
Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics

Status: Draft Amended Report for Panel Review
Release Date: May 10, 2019
Panel Date: June 6-7, 2019

The 2019 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.



Commitment & Credibility since 1976

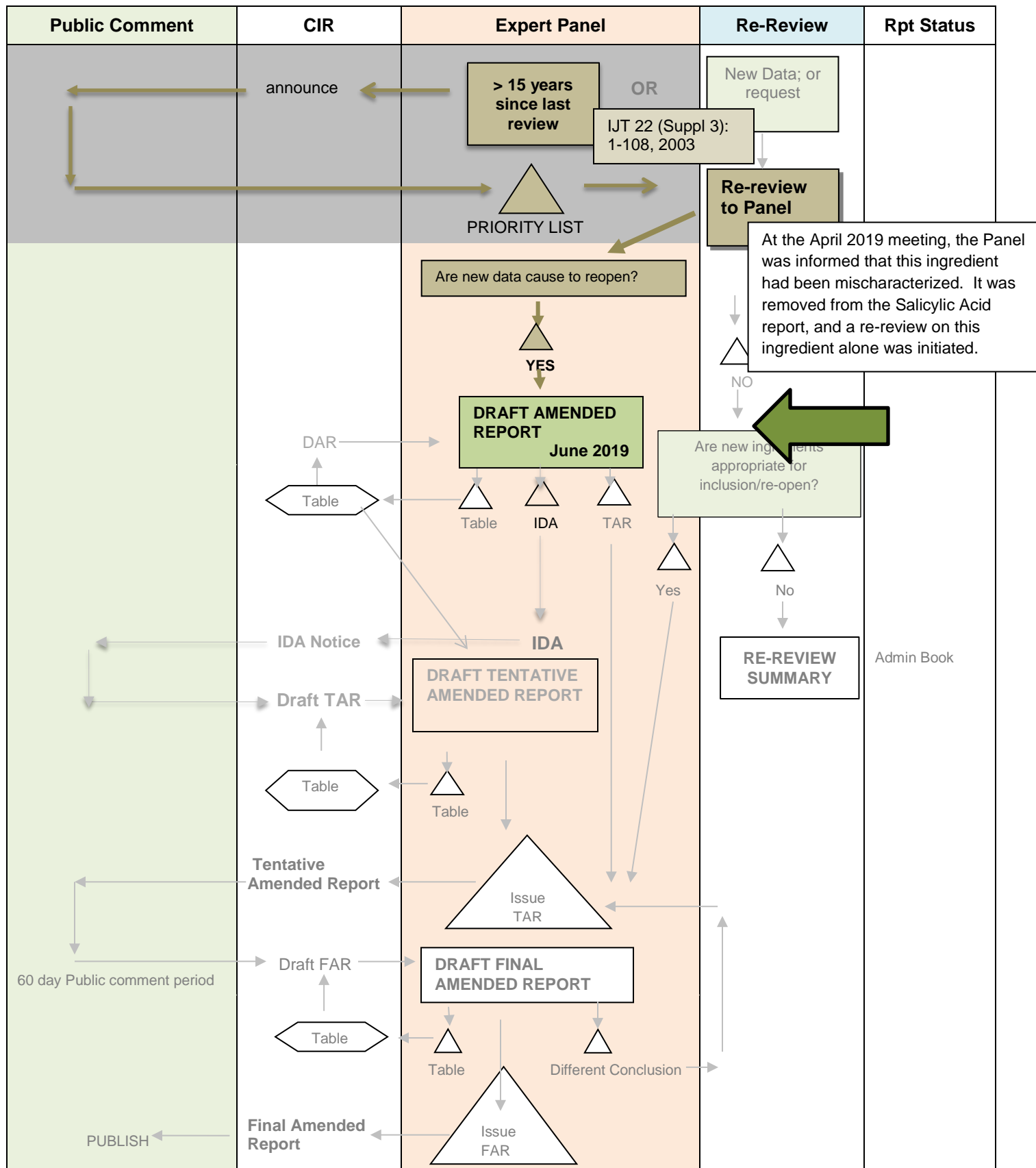
Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 10, 2019
Subject: Draft Amended Report on Capryloyl Salicylic Acid

Enclosed is a draft amended report on Capryloyl Salicylic Acid (*capryl062019rep*). This is the first time the Panel has assessed the safety of this ingredient correctly characterized as a ketone. At their April 2019 meeting, the Panel issued a final amended report on the 18 Salicylic Acid esters. Because the definition previously given for Capryloyl Salicylic Acid (previously defined as an ester) is incorrect and it is now correctly defined as a ketone, this ingredient is not included in the final amended report that was issued. Therefore, a separate re-review was initiated for this ingredient, and this draft amended report on Capryloyl Salicylic Acid was prepared for Panel review

Also included in this package for your review are the flow chart (*capryl062019flow*), literature search strategy (*capryl062019strat*), ingredient data profile (*capryl062019prof*), and 2019 FDA VCRP data (*capryl062019FDA*).

If the data included in this report adequately address the safety of Capryloyl Salicylic Acid, the Panel should be prepared to formulate a tentative conclusion, provide the rationale to be described in the Discussion, and issue a Tentative Amended Report for public comment. If the data are not sufficient for making a determination of safety, then an Insufficient Data Announcement (IDA) should be issued that provides a listing of the additional data that are needed.

RE-REVIEW FLOW CHARTINGREDIENT/FAMILY Capryloyl Salicylic AcidMEETING June 2019

*If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

CIR History of:

Capryloyl Salicylic Acid

Draft Amended Report, Teams/Panel: June 6-7, 2019

Capryloyl Salicylic was removed from the Salicylic Acid and Salicylates ingredient group (i.e., because it is a ketone, and not an ester) prior to the Panel's review of the Draft Final Amended Report at the April 2019 Panel meeting. A Final Amended Report on this group (minus Capryloyl Salicylic Acid) was issued at that meeting. A Draft Amended Report on Capryloyl Salicylic Acid that contains data on this ketone (identified by CAS No. 78418-01-6 and corresponding chemical names for this ketone) has been prepared for the Panel's review at this Panel meeting.

Capryloyl Salicylic Acid Data Profile* –June 6-7, 2019 Panel – Wilbur Johnson

[illegible]

* "X" indicates that data were available in a category for the ingredient

[Capryloyl Salicylic Acid]

Ingredient Names (for same ingredient)	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS*	NICNAS	NTIS	NTP	WHO	FAO	ECET-OC	Web
Capryloyl Salicylic Acid	78418-01-6	Yes	76/0	6/5	1/1	No	No	No	No	No	Not Searchable	Yes	No	No	No	No	No	
5-Octanoylsalicylic acid	78418-01-6		32/0	0	1/0	No	No	No	No	No	Ditto	No	No	No	No	No	No	
2-Hydroxy-5-octanoyl benzoic acid	78418-01-6		7/0	4/4	1/1	No	No	No	No	No	Ditto	Yes	No	No	No	No	No	
2-Hydroxy-5-octanoylbenzoic acid	78418-01-6		21/0	12/9	10/10	No	No	No	No	No	Ditto	No	No	No	No	No	No	
78418-01-6 (alone)	0		202/1	0	0/0	No	No	Yes	REACH dossier	No	Ditto	No	No	No	No	No	No	

*Database not searchable due to effects of Government Shutdown

Search Strategy*[document search strategy used for SciFinder, PubMed, and Toxnet]**[identify total # of hits /# hits that were useful or examined for usefulness]*

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - <http://www.personalcarecouncil.org/science-safety/line-infobase>

SciFinder (usually a combined search for all ingredients in report; list # of this/# useful) - <https://scifinder.cas.org/scifinder>

PubMed (usually a combined search for all ingredients in report; list # of this/# useful) -

<http://www.ncbi.nlm.nih.gov/pubmed>

Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – <https://toxnet.nlm.nih.gov/> (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm> (CFR); then, list of all databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>; then, <http://www.accessdata.fda.gov/scripts/fcn/fcnavigation.cfm?rpt=eafuslisting&displayall=true> (EAFUS); <http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm> (GRAS); <http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm> (SCOGS database); <http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives> (indirect food additives list); <http://www.fda.gov/Drugs/InformationOnDrugs/default.htm> (drug approvals and database); <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf> (OTC ingredient list); <http://www.accessdata.fda.gov/scripts/cder/iig/> (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - <http://ec.europa.eu/growth/tools-databases/cosing/>

ECHA (European Chemicals Agency – REACH dossiers) – <http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1>

IUCLID (International Uniform Chemical Information Database) - <https://iuclid6.echa.europa.eu/search>

OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)-

<http://webnet.oecd.org/hpv/ui/Search.aspx>

HPVIS (EPA High-Production Volume Info Systems) - <https://ofmext.epa.gov/hpvis/HPVISlogin>

NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- <https://www.nicnas.gov.au/>

NTIS (National Technical Information Service) - <http://www.ntis.gov/>

NTP (National Toxicology Program) - <http://ntp.niehs.nih.gov/>

WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

FAO (Food and Agriculture Organization of the United Nations) - <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/> (FAO);

FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

Web – perform general search; may find technical data sheets, published reports, etc

ECETOC (European Center for Ecotoxicology and Toxicology Database) - <http://www.ecetoc.org/>

Botanical Websites, if applicable

Dr. Duke's <https://phytochem.nal.usda.gov/phytochem/search>

Taxonomy database - <http://www.ncbi.nlm.nih.gov/taxonomy>

GRIN (U.S. National Plant Germplasm System) - <https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx>

Sigma Aldrich plant profiler <http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html>

Fragrance Websites, if applicable

IFRA (International Fragrance Association) – <http://www.ifraorg.org/>

RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers

Absorption

Acute

Allergy

Allergic

Allergenic

Cancer

Carcinogen

Chronic

Development

Developmental

Excretion

Genotoxic

Irritation

Metabolism

Mutagen

Mutagenic

Penetration

Percutaneous

Pharmacokinetic

Repeated dose

Reproduction

Reproductive

Sensitization

Skin

Subchronic

Teratogen

Teratogenic

Toxic

Toxicity

Toxicokinetic

Toxicology

Tumor

Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics

Status: Draft Amended Report for Panel Review
Release Date: May 10, 2019
Panel Date: June 6-7, 2019

The 2019 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.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of Salicylic Acid and 16 salicylates in 2003.¹ That safety assessment included Capryloyl Salicylic Acid, which was included in the grouping because at the time, it was mischaracterized and defined as an ester. However, it is now known that this ingredient is a ketone. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Capryloyl Salicylic Acid is reported to function as a skin conditioning agent.²

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 (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://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. Much of the data included in this safety assessment was found at the European Chemicals Agency (ECHA) and National Industrial Chemicals Notification and Assessment Scheme (NICNAS) websites.^{3,4} Please note that these websites provide summaries of information from other studies, and it is those summary data that are reported in this safety assessment when ECHA or NICNAS is cited.

CHEMISTRY

Definition and General Characterization

Capryloyl Salicylic Acid (CAS No. 78418-01-6) was previously, erroneously defined as the ester of salicylic acid and caprylic acid. However, it has become apparent that Capryloyl Salicylic Acid is instead the 5-capryl ketone of salicylic acid. As such, this chemical is structurally distinct from the salicylate carboxyl esters. It is now defined as the organic compound that conforms to Figure 1.²

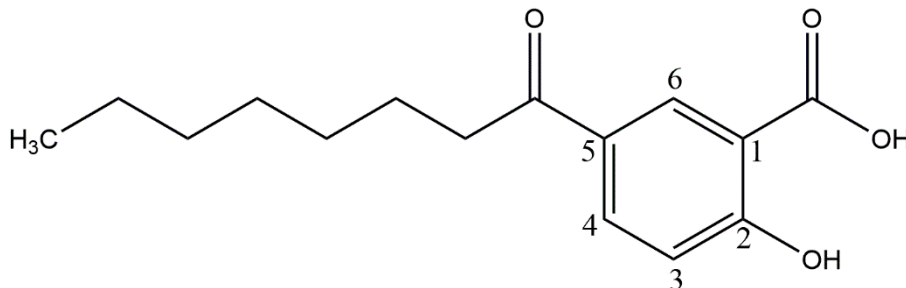


Figure 1. Capryloyl Salicylic Acid

Chemical and Physical Properties

Capryloyl Salicylic Acid has a molecular weight of 264 and has an 8-carbon acyl fatty chain linked to the fifth carbon of the benzene ring.⁵ This white powder is water soluble (29.7 mg/mL) and acidic (estimated pKa of 2.68). Further chemical and physical properties of Capryloyl Salicylic Acid are presented in Table 1.^{3,6}

Method of Manufacture

The synthetic method of manufacture for Capryloyl Salicylic Acid is based on Friedel-Crafts acylation of methyl salicylate by capryloyl chloride and aluminum trichloride to yield the methyl ester of Capryloyl Salicylic Acid.⁷ This ester is hydrolyzed with sodium hydroxide, after which acidification yields Capryloyl Salicylic Acid.

Impurities

It has been reported that the structural isomer, 3-capryloyl salicylic acid, is a highly plausible contaminant of Capryloyl Salicylic Acid.⁷

USE

Cosmetic

The safety of this cosmetic ingredient is evaluated based, in part, on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics.⁸ 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 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.⁹

According to 2019 VCRP data, Capryloyl Salicylic Acid is reported to be used in 104 cosmetic products (93 leave-on and 11 rinse-off).⁸ The results of a concentration of use survey conducted in 2018 indicate that Capryloyl Salicylic Acid is used at concentrations up to 0.5% (in moisturizing products, not spray), which is the highest reported maximum use concentration for leave-on formulations.⁹ In rinse-off products, Capryloyl Salicylic Acid is reported to be used at concentrations up to 0.4% (in paste masks and mud packs), which is the highest reported maximum use concentration for rinse-off formulations. Further use frequency and concentration of use data are presented in Table 2.

Cosmetic products containing Capryloyl Salicylic Acid may be applied to the skin at concentrations up to 0.5% (moisturizing products, not spray) and may come in contact with the eyes during use of eye lotions and other eye makeup preparations (use concentrations were not reported by industry). Capryloyl Salicylic Acid also could be incidentally ingested during product use (e.g., use concentrations up to 0.1% in lipsticks). Products containing Capryloyl Salicylic Acid 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.

Capryloyl Salicylic Acid is reported to be used in deodorant sprays (aerosolized) at concentrations up to 0.3%. 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.^{10,11,12,13} 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.^{10,11} There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.¹¹ However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. According to information submitted for the ECHA dossier, the particle size distribution of this ingredient as a raw material includes 13.23 – 26.71% of particles < 100 µm.³ However, the barring of these raw material particles sizes on the particle sizes of final consumer product formulations is not clear. Capryloyl Salicylic Acid is being used in face powders at concentrations up to 0.3%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.^{14,15,16}

According to information submitted for the ECHA dossier, the particle size distribution of this ingredient as a raw material, includes 13.23 – 26.71% of particles < 100 µm. However, the barring of these raw material particles sizes on the particle sizes of final consumer product formulations is not clear.

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

The penetration of Capryloyl Salicylic Acid through human skin was assessed using a Franz diffusion chamber and skin samples.⁵ The amount of Capryloyl Salicylic Acid that penetrated deeper than the stratum corneum after a 16-h contact time was significantly lower than its parent acid, salicylic acid, in the same vehicle. Thus, only approximately 6% of Capryloyl Salicylic Acid was found to penetrate deeper than the stratum corneum, after 16 h, versus 58% for salicylic acid.

Human

The skin penetration of Capryloyl Salicylic Acid was also assessed using a standard stripped skin method.⁵ Capryloyl Salicylic Acid was applied to the skin (number of subjects involved not stated), followed by rinsing with water/alcohol 30 min later. Strips of stratum corneum were then harvested, using adhesive tape, and analyzed for test material content. An estimation of the level of penetration through the skin over a 4-day period was determined using the

stored concentration method. Based on this method, 17.1% of the applied test material was found in the stratum corneum, versus 9.7% of salicylic acid applied.

Absorption, Distribution, Metabolism, and Excretion

Data on the absorption, distribution, metabolism, and excretion of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Capryloyl Salicylic Acid was studied using Sprague-Dawley rats (5 males, 5 females).³ The study was performed according to Organization for Economic Co-operation and Development (OECD) Test Guideline (TG) 402. A semi-occlusive patch (7 cm x 4 cm) containing the test substance (in peanut oil) was applied for 24 h to an area defined as 10% of the total body area. This amounted to a single dose exposure of 2000 mg/kg. Dosing was followed by a 14-day observation period, after which the animals were killed. Necropsy was performed, but tissues were not retained. None of the animals died during the observation period, but the following signs of toxicity were observed: hunched posture, lethargy, and piloerection during the first day. With the exception of 1 male rat, body weight gain was not affected by treatment. The following adverse dermal reactions were observed: edema and blanching and hard, light brown colored scabs at the application site. These findings were accompanied by loss of the upper layers of skin and fur, resulting in purple/pink areas. The distribution of toxicity signs/adverse dermal reactions in the dosed group was not reported. The LD₅₀ was > 2000 mg/kg.

Oral

The acute oral toxicity of Capryloyl Salicylic Acid (in peanut oil) was evaluated using groups of 10 Sprague-Dawley rats (5 males, 5 females/group).³ The four dose groups received single oral doses (by gavage) of 2530, 3000, 3557, and 4217 mg/kg, respectively. The study was performed according to OECD TG 401. A control group was not included in the study. Dosing was followed by a 14-day observation period. All animals were subjected to gross necropsy. The following major signs of toxicity were observed in all dose groups: hunched posture, piloerection, lethargy, ptosis, decreased or gasping respiration, red/brown staining around the snout or mouth, and ataxia and/or increased. Incidences of reduced body weight gain or body weight loss also occurred in all dose groups. Distended abdomen and/or emaciation were observed in animals of the 3 higher dose groups. Pallor of the extremities, with an isolated incidence of tiptoe gait, was observed in animals of the 3557 mg/kg dose group. Mortalities in all dose groups were reported as follows: 2530 mg/kg (1 female); 3000 mg/kg (4 males and 2 females); 3557 mg/kg (3 males, 3 females), and 4217 mg/kg (4 males, 4 females). The following abnormalities were observed at necropsy of animals that died during the study: hemorrhagic or abnormally red lungs; dark liver or patchy pallor of the liver; pale spleen; pale or dark kidneys; hemorrhage or sloughing of the glandular gastric epithelium; and hemorrhage of the small and/or large intestines. Abnormalities observed at necropsy of animals (2530 g/kg group) that were killed at the end of the study were described as occasional white foci (~1 mm x 1 mm covering 75% of the non-glandular gastric epithelium). At necropsy, there were no abnormalities in animals that received a dose of 3000 mg/kg or higher and were killed at the end of the study. The combined oral LD₅₀ (males + females) for the test material was 3354 mg/kg (95% confidence limit between 2834 and 3970 mg/kg).

Results relating to acute oral toxicity are included in a micronucleus test on Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle).⁴ The micronucleus test (described later in this report), performed in accordance with OECD TG 474, used groups of 10 (5 males, 5 females per group) Swiss CD-1 mice. A single dose of the test substance (500, 1000, and 2000 mg/kg) was administered by gavage to 3 groups, respectively. Two female mice and 1 male mouse dosed with 2000 mg/kg were found dead 24 h after dosing. Piloerection was observed in all animals on the same day of dosing with 1000 mg/kg. Piloerection and swollen abdomen were observed in the 2000 mg/kg dose group.

Results relating to acute oral toxicity are also included in an unscheduled DNA synthesis test on Capryloyl Salicylic Acid (in 0.5% in carboxymethylcellulose aqueous vehicle).⁴ The assay was performed in accordance with OECD TG 486 using groups of 4 Sprague-Dawley rats. In 2 tests, single doses of 500, 1000, and 2000 mg/kg were administered by gavage. The animals were killed at 14 h in one test and at 2 h in the other test. No mortalities or clinical signs were observed. (Results relating to genotoxicity are included in that section of this report.)

Short-Term Toxicity Studies

Dermal

A short-term dermal toxicity study (10-day study) on Capryloyl Salicylic Acid (in hexaethylene glycol (PEG-6)) was performed using groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain.³ The test substance was applied for 6 h directly to the back (not less than 10% of body area; constant volume of 2 mL/kg) once daily at concentrations of 2% and 5%. A third group was treated with vehicle only. The test protocol was similar to OECD TG 410. None of the animals died during the study. The animals were killed at the end of the 10-day dosing period and subjected to gross necropsy. Tissues were examined microscopically. There were no treatment-related changes in food consumption or body weight gain. The authors noted that occasional transient weight losses were observed which, because of the small group sizes, skewed the means. Other than the scabbing that was observed at necropsy, there were no other necropsy findings. The no-observed-effect-levels (NOEL) for local and systemic effects of Capryloyl Salicylic Acid were 2% and > 5%, respectively. Additional results from this study are included in the Skin Irritation section of this report.

The skin sensitization potential of Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) was evaluated in the guinea pig maximization test, according to OECD TG 406.⁴ Twenty Dunkin-Hartley guinea pigs (10 males, 10 females) were tested with this ingredient in this study. During topical induction, Capryloyl Salicylic Acid was applied at a concentration of 1%. One animal was found dead on day 18, but microscopic examination revealed no apparent abnormalities. None of the other animals had clinical signs; body weight gains were comparable to the control animals. Results relating to skin sensitization potential are included in that section of this report.

Oral

A short-term oral toxicity study on Capryloyl Salicylic Acid (in PEG-6) was performed using groups of 10 or 20 rats of the CRL:CD(SD)BR strain.³ The control group and highest dose group (initially, 300 mg/kg/day) each consisted of 20 rats (10 males, 10 females per group). Each of the remaining dose groups (10, 30, and 100 mg/kg/day) consisted of 10 rats (5 males, 5 females per group). The animals were dosed orally (by gavage) daily for 28 days in accordance with OECD TG 407. Two recovery groups (5 males, 5 females per group; for control and highest dose groups) were maintained un-dosed for an additional 14 days after the last day of dosing (day 28). The dose level in the highest dose group was reduced from 300 to 200 mg/kg/day on day 13 due to adverse clinical signs, including death. The animals were subjected to gross necropsy and microscopic examination of tissues at the end of the study. Five rats from the highest dose group died during the study, and the following clinical signs were observed: rough coat, piloerection, post-dose salivation. A slight reduction in body weight gain (13 to 14%) was also noted in males of the highest dose group during treatment and non-treatment periods, and in females of the 100 mg/kg dose group during treatment only. Hematology and blood chemistry evaluations did not reveal any adverse effects. At necropsy, a dose-related increase in the incidence of stomach abnormalities was observed (at the end of both the treatment and the treatment-free period) for animals dosed with 100 mg/kg/day and 300/200 mg/kg/day. Microscopic findings included hyperplasia of the non-glandular stomach in animals of the 300/200 mg/kg/day group. This finding was accompanied by chronic inflammation and ulceration. Hyperplasia was also observed in 1 male in the 100 mg/kg/day dose group. Similar, but less severe, hyperplastic lesions were also observed in recovery animals that were previously dosed with 300/200 mg/kg/day. Hyperplasia of the non-glandular mucosa of the stomach was less severe at the end of the treatment-free period, which indicates that some recovery had taken place. Additionally, reversibility was observed and the effects were limited to the non-glandular stomach, and, thus, were considered to be of doubtful relevance to humans. The no-observed-effect-level (NOEL) for local effects was 30 mg/kg/day, and the NOEL for systemic effects was > 100 mg/kg/day.

Subchronic Toxicity Studies

Data on the subchronic toxicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

Chronic Toxicity Studies

Data on the chronic toxicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Animal

Dermal

The developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 24 pregnant female Sprague-Dawley rats.³ The 2 test groups received doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. The vehicle control group was dosed with PEG-6. The test substance and vehicle control were each applied for 6 h directly to skin on the back (not less than 10% of the body area). On gestation day 20, all females were killed and subjected to necropsy. Numbers of corpora lutea and live and dead implantations were recorded. Live fetuses were examined for external and visceral abnormalities. One-half of the fetuses were subsequently examined for skeletal abnormalities. No premature deaths or treatment-related clinical signs were recorded during the study. There was no treatment-related effect on mean maternal food consumption and body weight. However, when compared to the control group, a statistically significant reduction in body weight gain values was reported for the 40 mg/kg/day dose group (gestation days 9 - 12) and for the 100 mg/kg/day dose group (gestation days 6 - 15). There were no treatment-related effects on pregnancy parameters, mean fetal weight, and incidences of major external, visceral, or skeletal abnormalities.

When compared to the background range, a higher (but not statistically significant) increase in the incidence of minor skeletal abnormalities and variants (including incomplete ossification of the sacral neural arch) was observed in the vehicle control group and both dose groups. The historical control range was from 0% to 9%, compared to a value of 18.3% for the incidence of sacral neural arch incomplete ossification in the vehicle control group. Therefore, the authors noted the likelihood that the incidence of the skeletal minor abnormalities observed in both dose groups was also overestimated. Furthermore, they noted that these statistically non-significant skeletal findings in both dose groups were likely related to the transient, but statistically significant, decrease in body weight gain observed in dams (gestation days 9 - 12). This decrease was attributed to the moderate or severe skin lesions that led to pain and stress in the animals. Therefore, it was determined that the increase in the incidence of skeletal variations reported for fetuses from both groups were likely secondary to maternal toxicity (induced by local effects leading to pain and stress) and not indicative of a teratogenic effect. Results relating to maternal skin irritation potential are included in the Skin Irritation section of this report.³ A no-observed-adverse-effect-level (NOAEL) was not reported in this study summary. However, the following conclusion is reported in a summary of this study from a different source: *The NOAEL for developmental toxicity was established as 40 mg/kg/day, based on an increase in the incidence of fetuses with incomplete ossification of the sacral neural arch at 100 mg/kg/day.*⁴ The NOAEL was not established for maternal toxicity, as treatment-related effects (local reaction at the site of administration and reductions in body weight gain) were observed at both doses tested.

Oral

The reproductive and developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 20 (10 males, 10 females per group) Wistar Hannover rats.³ The animals were dosed orally (by gavage) with the test substance once daily in accordance with OECD TG 421. The 3 dose groups received 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day, respectively (dose volume of 4 mL/kg/day). Male rats were dosed 2 weeks prior to mating, during the mating period, and up to 5 weeks post-mating (50 days total). Female rats were dosed 2 weeks prior to mating, during the mating period (up to 14 days), during gestation, and at least 4 additional days during the lactation period (40 to 49 days total). The vehicle control group was dosed with PEG-6. At the end of the dosing period, all parental animals were killed and subjected to gross necropsy. Histopathological examination of tissues was performed. There were no mortalities or clinical signs that were attributed to treatment with the test substance, and there were no effects on body weight and food consumption. The following parameters in treated animals were similar to those of the vehicle control group: reproductive performance of males and females, mating, fertility, gestation, and live birth indices. There were no treatment-related effects on weights of testes, epididymides, ovaries, uterus, and cervix. Furthermore, there were no treatment-related findings at necropsy or microscopic examination. There also were no effects on the clinical condition of pups, body weight, or sex ratio. No macroscopic findings were noted in pups that were killed on day 4 post-partum. The NOEL of Capryloyl Salicylic Acid was considered to be 100 mg/kg/day for the following: parental toxicity, embryo-fetal developmental toxicity, and pup development until day 4 post-partum.

GENOTOXICITY STUDIES

The following genotoxicity studies on Capryloyl Salicylic Acid that are summarized below are described in Table 3.

In Vitro

The genotoxicity of Capryloyl Salicylic Acid (in ethanol) was evaluated in the Ames test using the following bacterial strains, with and without metabolic activation: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvr A.³ Doses up to 1000 µg/plate were tested, and the test material was classified as non-genotoxic. The mammalian chromosome aberration test involving Chinese hamster ovary cells (with and without metabolic activation) was used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in ethanol) at concentrations of 50 µg/mL and 80 µg/mL.⁴ The test material was classified as clastogenic with, but not without, metabolic activation.

In Vivo

The genotoxicity of Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle) was evaluated in the micronucleus test using groups of 10 (5 males, 5 females per group) mice of the CD-1 strain.³ A single dose of the test substance (250, 500, and 1000 mg/kg) was administered by gavage to the 3 groups, respectively. The test material was classified as non-clastogenic. In a second micronucleus test, Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) was administered to groups of 10 (5 males, 5 females per group) Swiss CD-1 mice.⁴ A single dose of the test material (500, 1000, and 2000 mg/kg) was administered by gavage to the 3 groups, respectively. A slight increase in the polychromatic erythrocytes (PCEs)/normochromatic erythrocytes (NCEs) ratio was observed in males of the 2000 mg/kg dose group, only at the 24-h sampling time. This finding was indicative of an inhibitory effect on erythropoietic cell division. Results indicated that the test material was non-clastogenic in this assay. (Results relating to the acute oral toxicity of this test material are included in that section of this report.) The unscheduled DNA synthesis test was also used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose), using groups of 4 Sprague-Dawley rats.⁴ In 2 tests, single doses of 500, 1000, and 2000 mg/kg were administered by gavage, and the test material was classified as non-clastogenic in both. (Results relating to acute oral toxicity are included in that section of this report.)

CARCINOGENICITY STUDIES

Data on the carcinogenicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

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

The skin irritation potential of Capryloyl Salicylic Acid was evaluated in an occlusive patch test using 3 male New Zealand White rabbits.³ The animals were patch tested with 0.5 g of the test material, and results were negative. In a study involving groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain, Capryloyl Salicylic Acid (in PEG-6) was applied to the back (constant volume of 2 mL/kg) once daily for 10 days. The test material was applied at concentrations of 2% and 5%; only the 5% concentration caused very slight erythema (in 2 to 5 rats) and edema (3 or 4 rats). Minimal/moderate scabbing at the application site was also observed. (Additional results from this study are included in the Short-Term Dermal Toxicity section of this report.) Skin irritation data are reported in a developmental toxicity study (described previously) on Capryloyl Salicylic Acid (in PEG-6) involving 2 groups of 24 pregnant female Sprague-Dawley rats.³ The test material was applied to skin of the back (2 groups) at doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. Erythema and eschar formation were observed in both groups (number of animals not stated), the severity of which was dose-related. Slight edema was also reported, and scabbing and/or reddening at test sites was observed at necropsy.

Reactions described as cutaneous signs of slight intensity were observed in 5 of 49 subjects after application of a face product containing 0.3% Capryloyl Salicylic Acid to the face and eye contour twice daily for 4 weeks.⁴

The skin sensitization potential of Capryloyl Salicylic Acid (in peanut oil) was evaluated in the guinea pig maximization test, using 20 female Dunkin-Hartley guinea pigs.³ Induction involved intradermal injection and topical application of 1% and 0.5% concentrations, respectively. This was followed by challenge with 0.5% (occlusive patch). The test material was classified as a skin sensitizer. In another maximization test, 20 guinea pigs were tested with Capryloyl Salicylic Acid (in ethanol).⁴ Induction involved intradermal injection and topical application of 0.5% and 10% concentrations, respectively. There were no signs of skin irritation during induction at concentrations of 0.5% (injected intradermally) and 10% (topical application). The animals were challenged with 2%. Sensitization reactions were observed (at 24 h and 48 h) at the application sites of 5 guinea pigs. However, these findings were classified as limited evidence of skin sensitization. The skin sensitization potential of Capryloyl Salicylic Acid (in PEG-300) was also evaluated in the maximization test, using 20 guinea pigs.⁴ The induction phase involved concentrations of 25%, 15%, and 10%. When a

concentration of 25% was applied, several test animals (number not stated) had erythema scores of 2 or more at the application site after the first induction application. The concentration was decreased during induction because of skin irritation, and induction was followed by topical challenge with 5%. At 24 h, but not 48 h, sensitization reactions were observed at the application sites of 2 animals. These findings were classified as limited evidence of skin sensitization. Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) was evaluated for sensitization potential in the guinea pig maximization test, using 20 Dunkin-Hartley guinea pigs.⁴ A test concentration of 1% was used for topical induction and challenge. Skin reactions were not observed in any of the test animals during induction or the challenge phase, and the test material was classified as a non-sensitizer. Results relating to short-term dermal toxicity reported in this maximization test are included in that section of this report.

A cosmetic product containing 2% Capryloyl Salicylic Acid was classified as a non-sensitizer in a human repeated insult patch test (HRIPT) involving 102 subjects.⁴ Slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A face powder containing 2% Capryloyl Salicylic Acid and a deodorant aerosol product containing 2% Capryloyl Salicylic Acid were also classified as non-sensitizers in HRIPTs involving 105 subjects and 103 subjects, respectively.⁴ In 2 HRIPTs, involving 106 subjects in one study and 105 subjects in the other, a face serum product containing 0.5% Capryloyl Salicylic Acid was classified as a non-sensitizer.⁴ In the study involving 106 subjects, slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A cream product and a fluid cream product (each containing 0.5% Capryloyl Salicylic Acid) were also classified as non-sensitizers in HRIPTs involving 104 subjects and 106 subjects, respectively.

OCULAR IRRITATION STUDIES

Animal

The ocular irritation potential of Capryloyl Salicylic Acid was evaluated using 3 New Zealand White rabbits, according to OECD TG 405.³ The test substance (~ 65 mg) was instilled into the eye, and exposure was not followed by ocular rinsing. Reactions were scored at 24 h, 48 h, and 72 h after instillation, and the animals were observed for a total of 14 days after exposure. Diffuse corneal opacity, iridial inflammation, and moderate or severe conjunctivitis were observed in all treated eyes at 1 h post-instillation and in 2 treated eyes at 24 h, 48 h, and 72 h post-instillation. In the eye of 1 treated animal, corneal opacity increased and areas of opalescent corneal opacity with iridial inflammation and moderate to severe conjunctival irritation were observed at 48 h and 72 h post-instillation. Adverse effects observed on the nictitating and/or conjunctival membranes in the eye of this animal were described as pale appearance, small green-colored or white areas, and areas of hemorrhage. In another rabbit, diffuse corneal opacity, iridial inflammation, and minimal conjunctival irritation persisted in the treated eye on day 7; these effects were resolved by day 14. Circumcorneal vascularization and convoluted eyelids were also noted in this animal, and the nictitating membrane was also pale in appearance. In the third rabbit, corneal opacity increased and opalescent corneal opacity with pannus formation (indicative of irreversible ocular damage) had developed on day 14. It was not possible to assess iridial inflammation at this time, and minimal conjunctival irritation with convoluted eyelids were also observed. Capryloyl Salicylic Acid was classified as being a severe irritant to the rabbit eye.

Human

A face product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 49 subjects twice a day for 4 weeks.⁴ The group included subjects with sensitive skin, sensitive eyes, non-sensitive eyes, and contact lenses wearers. Observations were recorded before application and at least 10 min after the first application and the last application, respectively. Microscopic examinations of ocular and periocular structures revealed no appearance of ocular physical signs or palpebral signs. Colorimetric examinations of the cornea and the conjunctiva revealed a maximal corneal index of 0.50% and a maximal conjunctival index of 0%, indicating an absence of toxicity to the conjunctiva and a very slight toxicity to the cornea. Clinical examinations revealed an ocular irritation rate of 0.03% and an ocular comfort rate of 99.83%. Additionally, the product did not induce any pathology that was specific to contact lenses wearers. It was concluded that the face product yielded good ocular safety.

An eye contour product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 50 subjects twice a day for 4 weeks.⁴ The group included subjects with sensitive eyes, non-sensitive eyes, and contact lenses wearers. Observations were recorded before application and at least 10 min after the first application and the last application, respectively. The product induced moderate ocular burning in 1 subject with sensitive eyes, and slight ocular stinging in 1 contact lenses wearer. Biomicroscopic examinations of ocular and periocular structures revealed 2 bilateral occurrences of bulbar conjunctival redness in 2 subjects. Colorimetric examinations of the cornea and the conjunctiva revealed a maximal corneal index of 0% and a maximal conjunctival index of 0%, indicating an absence of toxicity to the conjunctiva and very slight toxicity to the cornea. Clinical examinations revealed an ocular irritation rate of 0.04% and an ocular comfort rate of 99.88%. Additionally, the product did not induce any pathology that was specific to contact lenses wearers. It was concluded that the eye contour product yielded good ocular safety.

CLINICAL STUDIES

Case Reports

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.¹⁷ 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 patch 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 (concentration not stated) 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 letter to the editor on the preceding 2 case reports, the author stated that Capryloyl Salicylic Acid is unlikely to be significantly allergenic, and is therefore unlikely to be the cause of the contact allergy reported.⁷ 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.

Other Clinical Reports

In a split-face study, 44 female volunteers with mild to moderate facial hyperpigmentation and fine lines/wrinkles were randomized and a Capryloyl Salicylic Acid containing peel was applied to one side of the face.¹⁸ 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.

SUMMARY

Capryloyl Salicylic Acid was previously, erroneously defined as the ester of salicylic acid and caprylic acid. However, it has become apparent that Capryloyl Salicylic Acid is, instead, the 5-capryl ketone of salicylic acid. Capryloyl Salicylic Acid can be manufactured via Friedel-Crafts acylation of methyl salicylate with capryloyl chloride and aluminum trichloride, to yield the methyl ester of Capryloyl Salicylic Acid, which is then hydrolyzed with sodium hydroxide, after which acidification yields this ketone, Capryloyl Salicylic Acid.

Capryloyl Salicylic Acid is reported to be used in 104 cosmetic products (93 leave-on and 11 rinse-off). The results of a concentration of use survey conducted in 2018 indicate that Capryloyl Salicylic Acid is used at concentrations up to 0.5% (in moisturizing products, not spray), which is the highest reported maximum use concentration for leave-on formulations. In rinse-off products, Capryloyl Salicylic Acid is used at concentrations up to 0.4% (in paste masks and mud packs), which is the highest reported maximum use concentration for rinse-off formulations.

In vitro skin penetration data (human skin samples) indicate that, after 16 h of contact, ~ 6% of the applied Capryloyl Salicylic Acid was found to “penetrate deeper than the stratum corneum.” Using a standard tape stripping method for determining skin penetration (number of subjects not stated), it was determined that 17.1% of Capryloyl Salicylic Acid applied to the skin of human subjects was found in the stratum corneum over a 4-day period.

The acute dermal toxicity of Capryloyl Salicylic Acid was studied using Sprague-Dawley rats (5 males, 5 females). An LD₅₀ of > 2000 mg/kg was reported. The following adverse dermal reactions were observed after a single oral dose of 2000 mg/kg: edema and blanching and hard, light brown colored scabs at the application site.

The acute oral toxicity of Capryloyl Salicylic Acid (in peanut oil) was evaluated using groups of 10 Sprague-Dawley rats (5 males, 5 females/group). The highest dose administered was 4217 mg/kg. The combined oral LD₅₀ (males + females) was 3354 mg/kg (95% confidence limit between 2834 and 3970 mg/kg). Abnormalities observed at necropsy of animals (2530 g/kg group) that were killed at the end of the study were described as occasional white foci (~1 mm x 1 mm covering 75% of the non-glandular gastric epithelium). At necropsy, there were no abnormalities in animals that received a dose of 3000 mg/kg or higher and were killed at the end of the study.

Results relating to the acute oral toxicity of Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle) are reported in a micronucleus test involving groups of 10 (5 males, 5 females per group) Swiss CD-1 mice. A single dose of the test substance (500, 1000, and 2000 mg/kg) was administered by gavage to the 3 groups, respectively. Two female mice and 1 male mouse dosed with 2000 mg/kg died. Results relating to acute oral toxicity of Capryloyl

Salicylic Acid (in 0.5% carboxymethyl-cellulose aqueous vehicle) were also reported in an unscheduled DNA synthesis test using groups of 4 Sprague-Dawley rats. Single doses of 500, 1000, and 2000 mg/kg were administered by gavage, and no mortalities or clinical signs were observed.

A short-term (10 day) dermal toxicity study on Capryloyl Salicylic Acid (in PEG-6) was performed using groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain. The test substance was applied for 6 h directly to the back once daily at concentrations of 2% and 5%. The NOEL for local and systemic effects was considered to be 2% and > 5%, respectively. Results relating to short-term oral toxicity of Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) are reported in a guinea pig maximization test involving 20 Dunkin-Hartley guinea pigs. One animal was found dead on day 18, but microscopic examination revealed no apparent abnormalities.

A short-term (28 day) oral toxicity study on Capryloyl Salicylic Acid (PEG-6) was performed using groups of 10 or 20 rats of the CRL:CD(SD)BR strain. The highest dose group (initially 300 mg/kg/day) consisted of 20 rats (10 males, 10 females per group). Each of the remaining dose groups (10, 30, and 100 mg/kg/day) consisted of 10 rats (5 males, 5 females per group). The NOEL for local effects was 30 mg/kg/day, and the NOEL for systemic effects was > 100 mg/kg/day.

The developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 24 pregnant female Sprague-Dawley rats. The test material was applied for 6 h directly to skin on the back (not less than 10% of the body area). One group was dosed with 40 mg/kg/day and the other group was dosed with 100 mg/kg/day on gestation days 6 to 15. The NOAEL for developmental toxicity was established as 40 mg/kg/day, based on an increase in the incidence of fetuses with incomplete ossification of the sacral neural arch at 100 mg/kg/day. The NOAEL was not established for maternal toxicity, as treatment-related effects (local reaction at the site of administration and reductions in body weight gain) were observed at both doses tested. The reproductive and developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 10 male and 10 female Wistar Hannover rats. The animals were dosed orally (by gavage) with the test substance once daily. The 3 dose groups received 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day, respectively (dose volume of 4 mL/kg/day). Males were dosed for 50 days total and females were dosed for 40 to 49 days total. The NOEL was considered to be 100 mg/kg/day for the following: parental toxicity, embryo-fetal developmental toxicity, and pup development until day 4 post-partum.

In the Ames test, Capryloyl Salicylic Acid (in ethanol) was non-genotoxic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvr A when evaluated at doses up to 1000 µg/plate with and without metabolic activation.. Capryloyl Salicylic Acid (in ethanol) was classified as clastogenic with, but not without, metabolic activation, in the mammalian chromosome aberration test involving Chinese hamster ovary cells. The test material was evaluated at concentrations of 50 µg/mL and 80 µg/mL in this assay.

Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) was classified as non-clastogenic when evaluated in in vivo micronucleus tests using groups of 5 male and 5 female mice of the CD-1 strain. Single doses of the test substance up to 2000 mg/kg were administered by gavage. The in vivo unscheduled DNA synthesis test was also used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) using groups of 4 Sprague-Dawley rats. Single doses of 500, 1000, and 2000 mg/kg were administered by gavage, and the test material was classified as non-clastogenic.

When 3 male New Zealand White rabbits were patch tested with 0.5 g of Capryloyl Salicylic Acid trade, skin irritation was not observed. In addition to these results, skin irritation was reported in other types of toxicity tests. In a short-term dermal toxicity study, daily (for 10 days) applications of Capryloyl Salicylic Acid (in PEG-6) at a concentration of 5% caused very slight erythema and edema in a group of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain. In a developmental toxicity study, Capryloyl Salicylic Acid (in PEG-6) was applied to the backs of pregnant female Sprague-Dawley rats (2 groups of 24) at doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. Erythema and eschar formation, dose-related in severity, were observed (number of animals not stated).

Reactions described as cutaneous signs of slight intensity were observed in 5 of 49 subjects after application of a face product containing 0.3% Capryloyl Salicylic Acid to the face and eye contour twice daily for 4 weeks.

Three maximization tests involved groups of 20 Dunkin-Hartley guinea pigs tested with Capryloyl Salicylic Acid (different vehicles used). A challenge concentration of 2% was sensitizing to 5 of 20 guinea pigs, and a challenge concentration of 5% was sensitizing to 2 of 20 guinea pigs. The absence of skin sensitization was noted in a group of 20 guinea pigs challenged with a concentration of 1%. Additionally, findings relating to skin irritation (number of animals with reactions not stated) during induction were reported in the 3 maximization tests. Test concentrations of 1% and 25% applied topically were irritating, whereas, 0.5% (injected intradermally) and 10% (topical application) were not.

In 2 HRIPTs involving 106 subjects and 105 subjects, respectively, face serum products containing 0.5% Capryloyl Salicylic Acid was classified as a non-sensitizer. In the HRIPT involving 106 subjects, slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A cream product and a fluid cream product (each containing 0.5% Capryloyl Salicylic Acid) were also classified as non-sensitizers in HRIPTs involving 104 subjects and 106 subjects, respectively. A cosmetic product containing 2% Capryloyl Salicylic Acid was classified as a non-sensitizer in an HRIPT involving 102 subjects. Slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A face powder containing 2% Capryloyl Salicylic Acid and a deodorant aerosol product containing 2% Capryloyl Salicylic Acid were also classified as non-sensitizers in HRIPTs involving 105 subjects and 103 subjects, respectively.

Capryloyl Salicylic Acid was classified as being a severe ocular irritant in a test involving 3 New Zealand White rabbits. The test substance (~ 65 mg) was instilled into the eye, and exposure was not followed by ocular rinsing.

A face product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 49 subjects twice a day for 4 weeks. Clinical examinations revealed an ocular irritation rate of 0.03%. In another test, an eye contour product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 50 subjects twice a day for 4 weeks, and clinical examinations revealed an ocular irritation rate of 0.04%

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.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES**Table 1.** Chemical and Physical properties of Capryloyl Salicylic Acid

Property	Value/Results	Reference
Capryloyl Salicylic Acid		
Form (at 20 °C and 1013 hPa)	White powder	3
Molecular weight	264.32	6
Specific Gravity (at 23 °C)	0.35	3
Boiling point (°C)	thermal decomposition occurs (at 264°C) before boiling	3
Melting/Freezing point (°C)	115	3
(at 101,325 Pa and 720 mm Hg)		
Water solubility (mg/L at 20 °C)	29.7	3
Vapor pressure (Pa at 21 °C)	97.3	3
log P _{ow} (at 20 °C)	0.32 (non-ionized form)	3
pK _a (at 25 °C)	2.68 ± 0.10 (estimated)	6

Table 2. Frequency (2019) and Concentration (2018) of Use According to Duration and Exposure.

	# of Uses	Max Conc of Use (%)
	Capryloyl Salicylic Acid	
	2019^a	2018^a
Totals*	104	0.1 -0.5
<i>Duration of Use</i>		
<i>Leave-On</i>	<i>93</i>	<i>0.1-0.5</i>
<i>Rinse-Off</i>	<i>11</i>	<i>0.1-0.4</i>
<i>Diluted for (Bath) Use</i>	<i>NR</i>	<i>NR</i>
Eye Area	9	NR
Incidental Ingestion	NR	0.1
Incidental Inhalation-Spray	35 ^a ;28 ^b	0.1
Incidental Inhalation-Powder	28 ^b	0.3; 0.3-0.5 ^c
Dermal Contact	104	0.1-0.5
Deodorant (underarm)	NR	not spray: 0.3 aerosol: 0.3
Hair - Non-Coloring	NR	0.1
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	0.1-0.3
Baby Products	NR	NR

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

^aIt is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

^bNot specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^cIt is possible that these products may be powders, but it is not specified whether the reported uses are powders.

Table 3. Genotoxicity Studies on Capryloyl Salicylic Acid.

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
<i>In Vitro</i>				
Capryloyl Salicylic Acid (in ethanol)	<i>Salmonella typhimurium</i> strains TA98, TA100, TA1535, and TA1537 and <i>Escherichia coli</i> strain WP2 uvr A.	Ames test, with and without metabolic activation. Test protocol equivalent or similar to OECD TG 471. Controls: vehicle (ethanol); positive, without metabolic activation (2-aminoacridine, 2-nitrofluorene, and sodium azide); and positive, with metabolic activation (2-aminoanthracene and 4-nitroquinoline-1-oxide)	1 st experiment: doses up to 1000 µg/plate (with and without metabolic activation). 2 nd experiment: doses up to 100 and 200 µg/plate (without metabolic activation)	No substantial increases in revertant colony numbers over vehicle control count in any bacterial strain. Non-genotoxic. ³
Capryloyl Salicylic Acid (in ethanol)	Chinese hamster ovary cells	Mammalian chromosome aberration test, with and without metabolic activation. Controls: vehicle (ethanol) and positive (mitomycin C and cyclophosphamide). Exposure and harvest times not reported.	Two experiments performed at concentrations up to 50 mg/mL and 80 mg/mL, respectively.	1 st test (with metabolic activation): statistically significant increases in chromosome aberrations at 1 st harvest observed at 50 µg/mL. (actual frequency was within background for this cell line). 2 nd test (with metabolic activation): statistically significant increases in chromosome aberrations at 1 st harvest observed at 80 µg/mL (actual frequency was above background for this cell line). No statistically significant increases in chromosome aberrations without metabolic activation. Results for positive controls confirmed validity of the test system. Clastogenic to Chinese hamster ovary cells. ⁴
<i>In Vivo</i>				
Capryloyl Salicylic Acid (0.5% in carboxymethylcellulose)	Groups of 10 (5 males, 5 females per group) mice of the CD-1 strain	Micronucleus test. Protocol similar to OECD TG 474, with minor deviations. Vehicle control group dosed with carboxymethylcellulose, and positive control group dosed with mitomycin C (injected intraperitoneally). Animals killed at 24 h, 48 h, and 72 h post-dosing. Bone marrow cells obtained and analyzed for micronuclei. Minimum of 1000 polychromatic erythrocytes (PCE) counted per animal.	3 groups received single oral doses (by gavage) of 250, 500, and 1000 mg/kg, respectively.	Micronuclei not induced at any administered dose of test material, despite decrease in PCE/normochromatic erythrocytes at dose of 1000 mg/kg at 24 h. Test material was non-clastogenic. Positive control induced appropriate increase in number of PCE. ³
Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose)	Groups of 10 (5 males, 5 females per group) Swiss CD-1 mice	Micronucleus test. Performed in accordance with OECD TG 474. Vehicle control group dosed with carboxymethylcellulose, and positive control group dosed with mitomycin C.	3 groups received single oral doses (by gavage) of 500, 1000, and 2000 mg/kg, respectively.	A slight increase in the polychromatic erythrocytes (PCEs)/normochromatic erythrocytes (NCEs) ratio was observed in males of the 2000 mg/kg dose group, only at the 24-h sampling time. No statistically significant increases in frequency of micronucleated PCEs. Test material was non-clastogenic. Positive and negative controls yielded satisfactory response, confirming validity of test system. ⁴

Table 3. Genotoxicity Studies on Capryloyl Salicylic Acid.

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose)	Groups of 4 Sprague-Dawley rats	Unscheduled DNA synthesis test. Performed in accordance with OECD TG 486. Vehicle control group dosed with carboxymethylcellulose, and 2-acetamidofluorene and methylnitrosourea served as positive controls.	In 2 tests, single doses of 500, 1000, and 2000 mg/kg were administered by gavage. In the 2 tests, animals were killed at 14 h and 2 h, respectively.	Treatment with the test material did not produce group mean net grain value that was greater than -0.88, and no more than 6% of the cells were found in repair. Test material was non-clastogenic. Positive and negative controls yielded satisfactory response, confirming validity of test system. ⁴

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Irritation (Animal)			
Capryloyl Salicylic Acid	3 male New Zealand White rabbits	OECD TG 404. Occlusive patch containing test material (0.5 g moistened with distilled water (0.5 ml)) applied for 4 h to 6.25 cm ² area on dorsal flank. Skin irritation evaluated according to Draize scale at 24 h, 48 h, and 72 h after patch application.	No skin irritation at any time after patch application. Test material classified as non-irritant. ³
Capryloyl Salicylic Acid (in PEG 300) tested at concentrations of 2% and 5%.	5 female rats of the Crl:CD(SD)BR (VAF plus) strain	Test protocol similar to OECD TG 410. Applied for 6 h directly to the back (not less than 10% of body area; constant volume of 2 ml/kg) once daily (for 10 days) at each concentration	In group that received 5% concentration, very slight erythema observed in 2 to 5 animals throughout dosing period (beginning at day 6), and well-defined erythema observed in 1 female between days 8 and 10 of dosing period. Very slight edema observed in 3 or 4 animals treated with 5%, beginning at day 7, and scabbing (minimal/moderate; observed at necropsy) at application site observed in all animals treated with 5%. ³
Irritation (Human)			
Face product containing a 0.3% Capryloyl Salicylic Acid	49 subjects	Product applied to face and eye contour twice a day for 4 weeks.	Cutaneous signs of slight intensity were observed in 5 subjects. ⁴
Sensitization (Animal)			
Capryloyl Salicylic Acid (in arachis oil), tested during induction (1% and 0.5%) and challenge (2%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	OECD TG 406. Guinea pig maximization test. Initially, following 3 pairs of intradermal induction injections (0.1 ml per injection) made in group of 20 animals: 1:1 mixture of Freund's complete Adjuvant in distilled water; 1% (w/v) dilution of test material in arachis oil; and 1% (w/v) dilution of test material in a 1:1 preparation of Freund's complete Adjuvant and arachis oil. These intradermal injections comprise 2 induction exposures during an exposure period of 7 days + 48 h. One week later, a 48-h topical application (induction) of 0.2 to 0.3 ml of 0.5% (w/w) test material in arachis oil over injection sites (shoulder region). At 2 weeks post-topical induction, a 24-h epicutaneous challenge with 2% (w/w) test material in arachis oil (occlusive patch) involved the left flank. Dose per cm ² for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h. Positive and vehicle controls were 2,4-dinitrochlorobenzene and arachis oil, respectively.	Positive reactions observed in 14 of 20 guinea pigs at 24 h after challenge. At 48 h, 4 guinea pigs had positive reactions. Test material classified as skin sensitizer because more than 30% of total number of guinea pigs tested (i.e., 70%) had positive response. Control animals treated with arachis oil did not have positive reactions. Positive control (2,4-dinitrochlorobenzene) induced sensitization. ³

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Capryloyl Salicylic Acid (in ethanol), tested during induction (10% and 0.5%) and challenge (2%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	Method similar to OECD TG 406. Guinea pig maximization test. During induction, animals injected intradermally with concentration of 0.5%, and received topical applications at a concentration of 10%. Challenged with a concentration of 2%. The dose per cm ² for induction and challenge applications was not stated. Challenge reactions were scored at 24 h and 48 h.	No signs of skin irritation during induction at concentrations of 0.5% (injected intradermally) and 10% (topical application). Positive (sensitization) reactions observed (at 24 h and 48 h) at the application sites of 5 guinea pigs. Classified as limited evidence of reactions indicative of skin sensitization. Adverse skin reactions not observed in control animals. ⁴
Capryloyl Salicylic Acid (in PEG 300), tested during induction (25%, 15%, and 10%) and challenge (5%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	OECD TG 406 (no significant protocol deviations). Guinea pig maximization test. During induction, test material applied topically at concentration of 25%. Due to severity of skin reactions after first induction application, concentration reduced to 15% for 2 nd induction, and to 10% for last induction. Animals challenged topically with a test substance concentration of 5%. Dose per cm ² for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h.	When a concentration of 25% was applied, several test animals (number not stated) had erythema scores of 2 or more at the application site after the first induction application. At 24 h, positive (sensitization) reactions observed at application sites of 2 animals. Positive reactions not observed in any animals at 48 h. Reactions classified as limited evidence of reactions indicative of skin sensitization. Adverse skin reactions not observed in control animals. ⁴
Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose), tested at 1% (induction and challenge)	Dunkin-Hartley guinea pigs (test: 10 males, 10 females; controls: 5 males, 5 females)	OECD TG 406. Guinea pig maximization test. Topical application during induction, followed by topical challenge. Dose per cm ² for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h. Ten positive control animals tested with 2,4-dinitrochlorobenzene.	Skin reactions not observed in any test animals during induction or challenge. No evidence of adverse skin reactions in negative control animals. Test material classified as non-sensitizer. Sensitization in 3 of 10 positive control animals. ⁴ [Results relating to short-term dermal toxicity in that section of this report.]
Sensitization (Human)			
Face serum product containing a 0.5% Capryloyl Salicylic Acid	106 subjects	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm ² area; application site not stated) 3 times per week (Tuesdays, Thursdays, and Saturdays) for total of 9 applications. Patches removed after 48 h (or 72 h for patches applied on Saturday). Sites graded 15 to 20 min after patch removal. Challenge phase initiated after 13-day non-treatment period. Challenge patch containing 0.02 mL of product applied to previously treated site and to new site for 48 h. Patch alone applied to new site served as negative control. Reactions scored at least 30 min and ~ 48 h after patch removal.	Slight skin irritation observed in a few subjects (number not stated) during induction phase and at first challenge reading. Sensitization not observed at 1 st challenge reading, and no adverse responses observed at final challenge reading. Product classified as non-sensitizer. ⁴ [
Face serum product containing a 0.5% Capryloyl Salicylic Acid	105 subjects.	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm ² area; application site not stated) 3 times per week (Mondays, Wednesdays, and Fridays) for total of 9 applications. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 10 to 14-day non-treatment period. Challenge patch containing 0.02 mL of product applied to previously treated site and to new site for 48 h, after which reactions. Reactions also scored at 72 h and 96 h post-application.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer. ⁴

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Cream product containing a 0.5% Capryloyl Salicylic Acid	104 subjects	HRIPT performed according to L'Oreal general protocol. Occlusive patches containing 0.02 mL of product applied to 50 mm ² area. Details relating to test protocol not included.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer. ⁴
Fluid cream product containing a 0.5% Capryloyl Salicylic Acid	106 subjects	HRIPT performed according to L'Oreal general protocol. Occlusive patches containing 0.02 mL of product applied to 50 mm ² area. Details relating to test protocol not included.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer. ⁴
Cosmetic product containing a 2% Capryloyl Salicylic Acid	102 subjects	HRIPT. During induction, semi-occlusive patches containing 0.2 mL of product applied (4 cm ² area; application site not stated) 3 times per week (Tuesdays, Thursdays, and Saturdays) for total of 9 applications. Patches removed after 48 ± 4 h (or 72 ± 4 h for patches applied on Saturday). Sites graded 15 to 30 min after patch removal. Challenge phase initiated after 13-day non-treatment period. Challenge patch containing 0.2 ml of product applied to previously treated site and to a new site for 48 ± 4 h. Patch alone applied to new site served as negative control. Reactions scored 30 to 35 min and ~ 48 ± 4 h after patch removal.	Slight skin irritation observed in a few subjects (number not stated) during induction phase and at first challenge reading. Sensitization not observed at 1 st challenge reading, and no adverse responses observed at final challenge reading. Product classified as non-sensitizer. ⁴
Face powder containing a 2 % Capryloyl Salicylic Acid	105 subjects	During induction, occlusive patches containing 0.02 mL of product applied (50 mm ² area; application site not stated) 3 times per week (Mondays, Wednesdays, and Fridays) for total of 9 applications. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 10- to 14-day non-treatment period. Challenge patch containing 0.02 ml of product applied to previously treated site and to new site for 48 h, after which reactions scored. Reactions also scored at 72 h and 96 h post-application.	No evidence of adverse responses during induction or challenge phases. Product classified as non-sensitizer. ⁴
Deodorant aerosol product containing a 2% Capryloyl Salicylic Acid	103 subjects	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm ² area; application site not stated) 9 times over period of 3 consecutive weeks. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 2-week non-treatment period. Challenge patch containing 0.02 ml of product applied to previously treated site and to new site for 48 h, after which reactions scored. Reactions also scored at 72 h and 96 h post-application. Patch alone applied to new site served as negative control.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer. ⁴

REFERENCES

1. Andersen FA (ed). Safety assessment of Salicylic Acid, Butyloctyl Saicylate, Calcium Salicylate, C12-15 Alkyl Salicylate, Capryloyl Salicylic Acid, Hexyldodecyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Magnesium Salicylate, MEA-Salicylate, Ethylhexyl Salicylate, Potassium Salicylate, Methyl Salicylate, Myristyl Salicylate, Sodium Salicylate, TEA-Salicylate, and Tridecyl Salicylate. *International Journal of Toxicology*. 2003;22(3):1-108.
2. Nikitakis, J. and Lange B. International Cosmetic Ingredient Dictionary and Handbook Online Version (wINCI). <http://webdictionary.personalcarecouncil.org/jsp/Home.jsp>. Washington, DC. Last Updated 2019. Date Accessed 5-5-2019.
3. European Chemicals Agency (ECHA). Registration, Evaluation, and Authorization of Chemicals (REACH) Dossier. 2-hydroxy-5-(1-oxooctyl)benzoic acid. <https://echa.europa.eu/registration-dossier/-/registered-dossier/1269>. Last Updated 2019. Date Accessed 3-20-2019.
4. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Public report. Benzoic acid, 2-hydroxy-5-(1-oxooctyl)- (INCI name: Capryloyl salicylic acid). File No. LTD/1817. https://www.nicnas.gov.au/data/assets/word_doc/0006/18771/LTD1817-FR-FINAL.DOCX. Last Updated 2015. Date Accessed 4-11-2019.
5. Saint-L  ger D, L  v  que J-L, and Verschoore M. The use of hydroxy acids on the skin: Characteristics of C₈-lipohydroxy acid. *Journal of Cosmetic Dermatology*. 2007;6:59-65.
6. Advanced Chemistry Development Labs (ACD Labs). Properties estimated using ACD Labs software. V11.02. 2019.
7. Roberts, D. W. and Aptula A. O. Contact allergy to capryloyl salicylic acid: a mechanistic chemistry and structure-activity perspective. *Contact Dermatitis*. 2015;72(5):347-351.
8. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD, 2019. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2019; received February 13, 2019).
9. Personal Care Products Council. Concentration of Use by FDA Product Category: Salicylates. Unpublished data submitted by the Personal Care Products Council on 6-11-2018. 2018. pp.1-5.
10. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104. PM:21669261.
11. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 20200. <http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf>. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.
12. Rothe H. Special aspects of cosmetic spray evaluation. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C. 2011.
13. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27. <http://www.spraytechnology.com/index.mv?screen=backissues>.
14. Aylott RI, Byrne GA, Middleton, J, and Roberts ME. Normal use levels of respirable cosmetic talc: preliminary study. *Int J Cosmet Sci*. 1979;1(3):177-186. PM:19467066.
15. Russell RS, Merz RD, Sherman WT, and Sivertson JN. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol*. 1979;17(2):117-122. PM:478394.
16. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 11-3-2015. Cosmetic Powder Exposure. Unpublished data submitted by the Personal Care Products Council.
17. de Groot, A. Rustemeyer T. Hissink D. and Bakker M. Contact allergy to capryloyl salicylic acid. *Contact Dermatitis*. 2014;71:176-190.
18. Oresajo, C. Yatskaer M. and Hansenne I. Clinical toledrance and efficacy of capryloyl salicylic acid peel compared to a glycolic acid peel in subjects with fine lines/wrinkles and hyperpigmented skin. *Journal of Cosmetic Dermatology*. 2008;7:259-262.

2019 VCRP Data

Capryloyl Salicylic Acid

03D - Eye Lotion	5
03G - Other Eye Makeup Preparations	4
07I - Other Makeup Preparations	1
11G - Other Shaving Preparation Products	2
12A - Cleansing	9
12C - Face and Neck (exc shave)	24
12D - Body and Hand (exc shave)	4
12F - Moisturizing	24
12G - Night	10
12J - Other Skin Care Preps	20
13C - Other Suntan Preparations	1
Total	104