixture containing 4% Amyl Salicylate was evaluated using groups of female CD rats or female Syrian hamsters.[36] The animals were exposed (whole body inhalation, in chamber) to the mixtures at 5 mg/m^3 (20 rats) or 9 mg/m^3 (12 rats and 12 hamsters), five days per week (4 h per day) for 13 weeks (62 to 67 exposures total). The doses used generally represented a 10- to 100-fold exaggeration of levels expected to be achieved during typical use by consumers. Particle sizes ranged from 0.5 to 7.5 µm. There were no exposure-related, toxicologically significant effects on the following: animal survival, behavior, body weights or weight gains, organ weights, or in hematology, clinical chemistry, or urinalysis parameters. Additionally, no test substance-related gross pathological or histopathological findings were observed.

Methyl Salicylate

Male white rats (number per group not specified) were exposed to 1.2, 8, or 40 mg/m^3 Methyl Salicylate for 4 months (4 h/day).[1] The highest dose caused changes in nervous system function. Also, pulmonary focal hemorrhages and hyperplasia were observed in the peribronchial lymphoid tissue. Focal hemorrhages in the kidneys were observed.

Chronic Toxicity Studies

Oral

Methyl Salicylate

In the study with the highest administered dose, groups of 5 male and 5 female rats were fed a diet containing 2000, 3550, 6300, 11,250, or 20,000 ppm Methyl Salicylate for 30 weeks.[1] During weeks 1 and 2, Methyl Salicylate was given at 50%, and, during weeks 3 and 4, it was given at 75% of the final dose. At week 10, animals of the 11,250 ppm and 20,000 ppm groups had positive increased bone density in the femur and tibia. The largest 2-year feeding studies, involved groups of 50 rats fed up to 2% Methyl Salicylate in the diet. One of the 2 studies had no gross or microscopic findings. In the other study, statistically significant growth inhibition was observed in animals of the 1% and 2% dietary groups. Also, in the 1% dietary group, relative organ-to-body weight ratios for the testes (males) and for the heart and kidneys (females) were significantly increased. Gross lesions of the pituitary gland were observed in 10 animals of the 0.5% dietary group, compared to 4 animals in the control group. In the 2% dietary group, pneumonia was observed in 29 of the 50 animals. When groups of Beagle dogs received oral doses of Methyl Salicylate up to 350 mg/kg for 2 years (6 days per week), animals of the 150 and 350 mg/kg groups had retarded growth and enlarged livers. When Beagle dogs received oral doses of Methyl Salicylate up to 800 mg/kg/day for 6.6 to 7.5 months. An increase in liver and kidney weight was observed in treated animals, but the 150 and 300 mg/kg doses did not induce lesions or other deleterious alterations.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In Vitro

Salicylic Acid

The effect of Salicylic Acid on human spermatozoa was determined after incubation with 50, 100, or 200 mg/L salicylate.[1] A dose response effect was observed, with significant inhibition of motility at all time points.

Post-implantation day 11 rat embryos were cultured for 24 h with 10, 100, or 1000 µg/ml Salicylic Acid.[37] The growth and development of each embryo was evaluated and compared with control embryos for the presence of any malformations. Salicylic Acid decreased all growth and developmental parameters in a concentration-dependent manner, when compared with controls. However, exposure to Salicylic Acid at 10 µg/ml culture did not show any significant effect on embryonic growth and development. Parallel to this, flow cytometric analysis (cell cycle and annexin V binding) and DNA fragmentation assay were carried out followed via quantitation by 3′-OH labeling of cultured rat embryos to evaluate the role of apoptosis in bringing about Salicylic Acid-induced teratogenesis. All results were found to be dose-dependent and an increase in apoptosis in embryonic tissues may be related to the increased risk of congenital malformations. The data suggested that apoptosis might be involved in mediating teratogenesis of Salicylic Acid in vitro.

Salicylic Acid and Sodium Salicylate

The effects of Salicylic Acid and Sodium Salicylate on early organogenesis and the interaction of these chemicals with free radicals was investigated.[38] Post-implantation Wistar rat embryos were cultured in vitro from day 9.5 of gestation

for 48 h; each test substance was added to whole rat serum at concentrations between 0.1 and 0.6 mg/ml. Also, each test substance (0.3 mg/ml) was added to the culture media in the presence of superoxide dismutase (30 U/ml) or glutathione (0.5 µmol/ml). The growth and development of embryos was compared, and each embryo was evaluated for the presence of malformations. When compared to the growth of control embryos, both chemicals decreased all growth and developmental parameters in a concentration-responsive manner. There was also a concentration-related increase in overall dysmorphology, including the following: hematoma in the yolk sac and neural system, open neural tube, abnormal tail torsion, and the absence of forelimb bud. When superoxide dismutase was added in the presence of Salicylic Acid, the incidence of malformations was decreased. However, the addition of superoxide dismutase did not affect the growth and developmental parameters of Salicylic Acid and Sodium Salicylate. The addition of glutathione significantly decreased the incidence of the malformations that were observed in the presence of Salicylic Acid. The authors noted that the effects of salicylates might involve free oxygen radicals by the non-enzymatic production of the highly teratogenic metabolites 2,3-dihydroxybenzoic acid and 2,5-dihydroxybenzoic acid. Furthermore, they noted that an enhanced production of these metabolites in embryonic tissues may be directly related to the increased risk of congenital malformations.

Animal

Dermal

Methyl Salicylate

Methyl Salicylate was applied (at 7 days 9 h of gestation) to dorsal skin of timed-pregnant LVG hamsters (number not stated), at doses of 350 and 525 mg/100 g.[1] *Few embryos from the high-dose group survived beyond 12 days of gestation, but, of the 19 litters produced in this group, there were 53% neural tube defects. Of the 6 litters produced in the lower dose group, 6% of the fetuses had neural tube defects. A peak salicylate level of 50 mg/100 ml was obtained 5 to 6 h after topical application of 350 mg/100 g and a peak of 120 mg/100 g with the 525 mg/100g topical treatment level. Thus dermal exposure to Methyl Salicylate is associated with reproductive and developmental toxicity as a function of blood levels reached as a result of exposure.*

Oral

Methyl Salicylate

Methyl Salicylate was delivered by oral intubation (1.75 g/kg) to timed-pregnant LVG hamsters at 7 days 9 h of gestation.[1] *Blood levels reached a peak at of 125 mg/100 ml at approximately 2 h after oral dosing. Of 35 litters (fetuses per litter not given) in the treatment group, 72% of the fetuses had neural tube defects. Groups of 24 to 27 rats were fed 4000 ppm or 6000 ppm Methyl Salicylate in a test diet containing calcium carbonate for 60 days prior to mating and through weaning at day 20 or 21. This procedure was repeated. Abnormalities were not observed in offspring. Neonate survival at weaning was greater in the test group than in the control group. Groups of F_0 generation mice (25/sex/group) and F_{1b} generation mice (30 males and 30 females/group) received 0.25% or 0.5% Methyl Salicylate in feed for 30 days prior to mating. The results are only from females in each generation that mated twice. There was no evidence of gross abnormalities in in any litter. All surviving neonates appeared normal, and no reproductive abnormalities were observed. Another experiment in the same study involved the same numbers of F_0 and F_{1b} animals (in this experiment, Wistar rats used) and the same concentrations of Methyl Salicylate administered in feed. The protocol was the same, except for the 60-day feeding period prior to mating. Gross abnormalities were not observed in any litter and all surviving neonates appeared normal. Mating performance and reproduction and viability indices were decreased, and the number of deaths between birth and day 5 were increased in the 0.5% group. Litter size was decreased in both test groups. Groups of F_0 generation Osborne-Mendel rats (10/sex/group) received 500, 1500, 3000, or 5000 ppm Methyl Salicylate in feed for 100 day, after which the animals were mated. There was no evidence of gross abnormalities. Various reproductive effects were observed, especially in the 2nd generation. In a continuous breeding reproductive toxicity study, male and female CD-1 mice (number not stated) were dosed orally with 25, 50, or 100 mg/kg Methyl Salicylate. Reproductive and fertility parameters were generally not affected. There also was no significant effect on mating behavior, fertility rate, or reproductive performance. Groups of CD-1 mice (20/sex/group) were dosed orally with 100, 250, or 500 mg/kg Methyl Salicylate in another continuous breeding reproductive toxicity study. A significant decrease in the mean number of litters, average number of pups/litter, proportion of live pups, and mean live pup weights was observed in the high dose group. CD rats (number not stated) received an oral dose of Methyl Salicylate (0.05 ml or 0.1 ml) on gestation day 10. The 0.1 ml dose group had decreased body weight gain, fewer and smaller neonates, and more resorptions and malformed neonates. Fetal kidney weight was decreased on gestation day 21, but was not different from the control on postnatal day 6.*

Salicylic Acid

Groups of 20 gravid Wistar rats were fed a diet containing 0.06%, 0.1%, 0.2%, or 0.4% Salicylic Acid on gestation days 8 to 14.[1] *Significant reproductive effects were observed in the 0.4% dietary group, and skeletal anomalies were*

observed in the 0.2% group. Only one dam gave birth to live neonates in the 0.4% dietary group, and skeletal anomalies were observed in 0.2% neonates. Groups of Wistar rats were dosed orally with Salicylic Acid at a dose of 75, 150, or 300 mg/kg on gestation days 8-14. Fetal mortality was 26% and 100% in the 150- and 300-mg/kg groups. Significant reproductive effects were observed in fetuses and neonates of the the 150 mg/kg group. Groups of 10 Sprague-Dawley rats were dosed twice daily with 10 mg/kg Salicylic Acid on gestation days 20 and 21, and the mean gestation period was increased.

Sodium Salicylate

New Zealand White rabbits (number not stated) were dosed orally with 100 mg/kg Sodium Salicylate on gestation days 4 to 7.[1] *The preimplantation ratio and average litter size were not affected, and teratogenic effects were not induced. Two groups of 21 albino rats each received 200 mg/kg Sodium Salicylate orally on gestation days 6 to 15. A significant increase in resorptions and decrease in viable fetuses was observed in one group. A significant increase in external and internal abnormalities was observed in the second group, and skeletal anomalies were observed in both groups. Groups of 17 to 19 Sprague-Dawley rats received an oral dose of 30, 90, or 180 mg/kg Sodium Salicylate on gestation days 6 to 15. The incidence of teratogenicity was 30% in the 180 mg/kg group; marked embryotoxicity was observed and maternal toxicity was low. Regarding the 90- and 180-mg/kg groups, a dose-dependent decrease in growth was reported. CD-1 mice and Sprague-Dawley rats (number not stated) received oral doses of 1500 mg/kg and 300 mg/kg Sodium Salicylate, respectively, on gestation days 7, 8, 9, 10, or 11. For mice, fetal mortality increased with dosing on day 10. Skeletal anomalies increased with dosing on days 8 and 9. For rats, skeletal anomalies increased with dosing on days 8 and 10. Groups of 19 or 37 CD-1 mice received doses of 2000 and 2600 mg/kg Sodium Salicylate on gestation day 8. Results for the 2000 mg/kg group were: 11% maternal mortality, 71% viable litters, 14% fetal mortality, and 7% of fetuses with malformations. Results for the 2600 mg/kg group were: 24% maternal mortality, 79% viable litters, 7% fetal mortality, and 3% of fetuses with malformations. Two groups of 2 CFE rats were dosed orally with 500 mg/kg Sodium Salicylate (on gestation day 8) or 100 mg/kg Sodium Salicylate (on gestation days 7 to 11). Results for the higher dose group included 50% maternal toxicity, 53% resorptions and dead fetuses, and 13% malformations. In the 100 mg/kg group, there was a 15% incidence of resorptions and dead fetuses. Twenty-two CD-1 mice received an oral dose of 800 mg/kg Sodium Salicylate on gestation days 8 to12. The average neonatal weight was decreased on postnatal days 1 and 3. Thirty ICR/SIM mice received an oral dose of 1600 mg/kg on gestation days 8 to 12, and 7 dams died. Neonate survival and the average number of viable neonates per litter on days 1 and 3* ~~*was*~~ [were] *significantly decreased and the number of dead neonates per litter on day 1 was significantly increased. Twenty-five A/Jax mice received an oral dose of 66.6 mg/ml Sodium Salicylate on gestation day 17. One dam delivered between 5-24 h. Fetal mortality was 47%, and the incidence of superficial, hepatic, and gastric hemorrhage was 6%, 1%, and 2% in animals killed at 24 h. Groups of 12 to 15 albino rats received an oral dose of 25, 75, or 150 mg/kg Sodium Salicylate on gestation days15 to 20. Parturition was delayed in one and two dams of the 25 and 150 mg/kg groups. In the 150 mg/kg group, neonatal mortality increased in a dose-dependent manner. In another experiment, in the same study, groups of 12 to 15 albino rats received an oral dose of 4.2, 12.5, or 25 mg/kg Sodium Salicylate on gestation days 20 to 21. In the 12.5 and 25 mg/kg groups, neonatal mortality increased in a dose-dependent manner. Groups of 10 Sprague-Dawley rats received an oral dose of 10 mg/kg Sodium Salicylate twice daily on gestation days 20 and 21. The duration of bleeding at parturition was increased. Thirteen of 121 neonates were born dead. Sprague-Dawley and Long-Evans rats (number not stated) received an oral dose of 125 or 175 mg/kg Sodium Salicylate on gestation days 8 to 10. No malformations were observed.*

Groups of 15 mated Crl:CD (SD)BR rats were given a single dose of 0 or 300 mg/kg (dose volume = 10 ml/kg) Sodium Salicylate (99.5% pure, in distilled water) on gestation day (GD) 9.[39] All fetal data, including all supernumerary ribs data, are presented as the percentage mean per litter. No statistical analysis was carried out on mean incidences of supernumerary ribs and the number of presacral vertebrae. In the treated group, adverse effects were noted on body weight changes and food consumption during the 2 days following dosing. At birth, a high majority of pups had extra ribs at the 300 mg/kg dose. Specifically, on postnatal day 1, 89% of pups from dams exposed to 300 mg/kg Sodium Salicylate had supernumerary ribs. For these pups, evidence of postnatal reversibility was observed in 10 out of 14 pups with rudimentary ribs and 26 presacral vertebrae. Radiographs done on postnatal days 1, 6, 14, 28 and 54 showed a reduction in the incidence of rudimentary ribs only, whereas extra ribs, often associated with 27 presacral vertebrae, had the same incidence from birth to adult stage. Furthermore, extra ribs seemed to exhibit similar growth evolution to the other thoracic ribs. The authors noted that dosing with Sodium Salicylate resulted in a significant increase in the incidence of supernumerary ribs. The length of gestation was not affected by treatment. At birth, the number of dead pups was slightly higher in the treated group (7 dead pups out of 15 litters) in comparison with the control group (3 out of 14 litters) but no external malformations were significantly increased in the treated group.

In a study involving mated female Sprague-Dawley rats, Sodium Salicylate was administered by gavage on GD 9 at a dose of 300 mg/kg (in distilled water).[40] Control animals received distilled water only. The females were killed on GD 13. The mean number of live embryos was slightly lower than the control group value (11.9 as compared to 14.7), mainly due to

a slight, but non-significant, increased number of early resorptions in the treated group. Because Sodium Salicylate is known to cause an increased incidence of supernumerary ribs (see preceding study), the molecular basis of this defect was evaluated in this study by analyzing the possible involvement of *Hox* genes, known to specify vertebrae identity. On GD 13, the expression of several *Hox* genes, selected according to the position of their anterior limit of expression, namely upstream (*Hoxa9*), at the level (*Hoxa10*) and downstream (*Hoxd9*) to the morphological alteration, were analyzed. Posterior shifts in the anterior limit of expression of *Hoxa10* and *Hoxd9* were observed following exposure to Sodium Salicylate, which could explain an effect at the level of the axial skeleton. This finding suggests that the appearance of ectopic ribs can be attributed to an anterior transformation of lumbar vertebrae identity into thoracic vertebrae identity. The authors noted that whether this transformation occurs with all compounds inducing supernumerary ribs in rats remains to be determined.

Sodium Salicylate served as the positive control in an embryo-fetal developmental toxicity study.[41] The positive control (in distilled water) was administered intragastrically (dose = 250 mg/kg/day; once daily) to a group of 22 to 24 gravid female Sprague-Dawley rats on GDs 8 to 10. Sodium Salicylate was administered at a dose volume of 10 ml/kg/day. There were 4.8% malformations in fetuses from the positive control group, including exencephaly, cranial meningocele, spina bifida, gastroschisis, and subcutaneous ecchymosis. The rate of abnormality was significantly higher than that of the vehicle control group ($p < 0.01$). Additionally, there were significant difference in the body and tail length, and mean body weight of fetuses in positive control group compared with the vehicle control group ($p < 0.01$).

Human

Dermal

Salicylic Acid

In the third trimester, the use of Salicylic Acid can potentially cause early closure of ductus arteriosus and oligohydramnios. Therefore, it should not be applied over large surface areas for prolonged time periods, or under occlusive dressings that may enhance systemic absorption.[42,43] Study details relating to dermal Salicylic Acid application and closure of the ductus arteriosus and oligohydramnios were not included.

Risk Assessment

In a risk assessment from the Scientific Committee on Consumer Safety (SCCS), a NOAEL of 75 mg/kg/day, derived from rat oral teratogenicity studies, was used in the margin of safety (MOS) calculation. According to the test procedures, acetylsalicylic acid or Salicylic Acid was administered by oral at various times during pregnancy (e.g., days 8 to 14 of gestation, days 9 and 11 of gestation, or days 7 to 17 of gestation) at daily doses of 75 to 500 mg/kg in rats. [44] The results indicated that Salicylic Acid was neither teratogenic nor embryotoxic up to 75 mg/kg/day in rodents. Above these dose levels, fetal malformations (skeletal malformations, cleft lip), resorptions and perinatal death were observed.

The human percutaneous absorption from topically applied 2 % Salicylic Acid containing products is in the range of 20%.[44] However, Salicylic Acid, as a medical peeling agent in rinse-off products, is currently used at concentrations up to 30%. [10] During a typical treatment procedure, a peel is left on for 3 - 5 mins.[45] For the purpose of this risk assessment, it is assumed that an adult is exposed to 0.19 g/day rinse-off peel products, in a manner similar to shower gel (applied on the whole body).[46] Utilization of these parameters for a medical application of Salicylic Acid as a peeling agent likely result in a very conservative MOS for cosmetic uses.

For rinse-off peel product, the relevant calculations are:

Systemic exposure dose (SED) = 0.19 g/day of product × 30 % maximum use concentration ÷ 60 kg person × 20 % skin absorption × 1000 mg/g conversion factor = 0.19 mg/kg day^{-1}

MOS (rinse-off peel product) = NOAEL (rat oral teratogenicity study) / SED (peel product) = 75 mg/kg/day / 0.19 mg/kg/day = 395

In order to determine the systemic burden after topical use of a skin care leave-on formulation (face and general creams) containing Salicylic Acid, another risk assessment was performed, taking into consideration the accumulative dose exposure to three leave-on skin care product types: body lotion, face cream, and hand cream. According to the Council's survey, Salicylic Acid is currently used in face and neck leave-on products at concentrations up to 2%, and in body and hand leave-on products at concentrations up to 0.2%.[10] For the purpose of this risk assessment, the estimated daily human exposure level to body lotion, face cream, and hand cream are 7.82, 1.54, and 2.16 g/day, respectively.[46]

For leave-on skin care products, the relevant calculations are:

SED of body lotion = 7.82 g/day of product × 0.2 % maximum use concentration ÷ 60 kg person × 20 % skin absorption × 1000 mg/g conversion factor = 0.052 mg/kg/day

SED of face cream = 1.54 g/day of product × 2 % maximum use concentration ÷ 60 kg person × 20 % skin absorption × 1000 mg/g conversion factor = 0.103 mg/kg/day

SED of hand cream = 2.16 g/day of product × 0.2 % maximum use concentration ÷ 60 kg person × 20 % skin absorption × 1000 mg/g conversion factor = 0.0144 mg/kg/day

MOS (leave-on skin care products) = NOAEL (rat oral teratogenicity study) / Overall SED (sum of the three leave-on skin care products SEDs) = 75 mg/kg/day / 0.169 mg/kg/day = 442

In 2002, the SCCS performed MOS calculations based on overall cosmetic exposure estimate; that MOS (equal to 133) is lower than those above because a cumulative global daily exposure of Salicylic Acid was considered therein. [44]

Oral

Salicylic Acid

An exposure assessment of a representative cosmetic product (containing ≤ 2% Salicylic Acid) used on a daily basis estimated that the exposure from the cosmetic product would be only 20% of the level seen with ingestion of a "baby" aspirin (81 mg) on a daily basis. This exposure assessment further contends that the reproductive and developmental toxicity from the daily use of a baby aspirin is not significant.[1]

GENOTOXICITY STUDIES

Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Salicylic Acid, Sodium Salicylate, and Tridecyl Salicylate

Studies on the genotoxic potential of Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Salicylic Acid, Sodium Salicylate, and Tridecyl Salicylate are negative, except that Salicylic Acid is positive in a B. subtilis rec assay (negative in seven other bacterial tests and one mammalian test). Methyl Salicylate is positive in Salmonella typhimurium strains TA98, and TA100 with metabolic activation (negative in in 2 other Ames tests). Sodium Salicylate is positive in an in vivo chromosome aberration study in mice; it is negative for sister chromatid exchanges in vivo in mice, and in 4 in vitro test systems.[1]

CARCINOGENICITY STUDIES

Salicylic Acid has been classified as a non-carcinogen (study details not provided).[1]

In Vitro

Salicylic Acid and Sodium Salicylate

Sodium Salicylate had dose-dependent inhibitory effects on adenoma, in vitro transformants of adenoma, and carcinoma cell lines. IC_{50} values of 1.65 to 7.28 mM were reported.

Animal

Dermal

Methyl Salicylate

A skin painting study was performed in which Methyl Salicylate was applied to the back of 39 mice, at biweekly intervals, for 400 days.[1] *Neoplasms were not induced.*

Parenteral

Groups of 15 male and 15 female A/He mice were dosed intraperitoneally with 100 or 500 mg/kg Methyl Salicylate in tricaprylin 3 times per week for 8 weeks (24 doses total).[1] *Two out of 13 males and 1 of 14 females of the low-dose group that survived until study termination had lung tumors. One out of 12 males and 5 of 13 females of the high-dose group that survived until study termination had pulmonary tumors. These compare with 10 of 46 males and 8 of 48 females with tumors in the untreated control group and 8 of 30 males and 10 of 28 females with tumors in the vehicle control group.*

Photocarcinogenicity

Salicylic Acid

In a National Toxicology Program (NTP) carcinogenicity study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing Salicylic Acid were evaluated.[47] Creams containing Salicylic Acid (0%, 2%, or 4%), were applied to the skin of groups of 18 male and 18 female hairless mice in the mornings. Additional groups of 36 male and 36 female mice were not exposed to the cream. In the afternoons, groups of animals were exposed to one of three strengths of synthetic solar light for 4 h. Other groups were not exposed to light and were control groups. The treatment and exposures were performed five days per week for 40 weeks, during which time the animals were monitored for the development of skin cancers. Greater strengths of light increased the incidences of skin cancers in mice not given a cream or given a cream with no acid included. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities. It was concluded that Salicylic Acid had some protective effect against photocarcinogenicity at lower intensities.

Tumor Promotion

Salicylic Acid inhibited tumor promoter 12-*O-tetradecanoylphorbol-13-acetate-induced transformation in a concentration-dependent (concentrations not stated) manner, in a culture model (mouse epidermal JB6 cells)that was used to study tumor promotion and anti-tumor promotion*.[1]

OTHER RELEVANT STUDIES

Estrogenic Activity

Butyloctyl Salicylate and Ethylhexyl Salicylate

The estrogenic activity of Butyloctyl Salicylate and Ethylhexyl Salicylate was studied.[48] A consensus modeling method to predict their qualitative and quantitative binding activity towards the estrogen receptor (ER) was used. The consensus modeling comprised two Decision Forest (DF) models that were built using two different training data sets. The two DF models were validated using 5-fold cross validations and external chemicals. Similar predictions were made on unrelated compounds. Prediction confidence was defined as a number between 0 and 1, for indication of confidence for a prediction; the smaller the number, the less confident the prediction. The experimental ER binding affinities were given as logarithmic relative binding affinity (logRBA) values to the nature hormone estradiol whose logRBA was set to 2. Ethylhexyl Salicylate was classified as an estrogen receptor non-binder. Butyloctyl Salicylate was classified as having binding activity to the ER (prediction confidence value = 0.827; logRBA = -0.853).

A recombinant yeast estrogen assay was used to assess the activity of Ethylhexyl Salicylate.[49] The ERα gene, together with expression plasmids (containing estrogen responsive elements and the lac-Z reporter gene encoding the enzyme β-galactosidase), were incubated in medium containing Ethylhexyl Salicylate (10 µl, serially diluted in ethanol) and the chromogenic substrate, chlorophenol red-β-D-galactopyranoside (CPRG). Active ligands (which bind to the receptor) induce β-galactosidase (β-gal). The relative potency of the test substance was determined only when the dose–response curve was parallel to that of 17-β-estradiol. To do so, the concentration of the test substance required to produce a half-maximal response (absorbance at 540 nm (A540) between 1.7 and 2.0) was divided by the concentration of 17-β-estradiol required to produce the same response. Compounds displaying a submaximal response were compared at the 10% response level. Ethylhexyl Salicylate generated a dose-response curve that was shallower than the one for 17-β-estradiol, and had a submaximal response for estrogenic activity (estrogenic potency relative to 17-β-estradiol = 1/2,000,000).

Effect on Cytokine Production

Methyl Salicylate

Six male BALB/c mice were exposed (head/nose-only) to Methyl Salicylate (30 mg/m^3) in a short-term exposure respiratory local lymph node assay (LLNA).[50] The animals were exposed for 45, 90, 180, or 360 min/day on 3 consecutive days (days 0, 1, and 2). For inhalation exposure, the chemical was evaporated in air without solvent. Controls were exposed to air only for 360 min/day. The vehicle (acetone:olive oil (4:1) solution (AOO)) control group consisted of 6 mice. Three days after the last inhalation exposure, the draining lymph nodes were excised and cytokine production was measured after ex vivo stimulation with Concanavalin A. Cytokine profiles were assessed. Skin application was used as a positive control in this study. The dermal route (single ear application; n = 3 male BALB/c mice) was used as a positive control. Methyl Salicylate (25%, 25 µl), dissolved in AOO, was applied on the dorsum of both ears (50 µl per animal) for 3 consecutive days (days 0, 1, and 2). On day 5, auricular lymph nodes were collected and used for ex vivo cell proliferation and cytokine measurements. After inhalation exposure and skin exposure, Methyl Salicylate did not induce a measurable IL-4 response (i.e., no significant cytokine production).

DERMAL IRRITATION AND SENSITIZATION STUDIES

The skin irritation and sensitization studies summarized below (except for italicized text) are presented in detail in Table 4. In addition to these studies, it should be noted that possible complications relating to the topical use of Salicylic Acid as a peeling agent include persistent erythema and pruritus (specific studies not included).[51]

Irritation

Animal

The application of 500 mg (in 0.5 ml) of Isodecyl Salicylate (6 male New Zealand white rabbits) and Tridecyl Salicylate (6 female Dunkin-Hartley albino guinea pigs), and Butyloctyl Salicylate (dose not stated) did not cause skin irritation.[1] Undiluted Ethylhexyl Salicylate produced mild skin irritation in rabbits (number not stated). Methyl Salicylate (concentration not stated) has been reported to cause severe skin irritation in guinea pigs (number not stated) and moderate skin irritation (abraded and intact skin) in rabbits (number not stated). Repeated applications of Methyl Salicylate (concentration not stated) to guinea pigs (number not stated) caused scaling, dryness, and isolated and multiple infiltrates by days 4 to 6. Threshold changes were noted with the application of a 50% oil solution. At concentrations of 1%, 3%, and 6% (in 70% ethanol), Methyl Salicylate was severely irritating to the skin of all 3 animals (species not stated) tested. However, this was not true for water suspensions of the 3 Methyl Salicylate concentrations.

The skin irritation potential of Amyl Salicylate (> 99.8%) was evaluated using 6 Albino angora rabbits and 6 male Hartley guinea pigs.[52] After 24 h, Amyl Salicylate was severely irritating to the skin of rabbits and mildly irritating to the skin of guinea pigs. The skin irritation potential of Amyl Salicylate (> 99.8%) was evaluated using 6 miniature swine of the Pitman-Moore Improved strain. Skin irritation was not observed following a 48-h application. When undiluted Ethylhexyl Salicylate was applied under occlusion to the skin of 4 rabbits for 24 h, mild erythema was observed.[3] These results are reported in the acute dermal toxicity study that is summarized earlier in this report.

Groups of 5 male hrBR outbred hairless albino guinea pigs received a single ~ 2 h application of Hexyl Salicylate at a concentration of 1%, 5%, 10%, or 50% (in 3:1 diethyl phthalate:ethanol) or at 100%. Skin irritation was not observed. In a test involving 4 male albino Dunkin/Hartley strain guinea pigs, the animals were treated topically with patches saturated with 10%, 25%, or 50% Hexyl Salicylate in acetone.[4] After 24 h, no irritation was observed at the 10% concentration, and very slight erythema was observed in 3 animals at the 2 highest concentrations. In another test (same protocol), the skin irritation potential of Hexyl Salicylate (0.1 to 2% in 0.01% dodecylbenzene sulphonate /saline) was evaluated using 4 male albino Dunkin/Hartley guinea pigs.[4] Very slight erythema was observed at a concentration of 0.1% and slight erythema and edema were observed at higher concentrations. The application of undiluted Hexyl Salicylate (20 µl/5 cm^2) to the skin of 2 miniature swine did not cause skin irritation.[4] In a study involving 3 or 4 female New Zealand white rabbits, Hexyl Salicylate was applied for 4 h to the skin at concentrations ranging from 10% to 100%. Skin irritation was not observed at concentrations of 10% and 25%, but irritation was observed at higher concentrations.[4] When undiluted Hexyl Salicylate was applied (5 g/kg) to the skin of 10 rabbits, skin irritation was observed in 8 animals.[4] Also, when undiluted Hexyl Salicylate (20 µl/5 cm^2) was applied to the skin of 6 hairless mice, skin irritation was not observed.[4]

The skin irritation potential of wintergreen oil (containing 80–99% Methyl Salicylate) was evaluated using 6 hairless mice and 2 miniature swine.[5] Flaking, hyperkeratosis and dry desquamation were observed. The application of Methyl Salicylate (3%) to the skin of 6 to 8 male and female outbred, Himalayan white-spotted guinea pigs for 21 days resulted in minimal skin irritation.[53] Also, when Methyl Salicylate (3%) was applied for 24 h to guinea pigs (6 to 8) of the same strain,

mild erythema was observed in at least 25% of the animals.[53] A single dermal dose (5 g/kg) of undiluted Methyl Salicylate caused slight erythema and edema in 2 of 9 rabbits and moderate erythema and edema in 7 of 9 rabbits (skin irritation results from acute dermal toxicity study).[5] In a mouse ear swelling test, the minimal irritating concentration of Methyl Salicylate was determined to be 20%.[54] Formulations containing 3.5%, 5.0%, and 7.5% Salicylic Acid caused significant macroscopic alterations (desquamation, inflammatory reaction and comedogenic effect), compared to the negative control, when applied daily to the ears of 6 male albino New Zealand rabbits.[55]

Intradermal Injection

After 0.1% Hexyl Salicylate (0.1 ml) was injected intradermally into the skin of 4 inbred Hartley strain albino guinea pigs, skin irritation was observed.[56] The intradermal injection of a higher concentration of Hexyl Salicylate (5%) into the skin of 4 guinea pigs (same strain) did not cause skin irritation. The vehicle was not reported in either experiment, and an explanation for the different results was not provided.

Human

Clinical tests for cumulative irritation are available for the following ingredients at the specified concentrations: Salicylic Acid (27 subjects; 2% - minimal cumulative irritation; 1.5% - slight or no irritation); TEA Salicylate (10% caused irritation in 1 of 12 subjects); Methyl Salicylate (12% to 50% - pain and erythema (5 subjects); 8% - no irritation (number of subjects not stated); 1% aerosol – erythema (4 subjects); Ethylhexyl Salicylate (4% - no irritation (number of subjects not stated)); and Tridecyl Salicylate (no irritation, 30 subjects).[1]

In a 48-h occlusive patch test, Amyl Salicylate (32% in acetone) was not irritating to the skin of 50 subjects.[52] In a 48-h closed patch test involving 23 male subjects, 4% Ethylhexyl Salicylate in petrolatum did not cause skin irritation.[3] Skin irritation was observed when undiluted Hexyl Salicylate was evaluated in a 4-h patch test using 30 volunteers.[57] In a 24-h patch test involving 56 subjects, Hexyl Salicylate was evaluated for skin irritation potential at concentrations of 0.3%, 3%, or 30% in 3:1diethyl phthalate:ethanol.[4] Results were negative. Skin irritation was not observed after 8% Methyl Salicylate (in petrolatum) was applied to the backs of 27 male subjects.[5] The same results were reported when or 12% wintergreen oil (containing 80 – 99% Methyl Salicylate) in petrolatum was applied to the backs of 25 subjects. Repeated applications of 30% and 60% Methyl Salicylate to the skin of 9 subjects resulted in skin irritation.[58]

Sensitization

In Vitro

In a genomic allergen rapid detection assay utilizing an in vitro model of dendritic cells, Hexyl Salicylate was predicted to be a skin sensitizer.[59] An integrated testing strategy for skin sensitization that focuses on 3 in vitro methods covering the first three steps of the adverse outcome pathway was used to determine the skin sensitization potential of Salicylic Acid.[60] The results were equivocal, but, ultimately, were considered positive. The allergen–peptide/protein interaction in vitro assay was also used to predict the sensitization potential of Salicylic Acid.[61] Mass spectra of both target peptides revealed neither any modification of peptide-21 nor of peptide-20 by Salicylic Acid under skin-related in vitro conditions. The modification of proteins by skin sensitizers is a pivotal step in T-cell mediated allergic contact dermatitis.

Animal

Maximization test data on Butyloctyl Salicylate indicate that none of the guinea pigs challenged with 100% Butyloctyl Salicylate had a sensitization response.[1] However, one of the 10 guinea pigs challenged with 50% Butyloctyl Salicylate had a clear dermal response. Maximization test data on Ethylhexyl Salicylate indicate that skin sensitization was not observed in guinea pigs(number not stated) challenged with a 25% solution of Ethylhexyl Salicylate in ethanol/diethyl phthalate (DEP) (1:1).[1] Results for Methyl Salicylate are negative at concentrations up to 25%, independent of vehicle, in the local lymph node assay.[1] A modified Magnusson-Kligman guinea pig maximization test on Methyl Salicylate was performed using 10 Dunkin-Hartley guinea pigs. The animals were challenged with 10% Methyl Salicylate in acetone, and results were negative. In another maximization test, albino Dunkin-Hartley guinea pigs (number not stated) were challenged with 10% Methyl Salicylate in acetone/PEG 400 (70:30). Test results were negative for skin sensitization. Although results for Salicylic Acid are positive in the LLNA at a concentration of 20% in acetone, this is not true for Salicylic Acid at a concentration of 20% in acetone/olive oil.[1]

In the murine local lymph node assay (LLNA), a very low EC3 (effective concentration that induces a 3-fold increase in local lymph node proliferative activity) was reported for Hexyl Salicylate.[60] The lower the EC3 value, the greater the sensitization potency. It was noted that the low value reported may have been due to possibly sensitizing impurities. Hexyl Salicylate was tested in a sensitization study involving 10 inbred Hartley albino guinea pigs.[56] Sensitization was observed after the second challenge with 0.1% Hexyl Salicylate (intradermal injection) and 5% Hexyl Salicylate (topical

application). In a sensitization test using groups of 5 Crl:IAF(HA)-hrBR outbred albino hairless guinea pigs, challenge with 50% Hexyl Salicylate in 3:1 DEP:ethanol and 100% Hexyl Salicylate did not induce sensitization.[4] A maximization test was performed to evaluate the sensitization potential of Hexyl Salicylate in a group of 10 albino Dunkin/Hartley guinea pigs.[4] Sensitization was not observed after challenge with 10% Hexyl Salicylate. The sensitization potential of Methyl Salicylate (0.7 µM) was evaluated using the LLNA.[62] Overall, the results were classified as negative. According to another source, 50% Methyl Salicylate was predicted to be a non-sensitizer using the LLNA.[63] Salicylic Acid has been tested and found to be a non-sensitizer in the LLNA.[64]

Human

In a maximization test involving 25 subjects challenged with 10% Salicylic Acid, results were negative.[1] Results were also negative for skin sensitization in an HRIPT (99 subjects) on a moisturizer cream containing 2% Salicylic Acid and in an HRIPT (101 subjects) on both a moisturizing cream and a moisturizing lotion containing 2% Salicylic Acid. Gels containing 2% Salicylic Acid were also non-sensitizers in HRIPTs involving 193 subjects and 198 subjects. In a maximization test involving 23 subjects, 4% Ethylhexyl Salicylate in petrolatum did not induce skin sensitization. Also, in a maximization test involving 27 subjects, 8% Methyl Salicylate in petrolatum did not induce skin sensitization.

Hexyl Salicylate has been classified as a Category 4 substance (infrequent cause of contact allergy in relation to level of exposure) with regard to its human skin sensitization potential.[64] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. Substances in Category 4 are rarely important clinical allergens, because they require considerable/prolonged exposure to higher dose levels to produce sensitization, which even then is unlikely to exceed 0.01% of those exposed. Furthermore, a human skin sensitization no-observed-effect-level (NOEL) of 35,433 µg/cm^2 has been reported for Hexyl Salicylate. Human repeated insult patch test (HRIPT) results for 30% Hexyl Salicylate in 3:1diethyl phthalate:ethanol were negative for skin irritation and sensitization.[4] In a human maximization test on Hexyl Salicylate, no induction was observed at a dose of 20,654 µg/cm^2.[60] In another maximization test involving 22 subjects patch tested with 3% Hexyl Salicylate, the results were negative for skin irritation and sensitization.[4]

Methyl Salicylate has been classified as a Category 5 substance (a rare cause of contact allergy except perhaps in special circumstances, e.g., use in topical medicaments) with regard to its human skin sensitization potential.[64] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. It was also noted that there are insufficient data (availability of specific data not mentioned) to define a human skin sensitization NOEL. Category 5 consists of substances that have a very low intrinsic ability to cause skin sensitization. Here, typically only exceptionally prolonged exposure in combination with high use levels will lead to skin sensitization, for example, routine use in medicaments for treatment of chronic skin conditions. For these materials, sensitization in the general population is likely to be (extremely) rare. In a maximization test involving 25 subjects, 12% wintergreen oil (containing 80 – 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%) in petrolatum did not induce skin sensitization.[5] In an HRIPT involving 39 subjects, 1.25% Methyl Salicylate was a non-sensitizer.[5] Salicylic Acid has been classified as a Category 6 substance with regard to its human skin sensitization potential.[64] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. Substances in Category 6 are essentially free from skin sensitizing activity (i.e., non-sensitizers). Further details were not included.

Photosensitization/Phototoxicity

The photosensitization/phototoxicity studies summarized below are presented in detail in Table 5.

In Vitro

Ethylhexyl Salicylate

The phototoxicity of Ethylhexyl Salicylate (0.1 to 316 µg/mL) was evaluated in the 3T3 neutral red uptake phototoxicity test, using a cell suspension of 3T3 fibroblasts.[65] Phototoxicity test results were classified as negative.

Animal

Hexyl Salicylate

Undiluted Hexyl Salicylate (20 µl) was not phototoxic in 6 Skh:hairless-1 mutant mice exposed to light from a long arc xenon lamp and fluorescent blacklight lamps .[4,66] Phototoxicity also was not observed in 2 miniature swine tested with undiluted Hexyl Salicylate (20 µl) according to the same procedure.[4,66] In a phototoxicity study in which two groups of 5

Crl:IAF(HA)-hrBR outbred, albino hairless guinea pigs were exposed to Hexyl Salicylate (concentrations up to 100%) and then ultraviolet radiation (UV) from a long-arc xenon water-cooled lamp, results were also negative.[4] Photoallergy was not observed in 2 groups of 5 Crl:IAF (HA)-hrBR outbred albino hairless guinea pigs exposed to Hexyl Salicylate (50% and 100%) plus UV.[4]

Methyl Salicylate

The phototoxicity of wintergreen oil (containing 80–99% Methyl Salicylate) in the presence of long-wavelength ultraviolet radiation (UVA) was evaluated using 2 miniature swine. Results were negative.[5]

Salicylic Acid

The contact photosensitization potential of Salicylic Acid was determined using groups of 5 female albino outbred ICR mice.[1] The animals were challenged with 25% Salicylic Acid in alcohol (20 µl), followed by irradiation for 2.5 h, and results were negative.

Tridecyl Salicylate

Ten male Hartley albino guinea pigs were used to determine the phototoxicity potential of Tridecyl Salicylate.[1] During induction 2% Tridecyl Salicylate (0.5 ml) was applied to the back daily for 3 weeks, and the test site was irradiated with UVA + [mid-wavelength ultraviolet radiation (*UVB*)]. *At challenge with 0.1% Tridecyl Salicylate in dehydrated alcohol, results were negative*.

Human

Hexyl Salicylate

In a study involving 56 subjects patch tested with Hexyl Salicylate (0.3%, 3% and 30% in 3:1 DEP:ethanol), followed by irradiation of sites with UVA and UVB, no reactions were observed.[4]

Ethylhexyl Salicylate and Salicylic Acid

Products containing 2% Salicylic Acid did not induce phototoxicity in studies involving groups of 10 human subjects. The same was true for these products in photallergenicity studies involving groups of 25 to 28 humans subjects.[1] *A cream containing 2% Salicylic Acid had a photoprotective effect in a study involving 5 subjects. The same was true for a formulation containing Ethylhexyl Salicylate (concentration not stated) in groups of ≤ 38 subjects*.

Computational Analyses/Predictions

Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate

A database of 259 heterogeneous organic compounds (including Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate) evaluated in the guinea pig maximization test was subjected to multivariate quantitative structure-activity relationship (QSAR) analysis, utilizing principal component analysis and linear discriminant analysis.[67] Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate were classified as non-sensitizers. A QSAR system for estimating skin sensitization potency that incorporates skin metabolism and considers the potential of parent chemicals and/or their activated metabolites to react with skin proteins has also been developed.[68] Amyl Salicylate was one of the chemicals that was identified to fall within the model domain accounting for the first neighbors of centered atoms, and was predicted to be a non-sensitizer.

A study was performed to validate a QSAR rank model for grading allergenic potency using a database of 74 known allergens and non-allergens that were chosen among fragrance chemicals in common use.[69] The model's scoring system for class levels was: Class 1 (non-allergic; scores = 0.63 to 1.97), Class 2 (weak to mild; scores = 1.24 to 3.10), Class 3 (moderate; scores = 1.81 to 4.14), and Class 4 (strong to extreme; scores = 2.66 to 4.88). Hexyl Salicylate and Methyl Salicylate were classified as non-allergic.

Hexyl Salicylate

An exposure-based quantitative risk assessment (QRA) methodology was used to determine acceptable exposure limits (in finished product) for Hexyl Salicylate and a new International Fragrance Association (IFRA) standard was issued.[70] Limitations for various finished product categories were established, ranging from 1.3% to 25.7%. The following

relevant sensitization data were used for implementation of the QRA: LLNA weighted mean EC3 value (45 µg/cm^2), human data: NOEL – HRIPT (induction) (35,433 µg/cm^2), experimental NOEL – MAX (induction) (2069 µg/cm^2), and weight of evidence (WoE) no expected sensitization induction level (NESIL) (35,400 µg/cm^2).[4]

OCULAR IRRITATION STUDIES

In Vitro

Sodium Salicylate

Sodium Salicylate was evaluated using the EpiOcular™ reconstructed human cornea-like tissue model.[71] The tissues are cultured from primary non-transformed human epidermal keratinocytes (NHEK) obtained from individual donors. The tissues were incubated with Sodium Salicylate (50 µl) for 30 minutes, and tissue viability was assessed using the MTT assay. If the treated tissue viability was ≤ 60% relative to negative control tissue viability, the test chemical was predicted as "in vitro irritant." Values for % viability were 5% (run #1) and 5.1% (run #2) for Sodium Salicylate, classifying the chemical as an ocular irritant.

Animal

Methyl Salicylate

A rabbit eye irritation test was conducted in 5 healthy albino rabbits. A 0.005 ml aliquot of neat Methyl Salicylate was applied to the center of the cornea while the lids were retracted.[72] One minute later the lids were released. The eyes were examined 18 - 24 h later in strong diffuse daylight and then stained with fluorescein. Methyl Salicylate caused necrosis on 13 to 37% of the cornea (visible after staining).

A rabbit eye test was conducted in 3 healthy albino rabbits.[5] One-tenth ml of 1.25% Methyl Salicylate in specially denatured alcohol (SDA) 39C was instilled into the right eye of each rabbit with no further treatment. The untreated left eye served as control. Observations were made every 24 h for 4 days and then again on day 7 according to the Draize method. Intense conjunctival irritation accompanied by chemosis and considerable discharge was observed in all 3 rabbits. The treated eyes were normal on day 7 of observation.

Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, and Tridecyl Salicylate

The ocular irritation potential was negative for the following ingredients: Butyloctyl Salicylate (concentration not stated; 6 animals tested) Ethylhexyl Salicylate (50% solution; number of animals not stated), Isodecyl Salicylate (10% in liquid paraffin; 6 New Zealand albino rabbits tested), and Tridecyl Salicylate (0.1 ml dose; 3 male New Zealand white rabbits).[1] *Methyl Salicylate was not irritating in one study using rabbits, but was severely irritating in another study to the eyes of guinea pigs (test concentrations and number of animals not stated in either study).*

CLINICAL STUDIES

Retrospective and Multicenter Studies

Amyl Salicylate

A total of 1323 patients (from 11 centers combined) were patch tested with fragrances.[73] Patch testing was performed with Finn chambers on Scanpor tape; patches were applied to the back for 2 days. Readings were made according to International Contact Dermatitis Research Group (ICDRG) guidelines on days 2 and 3, or on days 2 and 4. Twenty-eight irritant or doubtful reactions (on day 3 or 4) to a total of 19 fragrance materials were reported. Two reactions (irritant or doubtful) were reported for 1% Amyl Salicylate.

A population of 1855 patients (6 European dermatology departments combined), was patch tested with fragrances. [74] Finn Chambers on Scanpor tape were used in all centers except 1(at which van der Bend chambers were used). Readings were taken at most centers on days 2 and 4. The reading at day 3 or day 4 was used for overall evaluation of positive test results. Three patients had a positive reaction (+) to 5% Amyl Salicylate, and 5 had doubtful reactions.

Hexyl Salicylate

In a multicenter study, 218 fragrance sensitive patients with proven contact dermatitis were patch tested with various fragrance materials according to internationally accepted criteria.[75] No reactions were observed with 5% Hexyl Salicylate in petrolatum.

Case Reports

Capryloyl Salicylic Acid

A female patient who used day and night creams containing Capryloyl Salicylic Acid presented with dermatitis of the face, which was first observed 3 months earlier.[76] Positive patch test reactions (+) to both products and to Capryloyl Salicylic Acid (1% in alcohol) were reported. Another female patient who used the same night cream containing Capryloyl Salicylic Acid also presented with facial dermatitis and had a positive path test reaction to this ingredient (1% in alcohol).

A female patient presented with a pruritic erythematous rash that arose on her face 10 days after application of a cream containing Capryloyl Salicylic Acid.[77] Patch testing was performed, and reactions were scored at 48 h and 96 h. At 96 h, a positive reaction (++) to the cream was reported. A positive allergic reaction (++) to 1% Capryloyl Salicylic Acid in alcohol was observed in the patient (at 48 h and 96 h), but not in 15 healthy control subjects.

In a comment on the preceding 2 case reports, it is stated that Capryloyl Salicylic Acid is unlikely to be significantly allergenic, and is therefore unlikely to be the cause of the contact allergy reported.[78] However, the structural isomer, 3-capryloyl salicylic acid, is a highly plausible contaminant of Capryloyl Salicylic Acid, and is likely to be sufficiently allergenic to account for the observed contact allergy.

Methyl Salicylate

A man became acutely ill (within less than an hour) after using an herbal skin cream containing Methyl Salicylate (high concentration, value not stated) for the treatment of psoriasis.[79] The area of application was covered with an occlusive wrap. Signs of metabolic acidosis superimposed on respiratory alkalosis and a serum salicylate level of 48.5 mg/dL were reported. These signs declined after the patient received treatment for the metabolic acidosis and respiratory alkalosis. The author noted that the transcutaneous absorption (described as rapid) of Methyl Salicylate was enhanced due to the abnormal areas of skin and use of an occlusive dressing. It was concluded that acute salicylate toxicity may result from the topical administration of Methyl Salicylate.

Salicylic Acid

Although rare, toxicity can occur from topical application of Salicylic Acid (i.e., salicylism).[80] Salicylism can be acute or chronic and develops when blood concentrations of salicylate are greater than 35 mg/dL. Symptoms of salicylism include nausea, confusion, dizziness, delirium, psychosis, stupor, and coma.

Amyl Salicylate, Ethylhexyl Salicylate, Methyl Salicylate, Salicylic Acid, and Sodium Salicylate

A 48-year-old woman with a 12-year history of rosacea was advised to use a sunscreen that contained Ethylhexyl Salicylate during several months prior to intense pulsed-light treatment for facial telangiectasia.[81] One-half year later, the patient developed facial dermatitis. She had a positive (++) patch test reaction to 2% Ethylhexyl Salicylate in petrolatum, a positive (+) patch test reaction to 5% Ethylhexyl Salicylate in petrolatum, and a positive (++) patch reaction to the sunscreen product. Results of repeated open application tests (ROATs) with Ethylhexyl Salicylate, 2% and 5%, were positive from day 4 on. A total of 29 consecutive eczema patients acting as controls were negative to Ethylhexyl Salicylate (at 5% and 2% in petrolatum). The patient was retested after 1 year, and the (+) reaction to Ethylhexyl Salicylate was reproduced. Patch test results for the following other salicylates were negative: Amyl Salicylate (5% in petrolatum), Methyl Salicylate (2% in petrolatum), Salicylic Acid (2% in petrolatum), and Sodium Salicylate (2% in petrolatum).

Ethylhexyl Salicylate, Methyl Salicylate, Salicylic Acid, and Sodium Salicylate

A woman who used a sunscreen containing Ethylhexyl Salicylate and had a history of rhinitis and intrinsic bronchial asthma developed erythematous micropapules (that progressed to microvesicles and vesicles) on the back, chest, and abdomen.[82] A skin biopsy of the lesions revealed a dermal hypersensitivity reaction that was consistent with contact

dermatitis. Epicutaneous tests of the components of the sunscreen spray product were performed. Results were positive for Ethylhexyl Salicylate (test concentration not stated), but not for any of the other ingredients tested. Patch test results for the following other salicylates were negative: Methyl Salicylate, Sodium Salicylate, and Salicylic Acid. Photopatch test results were positive for Ethylhexyl Salicylate (test concentration not stated), but not for Methyl Salicylate, Sodium Salicylate, or Salicylic Acid.

Methyl Salicylate, Salicylic Acid, and Salicylates

Numerous case studies report toxic reactions to oral ingestion of salicylates.[1] *Dermal toxicity is described in the case literature as follows: dermal application of Salicylic Acid with concomitant oral administration of a nonsteroidal anti-inflammatory drug; following dermal application of a Salicylic Acid ointment in an elderly subject recovering from acute renal failure; topical application of Methyl Salicylate (and methanol) followed by the application of heat (skin and muscle necrosis and interstitial nephritis); and severe urticarial and angioedema with Methyl Salicylate exposure. In 20 patients with eczema or contact dermatitis, Methyl Salicylate at 67% is reported to cause irritation in 8 subjects; at 40%, 2 subjects; and at 38%, 15%, and 3.75% - no irritation in any subject. In 2 case studies of reactions to a wart paint containing Salicylic Acid, Salicylic Acid (tested at 3% in petrolatum) was not the causative agent. Methyl Salicylate (2%) in arachis oil and 2% aqueous Sodium Salicylate produced positive patch results in a patient with acute dermatitis who had been using an ointment containing menthol and camphor. Methyl Salicylate (12%) and Salicylic Acid (5%) in yellow soft paraffin produced positive patch tests in 4 patients with dermatitis and one with psoriasis, all with some history of exposure to salicylates.*

Other Clinical Reports

Capryloyl Salicylic Acid

In a split-face study, 44 female volunteers with mild to moderate facial hyperpigmentation and fine lines/wrinkles were randomized and Capryloyl Salicylic Acid peel was applied to one side of the face.[83] Increasing peel concentrations were applied (5 - 10% Capryloyl Salicylic Acid) based on the tolerance level of the subjects and clinical observations of an expert dermatologist for 12 weeks at biweekly intervals. Results indicated that there were no significant changes in erythema for Capryloyl Salicylic Acid from baseline values when compared with pre-peel to pre-peel and post-peel to post-peel at different weeks.

Salicylic Acid

In patients with venous leg eczema, Salicylic Acid augmented histidine release in 3/320 challenged with ragweed pollen.[1] *Salicylic Acid exacerbated urticarial reactions to aspirin; 13 of 18 patients in one study and 6 of 20 in another. At 5% in petrolatum, however, Salicylic Acid did not cause any urticarial reactions in atopic, urticarial, non-atopic, and non-allergic patients. Salicylic Acid is well-documented to have keratolytic action on normal human skin. It had a small therapeutic effect in patients with various forms of ichthyosiform dermatoses, but decreased clearing in 8 of 11 psoriasis patients when compared to UV therapy alone. Therapeutic toxicities include nausea, vomiting, tinnitus, dizziness, headache, dullness, confusion, sweating, rapid pulse and breathing, skin eruptions, and fever. One estimate is that a blood concentration > 300 µg/ml of a salicylate should be considered toxic. Toxic reactions occur more frequently in children. Care must be taken in prescribing salicylate-containing medications because systemic clearance of salicylates may be reduced with age. Severe poisoning can result in delirium, hallucinations, convulsions, coma, and respiratory or cardiovascular collapse. Reversible hearing loss and tinnitus are reported side effects of salicylates at therapeutic levels.*

Methyl Salicylate

Methyl Salicylate taken in quantities greater than or equal to 1 teaspoon are reported to be quite toxic (equivalent of the salicylate that could be derived from 20+ adult aspirin tablets.[1] *Accidental poisoning is not uncommon, especially in children; symptoms of poisoning include kidney irritation, vomiting, and convulsions. The average lethal dose of Methyl Salicylate is 10 ml for children and 30 ml for adults.*

Sodium Salicylate

Sodium Salicylate injected in the skin of aspirin intolerant individuals affected several parameters as follows: 1/23 had a positive skin test to Sodium Salicylate; 2/31 were positive in the passive cutaneous anaphylaxis test; and 2/26 were positive in the lymphocyte transformation test.[1]

Salicylates

A review of radiographs taken in 155 cases of juvenile arthritis in which various forms of salicylates had been administered at concentrations ranging from 0.1 to 3.24 g for several months did not find any evidence of bone lesions.[1]

RIFM SAFETY ASSESSMENT CONCLUSION ON SALICYLATES

A published toxicologic and dermatologic assessment of salicylates, when used as fragrance ingredients, by the Research Institute for Fragrance Materials (RIFM) is available; the RIFM Expert Panel's lengthy conclusion on these fragrance ingredients is stated in the paragraphs below.[84] This conclusion is based on a review of safety test data on salicylates that were available before and after publication of the initial CIR published final report on salicylates. Many of the studies are found in the original CIR Final Report on salicylates and in this re-review document. Studies on salicylates with aromatic sidechains (i.e., Benzyl Salicylate) are also mentioned in the RIFM safety assessment conclusion. CIR is conducting a separate safety assessment of Benzyl Salicylate; therefore such studies (on salicylates with aromatic sidechains) are not included in this re-review document or the original CIR Final Report, and, thus, are not relevant to this safety assessment. It should be noted that the conclusion stated in the paragraph below should not be considered alone, but along with the more recent data summaries that are included in this re-review document.

Based on the available data, and using the NOAEL values of 50 mg/kg body weight/day identified in subchronic and chronic toxicity studies, a margin of safety for systemic exposure of humans to the individual salicylates in cosmetic products may be calculated to range from 125 to 2,500,000 (depending upon the assumption of either 12–30% or 100% bioavailability following dermal application) times the maximum daily exposure.

SUMMARY

The Panel published a Final Report on the Safety Assessment of Salicylic Acid and 16 salicylates in 2003. In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years; therefore this re-review document has been prepared. MEA-Salicylate was recently re-reviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts; thus it is not included in this re-review.

The Final Report was reopened to add these structurally similar ingredients and revise the Panel's original conclusion. Thus, this re-review document relates to the ingredients in that original report (except MEA-Salicylate), as well as 3 additional salicylates that have been added to the safety assessment. This re-review document contains all of the current safety test data and other relevant data that were considered by the Panel.

Of the 19 ingredients that are included herein, the greatest use frequency of 3,474 uses is being reported for Ethylhexyl Salicylate. The results of a concentration of use survey conducted in 2018 indicate that Butyloctyl Salicylate is being used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest maximum use concentration that is being reported for the salicylates that are being reviewed in this safety assessment. Salicylic Acid is being used at concentrations up to 30% in rinse-off products (peels), the highest maximum ingredient use concentration that is being reported for rinse-off products.

In vitro skin penetration data (human or rat skin) indicated that Ethylhexyl Salicylate and Methyl Salicylate were percutaneously absorbed. Additionally, the conversion of Methyl Salicylate to Salicylic Acid in hairless mouse skin in vitro following topical application of 1% Methyl to the skin was evaluated. Less than 5% of applied dose was metabolized to Salicylic Acid.

In in vivo studies, the percutaneous absorption of Methyl Salicylate has been demonstrated in pigs and humans, and the percutaneous absorption of Ethylhexyl Salicylate has been demonstrated in humans. The in vivo absorption of a formulation containing 20% Methyl Salicylate was studied using male Wistar rats. The levels of unhydrolyzed Methyl Salicylate in tissues below the treated site were low, i.e., only 2 to 3 µg/ml throughout the study period. A mathematical method was used to estimate total body absorption of some salicylate esters including Hexyl Salicylate. The estimated total body absorption of Hexyl Salicylate per µg over 1.4 m^2 was 0.18 at 2 h, 4.1 at 6 h and 27 at 12 h. Reportedly, after oral ingestion, Methyl Salicylate is readily metabolized to Salicylic Acid.

In acute dermal toxicity studies of Ethylhexyl Salicylate, Hexyl Salicylate, and Methyl Salicylate involving rabbits, the LD_{50} was > 5 g/kg for each salicylate. The same was true in acute oral toxicity studies on Ethylhexyl Salicylate and Hexyl Salicylate involving rats. In acute oral toxicity studies on Methyl Salicylate involving mice, the LD_{50} was calculated to be 1.39 g/kg (95% CI of 1.25 to 1.54 g/kg) and a dose of 0.5 g/kg was selected as the maximum tolerated dose.

In a short-term inhalation toxicity study involving mice, there were no test substance-related gross pathological or histopathological findings after inhalation of a fragrance mixture containing 5.8% Amyl Salicylate. Also, in a short-term inhalation toxicity study evaluating respiratory sensitization potential, Methyl Salicylate did not induce a measurable IL-4

response. There were no test substance-related gross pathological or histopathological findings in rats in a subchronic inhalation toxicity study of a fragrance mixture containing 4% Amyl Salicylate.

In a toxicological and dermatological assessment of salicylates, when used as fragrance ingredients, a margin of safety for systemic exposure is mentioned. Based on NOAEL values of 50 mg/kg body weight/day in subchronic and chronic toxicity studies, a margin of safety for systemic exposure of humans to the individual salicylates in cosmetic products may be calculated to range from 125 to 2,500,000 (depending upon the assumption of either 12 - 30% or 100% bioavailability following dermal application) times the maximum daily exposure.

In an in vitro developmental toxicity study involving Salicylic Acid, post-implantation rat embryos were cultured with Salicylic Acid concentrations of 10 to 1000 µg/ml. Salicylic Acid decreased all growth and developmental parameters in a concentration-dependent manner. The same results were reported for rat embryos cultured with Salicylic Acid or Sodium Salicylate at concentrations in the 0.1 to 0.6 mg/ml range. On postnatal day 1, 89% of the pups from dams (rats) that had received a single oral dose of 300 mg/kg Sodium Salicylate had supernumerary ribs. No external malformations of pups were observed. In another study, a 4.8% malformations (including exencephaly and spina bifida) incidence was reported for fetuses from rats dosed with Sodium Salicylate (250 mg/kg/day) on gestation days 8 to 10. It has been reported that the use of Salicylic Acid in the third trimester can potentially cause closure of the ductus arteriosus and oligohydramnios.

Hairless mice were evaluated for skin cancer in a study in which the effects of synthetic solar light on the skin after application of a cream containing 2% or 4% Salicylic Acid were evaluated. It was concluded that Salicylic Acid had a protective effect against the photocarcinogenicity of light at lower intensities.

In an estrogen receptor binding study using a consensus modeling method, Ethylhexyl Salicylate was classified as an estrogen receptor non-binder, whereas Butyloctyl Salicylate was classified as having binding activity to the estrogen receptor. When the estrogenic activity of Ethylhexyl Salicylate was compared to 17-ß-estradiol in a recombinant yeast estrogen assay, the dose response curve for Ethylhexyl Salicylate was shallower than the one for 17-ß-estradiol and Ethylhexyl Salicylate had a submaximal response for estrogenic activity.

Undiluted Amyl Salicylate (0.1 g) was severely irritating to the skin of rabbits, but mildly irritating to the skin of guinea pigs. Undiluted Amyl Salicylate (0.05 g) did not cause skin irritation in miniature swine. Mild erythema was observed in the acute dermal toxicity study on Ethylhexyl Salicylate that is summarized in this safety assessment.

Following intradermal injection, 0.1% Hexyl Salicylate(vehicle not reported) produced an irritation reaction in guinea pigs, but 5% Hexyl Salicylate (vehicle not reported) did not. An explanation for these results was not provided. In an irritation test in which patches containing up to 2% Hexyl Salicylate (0.1 ml) were applied to Dunkin/Hartley albino guinea pigs, slight erythema and edema were observed at concentrations of 0.25%, 0.5%, 1%, and 2%; very slight erythema was observed at a concentration of 0.1%. Patches saturated with concentrations up to 50% Hexyl Salicylate were applied to Dunkin/Hartley albino guinea pigs in another test, and slight skin irritation was observed at concentrations of 25% and 50%, but not 10%. The patch testing of hairless guinea pigs with Hexyl Salicylate (0.3 ml per patch) at concentrations up to 100% yielded negative results. Skin irritation also was not observed in miniature swine tested with undiluted Hexyl Salicylate (20 µl/5 cm^2). When the irritation potential of Hexyl Salicylate at concentrations up to 100% was evaluated using rabbits, patch test (0.5 ml per patch) results for 10%, 25%, 50%, and 100% Hexyl Salicylate were negative. Slight to moderate edema and erythema was observed rabbits in an acute dermal toxicity study on Hexyl Salicylate that is summarized in this safety assessment. Skin irritation was not observed in hairless mice tested with Hexyl Salicylate (20 µl/5 cm^2).

Flaking, hyperkeratosis, and dry desquamation were observed after an aliquot of 20 µl of undiluted wintergreen oil (contained 80 to 99% Methyl Salicylate) was applied to miniature swine. When Methyl Salicylate was applied repeatedly (twenty-one 0.1 ml applications) to guinea pigs in an open epicutaneous test, the minimal irritating concentration was determined to be 3% Methyl Salicylate. A minimally irritating concentration of 20% was determined in a skin irritation test on Methyl Salicylate. Slight to moderate edema and erythema was observed rabbits in an acute dermal toxicity study on 5 g/kg Methyl Salicylate that is summarized in this safety assessment.

Skin irritation was not observed in a 48-h occlusive patch test on 32% Amyl Salicylate (in acetone) involving 50 subjects. Skin irritation also was not observed in a 48-h closed patch test on 4% Ethylhexyl Salicylate (in petrolatum) involving 23 subjects.

Using Hilltop® chambers on 30% Hexyl Salicylate involving 103 subjects, skin irritation was not observed. Skin irritation also was not observed in a 48-h patch test on 3% Hexyl Salicylate involving 22 subjects, in a 4-h patch (Hilltop® chamber) test on undiluted Hexyl Salicylate involving 30 subjects, or in a 24-h patch (Hilltop® chamber) test on Hexyl Salicylate at concentrations up to 30% in a study involving 56 subjects.

Skin irritation was not observed in a 48-h occlusive patch test involving 27 subjects or in a 48-h occlusive patch test on 12% wintergreen oil (containing 80 to 99% Methyl Salicylate) involving 25 subjects. In a study evaluating the skin irritation potential of Methyl Salicylate (in 80% ethanol and 20% deionized water) pipetted (25 ml) onto the skin of 9 subjects, 30% and 60% Methyl Salicylate caused skin irritation. It has been noted that possible complications relating to the topical use of Salicylic Acid as a peeling agent include persistent erythema and pruritus.

Formulations for vitiligo treatment containing up to 7.5% Salicylic Acid were applied to groups of 6 rabbits. The 3.5%, 5%, and 7.5% formulations cause desquamation, an inflammatory reaction, and a comedogenic effect.

Hexyl Salicylate was predicted to be a skin sensitizer in the Genomic Allergen Rapid Detection assay. Using an integrated testing strategy for skin sensitization that focuses on 3 in vitro methods that cover the first 3 steps of the adverse outcome pathway, results for the sensitization potential of Salicylic Acid were considered equivocal, but ultimately were considered positive results.

In the LLNA, a very low EC3 value (0.18%) was reported for Hexyl Salicylate, which may have been due to possibly sensitizing impurities. When Hexyl Salicylate was tested for sensitization potential in guinea pigs using a modified Draize procedure, sensitization was observed after intradermal challenge with 0.1% Hexyl Salicylate and topical challenge with 5% Hexyl Salicylate. In a photoallergy test involving hairless albino guinea pigs, sensitization reactions were not observed after challenge with 50% and 100% Hexyl Salicylate. In a Magnusson-Kligman guinea pig maximization test, skin sensitization was not observed in guinea pigs challenged with 10% Hexyl Salicylate in acetone.

Methyl Salicylate (50%) was predicted to be a non-sensitizer in the LLNA. The same was true for Salicylic Acid and 0.7 µM Methyl Salicylate.

A human skin sensitization NOEL of 35,433 µg/cm^2 (study details not provided) has been reported for Hexyl Salicylate. Also in a human maximization test on Hexyl Salicylate, no induction was observed at a dose of 20,654 µg/cm^2 (study details not included). In an HRIPT (Hilltop® chamber system) involving 103 subjects, sensitization reactions to 30% Hexyl Salicylate were not observed. Maximization test results for 3% Hexyl Salicylate in petrolatum were negative in 22 subjects.

In a human maximization test on wintergreen oil (contains 80 to 99% Methyl Salicylate) involving 25 volunteers, sensitization was not observed at a concentration of 12%. Maximization test results for 8% Methyl Salicylate were also negative in 27 subjects. In an HRIPT involving 39 subjects, 1.25% Methyl Salicylate did not induce skin sensitization.

Results for Ethylhexyl Salicylate were classified as negative in the 3T3 neutral red uptake phototoxicity test at concentrations ranging from 0.1 to 316 µg/ml. Undiluted Hexyl Salicylate was not phototoxic in studies involving mice or miniature swine. At concentrations ranging from 5% to 100%, Hexyl Salicylate was not phototoxic to albino hairless guinea pigs. Hexyl Salicylate did not induce photoallergenicity in groups of albino hairless guinea pigs tested with concentrations of 50% and 100%.

The phototoxicity of undiluted wintergreen oil (contained 80% to 99% Methyl Salicylate) was evaluated using miniature swine, and results were negative. There also was no evidence of phototoxicity in 56 subjects tested with Hexyl Salicylate at concentrations of 0.3%, 3%, and 30%.

Amyl Acetate was classified as a non-sensitizer in a QSAR system for estimating sensitization potency that incorporates skin metabolism and considers the potential of parent chemicals and their activated metabolites to react with skin proteins. Hexyl Salicylate and Methyl Salicylate were classified as non-allergenic in a study that was performed to validate a QSAR rank model for grading allergenic potency. An exposure-based QRA methodology has been used to determine acceptable exposure limits (in finished product) for Hexyl Salicylate. Limitations for various finished product categories have been established, ranging from 1.3% to 25.7%.

Sodium Salicylate was classified as an ocular irritant using the EpiOcular™ reconstructed human cornea-like tissue model, whereby the tissues were incubated with 50 µl of Sodium Salicylate. In an ocular irritation test involving rabbits, the instillation of Methyl Salicylate (0.0005 ml) caused a grade 3 reaction (necrosis on 13 to 37% of the cornea). Intense conjunctival irritation, accompanied by chemosis and considerable discharge, was observed in rabbits in which 1.25% Methyl Salicylate (0.1 ml) was instilled into the eyes.

In multicenter studies, an irritant or doubtful reaction was observed in 2 of 1323 patients patch (Finn chamber) tested with 1% Amyl Salicylate and 3 positive reactions and 5 doubtful reactions were observed in a population of 1855

patients patch tested with 5% Amyl Salicylate. No reactions were observed in a multicenter study in which 218 fragrance-sensitive patients with contact dermatitis were patch tested with 5% Hexyl Salicylate.

Positive patch test reactions to 1% Capryloyl Salicylic Acid have been reported in case reports, one of which reported no reactions in a control group of 15 subjects. It has been suggested that it is unlikely that 5-Capryloyl Salicylate is significantly allergenic, but that the structural isomer, 3-capryloyl salicylic acid, is a highly plausible contaminant and is likely to be sufficiently allergenic. Positive patch test reactions to 2% and 5% Ethylhexyl Salicylate were reported in another case report (patient with facial telangiectasia and history of rosacea), but reactions to these test concentrations were negative in the 29 consecutive eczema patients that served as controls. Also, patch test reactions to the following salicylates were negative in this case report: 5% Amyl Salicylate, 2% Methyl Salicylate, 2% Salicylic Acid, and 2% Sodium Salicylate. A contact dermatitis patient had a positive patch test reaction to Ethylhexyl Salicylate (concentration not stated), but not to Salicylic Acid, Methyl Salicylate, or Sodium Salicylate.

Due to concern over the potential reproductive toxicity of Salicylic Acid in humans, MOS calculations taking into consideration maximum use concentrations of this ingredient in rinse-off and leave-on cosmetic products were performed. The calculations yielded a MOS of 395 for rinse-off products containing 30% Salicylic Acid and a MOS of 442 for leave-on products (body lotion + face cream + hand cream) containing up to 2% Salicylic Acid.

DISCUSSION

The Panel published a safety assessment of Salicylic Acid and 16 salicylates in 2003. Based on the available data, the Panel concluded that the ingredients named in that report are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years. MEA-Salicylate was previously re-reviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts; thus it is not included in this re-review. After reviewing the available new data on the original group of ingredients and the available data on 3 additional, structurally similar salicylates (Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate), the Panel determined that the report should be re-opened to revise the original conclusion, add the 3 additional salicylates, and remove the qualification relating to formulating products to avoid increasing the skin's sun sensitivity. The reason for omitting this qualification is based on results from an NTP photocarcinogenicity study indicating that Salicylic Acid has some protective effect against photocarcinogenicity, at lower light intensities. In the NTP study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing 2% or 4% Salicylic Acid were evaluated. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities.

The Panel expressed concern over the reproductive toxicity of Salicylic Acid, having considered that, in the third trimester, the use of Salicylic Acid can potentially cause early closure of ductus arteriosus and oligohydramnios. Thus, the Panel requested that CIR calculate an MOS for Salicylic Acid exposure, taking into consideration the extent of dermal absorption during cosmetic product use (at the highest maximum use concentration in leave-on products). Because the highest reported maximum use concentration of Salicylic Acid in cosmetic products is 30% in a rinse-off product (peel) and the highest reported maximum use concentration of Salicylic Acid in leave-on products is 2% (face and neck products), two margins were calculated (one for rinse-offs and one for leave-ons). Furthermore, given the potential for whole-body exposure during the application of body and hand products (leave-on products) containing a highest maximum use concentration of 0.2% Salicylic Acid, it was determined that this concentration should also be included. The calculations yielded an MOS of 395 for rinse-off products containing up to 30% Salicylic Acid and an MOS of 442 for leave-on products (body lotion + face cream + hand cream) containing up to 2% Salicylic Acid.

CONCLUSION

The Panel concluded that the following ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating:

Butyloctyl Salicylate
Calcium Salicylate*
C12-15 Alkyl Salicylate*
Capryloyl Salicylic Acid
Ethylhexyl Salicylate
Hexyldodecyl Salicylate*
Isocetyl Salicylate*
Isodecyl Salicylate
Magnesium Salicylate
Methyl Salicylate
Myristyl Salicylate*
Potassium Salicylate*
Salicylic Acid
Sodium Salicylate
TEA-Salicylate
Tridecyl Salicylate
Amyl Salicylate
Hexyl Salicylate
Isotridecyl Salicylate*

**Not reported to be in current use. Were the ingredient in this group not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2; *CIR Staff*]

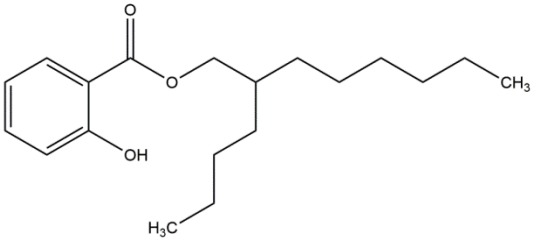
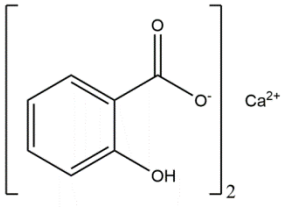
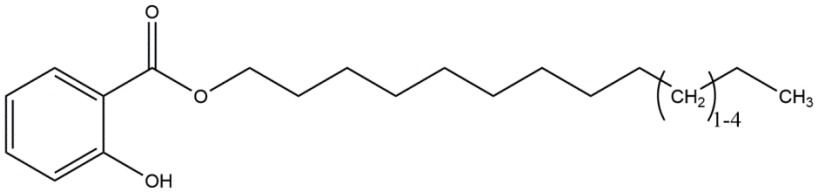
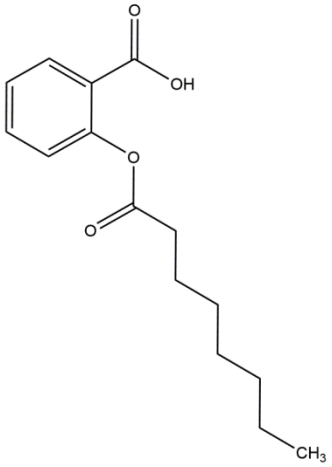
Ingredient CAS No.	Definition & Structures	Function(s)
Butyloctyl Salicylate 190085-41-7	Butyloctyl Salicylate is the organic compound that conforms to the formula: 	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous; Solvents
Calcium Salicylate 824-35-1	Calcium Salicylate is the calcium salt of Salicylic Acid that conforms to the formula: 	Preservatives
C12-15 Alkyl Salicylate	C12-15 Alkyl Salicylate is the ester of C12-15 alcohols and salicylic acid. It conforms generally to the formula: where R represents the C12-15 alkyl group. 	Skin-Conditioning Agents - Miscellaneous
Capryloyl Salicylic Acid 78418-01-6	Capryloyl Salicylic Acid is the ester of Salicylic Acid and caprylic acid. 	Skin-Conditioning Agents - Miscellaneous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2; *CIR Staff*]

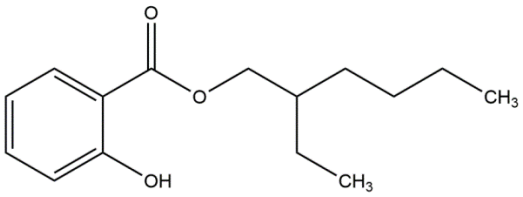
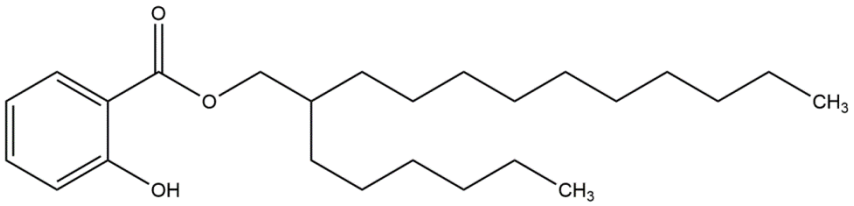
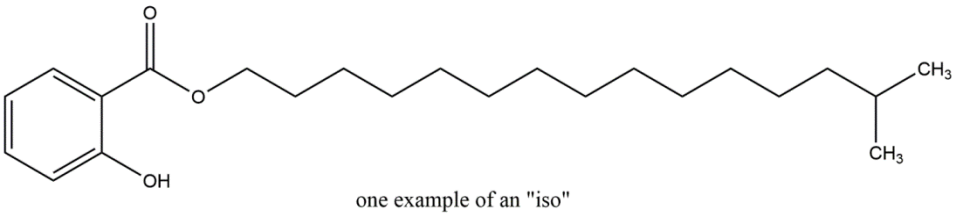
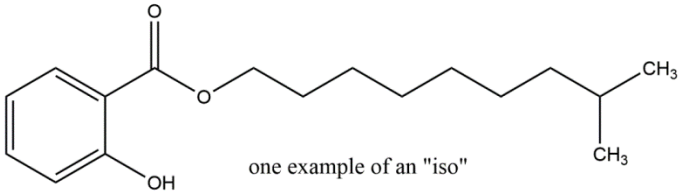
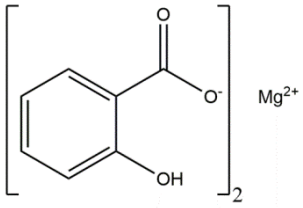
Ingredient CAS No.	Definition & Structures	Function(s)
Ethylhexyl Salicylate 118-60-5	Ethylhexyl Salicylate is the ester of 2-ethylhexyl alcohol and Salicylic Acid. It conforms to the formula: 	Fragrance Ingredients; Light Stabilizers; Sunscreen Agents
Hexyldodecyl Salicylate 220778-06-3	Hexyldodecyl Salicylate is the organic compound that conforms to the formula: 	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous; Solvents
Isocetyl Salicylate 138208-68-1	Isocetyl Salicylate is the ester of Isocetyl Alcohol and Salicylic Acid. It conforms to the formula:  one example of an "iso"	Skin-Conditioning Agents - Miscellaneous
Isodecyl Salicylate 85252-25-1	Isodecyl Salicylate is the ester of branched chain decyl alcohols and Salicylic Acid that conforms to the formula:  one example of an "iso"	Skin-Conditioning Agents - Miscellaneous
Magnesium Salicylate 18917-89-0 551-37-1	Magnesium Salicylate is the magnesium salt of Salicylic Acid that conforms to the formula: 	Preservatives

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2; *CIR Staff*]

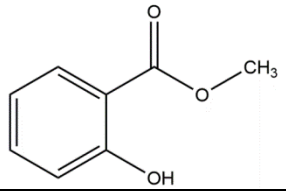
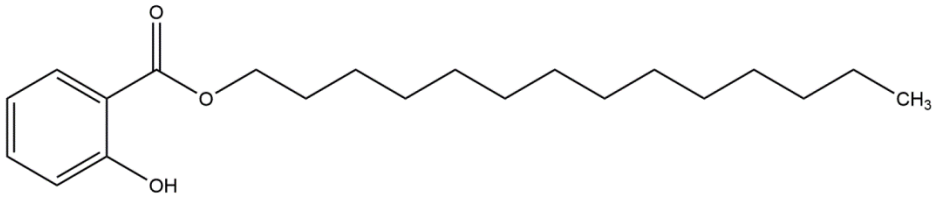
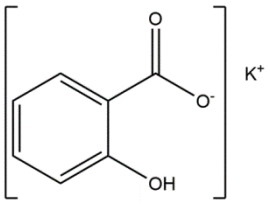
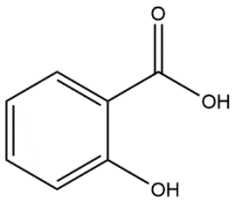
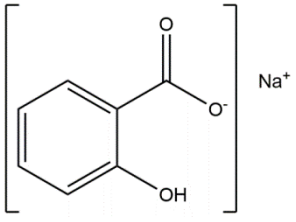
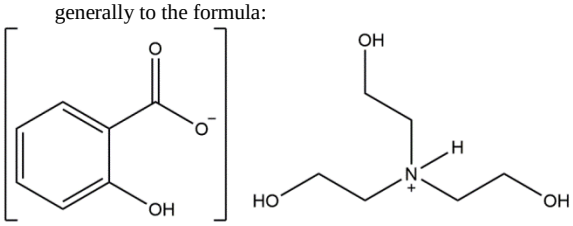
Ingredient CAS No.	Definition & Structures	Function(s)
Methyl Salicylate 119-36-8	Methyl Salicylate is the ester of methyl alcohol and SalicylicAcid. It conforms to the formula: 	Denaturants; External Analgesics; Flavoring Agents; Fragrance Ingredients; Oral Health Care Drugs
Myristyl Salicylate 19666-17-2	Myristyl Salicylate is the ester of myristyl alcohol and Salicylic Acid. It conforms to the formula: 	Not Reported
Potassium Salicylate 578-36-9	Potassium Salicylate is the potassium salt of Salicylic Acid that conforms to the formula: 	Cosmetic Biocides; Preservatives
Salicylic Acid 69-72-7	Salicylic Acid is the aromatic acid that conforms to the formula: 	Antiacne Agents; Antidandruff Agents; Corn/Callus/Wart Removers; Denaturants; Exfoliants; Fragrance Ingredients; Hair Conditioning Agents; Hair-Waving/Straightening Agents; Skin-Conditioning Agents - Miscellaneous
Sodium Salicylate 54-21-7	Sodium Salicylate is the sodium salt of Salicylic Acid that conforms to the formula: 	Denaturants; Preservatives
TEA-Salicylate 2174-16-5	TEA-Salicylate is the triethanolamine salt of Salicylic Acid that conforms generally to the formula: 	Light Stabilizers; Sunscreen Agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2; *CIR Staff*]

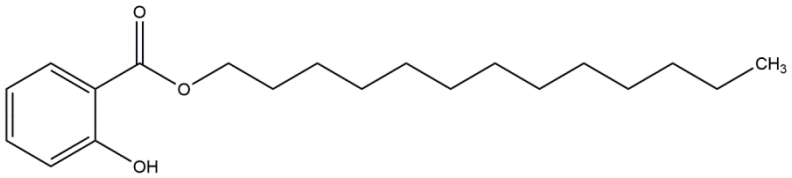
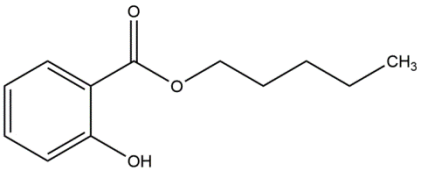
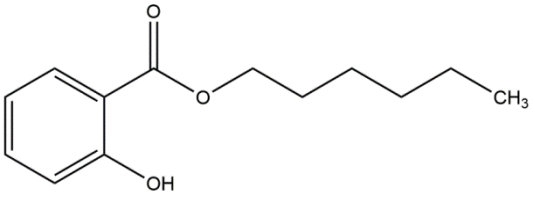
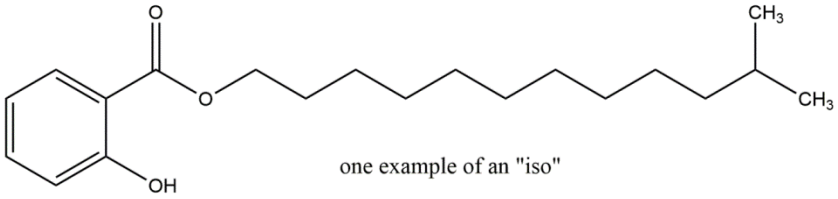
Ingredient CAS No.	Definition & Structures	Function(s)
Tridecyl Salicylate 19666-16-1	Tridecyl Salicylate is the ester of tridecyl alcohol and Salicylic Acid. It conforms to the formula: 	Skin-Conditioning Agents - Miscellaneous
Amyl Salicylate 2050-08-0	Amyl Salicylate is the ester of amyl alcohol and Salicylic Acid that conforms to the formula: 	Fragrance Ingredients
Hexyl Salicylate 6259-76-3	Hexyl Salicylate is the organic compound that conforms to the formula: 	Fragrance Ingredients; Skin-Conditioning Agents - Occlusive
Isotridecyl Salicylate 1863871-63-9	Isotridecyl Salicylate is the organic compound that conforms to the formula:  one example of an "iso"	Antistatic Agents; Skin-Conditioning Agents - Miscellaneous

Table 2. Chemical and Physical Properties of Salicylic Acid and Salicylates

Property	Value/Results	Reference
Butyloctyl Salicylate		
Molecular weight (Da)	306.45	6
log P	6.03 (estimated)	6
pK_a	10.3 (estimated)	6
Calcium Salicylate		
Formula weight (Da)	314.31	6
C12-15 Alkyl Salicylate		
Molecular weight (Da)	306.45 – 348.53	6
Capryloyl Salicylic Acid		
Molecular weight (Da)	264.32	6
log P	3.92 (estimated)	6
pK_a	3.29 (estimated)	6
Ethylhexyl Salicylate		
Form	Colorless liquid	3
Molecular weight (Da)	250.34	6
Water solubility (mg/l at 25ºC)	0.7171 (estimated)	3
Vapor pressure (mm Hg at 25ºC)	0.00000436	3
Flash point (ºC)	> 200	3
log K_{ow}	6.02 (estimated)	3
Hexyldodecyl Salicylate		
Molecular weight (Da)	390.61	6
log P	8.53 (estimated)	6
pK_a	10.3 (estimated)	6
Isocetyl Salicylate		
Molecular weight (Da)	326,55	6
log P	7.63 (estimated)	6
pK_a	10.4 (estimated)	6
Isotridecyl Salicylate		
Molecular weight (Da)	320.47	6
log P	6.37 (estimated)	6
pK_a	10.4 (estimated)	6
Magnesium Salicylate		
Formula weight (Da)	298.53	6
Methyl Salicylate		
Form	Clear, colorless liquid	5
Molecular weight (Da)	152.15	6
Specific gravity	1.18	5
Water solubility (mg/l at 25ºC)	1875 (estimated)	5
Vapor pressure (mm Hg at 25ºC)	0.09 (estimated)	5
Boiling point (ºC)	222	5
Flash point (ºF)	> 212	5
log K_{ow}	2.6 (estimated)	5

Table 2. Chemical and Physical Properties of Salicylic Acid and Salicylates

Property	Value/Results	Reference
Myristyl Salicylate		
Molecular weight (Da)	334.50	6
log P	6.88 (estimated)	6
pK_a	10.4 (estimated)	6
Potassium Salicylate		
Formula weight (Da)	176.21	6
Salicylic Acid		
Molecular weight (Da)	138.12	6
log P	1.2 (estimated)	6
pK_a	3.01 (1^{st}; estimated)	6
Sodium Salicylate		
Formula weight (Da)	160.10	6
TEA Salicylate		
Formula weight (Da)	287.31	6
Tridecyl Salicylate		
Molecular weight (Da)	320.47	6
log P	6.46 (estimated)	6
pK_a	10.4 (estimated)	6
Amyl Salicylate		
Molecular weight (Da)	208.26	6
log P	3.12 (estimated)	6
pK_a	10.4 (estimated)	6
Hexyl Salicylate		
Form	Colorless, oily liquid	4
Molecular weight (Da)	222.28	6
Water solubility (mg/l at 25ºC)	6.084 (estimated)	4
Vapor pressure (mm Hg at 20ºC)	< 0.001	4
Boiling Point (ºC)	> 200	4
Log K_{ow}	5.06 (estimated)	4
Isodecyl Salicylate		
Molecular weight (Da)	278.39	6
log P	5.12 (estimated)	6
pK_a	10.4 (estimated)	6

Table 3. Frequency and Concentration of Use of Salicylates According to Duration and Exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Amyl Salicylate				**Butyloctyl Salicylate**			
	2018[9]	**1998[1]**	**2018[10]**	**2000[1]**	**2018[9]**	**1998[1]**	**2018[10]**	**2000[1]**
Totals*	**10**	NS	***0.0023-0.26***	NR	**19**	NR	***1-35.9***	**0.5-5**
Duration of Use								
Leave-On	***1***	***NS***	***0.0023-0.23***	***NR***	***18***	***NR***	***1-35.9***	***0.5-5***
Rinse-Off	***9***	***NS***	***0.02-0.26***	***NR***	***1***	***NR***	***NR***	***NR***
Diluted for (Bath) Use	**NR**	***NS***	***NR***	***NR***	**NR**	***NR***	***NR***	***NR***
Eye Area	NR	NS	NR	NR	1	NR	3.6	NR
Incidental Ingestion	NR	NS	NR	NR	6	NR	35.9	NR
Incidental Inhalation-Spray	NR	NS	0.0023-0.0058;0.12[a]	NR	3[b]	NR	1-3	4-5[a]
Incidental Inhalation-Powder	NR	NS	NR	NR	3[b]	NR	3.6	0.5
Dermal Contact	1	NS	0.02-0.26	NR	13	NR	1-10	0.5-5 NR
Deodorant (underarm)	NR	NS	0.23	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	NS	0.0023-0.12	NR	NR	NR	NR	NR
Hair-Coloring	NR	NS	NR	NR	NR	NR	NR	NR
Nail	NR	NS	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NS	0.26	NR	6	NR	35.9	NR
Baby Products	NR	NS	NR	NR	NR	NR	NR	NR
	Capryloyl Salicylic Acid				**Ethylhexyl Salicylate**			
	2018[9]	**1998[1]**	**2018[10]**	**2000[1]**	**2018[9]**	**1998[1]**	**2018[10]**	**2000[1]**
Totals*	**100**	**5**	**0.1 -0.5**	**0.1-1**	**3474**	**83**	**0.0003-5.1**	**0.001-8**
Duration of Use								
Leave-On	***89***	***5***	***0.1-0.5***	***1***	***2762***	***80***	***0.0003-5.1***	***0.001-8***
Rinse-Off	***11***	***NR***	***0.1-0.4***	***0.1***	***701***	***3***	***0.001-0.21***	***0.001-0.005***
Diluted for (Bath) Use	***NR***	***NR***	***NR***	***NR***	***11***	***NR***	***0.2***	***NR***
Eye Area	9	NR	NR	NR	3	NR	0.1	NR
Incidental Ingestion	NR	NR	0.1	NR	54	2	4-4.5	8
Incidental Inhalation-Spray	26[b]	1[b]	0.1-0.3	0.1-1[b]	2307;98[b]	18;2[b]	0.00099-5;0.012-0.05[a]	0.001-0.01;0.001-5[b]
Incidental Inhalation-Powder	26[b]	1[b]	0.3	0.1-1[b]	3;98[b]	2[b]	NR	5; 0.001-5[b]
Dermal Contact	100	5	0.1-0.5	0.1-1	3280	45	0.0003-5.1	0.5-5
Deodorant (underarm)	NR	NR	0.3	NR	6	NR	0.0016	NR
Hair - Non-Coloring	NR	NR	0.1	NR	129	35	0.00099-0.2	0.001-0.01
Hair-Coloring	NR	NR	NR	NR	5	NR	0.012	NR
Nail	NR	NR	NR	NR	6	1	0.15	0.1
Mucous Membrane	NR	NR	0.3	NR	676	2	0.0012-4.5	8
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Hexyl Salicylate				**Isodecyl Salicylate**			
	2018[9]	**1998[1]**	**2018[10]**	**2000[1]**	**2018[9]**	**1998[1]**	**2018[10]**	**2000[1]**
Totals*	**2**	NS	**0.013-0.52**	NR	**19**	**3**	**2.5**	NR
Duration of Use								
Leave-On	***2***	***NS***	***0.013-0.12***	***NR***	***19***	***2***	***2.5***	***NR***
Rinse-Off	***NR***	***NS***	***0.032-0.52***	***NR***	***NR***	***1***	***NR***	***NR***
Diluted for (Bath) Use	***NR***	***NS***	NR	***NR***	***NR***	***NR***	***NR***	***NR***
Exposure Type								
Eye Area	NR	NS	0.00074	NR	1	NR	NR	NR
Incidental Ingestion	NR	NS	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[b]	NS	0.013-0.023; 0.11[a]	NR	7[b]	2[a]	NR	NR
Incidental Inhalation-Powder	1[b]	NS	NR	NR	7[b]	NR	NR	NR
Dermal Contact	2	NS	0.02-0.52	NR	19	3	2.5	NR
Deodorant (underarm)	NR	NS	0.097	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NS	0.013-0.21	NR	NR	NR	NR	NR
Hair-Coloring	NR	NS	0.5	NR	NR	NR	NR	NR
Nail	NR	NS	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NS	0.52	NR	NR	NR	NR	NR
Baby Products	NR	NS	NR	NR	NR	NR	NR	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.

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

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

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

NR - no reported use

Table 3. Frequency and Concentration of Use of Salicylates According to Duration and Exposure.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Magnesium Salicylate				**Methyl Salicylate**			
	2018[9]	**1998[1]**	**2018[10]**	**2000[1]**	**2018[9]**	**1998[1]**	**2018[10]**	**2000[1]**
Totals*	**10**	NR	**0.2**	NR	**36**	**25**	**0.00000006-1**	**0.0001-0.6**
Duration of Use								
Leave-On	***10***	***NR***	***0.2***	***NR***	***18***	***4***	***0.0000013-1***	***0.02***
Rinse-Off	***NR***	***NR***	***NR***	***NR***	***17***	***20***	***0.00000006-0.038***	***0.0001-0.6***
Diluted for (Bath) Use	***NR***	***NR***	***NR***	***NR***	***1***	***1***	***0.0016***	***NR***
Exposure Type								
Eye Area	10	NR	0.2	NR	NR	NR	0.0000013-0.000026	NR
Incidental Ingestion	NR	NR	NR	NR	12	14	0.038-0.23	0.03-0.2
Incidental Inhalation-Spray	NR	NR	NR	NR	8[b]	1[b]	0.0000051-0.5;0.000065-0.23[b]	0.1;0.02-0.2[b]
Incidental Inhalation-Powder	NR	NR	NR	NR	8[b]	1[b]	0.000065-0.23[b]	0.02-0.2[b]
Dermal Contact	2	NR	0.2	NR	23	6	0.00000006-1	0.0001-0.6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	1	3	0.0000051-0.0011	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	0.00000002	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	17	17	0.000018-0.23	0.0001-0.2
Baby Products	NR	NR	NR	NR	1	NR	NR	NR
	Salicylic Acid				**Sodium Salicylate**			
	2018[9]	**1998[1]**	**2018[10]**	**2000[1]**	**2018[9]**	**1998[1]**	**2018[10]**	**2000[1]**
Totals*	**1300**	**107**	**0.00001-30**	**0.0008-3**	**165**	**7**	**0.0008-0.5**	**0.09-2**
Duration of Use								
Leave-On	***608***	***62***	***0.00001-2***	***0.02-3***	***70***	***5***	***0.0015-0.1***	***2***
Rinse-Off	***689***	***45***	***0.01-30***	***0.0008-3***	***95***	***2***	***0.0008-0.5***	***0.09-0.3***
Diluted for (Bath) Use	***3***	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***
Exposure Type								
Eye Area	26	2	0.00001-0.2	0.2-2	5	NR	NR	NR
Incidental Ingestion	1	NR	NR	1	NR	2	NR	0.09-0.2
Incidental Inhalation-Spray	5;248[b]	3;10[b]	0.1-0.5;0.004-0.5[a]	0.02-3[b]	41[b]	1[b]	NR	0.09-2[b]
Incidental Inhalation-Powder	7;248[b]	1;10[b]	NR	0.2-0.6; 0.02-3[b]	41[b]	1[b]	NR	0.09-2[b]
Dermal Contact	999	77	0.00001-30	0.0008-3	155	3	0.0015-0.5	2
Deodorant (underarm)	6	1	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	254	28	0.004-4	0.002-0.2	9	2	0.0008-0.5	0.2
Hair-Coloring	42	2	0.015-0.1	0.1	1	NR	NR	NR
Nail	3	NR	NR	0.2	NR	NR	NR	NR
Mucous Membrane	190	2	0.064-0.2	0.0008-2	82	2	0.25-0.37	0.09-0.2
Baby Products	2	NR	NR	NR	NR	NR	0.31	NR
	TEA Salicylate				**Tridecyl Salicylate**			
	2018[9]	**1998[1]**	**2018[10]**	**2000[1]**	**2018[9]**	**1998[1]**	**2018[10]**	**2000[1]**
Totals*	**5**	**5**	**NR**	**0.0001-0.75**	**14**	**2**	**NR**	**0.01**
Duration of Use								
Leave-On	***4***	***5***	***NR***	***0.0001-0.75***	***12***	***2***	***NR***	***0.01***
Rinse-Off	***1***	***NR***	***NR***	***0.0002***	***2***	***NR***	***NR***	***NR***
Diluted for (Bath) Use	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***	***NR***
Exposure Type								
Eye Area	NR	NR	NR	NR	2	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	1[b]	NR	0.001[b]	4[b]	2[b]	NR	0.01[b]
Incidental Inhalation-Powder	NR	1[b]	NR	0.001[b]	4[b]	2[b]	NR	0.01[b]
Dermal Contact	NR	5	NR	0.0001-0.75	14	2	NR	0.01
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	5	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	0.0002	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	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.

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

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

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

NR - no reported use

NS – not surveyed

Table 3. Frequency and Concentration of Use of Salicylates According to Duration and Exposure.

	# of Uses		*Max Conc of Use (%)*	
	Isocetyl Salicylate			
	2018[9]	**1998[1]**	**2018[10]**	**2000[1]**
Totals*	NR	NR	**NR**	**3-5**
Duration of Use				
Leave-On	***NR***	***NR***	***NR***	***3-5***
Rinse-Off	***NR***	***NR***	***NR***	***NR***
Diluted for (Bath) Use	***NR***	***NR***	***NR***	***NR***
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	5[a]
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	3-5
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	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.
[a] It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[c] It is possible that these products may be powders, but it is not specified whether the reported uses are powders
NR - no reported use
NS – not surveyed

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Irritation (Animal)			
Amyl Salicylate (undiluted)	6 Albino angora rabbits	Test substance (0.1 g) applied (using glass syringe) for 24 h to 3 x 3 cm area on dorsal surface. Plastic collar (25-cm diameter) wrapped around the neck. Application repeated 30 min after end of 24-h contact period. Reactions scored 24 h after first application and 48 h and 72 h after 2nd patch application	Amyl Salicylate was severely irritating.[52]
Amyl Salicylate (undiluted)	6 male Hartley guinea pigs	Same protocol, but application to dorsal, mid-lumbar region	Amyl Salicylate was mildly irritating.[52]
Amyl Salicylate (undiluted)	6 miniature swine of the Pitman-Moore Improved strain	Test substance (0.05 g) applied, under 15 mm diameter patch, to dorsal skin for 48 h.	Amyl Salicylate was a non-irritant.[52]
Ethylhexyl Salicylate (undiluted)	4 rabbits (strain not stated)	Test substance applied (under occlusion) to intact or abraded skin for 24 h.	Mild erythema, lasting 24 h, was observed.[3]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Hexyl Salicylate (1 to 100%)	Groups of 5 male hrBR outbred hairless albino guinea pigs	Single 0.1 ml application at a concentration of 1%, 5%, 10%, or 50% (in 3:1 diethyl phthalate:ethanol) or undiluted. Applied to dorsal skin using 25 mm Hilltop® chambers. Chambers removed after 2 h (± 15 min). Reactions scored at 1h and 4 h after removal and at 1, 2, and 3 days post-administration.	Skin irritation was not observed at any of the concentrations tested.[4]
Hexyl Salicylate (10 to 50%)	4 male albino Dunkin/Hartley guinea pigs	Topical treatment with 8 mm diameter filter paper patches saturated with 10%, 25%, or 50% Hexyl Salicylate (in acetone), using 1 mm aluminum patch test cups. Patch removal after 24 h, and reactions scored at 24 h and 48 h post-removal.	No evidence of skin irritation (at 10% concentration). Very slight erythema (at 25% and 50%, 3 animals).[4]
Hexyl Salicylate (5%)	4 inbred Hartley albino guinea pigs	Test substance (0.1 ml) injected intradermally into the shaved flank. Reactions read 24 h after injection.	Skin irritation was not observed.[56]
Hexyl Salicylate (0.1 to 2%, in 0.01% dodecylbenzenesulfonate /saline)	4 male albino Dunkin/Hartley guinea pigs	Same protocol	Very slight erythema (at 0.1%) and slight erythema and edema (at 0.25%, 0.5%, 1%, and 2%).[4]
Hexyl Salicylate (0.1%)	4 inbred Hartley albino guinea pigs	Same protocol.	Skin irritation was observed.[56]
Hexyl Salicylate (undiluted)	2 miniature swine	Test substance (20 µl/5 cm^2) applied to back	Skin irritation was not observed.[4]
Hexyl Salicylate (10 to 100%)	3 or 4 female New Zealand white rabbits	Surgical lint square (2.5 cm^2) containing 0.5 ml of 10%, 25%, or 50% Hexyl Salicylate in diethyl phthalate, or undiluted ingredient. Lint square (semi-occlusive patch) placed on 6 cm^2 area of clipped, intact dorsal skin for 4h. Reactions assessed at 1 h, 24 h, 48 h, 72 h, and 168 h after patch removal.	Skin irritation was not observed at concentrations of 10% and 25%, but was observed at higher concentrations.[4]
Hexyl Salicylate (undiluted)	10 rabbits (strain not stated)	Single dermal dose of 5 g/kg [skin irritation data from acute dermal toxicity study]	Skin irritation was observed: moderate edema (7 animals), slight edema (3 animals), moderate erythema (8 animals), and slight erythema (2 animals).[4]
Hexyl Salicylate (undiluted)	6 hairless mice	Test substance (20 µl/5 cm^2) applied to back	Skin irritation was not observed.[4]
Methyl Salicylate (undiluted)	9 rabbits (strain not stated)	Single dermal dose of 5 g/kg	Slight erythema and edema (2 animals) and moderate erythema and edema (7 animals).[5]
Wintergreen oil (contains 80 to 99% Methyl Salicylate)	6 hairless mice and 2 miniature swine	Test substance (20 µl) applied to 5 cm^2 area on back	Flaking, hyperkeratosis, and dry desquamation observed.[5]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Methyl Salicylate	Mice (strain not stated)	Mouse ear swelling test. Test substance (in 4:1 acetone to olive oil) applied in 4-day dosing protocol. The minimal irritating concentration (lowest concentration to produce a % ear swelling significantly greater than the vehicle) was determined.	Minimal irritating concentration was 20%.[54]
Methyl Salicylate (3%)	6 to 8 outbred Himalayan, white-spotted male and female guinea pigs	Test substance (0.1 ml) applied to 8 cm^2 area on clipped flank (uncovered) daily for 21 days	Minimal skin irritation.[53]
Methyl Salicylate (3%)	6 to 8 outbred Himalayan, white-spotted male and female guinea pigs	Test substance (0.025 ml) applied for 24 h to 2 cm^2 area on clipped flank (uncovered)	Mild erythema in at least 25% of animals.[53]
Salicylic Acid (formulations containing 3.5%, 5%, and 7.5%)	Groups of 6 adult male albino New Zealand rabbits	Formulations applied to concave side of left ears. Distilled water (control) applied to right ears. Macroscopic evaluations performed daily	All 3 formulations caused significant macroscopic alterations (desquamation, inflammatory reaction, and comedogenic effect) when compared to the control.[55]
Irritation (Human)			
Amyl Salicylate (32% in acetone)	50 adult male subjects	A 15 mm diameter occlusive patch containing 0.05 ml of test substance applied for 48 h. Reactions scored 30 min after patch removal	Skin irritation was not observed.[52]
Ethylhexyl Salicylate (4% in petrolatum)	23 male subjects	48-h closed patch test	Skin irritation was not observed.[3]
Hexyl Salicylate (undiluted)	30 subjects	4-h patch (25 mm Hilltop® chamber) test. Patch contained 0.2 ml of test substance. Reactions read at 24 h, 48 h, and 72 h after patch removal	Skin irritation was not observed.[57]
Hexyl Salicylate (0.3%, 3%, or 30%, in 3:1 diethyl phthalate:ethanol)	56 subjects (15 males, 41 females)	24-h patch test. Test substance (0.3 ml) applied to back using 25 mm Hilltop® chambers. Duplicate patches placed on both sides of spine. Sites evaluated at ~1 h, 24 h, 48 h, and 72 h after patch removal	Skin irritation was not observed.[4]
Methyl Salicylate (30% and 60%)	9 subjects (3 males, 6 females)	25 ml of test substance (in 80% ethanol and 20% deionized water vehicle) pipetted onto the skin (forearm). A PTFE cap was placed over the application site to prevent evaporation. Test substance was applied every 48 h for a total of 6 applications.	Skin irritation was observed at both concentrations.[58]
12% wintergreen oil (contains 80 to 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%)	25 male subjects	48-h patch test (occlusive patches)	Skin irritation was not observed.[5]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Methyl Salicylate (8% in petrolatum)	27 male subjects	48-h patch test (occlusive patches)	Skin irritation was not observed.[5]
Sensitization (In Vitro)			
Hexyl Salicylate	In vitro model of dendritic cells	Genomic allergen rapid detection (cell-based alternative to animal testing). Assay based on a biomarker signature comprising 200 genes measured in in vitro model. Assay consistently reports predictive performances of ~90% .	Hexyl Salicylate was predicted to be a skin sensitizer.[59]
Salicylic Acid	Keratinocytes, dendritic cells, and peptides	Integrated testing strategy focusing on the following 3 in vitro methods covering the first 3 steps of the adverse outcome pathway: direct peptide reactivity assay, keratinocyte activation assay, and dendritic cell line activation assay. Results compared to in vivo data (especially human)	The results for Salicylic Acid were equivocal, but, ultimately, were considered positive results.[60]
Salicylic Acid	Peptides	Allergen-peptide/protein interaction assay, which permits the profiling of all amino acid specific allergen-peptide interactions. Mass spectrometry of target peptides performed	No modifications of peptide-21 or peptide-20 by Saslicylic Aid. Non-allergenic Salicylic Acid did not interfere with Cys containing peptide-21 or Cys-free peptide-20.[61]
Sensitization (Animal)			
Hexyl Salicylate	Mice	LLNA. EC3 determined.	A very low EC3 (0.18%) was reported., and thought to have been due to possibly sensitizing impurities.[60]
Hexyl Salicylate	10 inbred Hartley albino guinea pigs	Modified Draize procedure: Induction injections at 0.25%; challenge at 0.1% (injection) and at 5% (topical application). Induction consisted of 4 intradermal injections into flank (0.1 ml each), and challenge (left and right flanks) occurred 14 days later. Second challenge performed 7 days after first	Sensitization was observed after the second challenge.[56]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Hexyl Salicylate	Groups of 5 Crl:IAF(HA)-hrBR outbred albino hairless guinea pigs	Induction phase involved intradermal injection of a sterile water and Freund's complete adjuvant mixture (0.1 ml) into 2.5 cm^2 nuchal area of skin, and 2-h topical application (0.3 ml) of 100% Hexyl Salicylate in 3:1 diethyl phthalate:ethanol using 25 mm Hilltop® chamber patches. Procedure repeated on days 3, 5, 7, 10, and 12. On day 22, topical challenge with 50% Hexyl Salicylate in vehicle and 100% Hexyl Salicylate. Sites observed for up to 3 days post-application	Sensitization was not observed.[4]
Hexyl Salicylate	10 albino Dunkin/Hartley guinea pigs	Magnusson-Kligman maximization test. Induction involved 6 intradermal injections of 1% Hexyl Salicylate to a 2 x 4 cm area in dorsal shoulder region. 7 days later, occlusive patch containing 40% Hexyl Salicylate applied to shoulder for 48 h. At 13 to 14 days post-application of occlusive patch, 24-h challenge (flank) with 8 mm diameter occlusive patch containing 10% Hexyl Salicylate. Three additional challenge applications (on contralateral flanks) at weekly intervals.	Sensitization was not observed.[4]
Methyl Salicylate (50%)	Mice	LLNA	Non-sensitizer.[63]
Methyl Salicylate (0.7 µM)	Mice	LLNA	Number of positive tests/number of total tests was 1 in 4 (25% positive response). Overall, results were classified as negative (non-sensitizer).[62]
Sensitization (Human)			
Hexyl Salicylate (30% in 3:1 diethyl phthalate:ethanol)	103 subjects (29 males and 74 females)	HRIPT. Induction (3 weeks): Occlusive patches (25 mm Hilltop® chamber system) containing test substance (0.3 ml) applied for 24 h to left side of back for 9 applications. Challenge: After 2-week non-treatment period, occlusive challenge patch containing test substance applied for 24 h. Reactions scored at 48 h, 72 h, and 96 h after application.	Neither irritation nor sensitization was observed.[4]
Hexyl Salicylate	Human subjects (number not stated)	Protocol not stated	Human skin sensitization no-observed –effect – level of 35,433 µg/cm^2.[64]
Hexyl Salicylate	Human subjects (number not stated)	Maximization test	No induction was observed at a dose of 20,654 µg/cm^2.

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Hexyl Salicylate (3% in petrolatum)	22 subjects	Maximization test. Pre-treatment of test site for 24 h with 5% aqueous sodium lauryl sulfate (SLS), under occlusion. Test substance application, under occlusion, to same site on volar forearm or back for 5 alternate-day-48-h periods. After 10-day non-treatment period, occlusive challenge patches applied for 48 h to 2 new sites (SLS pre-treat-ment and no pre-treatment). Reactions were scored at the time of patch removal and 24 h later.	Neither irritation nor sensitization was observed.[4]
12% Wintergreen oil (contains 80 to 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%) in petrolatum	25 subjects	Maximization test. Induction: Test substance applied, under occlusion, to same site on volar forearm for 5 alternate-day 48-h periods. Prior to initial application only, site pre-treated with 5% aqueous SLS for 24 h. Challenge: After 10- to 14-day non-treatment period, 48-h occlusive challenge patch application (2 patches; pretreatment with 5% SLS for 30 min and no pre-treatment) to new sites. SLS-treated sites served as controls.	Sensitization was not observed.[5]
Methyl Salicylate (8% in petrolatum)	27 subjects	Maximization test. Same protocol, except SLS pre-treatment between patch applications during induction and pre-treatment of challenge site with 10% SLS 1 h before challenge. Reactions read when patches removed and 24 h later	Sensitization was not observed.[5]
Methyl Salicylate (1.25%)	39 subjects (13 males, 26 females)	HRIPT. Induction: 24-h occlusive patch (1-inch square, at center of 1 x 3 inch adhesive bandage) containing 0.5 ml of test substance). 9 applications to same site over 3-week period. Challenge: On Monday of week 6, 24-h challenge patch containing test substance applied to new site. Reactions scored at 24 h and 72 h after patch removal	Sensitization was not observed.[5]

Table 5. Photosensitization/Phototoxicity Studies on Salicylates

Test Substance	Animals/Subjects/Cells Tested	Test Protocol	Results
Phototoxicity (In vitro)			
Ethylhexyl Salicylate (0.1 to 316 µg/ml)	Cell suspension of 3T3 fibroblasts (1 x 10^5 cells/ml, 1 x 10^4 cells/well)	3T3 neutral red uptake phototoxicity test. Concentrations applied (in sextuplicate) in 96-well plates. After 1 h of incubation, irradiation with UVA light. Neutral red medium added after second incubation. Photoirritation factor (PIF, ratio of toxicity with and without UV light) was calculated., and value for mean photoeffect (MPE, statistical comparison of dose response curves obtained with and without UV) was determined . PIF > 1 (potential phototoxic hazard). MPE > 0.1 (predicted to be phototoxic.	PIF = 1.756 (1^{st} run) and 1.043 (2^{nd} run). MPE = 0.109 (1^{st} run) and 0.109 (2^{nd} run). Phototoxicity test results were classified as negative.[65]
Phototoxicity/Photosensitization (Animal)			
Hexyl Salicylate (undiluted)	12 Skh:hairless-1 mutant mice)	Single application of test substance (20 µl/2 cm^2) on back (6 mice). Application followed by exposure to 6 kW long arc xenon lamp (distance = 1 m; intensity = 0.1667 W/m^2) for 40 min and 4 fluorescent blacklight lamps (intensity of 3 W/m^2) for 1 h. Six controls treated with test substance only. Positive control group was treated with 8-methoxy-psoralen in methanol (0.01% w/v) . Sites evaluated at 4 h, 24 h, 48 h, 72 h, and 96 h.	No reactions were observed.[4,66]
Hexyl Salicylate (undiluted)	2 miniature swine	Single application of test substance (20 µl/5 cm^2) on back. Irradiation performed for 40 min using same light source and procedure as above.	Phototoxicity was not observed.[4,66]
Hexyl Salicylate (5%, 10%, 50%, or 100%)	2 groups of 5 hairless albino guinea pigs of the Crl:IAF(HA)-hrBR outbred strain	Each concentration (volume = 0.3 ml) applied to dorsal skin along midline using 25 mm Hilltop® chamber. 2 h later, patches removed and sites irradiated for ~ 2.25 h with UVR (2.25 x minimal erythemal dose [MED]) using 6.5 kW long-arc xenon water-cooled lamp with filter used to attenuate mid-range UVB. Sites evaluated immediately and 1h and 2 h later, and at 1, 2, and 3 days after application.	Phototoxicity was not observed.[4]

Table 5. Photosensitization/Phototoxicity Studies on Salicylates

Test Substance	Animals/Subjects/Cells Tested	Test Protocol	Results
Hexyl Salicylate (50% and 100%, in 3:1 diethyl phthalate:ethanol)	2 groups of 5 Crl:IAF (HA)-hBR outbred albino, hairless guinea pigs	Induction: test substance (0.3 ml, on 25 mm-diameter Hill Top® patch) applied for 2 h to nuchal area of skin (2.5 cm^2). After patch removal, application site exposed for 2.25 h to UVR (2.25 x MED) from 6.5 kW long-arc xenon water-cooled lamp with filter used to attenuate mid-range UVB. Procedure repeated (once daily) on days 3, 5, 8, 10, and 12. Challenge: On day 22, patch containing test substance applied for 2 h. Exposure of site to UVR for 2.25 after patch removal. Sites scored at 1 h and 4 h after patch application.	Photoallergy was not observed.[4]
Undiluted w2 intergreen oil (contains 80 to 99% Methyl Salicylate)	2 miniature swine	Test substance (20 µl/5 cm^2) applied to back. Site exposed for 1 h to UVA light (10 watts/m^2) from fluorescent black light lamps, filtered to limit exposure to long wave UV light only. The negative and positive controls were methanol and 8-methoxy-psoralen (in methanol), respectively	Phototoxicity was not observed.[5]
Phototoxicity (Human)			
Hexyl Salicylate (0.3%, 3%, and 30% in 3:1 diethyl phthalate:ethanol)	56 subjects (41 females, 15 males)	Test substance applied to duplicate patches (25 mm Hilltop® chambers) that were placed on the back (both sides of the spine, 24-h contact period). Each subject had 3 patches containing Hexyl Salicylate (applied to left paraspinal region) and 3 control patches (vehicle and saline controls at non-irradiated sites in right paraspinal region) applied. After removal of patches from the left paraspinal region, the sites were irradiated with 16 J/cm^2 of UVA for 10 min, and, then, with UVB (0.75 MED). Sites evaluated at 1 h, 24 h, 48 h, and 72 h after irradiation	No reactions were observed.[4]

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