Safety Assessment of Hydroxyacetophenone as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	February 11, 2022
Panel Meeting Date:	March 7-8, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi Raj, Senior Scientific Analyst/Writer, CIR.

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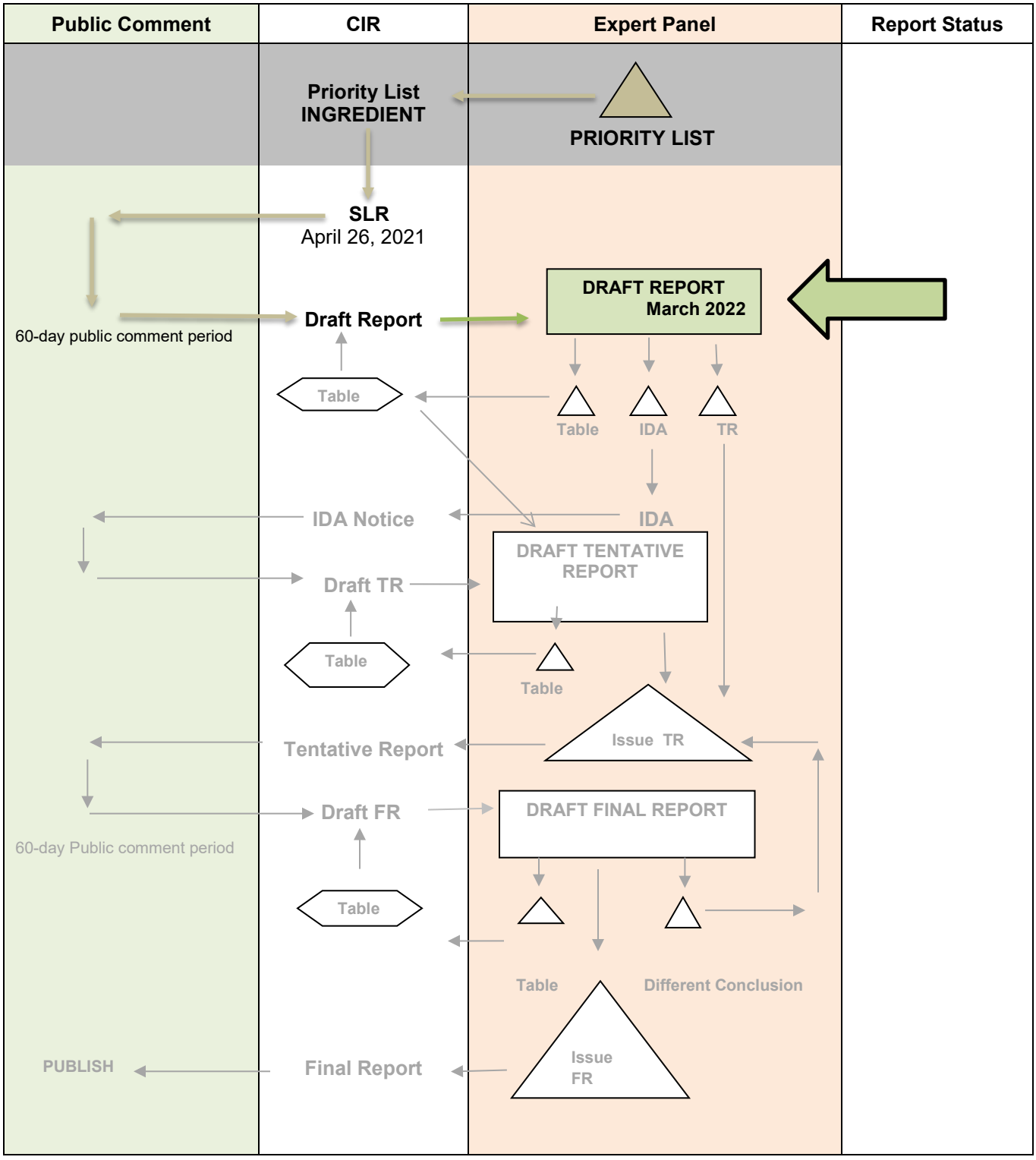
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Hydroxyacetophenone

MEETING March 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst, CIR
Date: February 11, 2022
Subject: Safety Assessment of Hydroxyacetophenone as Used in Cosmetics

Enclosed is the Draft Report of the Safety Assessment of Hydroxyacetophenone as Used in Cosmetics (identified as *report_Hydroxyacetophenone_032022* in the pdf). This is the first time the Panel is seeing a safety assessment of this cosmetic ingredient. A Scientific Literature Review (SLR) was announced on April 26, 2021. Following the announcement of the SLR, the following data were received:

data1_Hydroxyacetophenone_032022

- Anonymous. (2018) Human patch test of a SPF product containing 0.05% Hydroxyacetophenone
- Anonymous. (2017) 21-Day cumulative irritation assay of a SPF 70 cream containing 0.05% Hydroxyacetophenone
- Anonymous. (2017) Repeated insult patch test of a SPF 70 cream containing 0.5% Hydroxyacetophenone

data2_Hydroxyacetophenone_032022

- Life Science Research. (1977) Delayed contact hypersensitivity in guinea pigs (Buehler test) of Parahydroxyacetophenone
- Life Science Research. (1977) Rabbit closed patch study of Parahydroxyacetophenone

Correspondence from a supplier providing permission for use of the data below are also included as *Symrise_Hydroxyacetophenone_032022.*

data3_Hydroxyacetophenone_032022

- Symrise. (2021) Certificate of analysis of Hydroxyacetophenone
- Symrise. (2021) Production flow chart of Hydroxyacetophenone
- Symrise. (2021). Summary of a dermal irritation study of Hydroxyacetophenone
- Symrise. (2013). Summary of an HRIPT of Hydroxyacetophenone

Comments on the SLR (*PCPCcomments_Hydroxyacetophenone_032022*) that were received from the Council have been addressed, and follow this memo. A comments response checklist is also included (*response-PCPCcomments_Hydroxyacetophenone_032022*).

Also included in this package, for your review, are:

- a flow chart (*flow_Hydroxyacetophenone_032022*)
- literature search strategy (*search_Hydroxyacetophenone_032022*)
- data profile (*dataprofile_Hydroxyacetophenone_032022*)
- ingredient history (*history_Hydroxyacetophenone_032022*)
- 2022 FDA VCRP data (*VCRP_Hydroxyacetophenone_032022*)
- 2020 concentration of use data (*data4_Hydroxyacetophenone_032022*)

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: May 6, 2021

SUBJECT: Scientific Literature Review: Safety Assessment of Hydroxyacetophenone as Used in Cosmetics (release date April 26, 2021)

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Hydroxyacetophenone as Used in Cosmetics.

Key Issue
Cosmetic Use - Aerosol shaving products should not be considered as having potential incidental inhalation exposure, especially for a non-volatile ingredient. The key to how CIR classifies FDA product categories in the frequency and concentration of use table has been removed from the CIR website. This classification should be publicly available and needs to be put back on the CIR website (perhaps in the Resource Document section).

Additional Considerations
Genotoxicity – As in Table 3, this section should note that at least some of the positive results were observed only at concentrations that were highly toxic.

Irritation, Animal – Since Hydroxyacetophenone was diluted in four different solvents, it should not state that it was applied "neat".

Summary – Please revise the following sentence: "In 2021 VCRP data, Hydroxyacetophenone has the highest reported use of 531 formulations, of which the two highest reported leave-on uses are in 165 face and neck products and 139 moisturizing products." This sentence can be misread as indicating that the highest use concentrations were in 165 face and neck products and 139 moisturizing products. It would be clearer if it stated that the "highest number of reported leave-on uses were…"

Table 3 – At what concentration(s) was Hydroxyacetophenone clastogenic in mouse lymphoma L5178Y cells (reference 2)?

Table 3 – In the study in BALB/C-3T3 cells, how did they know a chemical was a carcinogen? This is implying that Hydroxyacetophenone is a carcinogen, and there is no data in the CIR report to support carcinogenicity. If the "chemical carcinogens" are something other than Hydroxyacetophenone, they should be identified.

Hydroxyacetophenone - March 7-8th, 2022 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: May 6, 2021 (comments received on SLR after April 26, 2021 posting)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Cosmetic Use: Key to how CIR classifies FDA categories is needed on website	The following link is available online under Resource Docs: https://cir-safety.org/sites/default/files/CIR%20Use%20Categorization.pdf	
2	Genotox: - section should highlight that some of the positive results were only observed at highly toxic concentrations (as implied in Table 3)	Have revised	
3	Irritation, Animal: don't state 'applied neat' when test substance was diluted in 4 solvents	Have revised	
4	Summary – revise Cosmetic use sentence	addressed	
5	Table 3 – clarify at which concentration(s) Hydroxyacetophenone was clastogenic	Have revised	
6	Tab;e 3 – in the study with BALB/C-3T3 cells, clarify mention of 'carcinogenicity'	It seems like the objective was to evaluate the 'cellular transforming potential of Hydroxyacetophenone' in cells that were exposed to carcinogens (which are not identified)	

CIR History of:

Hydroxyacetophenone

January 2021

-Concentration of use data submitted by Council (survey conducted in 2020)

January 2021

-FDA frequency of use data obtained

April 2021

- SLR posted on the CIR website; received SLR comments in May

Data received, by date:

May 3, 2021:

- single occlusive patch test of a SPF product containing 0.05% Hydroxyacetophenone
- 21-d cumulative irritation assay using a SPF 70 cream containing 0.05% Hydroxyacetophenone
- HRIPT of a SPF 70 cream containing 0.5% Hydroxyacetophenone

June 21, 2021:

- Buehler test of guinea pigs (20% aqueous Hydroxyacetophenone)
- Single occlusive patch test of rabbits (1%, 10%, 50% aqueous Hydroxyacetophenone)

June 22, 2021:

- Certificate of analysis, production flow chart, dermal irritation study summary, and HRIPT summary data

January 2022

-Updated FDA frequency of use data obtained

March 2022

-A Draft Report is being presented to the Panel.

Hydroxyacetophenone Data Profile* – March 7-8, 2022 – Preethi Raj																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Hydroxyacetophenone	X	X	X	X			X	X			X	X		X	X	X				X	X		X	X			X		X

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

Hydroxyacetophenone – 1 ingredient

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Hydroxyacetophenone	99-93-4	✓*	NR	NR	NR	✓	✓*	✓	✓*	✓	NR	NR	NR	NR	✓	✓	

✓- data available
✓*- mentioned but relevant data not available
NR – not reported

Search Strategy (PubMed) [*total # of hits / # hits that were useful*]

Updated search on 01/21/21: (((((hydroxyacetophenone) OR (Ethanone, 1-(4-hydroxyphenyl)-)) OR (p-hydroxyacetophenone)) OR (parahydroxyacetophenone)) OR (4-Hydroxyacetophenone)) AND (toxicity)- 50 hits/ 0 useful

Ethanone, 1-(4-hydroxyphenyl) + toxicity- 10- 27 hits/0 useful
p-Hydroxyacetophenone toxicity – 137 hits/0 useful
4-Hydroxyacetophenone- 313 hits/ 0 useful
Piceol – 325 hits/ 0 useful
(((((Hydroxyacetophenone) OR (Ethanone, 1-(4-hydroxyphenyl))) OR (p-Hydroxyacetophenone)) OR (4-Hydroxyacetophenone)) OR (piceol))
AND (cosmetic toxicity) – 1 hit/0 useful
AND (method of manufacture) – 2 hits/ 0 useful
AND (impurities) – 5 hits/ 0 useful
AND (dermal penetration) – 0 hits
AND (toxicokinetics) – 20 results/ 1 useful
AND (dermal toxicity) – 14 results/ 1 useful
AND (oral toxicity) – 92 results /0 useful
AND (inhalation toxicity) – 11 results/ 0 useful
AND (repeated dose toxicity)- 43 results/ 0 useful
AND (repeated dose oral toxicity)- 22 results/0 useful
AND (repeated dose dermal toxicity)- 4 hits/ 1 useful
AND (repeated dose inhalation toxicity) – 2 hits/0 useful
AND (developmental toxicity) – 29 hits/0 useful
AND (reproductive toxicity) – 24 hits/ 0 useful
AND (genotoxicity/ mutagenicity) – 21-22 hits/ 0 useful
AND (carcinogenicity) – 22 hits/0 useful
AND (dermal irritation) – 5 hits/ 1 useful
AND (dermal sensitization) – 4 hits/ 0 useful
AND (phototoxicity) – 6 hits/ 0 useful
AND (ocular irritation) – 2 hits/ 0 useful
AND (clinical studies) – 38 hits/ 0 useful

General Web Search (Google)

Hydroxyacetophenone Australian industrial chemicals introduction scheme risk assessment – 27300 hits/ 0 useful
Ethanone, 1-(4-hydroxyphenyl) safety assessment- 20,300 hits/ 0 useful
p-Hydroxyacetophenone dermal irritation– 46 hits/ 0 useful
p-hydroxyacteophenone EU risk assessment – 25 hits/ 0 useful
p-hydroxyacetophenone European medical assessment – 143,000 hits/ 0 useful; 4-Hydroxyacetophenone dermal sensitization – 38,500 hits/ 5 useful
Where is piceol found – 6,60 hits/ 4 useful; CAS 99-93-4 toxicity – 82 hits/ 1 useful

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Connected Papers (https://www.connectedpapers.com)

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

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
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – https://ifrafragrance.org/
- Research Institute for Fragrance Materials (RIFM) - https://www.rifm.org/#gsc.tab=0

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ABBREVIATIONS

CAS	Chemical Abstracts Service
CII	cumulative irritation index
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturing Association
GRAS	generally recognized as safe
HRIPT	human repeat insult patch test
ICDRG	International Contact Dermatitis Research Group
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD	lethal dose
MMAD	mass median aerodynamic diameter
MeOH	methanol
MW	molecular weight
N/A	not applicable
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NR	not reported/none reported
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PDII	primary dermal irritation index
PII	primary irritation index
SIOPT	single insult occlusive patch test
SLS	sodium lauryl sulfate
TG	test guideline
THF	tetrahydrofuran
US	United States
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This assessment reviews the safety of Hydroxyacetophenone as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), this ingredient is reported to function in cosmetics as an antioxidant and skin-conditioning agent.[1]

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

Much of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[2] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

Hydroxyacetophenone (CAS No. 99-93-4) is the organic compound that conforms to the structure depicted in Figure 1.

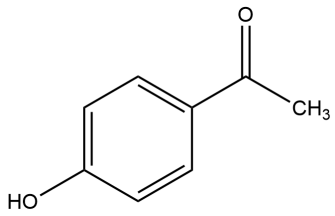

Figure 1. Hydroxyacetophenone

Chemical Properties

Hydroxyacetophenone has a molecular weight (MW) of 136.15 g/mol and an estimated log K_{ow} of 1.65.[2,3] The chemical properties of Hydroxyacetophenone are further outlined in Table 1.

Natural Occurrence

Hydroxyacetophenone, also known as piceol, and its glucoside, picein, have been found at concentrations of 0.4% - 1.1% and 1.8 - 2.2%, dry weight, respectively, in Norway spruce (*Picea abies*) needles.[4]

Method of Manufacture

According to a supplier, a sample of Hydroxyacetophenone is manufactured as described below.[5] Firstly, phenol and acetic anhydride are combined to produce phenylacetate. The phenylacetate is converted to 4-Hydroxyacetophenone via a Fries rearrangement, after which it is purified.

Impurities

According to data in ECHA, the test substance Hydroxyacetophenone is reported at a purity of up to > 99%.[2] Gas liquid chromatography of a Hydroxyacetophenone sample in a supplier-provided certificate of analysis confirmed up to 99.5% purity.[6] No further impurities data were found in the published literature, and unpublished data were not submitted.

USE

Cosmetic

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

According to 2022 VCRP survey data, Hydroxyacetophenone is reported to be used in 791 formulations, of which 671 are leave-on products; there are 236 reported uses in moisturizing products and 202 reported uses in face and neck products (Table 2).[7] Results from the 2020 concentration of use survey conducted by the Council indicate that the highest concentration of use reported for Hydroxyacetophenone is 5%, in non-spray night products and in paste masks and mud packs; the night product use represents the greatest maximum concentration of use for leave-on dermal exposure.[8]

This ingredient has been reported to be used in products that may come into contact with the eyes; for example, Hydroxyacetophenone is reported to be used at up to 0.23% in eye lotions and eye makeup removers. Reported use of Hydroxyacetophenone in lipsticks also indicates the possibility for incidental ingestion. Hydroxyacetophenone is also reported to be used at up to 0.6% in formulations that could come in contact with mucous membranes, such as bath soaps and detergents. Hydroxyacetophenone is reported to be used in 7 baby products; concentration of use data were not provided for this type of exposure.

Hydroxyacetophenone is reported to be used in cosmetic formulations that could be incidentally inhaled. For example, it is reported to be used in aerosol hair sprays (at up to 0.5%) and in face powder (concentration of use not reported). Additionally, Hydroxyacetophenone is reported to be used in moisturizing spray (at 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 < 10 µm compared with pump sprays.[9,10] Therefore, most droplets/ particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[11,12]. 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.[13-15]

Hydroxyacetophenone is not restricted from use in any way under the rules governing cosmetic products in the European Union.[16]

Non-Cosmetic

In 2011, the Joint Expert Committee on Food Additives (JECFA) mentioned Hydroxyacetophenone as a flavoring agent, and that it posed no safety concerns.[17] In Europe, Hydroxyacetophenone dietary exposure was estimated as 0.0002 µg/kg bw/d, while in Japan, Hydroxyacetophenone dietary exposure was estimated as 0.0059 µg/kg bw/d. Hydroxyacetophenone also has a Flavoring, Extract, and Manufacturing Association (FEMA) generally recognized as safe (GRAS) designation, under FEMA No. 4330.[18]

TOXICOKINETIC STUDIES

Toxicokinetics studies were not found in the published literature, and unpublished data were not submitted

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Hydroxyacetophenone (99.97% pure) was investigated following a single, occlusive application to New Zealand white rabbits.[2] Five male and 5 female New Zealand white rabbits (no controls used) were exposed to a single, undiluted dose of 2000 mg/kg Hydroxyacetophenone for 24 h, and were observed for mortality and clinical abnormalities for 14 d. No animals died during the observation period. All animals exhibited abnormal stools, ocular discharge, erythema, and edema at the test site; by day 13, all external abnormalities had resolved. Upon necropsy, no visible lesions were observed. The acute dermal LD_{50} in rabbits was > 2000 mg/kg bw.

Oral

The acute oral toxicity of Hydroxyacetophenone (99.97% pure) was determined in groups of 5 male and 5 female Sprague-Dawley rats using a single gavage exposure of 0, 1000, 2000, or 5000 mg/kg Hydroxyacetophenone, in corn oil.[2] The animals were observed for 14 d prior to necropsy. No animals in the control and 1000 mg/kg group died, while 3 male and 3 female rats from the 2000 mg/kg group and 4 male and all 5 female rats from the 5000 mg/kg group died; all animals died within 24 h of exposure. During the 14-d observation period, 8 of the 5000 mg/kg group animals, all 10 of the 2000 mg/kg group animals, and 8 of the 1000 mg/kg group animals exhibited one of the following: oral discharge, nasal discharge, ocular discharge, alopecia, abnormal respiration, tremors, abnormal stools, lethargy, and/or moribundity. Two of the control animals exhibited abnormal stools on day 0 while 1 animal exhibited a stained coat on day 3-9 of the observation period. Upon post-mortem examination, fluid was found in either the stomach, duodenum, jejunum, and/or ileum. The acute oral LD_{50} was determined to be 2240 mg/kg bw.

Short-Term Toxicity Studies

Oral

In a 28-d oral toxicity study, Hydroxyacetophenone (99.8% pure) was administered in propylene glycol, once daily by gavage, to groups of 5 male and 5 female Crl:WI(Han) rats at doses of 0, 40, 150, or 600 mg/kg bw, in accordance with Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 407.[2] No substance-related mortality or body weight gain occurred during the study period. No toxicologically significant changes were noted in hematology, clinical pathology, or organ weights, or upon gross and microscopic examination. The no-observed-adverse-effect-level (NOAEL) of Hydroxyacetophenone in rats was determined to be 600 mg/kg bw/d.

Inhalation

In an inhalation toxicity study, 10 male Sprague-Dawley rats and concurrent controls (number not specified) were exposed, whole body, 6 h/d and 5 d /wk for 4 wk, to a dust concentration of 42 mg/m^3 Hydroxyacetophenone (99.7% pure).[2] No mortality occurred during observation. The average mass median aerodynamic diameter (MMAD) was measured as 11 µm, with a standard deviation of 2.0 µm. More than 48% of the detected particles were found to be ≤ 10 µm. A statistically significant decrease in albumin was observed after the first week of exposure, however these values returned to normal levels by the fourth week. The no-observed-adverse- effect-concentration (NOAEC) for inhalation toxicity in rats was determined to be 42 mg/m^3.

Subchronic Toxicity Studies

Oral

Groups of 20 male and 20 female Sprague-Dawley rats were dosed with 0, 5, 15, or 45 mg/kg Hydroxyacetophenone (100% pure), in corn oil, via gavage, in accordance with OECD TG 408, for 90 d.[2] One mid-dose female was sacrificed moribund on day 57, 1 control male was found dead on day 12, and mortality in 7 animals distributed across the groups was considered due to accidental deaths. Several (1-3) male animals from the control and most treated groups exhibited chromodacryorrhea or lacrimation, which were not considered treatment-related. No treatment-related effects were seen upon body weight, ophthalmoscopic examination, urinalysis data, and pathology. Mean food consumption was slightly elevated in males from the 45 mg/kg group during the last 4 wk, but these increases were generally not dose-related and therefore were not considered toxicologically significant. A month and a half into the study, a dose-related increase in reticulocytes was seen in males and females (groups not specified), which was not statistically significant. The NOAEL for Hydroxyacetophenone in rats was determined to be 45 mg/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Groups of 5 male and 5 female Crl: WI (Han) rats were dosed with 0, 40, 150, or 600 mg/kg bw/d Hydroxyacetophenone, in propylene glycol, via gavage, in accordance with OECD TG 422.[2] Males were exposed for 30 d, including 2 wk prior to mating, up to the day before necropsy; females were exposed from 2 wk prior to mating up to at least 4 d of lactation, for a total of up to 46 d. Males were killed and examined shortly after mating, while females and pups were killed and examined after day 4 of lactation. One female in the 600 mg/kg group experienced total litter loss after delivery and was killed after 24 h; since other litters of the same group were comprised of live offspring, this finding was not considered toxicologically significant. No toxicologically significant changes or differences in fetal or pup body weights, viability, litter size, sex ratios, maturation, gross pathology, or developmental parameters were observed for any group. The NOAEL was determined to be 600 mg/kg bw/d for both males and females in the parental generation, as well as the F_1, generation.

GENOTOXICITY STUDIES

Details of the genotoxicity studies summarized below are described in Table 3.

Hydroxyacetophenone was not genotoxic in 3 separate bacterial reverse mutation assays, with concentrations ranging from 3 µmol/plate to 10,000 µg/plate.[2] In two gene mutation assays with L5178Y mouse lymphoma cells treated with concentrations of up to 1400 µg/ml Hydroxyacetophenone in the absence and presence of metabolic activation, diminished cell growth rate and increased mutant frequencies were observed only at very high toxicities, and, specifically, in the absence of metabolic activation for one study.[2] Hydroxyacetophenone was not genotoxic at concentrations of up to 157 µg/ml in Chinese hamster ovary cell lines, with or without metabolic activation, in a sister chromatid exchange assay, or, in an in vitro cell transformation assay at concentrations of up to 1125 mg/ml using BALB/C-3T3 cell lines.[2] Groups of 5 male and 5 female ICR mice dosed with up to 450 mg/kg Hydroxyacetophenone in a micronucleus assay exhibited minimal clinical abnormalities, and 1 male from the 450 mg/kg group died on the third day following exposure; no significant increase in micronucleated polychromatic erythrocytes was noted in either sex at any dose.[2]

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below are described in Table 4.

Slight dermal irritation, including minimal erythema, without edema, was reported for 3 of 4 New Zealand white rabbits tested with a single, occlusive, 6 cm^2, application of 0.5 g Hydroxyacetophenone.[19] In a similar irritation study, a 4-h, 1 in^2 occlusive application of 0.5 g of Hydroxyacetophenone was not irritating to the skin of 6 New Zealand white rabbits.[2] Groups of 6 New Zealand white rabbits were exposed to 0.5 ml of Hydroxyacetophenone at 3%, 5%, 15%, and 30% in 4 different vehicles: tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), methanol (MeOH), or *N,N*-dimethylformamide

(DMF; which were also tested for irritation potential in the absence of the test article), for 4 h.[2] Hydroxyacetophenone in THF produced the maximum mean Draize score of 7.5 at the 3% concentration, and 5.5 at the 30% concentration (with average PDIIs of 6.8 and 5.1, respectively); the test article did not significantly increase the dermal irritancy of any vehicle. No edema or erythema occurred when 1%, 10%, or 50% aqueous Hydroxyacetophenone was applied to the abraded and intact skin of New Zealand white rabbits (3/group), under occlusion.[20] In a Buehler test, performed in 19 Dunkin Hartley guinea pigs, 20% aqueous Hydroxyacetophenone was shown to be a non-sensitizer.[21] In a maximization test, male Hartley guinea pigs induced twice with 5% Hydroxyacetophenone in propylene glycol, and challenged with a topical application of 0.5 g of 75% in petrolatum for 24 h, were not sensitized.[2]

In a single insult occlusive test (SIOPT), application of an SPF cream containing 0.05% Hydroxyacetophenone, tested as supplied (amount not specified), was not irritating to 22 subjects.[22] In another SIOPT, an occlusive application of 0.2 ml Hydroxyacetophenone was not irritating to 53 subjects.[23] In a 21-d cumulative irritation test of 32 subjects, using an SPF 70 cream, containing 0.05% Hydroxyacetophenone, repetitive application of 0.05 ml of the test article exhibited negligible potential for irritation with a total irritation score of 86, a mean cumulative irritation score of 2.69, a mean daily irritation score of 0.18, and a cumulative irritation index (CII) of 0.06 (compared to 773, 24.16, 1.61, and 0.54 for positive controls).[24] An SPF cream containing 0.5% Hydroxyacetophenone was tested in an HRIPT in 103 subjects; the test article was deemed non-sensitizing.[25] According to summary details from an HRIPT of 104 subjects, a test article containing 5% (in glycerin) of 99% pure Hydroxyacetophenone was deemed not sensitizing; 1 subject presented with two, grade 0.5 skin reactions during induction.[26]

OCULAR IRRITATION STUDIES

Animal

The eyes of 4 healthy New Zealand white rabbits were treated with 0.1 g of undiluted Hydroxyacetophenone (99.97% pure) for 24 h.[2] The untreated eye of each animal served as the control, and both eyes were observed for up to 21 d after exposure. Potential for ocular irritancy was examined in the first animal leaving the treated eye unrinsed. In the remaining 3 animals, anesthetic was used prior to dosing, even for control eyes, and treated eyes were rinsed with approximately 120 ml of 0.9% saline, for 30 sec. In the animal with the unrinsed eye, corneal opacity, conjunctival redness, iridial irritation, chemosis, and discharge were noted, all of which resolved by 21 d. A maximum Draize score of 63, out of a maximum score of 110, was recorded for the unrinsed eye, 48 h after treatment; this score is categorized as a severe irritant. In the animals with rinsed treated eyes, milder conjunctival effects were seen, but resolved within 7 d; the mean Draize score calculated for the 3 animals with rinsed eyes was 22, categorizing the test article as a moderate irritant.

The ocular irritancy potential of Hydroxyacetophenone was investigated in the eyes of 4 healthy New Zealand white rabbits.[19] The right eyes of the animals were treated with 0.1 ml of finely ground Hydroxyacetophenone (duration not provided), and ocular lesions were scored approximately 24 h and 7 d following treatment by the Draize method. The treated eyes showed signs of moderate to severe discharge, moderate chemosis (swelling) and moderate to severe redness at the 24 h observation. Corneal opacity, severe ulceration, and mild iritis was observed in all 4 treated eyes. Three of the 4 treated eyes were free of corneal effects 7 d after treatment; moderate redness and chemosis persisted through day 7 for all 4 test animals. Hydroxyacetophenone was considered a severe eye irritant to rabbit eyes under these study conditions.

CLINICAL STUDIES

Case Reports

A 79-yr-old man experienced dermatitis for 7 mo on the right upper and lower eye lid with the use of prescription eyedrops and a facial cream containing Hydroxyacetophenone (concentration in cream not provided).[27] In spite of the eyedrop prescription being changed several times, these lesions did not subside. A 2-d patch test was conducted on the back, with allergens found in the Spanish baseline series, Chemotechnique fragrance series, all previously used eye drops, and the facial cream. All patch test results were negative on day 2 and 4, except for a ?+ reaction to the face cream. Results from a repeated open application test conducted on the upper arm with the facial cream showed erythema, infiltration, and papules. Further patch tests conducted on manufacturer-supplied, individual ingredients in the face cream, revealed positive reactions only to 0.6% aqueous Hydroxyacetophenone (+ on day 2 and ++ on day 4). Furthermore, eczematous lesions resolved within 5- d use of tacrolimus, and lesions did not develop after discontinued use of the face cream. Patch test results for Hydroxyacetophenone in 10 controls were all negative.

SUMMARY

The safety of Hydroxyacetophenone, as used in cosmetics, is reviewed in this safety assessment. According to the *Dictionary*, Hydroxyacetophenone is reported to function as an antioxidant and skin-conditioning agent.

In 2022 VCRP data, Hydroxyacetophenone has the highest number of reported uses, at 791 formulations, of which the two highest number of reported leave-on uses are 236 in moisturizing products and 202 in face and neck products.

Concentration of use survey data from a 2020 survey indicate that Hydroxyacetophenone has the highest reported maximum concentration of use of 5% in non-spray night products and in paste masks and mud packs.

The acute dermal LD_{50} of Hydroxyacetophenone was > 2000 mg/kg bw in New Zealand white rabbits. Groups of 5 Sprague-Dawley rats were administered a single oral dose of up to 5000 mg/kg Hydroxyacetophenone, in corn oil, via gavage. Three male and 3 female rats from the 2000 mg/kg group, and 4 male and 5 female rats from the 5000 mg/kg group died within 24 h. During the 14-d observation period, 8 animals from the 5000 mg/kg group, all 10 in the 2000 mg/kg group, and 8 from the 1000 mg/kg group exhibited either oral discharge, nasal discharge, ocular discharge, alopecia, abnormal respiration, tremors, abnormal stools, lethargy, and/or moribundity; 2 control animals exhibited abnormal stools on day 0. The acute oral LD_{50} of Hydroxyacetophenone was determined to be 2240 mg/kg bw.

In a 28-d oral toxicity study, no toxicologically significant changes were noted in rats administered up to 600 mg/kg bw Hydroxyacetophenone; the NOAEL was determined to be 600 mg/kg bw/d. In an inhalation study, no mortality occurred in rats exposed, whole body, 6 h/d and 5 d/wk, for 4 wk, with 42 mg/m^3 Hydroxyacetophenone; a statistically significant decrease in albumin after the first week of exposure returned to normal levels by the fourth week. The NOAEC for inhalation toxicity in rats was, therefore, determined to be 42 mg/m^3.

Groups of 20 male and 20 female Sprague-Dawley rats were dosed with up to 45 mg/kg Hydroxyacetophenone, in corn oil, via gavage, for 90 d. One control male was found dead on day 12, and mortality in 7 animals across the dose groups (number not specified) was considered accidental deaths. Dose-related increases in the mean food consumption of males in the 45 mg/kg group and the reticulocytes in male and females (groups not specified) were not statistically significant. The NOAEL for Hydroxyacetophenone in rats was determined to be 45 mg/kg bw/d.

In an oral reproductive and developmental toxicity study, groups of 5 male and 5 female Crl: WI (Han) rats were dosed with 0, 40, 150, or 600 mg/kg bw/d Hydroxyacetophenone, in propylene glycol, via gavage, for up to 46 d. One dam in the 600 mg/kg group experienced total litter loss; however, because other litters of the same group were comprised of live offspring, this finding was not considered toxicologically significant. No toxicologically significant changes or differences in fetal developmental parameters were seen and the NOAEL was determined to be 600 mg/kg bw/d Hydroxyacetophenone for both males and females in the parental, as well as the filial, generation.

Hydroxyacetophenone was not genotoxic in 3 separate bacterial reverse mutation assays, at concentrations of up to 10,000 µg/plate, in the presence or absence of metabolic activation. In 2 gene mutation assays, L5178Y mouse lymphoma cells treated at concentrations of up to 1400 µg/ml Hydroxyacetophenone, in the presence or absence of metabolic activation, exhibited a diminished cell growth rate and increase in mutant frequencies only at very high toxicities, and specifically, in the absence of metabolic activation for one study. Hydroxyacetophenone was not genotoxic in a sister chromatid exchange assay, in which Chinese hamster ovary cell lines were treated with concentrations of up to 157 µg/ml, or in an in vitro cell transformation assay in which BALB/C-3T3 cell lines were treated with concentrations of up to 1125 mg/ml Hydroxyacetophenone. A significant increase of micronucleated polychromatic erythrocytes was not observed in ICR mice administered up to 450 mg/kg Hydroxyacetophenone.

Slight dermal irritation was reported for 3 of 4 New Zealand white rabbits treated with an occlusive, 6 cm^2 patch of 0.5 g Hydroxyacetophenone, moistened with saline, for 4 h. In a similar study, 0.5 g of Hydroxyacetophenone applied to rabbit skin in a 1 in^2, occlusive patch for 4 h, did not cause dermal irritation to control or treated sites. In a study comparing the dermal irritation potential of THF, DMSO, MeOH, or DMF, individually, and when 0.5 ml Hydroxyacetophenone was added to each, the test article did not increase the irritancy of any vehicle. Guinea pigs were not sensitized to 20% aqueous Hydroxyacetophenone in a Buehler test. In a maximization test, no sensitization occurred when male Hartley guinea pigs were induced twice with 5% Hydroxyacetophenone, in propylene glycol, and challenged with a topical application 0.5 g of 75% Hydroxyacetophenone in petrolatum for 24 h.

Hydroxyacetophenone was not irritating in 2 separate SIOPTs, either at 0.05% in an SPF product tested in 22 subjects, or at a dose of 0.2 ml, tested in 53 subjects. In a 21-d cumulative irritation test, a SPF cream, containing 0.05% Hydroxyacetophenone, was determined to have a negligible potential for irritation in 32 subjects, due to a total irritation score of 86, a mean cumulative irritation score of 2.69, and mean daily irritation score of 0.18, and a CII of 0.06. A SPF cream containing 0.5% Hydroxyacetophenone was found to be non-sensitizing in an HRIPT of 103 subjects. In spite of 1 subject presenting with 2, grade 0.5 reactions during induction, 5% Hydroxyacetophenone, in glycerin, was deemed a non-sensitizer in 104 subjects.

New Zealand white rabbit eyes treated with 0.1 g of undiluted Hydroxyacetophenone, unrinsed, produced a Draize score of 63, categorized as a severe irritant, while eyes rinsed with 0.9% saline for 30 sec produced a Draize score of 22, categorized as a moderate irritant. In another study, New Zealand white rabbit eyes treated with 0.1 ml, finely ground Hydroxyacetophenone showed signs of moderate to severe discharge, moderate chemosis, and moderate to severe redness when scored 24 h following treatment. Corneal effects dissipated in 3 of the 4 treated eyes within 7 d after treatment; moderate redness and chemosis persisted through day 7 for all treated eyes.

A 79- yr-old man presented with dermatitis for 7 mo on the right upper and lower eye lid with the use of prescription eyedrops and a facial cream containing Hydroxyacetophenone (concentration in cream not provided). Positive patch-test

reactions occurred for 0.6% aqueous Hydroxyacetophenone, which resolved with use of tacrolimus and discontinuation of cream use.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1, Chemical properties of Hydroxyacetophenone

Property	Value	Reference
Physical Form (@ 20 °C and 1013 hPa)	Solid	[2]
Color	White to beige	[6]
Molecular Weight (g/mol)	136.15	[3]
Specific Gravity (@ 20 ºC)	1.27	[2]
Vapor pressure (mmHg @ 20 ºC)	0.000015	[2]
Melting Point (°C @ 1013 hPa)	110	[2]
Water Solubility (g/l @ 22 ºC)	10	[2]
log K_{ow} (@ 25 °C)	1.35 (estimated)	[2]
Disassociation constants (pK_a @ 25 ºC)	8.05	[2]

Table 2. Frequency (2022) and concentration (2020) of use of Hydroxyacetophenone

	# of Uses[7]	Max Conc of Use (%)[8]
Totals*	**791**	**0.00009 - 5**
Duration of Use		
Leave-On	*671*	*0.02 - 5*
Rinse-Off	*119*	*0.000099 -5*
Diluted for (Bath) Use	*1*	*0.25*
Exposure Type		
Eye Area	47	0.23
Incidental Ingestion	2	NR
Incidental Inhalation-Spray	4; 265[a]; 232[b]	0.3 – 0.5; 0.5[a]
Incidental Inhalation-Powder	3; 232[b]; 3[c]	0.075 – 0.3[c]
Dermal Contact	754	0.000099 - 5
Deodorant (underarm)	5[a]	NR
Hair - Non-Coloring	33	0.02 – 0.5
Hair-Coloring	NR	NR
Nail	2	NR
Mucous Membrane	23	0.000099 – 0.6
Baby Products	7	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 these products are sprays, but it is not specified whether the reported uses are sprays.

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

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

NR – not reported

Table 3. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
Hydroxyacetophenone	3 µmol/plate, with and without metabolic activation	ethanol	*Salmonella typhimurium* strains TA 98, 100	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive control gave expected results.	[28]
Hydroxyacetophenone, 99.97% purity	Up to 5000 µg/plate, with and without metabolic activation	DMSO	*S. typhimurium* TA 98, 100, 1535, 1537, 1538	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive control gave expected results.	[2]
Hydroxyacetophenone	1.0 -10,000 µg/plate, with and without metabolic activation	DMSO	*S. typhimurium* strains TA 98, 100, 1535, 1537, 1538	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone, 99.97% purity	100- 1400 µg/ml without metabolic activation; 10-800 µg/ml with metabolic activation	DMSO	Mouse lymphoma L5178Y cells	Mammalian gene mutation assay	Clastogenic; the test article was positive for genotoxicity in the absence of exogenous metabolic activation, and the observed mutant frequencies roughly increased at the highest tested concentrations; genotoxicity was ambiguous in the presence of metabolic activation. Non-metabolically activated cultures treated with doses of 100-1400 µg/ml of the test article exhibited a growth rate of 103% to 34%, respectively, while activated cultures treated with concentrations of 10-800 µg/ml test article exhibited a growth rate of 76% to 13%, respectively. The non-activated portion of the study was repeated in order to obtain cultures with less than 34% growth rate; cloned cultures treated with 1570 to 1020 µg/ml of the test article exhibited growth rates from 8% to 72%. Four of these non-activated clone cultures, with growth rates > 10%, exhibited mutant frequencies at least twice the mean mutant frequency of solvent controls. A dose-dependent response was not noted in the treated cultures. An increase in the frequency of small colonies in treated cultures, compared to control cultures, was consistent with damage to multiple loci on chromosome 11 in addition to loss of the TK locus. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone	188-1250 µg/ml without metabolic activation; 31.5- 500 µg/ml	DMSO	Mouse lymphoma L5178Y cells	Mammalian gene mutation assay	Ambiguous genotoxicity; without metabolic activation, mutant cell frequencies were significantly increased only at very high toxicities (4.7 % relative growth). In the presence of metabolic activation, the test material was converted to more active form or forms. Treatments with 31.5 - 500 µg/ml test article when assayed produced mutant frequencies of 3.4- 5.6 fold, over a wide range of toxicities. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone	4.7-157 µg/ml without metabolic activation or 47-1570 µg/ml with metabolic activation	DMSO	Chinese hamster ovary cell line	Sister chromatid exchange assay	Not genotoxic. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone	62.5, 250, 400, 700, or 1125 mg/ml	NR	BALB/C-3T3 cells	In vitro cell transformation assay. BALB/C-3T3 cells were treated with chemical carcinogens (not identified), to test for cellular abnormalities in vitro and tumor growth when injected in animals.	Not genotoxic; No significant increase in the frequency of transformed foci was observed, corresponding to 19-114% cell survival for cultures treated with the lowest and highest concentration of the test substance. Appropriate negative and positive controls gave expected results.	[2]
			IN VIVO			
Hydroxyacetophenone, > 99% purity	0,113,225,450 mg/kg	Corn oil	Groups of 5 male and 5 female ICR mice	Micronucleus assay. Animals were given a single intraperitoneal dose; cyclophosphamide was used for the positive controls.	Not genotoxic; clinical abnormalities after dosing included lethargy, rough hair coat, and hunched posture. One male from the 450 mg/kg group died on the third day after treatment. No significant increase in micronucleated polychromatic erythrocytes was noted in either sex or for any dosage. Appropriate negative and positive controls gave expected results.	[2]

DMSO – dimethyl sulfoxide
NR – not reported

Table 4. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL					
Irritation					
Hydroxyacetophenone	0.5 g, moistened with saline	4 New Zealand white rabbits	A single, 6 cm^2, occlusive application of the test article, moistened with saline, was made to clipped skin, for 4 h. Test sites were evaluated 72 h after patch removal, using the Draize scoring system.	Slight dermal irritation was reported for 3 of the 4 animals, including minimal erythema, without edema. (No further details provided).	[19]
Hydroxyacetophenone; 99.97% pure	0.5 g, moistened with sterile water	6 New Zealand white rabbits	A single, occlusive application of the test article, moistened with sterile water, was made neat to a shaved skin area of 1 in^2 for 4 h; an untreated skin site on the same animal was used as the control. The test sites were observed for up to 72 h.	All control and treated sites were free of dermal irritation throughout the study period.	[2]
Hydroxyacetophenone; 99.87% pure	0.5 ml, at 3%, 5%, 15%, 30% (in THF, DMSO, MeOH, or DMF); 0.5 ml	New Zealand white rabbits (6/group)	The test articles (0.5 ml) were applied under occlusion to a shaved area of 6 cm^2 for 4 h. An adjacent site on each treated animal was exposed to the respective vehicle (neat), and served as a vehicle control; an untreated site served as a negative control. After exposure, skin was wiped free of excess test material with an adsorbent pad and test sites were observed for up to 14 d. Test sites were evaluated for irritation using the Draize method, and all sites were scored 1, 24, 48, and 72 h after patch removal; test sites at which DMF and THF were used as the vehicle were observed at 7 d and up to 14 d, respectively. The maximum possible Draize score was 8.0. The primary dermal irritation index (PDII) was calculated using Draize scores recorded at 1, 24, 48, and 72 h after exposure.	After 72 h, THF was shown be the most irritating vehicle, with a maximum mean Draize score of 7.5 (and average PDII of 6.5); Hydroxyacetophenone in THF produced maximum mean Draize scores of 7.5 at the 3% concentration, and 5.5 at the 30% concentration (with average PDIIs of 6.8 and 5.1, respectively). Lower scores were observed with the use of the other vehicles, and scores were comparable across the concentrations with each vehicle; at the 30% concentration, Hydroxyacetophenone in DMSO had a maximum mean Draize score of 1.2 (and average PDII of 0.3), in MeOH had a maximum mean Draize score of 0.7 (and average PDII of 0.2), and in DMF had a maximum mean Draize score of 0.3 (and average PDII of 0.1). Recovery times were > 14 d for THF, 7 d for DMF, and 3 d for DMSO and MeOH. The test article did not significantly increase the dermal irritancy of any vehicle.	[2]
Hydroxyacetophenone	1%, 10%, and 50% (aqueous)	New Zealand white rabbits (3/group)	Fur was removed from the test site 24 h prior to intended application; an occlusive application was made to both abraded and intact skin. Reactions were scored 24 and 72 h after application, averaged separately for erythema and edema, and then summed to arrive at the PII.	Not irritating; PII = 0 for all test concentrations	[20]

Table 4. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			Sensitization		
Hydroxyacetophenone	20% w/v (aqueous)	Dunkin-Hartley guinea pigs (19 animals in the test group; 10 animals in the control group)	Delayed contact hypersensitivity test (Buehler test). Animals were patched with 20% aqueous test article at pH 5.3 (amount not specified) for both topical induction and challenge applications. (Specific details not provided). Readings for potential erythematous or sensitization reactions were taken 24 and 48 h after patch removal. Bodyweights were also monitored over the study duration of 4 wk.	Not sensitizing; all irritancy and severity scores were 0. One animal died during the test, but this death was not treatment-related. No significant body weight changes occurred.	[21]
Hydroxyacetophenone	5% during induction in propylene glycol; 75% during challenge in petrolatum	20 male Hartley guinea pigs	Guinea pig maximization test. An intradermal injection of 5% test article (in propylene glycol, with and without FCA) was made during induction. Eight days later, the animals were induced for a second time with a topical application of 5% Hydroxyacetophenone in propylene glycol. Two wk after the second induction, a topical challenge application was made with 0.5 g of 75% Hydroxyacetophenone in petrolatum for 24 h. Dinitrochlorobenzene was used as a positive control (number of controls not specified).	Not sensitizing	[2]
			HUMAN		
			Irritation		
SPF 50 cream containing 0.05% Hydroxyacetophenone	applied neat	22	SIOPT; the test article (amount not specified) was applied for 24 h. An SPF 70 gel cream product was used as the control.	Not irritating; PII of 0.0	[22]
Hydroxyacetophenone	0.2 ml	53	SIOPT; A single, occlusive application of the test material was applied to the back using a 0.75 in^2 patch for 48 h. Readings were performed 48 and 72 h after application.	Not irritating	[23]
SPF 70 cream containing 0.05% Hydroxyacetophenone	applied neat; 0.05 ml	32	21-d cumulative irritation test. The test article was used as supplied. Occlusive applications were made using a 15 mm Webril patch, and scored on a 5-pt ICDRG grading scale upon removal, 5 d/wk for 3 consecutive weeks; patches applied on Friday remained in place until Monday. One site was also treated with 0.05 ml of 0.25% SLS as a positive control, and a plain cotton patch was applied as a negative control.	Negligible potential for irritation; the test article produced a total irritation score of 86, a mean cumulative irritation score of 2.69, a mean daily irritation score of 0.18, and a CII of 0.06 (compared to 773, 24.16, 1.61, and 0.54, respectively, for the positive controls).	[24]
			Sensitization		
SPF 70 cream containing 0.5% Hydroxyacetophenone	applied neat; 0.2 g (induction and challenge)	103	In an HRIPT, 24- h occlusive patches containing 0.2 g of the test material were applied 3x/wk, for 3 wk, for a total of 9 induction applications. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored at 24, 48, 72, and 96 h after application.	Not sensitizing	[25]
Hydroxyacetophenone 99% pure	5% in glycerin	104	An HRIPT was conducted (no further details were provided).	Not sensitizing; 1 subject presented with two, grade 0.5 skin reactions during induction	[26]

Abbreviations: CII- cumulative irritation index; DMF- *N,N*-dimethylformamide; DMSO – dimethyl sulfoxide; FCA – Freund's complete adjuvant; HRIPT- human repeat insult patch test; ICDRG- International Contact Dermatitis Research Group; MeOH – methanol; PDII – primary dermal irritancy index; PII – primary irritation index; SIOPT – single insult occlusive patch test; SLS- sodium lauryl sulfate; THF- tetrahydrofuran

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 3, 2021

SUBJECT: Hydroxyacetophenone

Anonymous. 2018. Human patch test SPF product containing 0.05% Hydroxyacetophenone.

Anonymous. 2017. 21-Day cumulative irritation assay Sample: SPF 70 cream containing 0.05% Hydroxyacetophenone.

Anonymous. 2017. Repeated insult patch test of an SPF 70 cream containing 0.5% Hydroxyacetophenone.

[redacted] [redacted]

[redacted] **REPORT: HUMAN PATCH TEST**

This test follows the procedure described in SOP, HPT.1 **TO:** [redacted]

PRODUCT PROFILE NO: [redacted] REPORT DATE: October 10, 2018 LAB REF.: [redacted]

TEST DATES: June 27,2018 to June 29,2018

1. TEST MATERIAL: [redacted] Sun SPF50 [redacted] contains 0.05% Hydroxyacetophenone

2. CONTROL MATERIAL: [redacted] SPF70 Gel Cream [redacted]

3. TEST PROCEDURE:

Single-Insult (24hr.) X Occlusive Patch X Semi-Occlusive Patch_____.

4. CONCENTRATION:

Full-Strength X Aqueous _____ Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

_____Volatiles were allowed to evaporate ~15 minutes prior to occlusion on the patch
_____Patch was hydrated just prior to application to skin.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	+	1	1+	2	2+	3	3+	4	PII
[redacted] Sun SPF50 [redacted]	22	22	0	0	0	0	0	0	0	0	0.00
[redacted] SPF70 Gel Cream [redacted]	22	20	2	0	0	0	0	0	0	0	0.05

___ Skin staining noted. Erythematous response was read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). X .

B. _____.
_____.
_____.

Study Conducted By: [redacted]

Written By: [redacted]

* SCORE
0 = No evidence of any effect.
+ (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

CC:

[redacted]

Final Report for

[redacted]

[redacted] # ASF 05/01/17

21-DAY CUMULATIVE IRRITATION ASSAY
Sample: SPF 70 Cream coded [redacted]
(tested as supplied)

contains 0.05% Hydroxayacetophenone

Submitted by:

[redacted]
[redacted], MD

June 2, 2017
Date

STATEMENT OF QUALITY CONTROL

All study-related documents underwent quality control (QC) review in accordance with [redacted] QC standard operating procedures. The study report was reviewed and accurately reflects the data for this study.

[redacted]

[redacted]

Table of Contents

Contents

I. BACKGROUND

Patch testing is an established diagnostic procedure used to identify skin sensitizing substances [1]. Dilute substances are applied to small areas of skin under occlusion (i.e., a patch) for variable periods of time. In clinical practice, patch testing is performed with common skin sensitizing substances over 1-2 days and results in positive reactions at a rate greater than 0.5% to 1.0% [2]. In product safety testing of new substances or formulations, repeat insult patch testing (RIPT) is performed over 1-5 weeks.

The 21-Day Cumulative Irritation Assay is a RIPT intended to identify substances capable of inducing a non-immunologic, primary irritancy reaction (irritant contact dermatitis) [3 -6].

II. OBJECTIVES

The objective of this study is to assess the primary irritancy potential of topically applied substances in human skin using a RIPT over twenty-one (21) days.

III. EXPERIMENTAL DESIGN

Principal Investigator: [redacted], M.D. – Board Certified Dermatologist

Project Technician: [redacted]

Test Facility: [redacted]

Study Sponsor: [redacted].

Study Contact: [redacted]

Investigational Review Board: IntegReview IRB
3815 S. Capital of Texas Hwy, Suite 320
Austin, TX 78704

Design of Study

This RIPT is an open-label, single arm (cell), randomized, evaluator-blinded study wherein test products are applied under an occlusive dressing to the upper back or arm continuously and repeatedly to the same site for a period of 21 days. The sample size is a minimum of 30 subjects. Up to five (5) test products are applied to the skin of each subject. In addition to the test products, one site will also be treated with 0.05ml of 0.25% sodium lauryl sulfate (SLS) as a positive control and another site will be treated with a plain Webril patch (cotton cloth) and will serve as a negative control. The evaluator will grade the level of irritation at each test site and be blinded as to the identity of the test products. See study schema below.

Study Dates

May 1, 2017 through May 22, 2017

Pre-Study

Recruitment of prospective subjects was accomplished by telephone contact. Candidate subjects were assigned an appointment time at the testing facility. During this visit, written informed consent was obtained and the following was completed:

- Informed Consent Form
- Medical History and Concomitant Medications
- Child-Bearing Potential
- Inclusion/Exclusion

Study Schedule

Day:	M 0	T 1	W 2	Th 3	F 4	S 5	S 6	M 7	T 8	W 9	Th 10	F 11	S 12	S 13	M 14	T 15	W 16	Th 17	F 18	S 19	S 20	M 21
Test Material Application*	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			^

(□) Test site graded and test material re-applied

(□) Final skin grading

Procedures

Screening (Day -7 to Day 1)

After the subject has provided written informed consent, the following procedures were performed in the order listed:

1. Obtained demographic information and medical history, including information on all medications used within the past 30 days. Included herbal therapies, vitamins, and all over-the-counter as well as prescription medications.
2. Examined test sites for any scars, moles or other blemishes that can interfere with the study.
3. Completed child-bearing potential if female.
4. Reviewed inclusion /exclusion criteria.

RIPT (Day 0 – Day 21)

Approximately 0.05ml of each test material was spread uniformly onto a 15mm diameter circular disc of non-absorbing cotton cloth (Webril), using micropipettes or plastic tuberculin syringes. The treated circular disc was then applied to a designated skin site measuring 15mm in diameter on the arm or back following the randomization scheme (**Appendix A**). The site was then covered with an occlusive tape (Blenderm, 3M) and the entire patch fastened to the skin with Scanpor or Hypafix Tape to ensure intimate contact with the skin. The initial patch was applied on Day 0 and grading began on Day 1.

The subjects returned to the testing facility once daily (Monday to Friday). At each visit, the patches were removed and the test sites graded for irritation or inflammation using the 5-point International Contact Dermatitis Research Group (ICDRG), followed by fresh re-applications of the test materials and occlusive patches. This procedure was repeated daily Mondays through Fridays for three consecutive weeks, with patches remaining in place over the weekends (Friday to Monday). The entire duration of the study was 22 days with final grading of skin sites on Day 21. In addition to the test products, one site was also treated with 0.05ml of 0.25% SLS (sodium lauryl sulfate) as a positive control and another site was treated with a plain Webril patch (cotton cloth) as a negative control.

Assessment and Grading of Skin Irritation

Irritant reactions provoked during the study were recorded daily (except for Saturdays and Sundays). All test sites were graded daily after removal of the patches for possible irritation using the 5-point ICDRG grading scale (0-4) of skin irritation:

SCORING SCALE
0 = no visible redness
1 = faint redness, poorly defined margins
2 = moderate redness, well defined margins

3 = intense redness
4 = caustic erythema – erosive and/or necrotic aspect

OTHER NOTATIONS
V = Vesicles
E = Erosions
F = Fissuring

Test sites achieving a grade 3 or greater score were discontinued and that grade was carried through for the remainder of the test days for the purpose of calculating the cumulative irritation index.

Cumulative Irritation Index (CII) and Irritancy Potential

The CII is the ratio calculated by dividing the sum of the cumulative irritation scores (SCS) from all subjects by the number of subjects in the panel x the maximum tolerated score per patch site (3) x the number of evaluation days (15) [6]. See **Appendix B**.

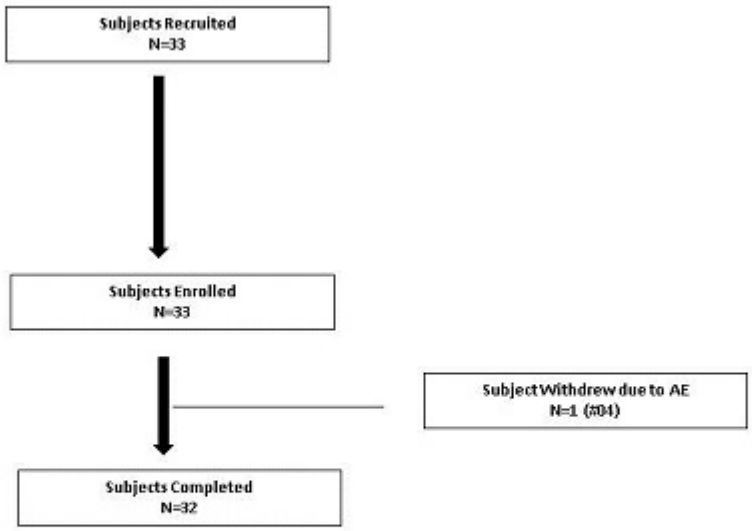
The range of the CII scores is correlated to the Irritancy Potential [6] as below:

CII SCORING	IRRITANCY POTENTIAL
0.0-0.06	**negligible or no significant irritation**
0.07-0.15	**minimal or weak irritancy potential**
0.16-0.22	**mild irritancy potential**
0.23-0.33	**moderate irritancy potential**
0.34-0.55	**severe irritancy potential**

IV. RESULTS

Panelist Accountability

Disposition of Subjects



A total of 33 subjects who satisfied the inclusion/exclusion criteria were enrolled into the study. Subject #04 had an adverse event and was withdrawn (see section C below). 32 subjects completed this investigation as outlined in the standard study protocol.

Demographic Data

There were 14 females and 19 males. Their ages ranged from 23 to 70 years. The demographic data is shown in Table 1 below.

TABLE 1

Subject Demographic Data			
Subject Number	**Age**	**Gender**	**Race**
01	60	M	C
02	69	M	C
03	49	F	C
04	59	F	C
05	63	M	C
06	50	F	C
07	57	M	C
08	34	F	C
09	49	M	C
10	27	M	C
11	26	F	C
12	37	F	C
13	59	M	C
14	65	M	C
15	66	M	C
16	65	F	C
17	63	M	C
18	23	F	C
19	60	F	C
20	64	F	C
21	61	M	C
22	59	F	C
23	60	M	C
24	67	F	C
25	70	M	C
26	40	M	C
27	52	M	C
28	53	M	C
29	51	M	C
30	62	M	C
31	41	F	C
32	45	M	C
33	48	F	C

C = Caucasian

Adverse Events

There was one adverse event during the course of this study. There were no product related adverse events.

- Subject # 04 – Kidney stones- withdrew 5/18/17

Protocol Deviations

There were no protocol deviations during the course of this study.

Irritation Results

No unexpected reactions were seen in any of the subjects during the study. The individual daily and cumulative irritation scores for each test site are shown in the tables in **Appendix C**. The test products labeled SPF70 Cream coded [redacted] (tested as supplied) produced a total cumulative irritation score of 86 and a CII of 0.06. The plain cotton Webril control produced a total cumulative irritation score of "19" and a CII of 0.01. In contrast, the 0.25% Sodium Lauryl Sulfate produced a total cumulative irritation score of "773" and a CII of 0.54. The mean irritation scores and Cumulative Irritation Indices are summarized in Table 2.

TABLE 2

	SPF70 Cream coded [redacted]	Webril Cotton (negative control)	0.25% Sodium Lauryl Sulfate (positive control)
Sum of Cumulative Scores	86	19	773
Mean Cumulative Irritation Score	2.69	0.59	24.16
Mean Daily Irritation Score	0.18	0.04	1.61
Cumulative Irritation Index	0.06	0.01	0.54
Irritation Potential	**□egligible**	**□egligible**	**Severe**

V. CONCLUSION

The test product SPF70 coded [redacted] was found to possess a "Negligible" irritation potential in human skin.

VI. REFERENCES

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Appendix A:

Randomization Scheme

Subject #	Site 1	Site 2	Site 3	Site 4
1	D	C	A	B
2	B	A	C	D
3	A	C	B	D
4	B	D	C	A
5	C	B	A	D
6	D	C	B	A
7	B	C	D	A
8	A	B	D	C
9	B	D	A	C
10	D	B	C	A
11	C	B	D	A
12	A	C	D	B
13	C	A	D	B
14	A	D	C	B
15	D	A	C	B
16	C	D	B	A
17	D	B	A	C
18	C	D	A	B
19	C	A	B	D
20	B	A	D	C
21	A	D	B	C
22	B	C	A	D
23	A	B	C	D
24	D	A	B	C
25	B	A	C	D
26	C	B	A	D
27	D	A	B	C
28	C	B	D	A
29	C	A	B	D
30	C	D	B	A
31	D	C	A	B
32	A	C	D	B
33	B	D	A	C
34	A	D	C	B
35	B	C	D	A
36	D	C	B	A

A=SPF Cream coded [redacted]
B= BB Cream coded [redacted]
C= Webril Cotton (negative control)
D= 0.25% Sodium Lauryl Sulfate (positive control)

Appendix B: Irritation Indices Calculations for 21-Day Cumulative Irritation Assay & Irritancy Potential

[redacted]

(Adapted from reference 6)

1. Cumulative Irritation Score (CIS): The total of the 15 individual daily scores from each patch site.

2. Sum of Cumulative Scores (SCS): The total of all of the CIS from each patch site for all of the subjects.

3. Mean Cumulative Irritation Score (MCIS): The mean CIS per subject calculated by dividing the SCS by the number of evaluable subjects who completed the study (N).

   MCIS = $\frac{SCS}{N}$

4. Mean Daily Irritation Score (MDIS): The daily mean CIS for the 15 evaluation days in the 21-day Cumulative Irritation Assay calculated by dividing the MCIS by 15.

   MDIS = $\frac{MCIS}{15}$

5. Cumulative Irritation Index (CII): The ratio calculated by dividing the SCS by the number of subjects in the panel (N) x the maximum tolerated score per patch site (3) x the number of evaluation days (15).

   CII = $\frac{SCS}{N \times 3 \times 15}$

6. Correlation of CII with Irritancy Potential

CII SCORING	IRRITANCY POTENTIAL
0.0-0.06	**negligible or no significant irritation**
0.07-0.15	**minimal or weak irritancy potential**
0.16-0.22	**mild irritancy potential**
0.23-0.33	**moderate irritancy potential**
0.34-0.55	**severe irritancy potential**

Appendix C: Individual Daily and Cumulative Irritation Scores by Test Product

DAILY AND CUMULATIVE IRRITATION SCORES																						
Sample: A SPF 70 Cream coded [redacted] Tested as Supplied																						
Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**Cumulative**
Number	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	**Score**
1	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
2	0	0	0	0			0	0	0	0	0			0	1	1	1	1			1	5
3	0	1	0	0			0	0	0	1	1			0	1	1	1	0			0	6
4*																						
5	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
6	0	0	0	0			0	0	0	0	0			0	1	1	1	1			1	5
7	0	0	0	0			0	0	0	0	0			0	1	1	1	1			1	5
8	1	1	0	0			0	0	0	0	0			0	1	1	1	2			2	9
9	0	0	0	0			0	0	0	0	0			0	0	0	0	0			1	1
10	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
11	0	0	0	0			1	1	0	0	0			0	1	1	1	1			1	7
12	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
13	0	0	0	0			0	1	1	0	1			1	1	1	1	1			1	9
14	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
15	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
16	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
17	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
18	0	0	0	0			0	0	0	1	1			0	0	1	0	0			0	3
19	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
20	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
21	0	0	0	0			0	0	0	0	0			0	1	1	1	1			1	5
22	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
23	0	0	0	0			0	0	0	0	0			0	1	1	1	1			1	5
24	0	0	0	0			1	1	0	0	0			0	1	1	1	1			1	7

DAILY AND CUMULATIVE IRRITATION SCORES

Sample: A (cont.)

Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	Cumulative
Number	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	Score
25	0	0	0	0			0	0	0	0	0			1	1	1	1	1			0	5
26	0	0	0	0			0	0	0	0	0			0	0	0	1	1			1	3
27	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
28	0	0	0	0			0	0	0	0	0			1	1	1	1	1			0	5
29	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
30	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
31	0	0	0	0			0	0	0	0	0			1	1	0	0	0			1	3
32	0	0	0	0			0	0	0	1	0			0	1	0	0	0			0	2
33	0	0	0	0			0	1	0	0	0			0	0	0	0	0			0	1
Σ	**1**	**2**	**0**	**0**			**2**	**4**	**1**	**3**	**3**			**4**	**14**	**13**	**13**	**13**			**13**	**86**

Mean Cumulative Irritation Score	2.69	Mean Daily Irritation Scores	0.18	Cumulative Irritation Index (CII)	0.06

Subject withdrawn from study

DAILY AND CUMULATIVE IRRITATION SCORES																						
Sample: C Webril Cotton (negative control)																						
Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**Cumulative**
Number	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	**Score**
1	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
2	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
3	0	0	0	0			0	0	0	1	0			1	0	1	0	0			1	4
4*																						
5	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
6	0	0	0	0			0	0	0	0	1			1	0	1	0	0			0	3
7	0	0	0	0			0	0	0	0	0			0	1	0	0	0			0	1
8	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
9	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
10	0	0	0	0			0	0	0	0	0			0	0	0	0	0			1	1
11	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
12	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
13	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
14	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
15	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
16	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
17	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
18	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
19	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
20	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
21	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
22	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
23	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
24	0	0	0	0			0	0	0	0	1			1	1	0	0	0			2	5

DAILY AND CUMULATIVE IRRITATION SCORES

Sample: C (cont.)

Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	Cumulative
Number	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	Score
25	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
26	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
27	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
28	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
29	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
30	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
31	0	1	0	0			0	0	0	0	0			0	0	0	0	0			1	2
32	0	0	0	0			0	0	0	0	0			0	0	0	0	0			0	0
33	0	0	0	0			0	0	1	1	1			0	0	0	0	0			0	3
Σ	**0**	**1**	**0**	**0**			**0**	**0**	**1**	**2**	**3**			**3**	**2**	**2**	**2**	**2**			**5**	**19**

Mean Cumulative Irritation Score	0.59	Mean Daily Irritation Scores	0.04	Cumulative Irritation Index (CII)	0.01

Subject withdrawn from study

[redacted]

DAILY AND CUMULATIVE IRRITATION SCORES																						
Sample: D 0.25% Sodium Lauryl Sulfate (positive control)																						
Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**Cumulative**
Number	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	**Score**
1	0	0	1	1			1	1	1	1	2			2	2	3	3	3			3	24
2	0	0	0	1			1	2	2	3	3			3	3	3	3	3			3	30
3	0	1	0	0			1	1	1	2	3			3	3	3	3	3			3	27
4*																						
5	0	0	1	2			3	3	3	3	3			3	3	3	3	3			3	36
6	0	0	0	0			0	1	1	1	2			3	3	3	3	3			3	23
7	0	1	1	2			2	2	3	3	3			3	3	3	3	3			3	35
8	0	0	0	1			1	1	1	1	1			1	2	3	3	3			3	21
9	0	0	0	0			0	1	1	1	1			1	2	3	3	3			3	19
10	0	0	1	2			2	2	3	3	3			3	3	3	3	3			3	34
11	0	0	0	0			0	0	1	1	1			2	3	3	3	3			3	20
12	0	0	0	0			0	0	0	0	0			0	0	0	0	1			0	1
13	0	0	0	0			1	1	1	1	2			3	3	3	3	3			3	24
14	0	0	0	0			0	0	0	0	1			1	1	2	3	3			3	14
15	0	0	0	0			0	1	1	1	1			2	2	3	3	3			3	20
16	0	0	0	0			0	1	1	1	1			1	1	1	2	2			2	13
17	0	0	0	0			0	1	1	1	1			1	1	2	3	3			3	17
18	0	0	0	1			1	1	1	1	1			1	1	1	2	2			1	14
19	0	0	1	0			1	1	1	1	1			1	1	1	2	2			2	15
20	0	0	0	1			0	0	1	1	1			3	3	3	3	3			3	22
21	1	1	1	1			1	1	1	3	3			3	3	3	3	3			3	31
22	0	0	1	2			2	2	3	3	3			3	3	3	3	3			3	34
23	0	1	1	2			3	3	3	3	3			3	3	3	3	3			3	37
24	0	1	1	1			3	3	3	3	3			3	3	3	3	3			3	36

[redacted]

DAILY AND CUMULATIVE IRRITATION SCORES
Sample: D(cont.)

Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	Cumulative
Number	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	Score
25	0	0	1	2			2	2	3	3	3			3	3	3	3	3			3	34
26	0	0	0	0			0	0	0	0	1			1	2	2	3	3			3	15
27	0	0	0	0			0	0	0	1	1			1	1	1	2	3			3	13
28	0	0	0	0			0	1	1	2	3			3	3	3	3	3			3	25
29	0	0	0	1			2	2	3	3	3			3	3	3	3	3			3	32
30	0	0	1	1			1	1	1	1	3			3	3	3	3	3			3	27
31	0	0	0	0			0	0	0	0	1			2	3	3	3	3			3	18
32	0	0	0	1			1	1	1	1	2			2	3	3	3	3			3	24
33	0	1	2	2			3	3	3	3	3			3	3	3	3	3			3	38
Σ	**1**	**6**	**13**	**24**			**32**	**39**	**46**	**52**	**63**			**70**	**76**	**82**	**89**	**91**			**89**	**773**

Mean Cumulative Irritation Score	24.16	Mean Daily Irritation Scores	1.61	Cumulative Irritation Index (CII)	0.54

Subject withdrawn from study

[redacted]

[redacted]

[redacted]

contains 0.5% Hydroxyacetophenone

[redacted] #17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

PURPOSE:	To evaluate the potential of the Test Material, as a result of repeated applications, to induce dermal sensitization in human subjects.
IRB APPROVAL:	Both the [redacted] Standard Protocol #100 and the Informed Consent were approved by the Clarus Institutional Review Board (CIRB) on January 20, 2017. A Sponsor-signed Protocol is retained in [redacted] files.
SPONSOR:	[redacted]
SPONSOR AUTHORIZATION:	April 7, 2017
SAFETY ASSURANCE:	April 7, 2017
PRINCIPAL INVESTIGATOR:	[redacted], PhD
CO-INVESTIGATORS:	[redacted] Board-Certified Dermatologist [redacted], MD, PhD, Board-Certified Dermatologist [redacted] DO, Board-Certified Dermatologist
TEST FACILITY:	[redacted]
TEST MATERIAL:	Test Material SPF 70 Cream; Code# [redacted] a white creme, was received on April 17, 2017, with the following instructions: Test as received; patch occlusively.
SUBJECTS:	A total of 119 subjects were enrolled; 103 subjects completed the test. One subject, #098 ([redacted] #46005), informed [redacted] that she is pregnant; she was discontinued from the test. One subject, #095 ([redacted] #45649), was discontinued prior to being patched. Fourteen subjects discontinued due to personal reasons. No subject discontinued due to test material reaction.

- continued -

[redacted]

[redacted]

[redacted]**#17-110**

Test Material #1: SPF 70 Cream; Code# [redacted]

METHOD:	This test was conducted according to [redacted] Standard Protocol #100 and [redacted] Standard Operating Procedures (including any Sponsor alterations).
TEST DATES:	April 19, 2017 through May 26, 2017.
SCORING SYSTEM:	See Tables I-II.
RESULTS:	See Tables I-II. No adverse reactions or adverse events were reported / observed in any of the subjects. During the Induction Phase and the Challenge, no reactions were exhibited.
CONCLUSION:	In this Repeated Insult Patch Test, Test Material SPF 70 Cream; Code# [redacted] did not induce dermal sensitization in human subjects.
QUALITY ASSURANCE (QA):	The QA Unit performed an in-phase audit of this study.

[redacted]

Co-Investigator
Board-Certified Dermatologist

Project Manager

Principal Investigator

Date: 5/31/17

[redacted]
[redacted]#17-110
Test Material #1: SPF 70 Cream; Code#[redacted]

SUBJECTS: Each potential subject completed an [redacted] Subject History Form ([redacted]Form:SHF), including relevant medical history. (An updated Subject History Form is secured approximately every eighteen months.) Each accepted subject was assigned a permanent HRL Identification Number. No subject was used if he or she exhibited any dermatological or other medical or physical condition that would preclude topical application of the Test Material. Upon enrollment, no subject reported using any medication that would interfere with the sensitization results. No known pregnant nor nursing women were used on this RIPT. No minor subjects were used on this RIPT.

An appropriate clearance period had elapsed since a subject was patched on a Repeated Insult Patch Test (RIPT) or a Photoallergy Test (PA) before being used in this RIPT.

Legally valid written IRB-approved Informed Consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

METHOD: Induction Phase: A webril/adhesive patch (Covidien Patch #4022 or equivalent) was used occlusively. Approximately 0.2 gm of the Test Material was applied to each patch. As per [redacted] Standard Operating Procedures (SOP) ([redacted] Form:SOP/RIPT), the left side of the back was usually the test area for the Induction Phase. The subject's skin was marked with gentian violet surgical marker at the left side of the test site. The test site was recorded on the anatomical diagram of each subject's individual Data Form. In addition, at that time, the prospective placement of the Challenge test site was also recorded on the anatomical diagram.

Each subject was instructed that the patch was to remain in place and kept dry for approximately 24 hours, at which time the patch was to be removed by the subject. An approximately 24-hour period, during which no test material was applied, followed the weekday patch removals; an approximately 48-hour period followed the weekend patch removals.

Each subject returned to [redacted] on the appropriate day. The test site was observed by the [redacted] technician, and the reaction scored and recorded (see **SCORING SYSTEM**, below). The identical test site was then repatched until nine (9) Induction patchings were completed.

In accordance with [redacted] SOP, if a subject was unable to make up a missed patching during the same week, the subject was either patched four days the following week or was patched at the end of the Induction Phase. Any absences and make-up days are noted by the dates on the individual Data Form.

A series of nine (9) Induction patchings was completed over a period of approximately three weeks.

[redacted]

[redacted]

[redacted] #17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

METHOD: (continued)

Rest Period: A Rest Period of approximately two weeks followed the last Induction patching; no test material was applied during the Rest Period. Subjects were instructed to notify [redacted] if they experienced any reaction during the Rest Period.

Challenge Phase: At the Challenge Phase, the original Induction test site was observed and each subject queried as to whether any reaction was experienced during the Rest Period. Any reactions were recorded on the Data Form. A webril/adhesive patch (Covidien Patch #4022 or equivalent) was used occlusively. Approximately 0.2 gm of the Test Material was applied to each patch. As per [redacted] RIPT SOP, the opposite side of the back was usually the virgin test site for the Challenge Phase.

As per [redacted] RIPT SOP, the Challenge patch was applied to the virgin site only. Each subject was again instructed to keep the patch on and dry.

Each subject reported to [redacted] approximately 24 hours later (Challenge Reading 1), at which time the patch was removed and the Challenge site scored and recorded by the [redacted] technician. The original test site was also observed. (See **RESULTS**, below.)

Each subject reported to [redacted] at approximately 48 hours (Challenge Reading 2), approximately 72 hours (Challenge Reading 3) and approximately 96 hours (Challenge Reading 4) post-patching for additional observations; reactions were scored and recorded.

SCORING SYSTEM: See Tables I-II. The test sites were scored using the modified scoring scale of the International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27.

RESULTS: See Tables I-II. No adverse reactions or adverse events related to the Test Material were exhibited / reported by any subject during this test. Erythema, edema, dryness, staining, peeling and hyperpigmentation / hypopigmentation are possible, expected endpoints and not considered Adverse Reactions. This test was conducted under the supervision of a Board-Certified Dermatologist, a Co-Investigator. At Challenge Reading 3, the Dermatologist participated in the scoring of the subjects. A total of 103 subjects completed the test; 24 male and 79 female. The subjects range in age from 18 to 69.

RETENTION: All original Data Forms will be retained at [redacted] for a period of three years, or such other time as may be required by law. A laboratory retainer bottle of the Test Material shall be retained, in ambient conditions, for at least two years, or as required by law. Return or disposal of unused Test Material shall be as per the Sponsor's instructions—to be communicated within 30 days of receipt of this Final Report. [redacted] shall appropriately dispose of any Test Material after six months if no Sponsor instructions have been communicated.

[redacted]

[redacted] #17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS ENROLLED: 119
TOTAL NUMBER OF SUBJECTS COMPLETED: 103

Reaction	Induction Reading									Challenge Reading			
Grade	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**1**	**2**	**3**	**4**
0	114	111	111	109	109	107	106	104	104	103	101	103	101
±													
1													
1E													
2													
2E													
3E													
4E													
-											2		2
N9R													
Total	114	111	111	109	109	107	106	104	104	103	103	103	103

SCORING SYSTEM:

0	= No visible reaction
±	= Faint, minimal erythema
1	= Erythema
2	= Intense erythema, induration
3	= Intense erythema, induration, vesicles
4	= Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	= Edema
-	= No reading
N9R	= No 9th reading

[redacted] #17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

					Induction Reading									Challenge Reading			
Sub	HRL	Ini	Sex	Age	1	2	3	4	5	6	7	8	9	1	2	3	4
1	36757	AL	M	47	0	0	0	0	0	0	0	0	0	0	0	0	0
2	30680	EK	M	56	0	0	0	0	0	0	0	0	0	0	0	0	0
3	40761	WW	F	63	0	0	0	0	0	0	0	0	0	0	0	0	0
4	18039	JR	M	53	0	0	0	0	0	0	0	0	0	0	0	0	0
5	36461	MW	M	52	0	0	0	0	0	0	0	0	0	0	0	0	0
6	45493	KH	F	27	0	0	0	0	0	0	0	0	0	0	0	0	0
7	46299	AS	F	54	0	0	0	0	0	0	0	0	0	0	0	0	0
8	41939	MG	F	59	0	0	0	0	0	0	0	0	0	0	0	0	0
9	18616	BC	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
10	44687	EG	M	41	0	0	0	0	0	0	0	0	0	0	0	0	0
11	46269	GH	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
12	22288	MR	F	69	0	0	0	0	0	0	0	0	0	0	0	0	0
13	18968	NP	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0
14	44797	SD	F	25	0	0	0	0	0	0	0	0	0	0	0	0	0
15	32641	MM	F	31	0	0	0	0	0	0	0	0	0	0	0	0	0
16	27639	CF	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0
17	41618	CD	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0
18	14892	VH	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
19	34051	KB	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0
20	30255	LU	M	33	0	0	0	0	0	0	0	0	0	0	0	0	0
21	22173	CP	F	63	0	0	0	0	0	0	0	0	0	0	0	0	0
22	41605	MC	F	27	0	0	0	0	0	0	0	0	0	0	0	0	0
23	44290	AS	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0
24	45543	DC	F	50	0	0	0	0	0	0	0	0	0	0	0	0	0
25	25099	KP	F	55	0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted]

[redacted]#17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

					Induction Reading									Challenge Reading			
Sub	HRL	Ini	Sex	Age	1	2	3	4	5	6	7	8	9	1	2	3	4
26	41891	JM	F	23	0	0	0	0	0	0	0	0	0	0	0	0	0
27	46300	JP	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0
28	45741	PA	F	34	0	0	0	0	0	0	0	0	0	0	0	0	0
29	37066	SV	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0
30	30552	BR	M	28	0	X	X	X	X	X	X	X	X	X	X	X	X
31	29512	DC	F	60	0	0	0	0	0	0	0	0	0	0	0	0	0
32	37261	LC	F	67	0	0	0	0	0	0	0	0	0	0	0	0	0
33	46287	JH	M	68	0	0	0	0	0	0	0	0	0	0	0	0	0
34	44949	MR	F	64	0	0	0	0	0	0	0	0	0	0	0	0	0
35	44858	HB	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0
36	39457	CD	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0
37	46304	AG	M	57	0	0	0	X	X	X	X	X	X	X	X	X	X
38	46305	CA	F	31	0	0	0	0	0	0	0	0	0	0	0	0	0
39	42232	TD	F	24	0	0	0	0	0	0	0	X	X	X	X	X	X
40	26740	CW	F	59	0	0	0	0	0	0	0	0	0	0	0	0	0
41	27931	TJ	M	35	0	0	0	0	0	0	0	0	0	0	0	0	0
42	19424	SL	F	36	0	0	0	0	0	0	0	0	0	0	0	0	0
43	35008	SW	F	40	0	0	0	0	0	0	0	0	0	0	0	0	0
44	45244	MM	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0
45	36003	AD	M	57	0	0	0	0	0	0	0	0	0	0	-	0	0
46	46306	AR	M	23	0	0	0	0	0	0	X	X	X	X	X	X	X
47	41692	ML	F	22	0	0	0	0	0	0	0	0	0	0	0	0	0
48	17665	CB	F	54	0	0	0	0	0	X	X	X	X	X	X	X	X
49	44912	AM	F	34	0	0	0	0	0	0	0	0	0	0	0	0	-
50	42819	MS	F	36	0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted]

[redacted]#17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

					Induction Reading									Challenge Reading			
Sub	HRL	Ini	Sex	Age	1	2	3	4	5	6	7	8	9	1	2	3	4
51	45814	MD	F	48	0	0	0	0	0	0	0	0	0	0	-	0	0
52	23059	FP	F	37	0	0	0	0	0	0	0	0	0	0	0	0	0
53	34249	TV	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0
54	38396	CM	F	54	0	0	0	0	0	0	0	0	0	0	0	0	0
55	24218	KA	F	44	0	0	0	0	0	0	0	0	0	0	0	0	0
56	32314	SN	M	45	0	0	0	0	0	0	0	0	0	0	0	0	0
57	46307	AW	F	25	0	X	X	X	X	X	X	X	X	X	X	X	X
58	42959	HJ	F	35	0	0	0	0	0	0	0	0	0	0	0	0	0
59	43066	TM	M	38	0	0	0	0	0	0	0	0	0	0	0	0	0
60	46308	SW	F	28	0	0	0	0	0	0	0	0	0	0	0	0	0
61	29462	JD	F	28	0	0	0	0	0	0	0	0	0	0	0	0	0
62	46109	AA	F	18	0	0	0	0	0	0	0	0	0	0	0	0	0
63	27611	RC	F	64	0	0	0	0	0	0	0	0	0	0	0	0	0
64	45811	BH	M	36	0	0	0	0	0	0	0	0	0	0	0	0	0
65	40929	HB	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0
66	41782	SG	F	26	0	0	0	0	0	0	0	0	0	0	0	0	0
67	28785	GC	F	55	0	0	0	0	0	0	0	0	0	0	0	0	0
68	34426	LA	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0
69	33496	DF	M	52	0	0	0	0	0	0	0	0	0	0	0	0	0
70	42276	WV	M	54	0	0	0	0	0	0	0	0	0	0	0	0	0
71	42295	ML	F	37	0	0	0	0	0	0	0	0	0	0	0	0	0
72	42504	DP	F	40	0	0	0	0	0	0	0	0	0	0	0	0	0
73	34616	EH	M	35	0	0	0	0	0	0	0	0	0	0	0	0	0
74	38429	YC	F	32	0	0	0	0	0	0	0	0	0	0	0	0	0
75	19863	DB	F	60	0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted] #17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

					Induction Reading									Challenge Reading			
Sub	HRL	Ini	Sex	Age	1	2	3	4	5	6	7	8	9	1	2	3	4
76	46294	JR	M	55	X	X	X	X	X	X	X	X	X	X	X	X	X
77	46293	RB	M	47	0	0	0	0	0	0	0	0	0	0	0	0	0
78	18355	LP	F	48	X	X	X	X	X	X	X	X	X	X	X	X	X
79	46309	SL	F	28	X	X	X	X	X	X	X	X	X	X	X	X	X
80	24935	JR	M	53	0	0	0	0	0	0	0	0	0	0	0	0	0
81	46311	RP	M	60	0	0	0	0	0	0	0	0	0	0	0	0	0
82	42283	FZ	M	52	0	0	0	0	0	0	0	0	0	0	0	0	0
83	44951	XB	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0
84	46301	DB	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0
85	42011	AL	F	67	0	0	0	0	0	0	0	0	0	0	0	0	0
86	37005	IR	F	63	0	0	0	0	0	0	0	0	0	0	0	0	0
87	37004	AM	M	64	0	0	0	0	0	0	0	0	0	0	0	0	0
88	41084	KM	F	32	0	0	0	0	0	0	0	0	0	X	X	X	X
89	46313	MG	M	25	0	0	0	X	X	X	X	X	X	X	X	X	X
90	24334	PC	F	69	0	0	0	0	0	0	0	0	0	0	0	0	0
91	37335	SC	F	66	0	0	0	0	0	0	0	0	0	0	0	0	0
92	44272	BB	M	20	0	0	0	0	0	0	0	0	0	0	0	0	0
93	36150	BB	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0
94	36342	TS	F	31	0	0	0	0	0	0	0	0	0	0	0	0	0
95	45649	JC	F	52	X	X	X	X	X	X	X	X	X	X	X	X	X
96	30805	FS	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0
97	31247	AT	F	56	X	X	X	X	X	X	X	X	X	X	X	X	X
98	46005	AF	F	27	0	X	X	X	X	X	X	X	X	X	X	X	X
99	25030	GC	F	59	0	0	0	0	0	0	0	0	0	0	0	0	0
100	46314	JM	M	33	0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted]

[redacted] #17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

					Induction Reading									Challenge Reading			
Sub	HRL	Ini	Sex	Age	1	2	3	4	5	6	7	8	9	1	2	3	4
101	44103	EM	F	45	0	0	0	0	0	0	0	X	X	X	X	X	X
102	45115	KJ	F	43	0	0	0	0	0	0	0	0	0	0	0	0	0
103	37683	KS	F	58	0	0	0	0	0	0	0	0	0	0	0	0	0
104	41291	AJ	F	53	0	0	0	0	0	0	0	0	0	0	0	0	-
105	35137	PH	M	41	0	0	0	0	0	0	0	0	0	0	0	0	0
106	43245	ZV	F	61	0	0	0	0	0	0	0	0	0	0	0	0	0
107	41075	CC	F	67	0	0	0	0	0	0	0	0	0	0	0	0	0
108	41106	GM	M	67	0	0	0	0	0	0	0	0	0	0	0	0	0
109	26717	MD	F	33	0	0	0	0	0	0	0	0	0	0	0	0	0
110	42952	GH	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0
111	44936	MS	F	20	0	0	0	0	0	0	0	0	0	0	0	0	0
112	35212	ET	F	53	0	0	0	0	0	0	0	0	0	0	0	0	0
113	45189	EJ	F	37	0	0	0	0	0	0	0	0	0	0	0	0	0
114	46069	LS	F	55	0	0	0	0	0	0	0	0	0	0	0	0	0
115	40017	MJ	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0
116	44221	KD	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0
117	43263	CJ	F	55	0	0	0	0	0	0	0	0	0	0	0	0	0
118	36058	FJ	F	58	0	0	0	0	0	0	0	0	0	0	0	0	0
119	43690	AB	F	33	0	0	0	0	0	X	X	X	X	X	X	X	X

[redacted]

[redacted] #17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

SCORING SYSTEM*:

0	=	No visible reaction
±	=	Faint, minimal erythema
1	=	Erythema
2	=	Intense erythema
3	=	Intense erythema, induration, vesicles
4	=	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	=	Edema
DR	=	Dryness
P	=	Peeling
S	=	Staining
^	=	Hyperpigmentation / Hypopigmentation
TR	=	Tape Reaction
C	=	Change of test site
N9R	=	No 9th reading
-	=	No reading
X	=	Discontinued

*International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27. (Modified)

[redacted]

[redacted]#17-110

Test Material #1: SPF 70 Cream; Code# [redacted]

QUALITY ASSURANCE MEMORANDUM

This Final Report was reviewed for accuracy and conformity with both [redacted] Standard Protocol #100 and [redacted] Standard Operating Procedures (including any Sponsor alterations) and any written communication from the Sponsor.

Inspections were accomplished by a random sampling approach and reported to the Project Manager and the Principal Investigator immediately following their completion.

Any known protocol deviations have been noted in the Final Report and/or Individual Data Form.

The raw data for this study are retained at [redacted]

[redacted]

[redacted]

Quality Assurance Manager

QUALITY ASSURANCE UNIT

Date: 5/31/17

[redacted]

January 19, 2017

[redacted]

ATTN: [redacted]

Dear [redacted],

All dermal patch tests at [redacted] are conducted under the supervision of [redacted], PhD, Principal Investigator, and the following Board-Certified Dermatologists: [redacted] The Principal Investigator and Co-Investigators delegate authority to qualified individuals who are trained. The training is documented and updated as necessary, and at least annually. Protocols are structured upon the guidelines outlined in Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, April 1996, as appropriate for cosmetic products. The Board Certified Dermatologists oversee testing, scoring, review documents and sign reports.

[redacted]
[redacted], PhD, Principal Investigator

[redacted]
[redacted], MD, Co-Investigator
Board-Certified Dermatologist

[redacted]
[redacted], MD, PhD, Co-Investigator
Board-Certified Dermatologist

[redacted]
[redacted], DO, Co-Investigator
Board-Certified Dermatologist

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: June 21, 2021

SUBJECT: Hydroxyacetophenone

Life Science Research. 1977. Delayed contact hypersensitivity in guinea-pigs (Buehler test) Parahydroxyacetophenone.

Life Science Research. 1977. Rabbit closed patch study Parahydroxyacetophenone.

[redacted]

[redacted]

DELAYED CONTACT HYPERSENSITIVITY IN GUINEA-PIGS (BUEHLER TEST) : [redacted]

[redacted] Parahydroxyacetophenone

Subjects
Guinea Pig Sensitisation
Parahydroxyacetophenone

[redacted]

[redacted]

From:
J.E. Lightowler,
J.R. Gardner,
Life Science Research,
Stock,
Essex.
CM4 9PE

26 May 1977

DELAYED CONTACT HYPERSENSITIVITY IN GUINEA-PIGS
(BUEHLER TEST) :
[redacted]

[redacted]

We, the undersigned, hereby declare that the report following constitutes a true and faithful account of the procedures adopted, and the results obtained, in the performance of this study.

J.E. Lightowler, B.Sc., M.I.Biol.
(Head, Short-Term Toxicology)

J.R. Gardner, B.Sc.
(Deputy Head, Short-Term Toxicology)

CONTENTS

p-hydroxyacetophenone (CAS 99-93-4)

p-hydroxyacetophenone

[redacted]

1. SUMMARY

p-Hydroxyacetophenone

1.1 [redacted] was examined for the provocation of delayed contact hypersensitivity in guinea-pigs in accordance with the Standard Procedure [redacted]

1.2 Under the conditions of this test no evidence of sensitizing activity was obtained.

1.3 All guinea-pigs, except one 'natural mortality', remained healthy and made normal weight changes during the period of this test.

1.4 Both the incidence and severity of response, as defined, were zero.

[redacted]

2. INTRODUCTION

The objective of the delayed contact hypersensitivity test is the detection of sensitization potential. This method has been applied to toiletries and household products to screen out sensitizers before testing in man.

3. MATERIAL

p-hydroxyacetophenone

21g of [redacted], a white crystalline powder, were received on 17 March 1977.

[redacted]

4. METHODS

The method follows Standard Procedure [redacted]

4.1 Animals

Albino guinea-pigs of the Dunkin-Hartley strain within the weight range 231-325g were used. All animals were maintained in galvanized cages with grid floors and had free access to tap water and to a complete pelleted guinea-pig diet, plus daily supplement of fresh green vegetables.

4.2 Preparation of the test material

Preliminary studies confirmed that p-hydroxyacetophenone [redacted] was without primary irritance to the skin on topical application when applied as a 20% w/v aqueous solution of pH 5.3.

For induction and challenge procedures, p-hydroxyacetophenone [redacted] was prepared as a 20% w/v aqueous solution.

[redacted]

5. RESULTS (Tables 1 and 2)

p-hydroxyacetophenone

No guinea-pig challenged with [redacted] produced any response at 24 hours and 48 hours, consequently both the irritance and the severity rated zero scores. One animal No. 399 died during the test; this was considered to be a 'natural mortality' not attributable to treatment per se.

All other animals remained in good health and made normal bodyweight changes during the period of the test.

6. CONCLUSION

p-Hydroxyacetophenone [redacted] produced no evidence of sensitization under the conditions of this test.

[redacted]

TABLE 1 p-hydroxyacetophenone

Dermal sensitization response to [redacted] 20% w/v aqueous in the guinea-pig

CHALLENGE

Preparation p-hydroxyacetophenone	Number of animals in the group	Number showing positive sensitization			
		at 24 hours		at 48 hours	
		Incidence	Severity	Incidence	Severity
[redacted] (20% w/v aqueous)	19	0	0	0	0
Control	10	0	0	0	0

TABLE 2

Individual sensitization (erythema) responses to challenge with [redacted], 20% w/v aqueous, and bodyweights

p-hydroxyacetophenone

Treatment	Animal number	Erythematous response to challenge		Bodyweight (g)				
		1st reading (24-hour)	2nd reading (48-hour)	Start	Week 1	Week 2	Week 3	Week 4
Control	56 ♂	0	0	344	400	445	502	535
	57 ♂	0	0	332	400	465	514	595
	58 ♂	0	0	324	382	430	502	550
	59 ♂	0	0	320	360	395	439	455
	60 ♂	0	0	295	365	415	474	520
	56 ♀	0	0	315	365	414	456	498
	57 ♀	0	0	334	355	382	384	430
	58 ♀	0	0	315	352	390	448	476
	59 ♀	0	0	299	340	395	434	485
	60 ♀	0	0	330	370	390	427	455
p-hydroxyacetophenone [redacted] (20% w/v aqueous: pH 5.3)	11 ♂	0	0	325	354	380	420	450
	12 ♂	0	0	365	390	429	450	512
	13 ♂	0	0	346	385	417	440	485
	14 ♂	0	0	330	360	424	465	495
	15 ♂	0	0	394	427	478	500	535
	16 ♂	0	0	350	395	446	460	515
	17 ♂	0	0	350	375	405	450	472
	18 ♂	0	0	334	375	427	455	510
	19 ♂	0	0	358	390	410	465	510
	20 ♂	0	0	285	307	341	370	410
	31 ♀	0	0	334	362	436	490	535
	32 ♀	0	0	325	335	367	425	480
	33 ♀	0	0	310	345	391	435	468
	34 ♀	0	0	266	327	375	400	475
	35 ♀	0	0	331	352	387	432	470
	36 ♀	0	0	285	325	351	390	420
	37 ♀	0	0	335	355	382	430	490
	38 ♀	0	0	315	330	375	395	425
	39 ♀*	-	-	305	-	-	-	-
	40 ♀	0	0	300	323	367	415	465

Found dead in cage on Day 6.

[redacted]

[redacted]

RABBIT CLOSED PATCH STUDY

[redacted]

[redacted] Parahydroxyacetophenone

Subjects
Rabbit Skin Irritation
Parahydroxyacetophenone

[redacted]

[redacted]

From:
J.E. Lightowler,
J.R. Gardner,
Life Science Research,
Stock,
Essex.
CM4 9PE

6 May 1977

RECEIVED [illegible] 1977

CONTENTS

TABLES

1. SUMMARY

1.1 The effects of 1%, 10% and 50% w/v aqueous solutions of [redacted] (p-hydroxyacetophenone) upon intact and abraded skin were evaluated in New Zealand White rabbits, in accordance with Standard Procedure [redacted]

1.2 Under the conditions of this test, the three solutions produced no responses and were therefore deemed to be 'non-irritant' to the skin.

2. INTRODUCTION

The objective of the Primary Skin Irritance test is to determine relative levels of primary skin irritation.

3. MATERIAL

21g of p-hydroxyacetophenone [redacted], a white crystalline powder, were received on 17 March 1977.

4. METHODS

The method follows Standard Procedure [redacted]

4.1 Animals and husbandry

Nine young albino rabbits of an outbred New Zealand White strain, each weighing in excess of 2.0kg, were housed individually in suspended galvanized and stainless steel cages measuring 0.6 x 0.6 x 0.4m and fitted with mesh floors and automatic watering. The animals had free access to a complete pelleted rabbit diet (Diet RAB, modified, from Labsure Animal Foods, Poole, Dorset). Room temperature was controlled within the range $15^0 \pm 2^0$C and a 12-hour lighting cycle was in operation.

Upon arrival in the test laboratories, all rabbits were held for a minimal period of seven days before entering the study. Any animal showing signs of disease or abnormality in this time was replaced.

4.2 Preparation of animals

Each animal was weighed and allocated to one of three treatment groups, so that each group comprised three animals which were identified by numbered ear-tags.

Twenty-four hours before intended application, fur was removed from the test site by means of electric clippers.

4.3 Preparation of the test material

Solutions of p-hydroxyacetophenone [redacted] were prepared at three concentrations, 1%, 10% and 50% w/v in water.

4.4 Evaluation of skin reactions

Resultant reactions were evaluated on the basis of the cumulative scores at 24 and 72 hours for both abraded and intact skin, being averaged separately for erythema and oedema, and then summed to arrive at the Primary Irritation Index. The Primary Irritation Index allows classification within the following scheme:

Index		Description
0 - 2	=	mild
3 - 4	=	moderately irritating
5	=	moderately to severely irritating
6 - 8	=	severely irritating.

5. RESULTS

1%, 10% and 50% w/v aqueous dispersions of [redacted] p-hydroxyacetophenone (Tables 1, 2 and 3)

No responses were elicited after application to the skin, of the three concentrations of [redacted] p-hydroxyacetophenone

6. CONCLUSION

Aqueous concentrations of [redacted] p-hydroxyacetophenone up to 50% w/v were deemed to be non-irritant to the skin.

TABLE 1

Scoring of irritance responses elicited by a single dermal application of [redacted] at a concentration of 1% w/v in water

p-hydroxyacetophenone

Animal number	Response	Score				Average
		24 hours		72 hours		
		Intact skin	Abraded skin	Intact skin	Abraded skin	
368	Erythema	0	0	0	0	0
369		0	0	0	0	
370		0	0	0	0	
368	Oedema	0	0	0	0	0
369		0	0	0	0	
370		0	0	0	0	

Primary Irritation Index = Sum of Averages = zero

TABLE 2

Scoring of irritance responses elicited by a single dermal application of [redacted] at a concentration of 10% w/v in water

p-hydroxyacetophenone

Animal number	Response	Score				Average
		24 hours		72 hours		
		Intact skin	Abraded skin	Intact skin	Abraded skin	
371	Erythema	0	0	0	0	0
372		0	0	0	0	
373		0	0	0	0	
371	Oedema	0	0	0	0	0
372		0	0	0	0	
373		0	0	0	0	

Primary Irritation Index - $\frac{\text{Sum of Averages}}{}$ = zero

TABLE 3

Scoring of irritance responses elicited by a single dermal application of [redacted] at a concentration of 50% w/v in water

p-hydroxyacetophenone

Animal number	Response	Score				Average
		24 hours		72 hours		
		Intact skin	Abraded skin	Intact skin	Abraded skin	
374 375 376	Erythema	0 0 0	0 0 0	0 0 0	0 0 0	0
374 375 376	Oedema	0 0 0	0 0 0	0 0 0	0 0 0	0

Primary Irritation Index = Sum of Averages = Zero

symrise

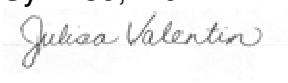
Personal Care Products Council
1620 L Street, Suite 1200
Washington DC 20036
Attn: Carol Eisenmann, Ph.D.

Re: SymSave® H (Hydroxyacetophenone)

Dear Dr. Eisenmann,

We hereby give permission to PCPC to forward the submitted documents, on the above trade name material, to CIR. We understand that the provided information will be published, cited in a report, and made available to the public.

Teterboro, 06/22/2021
Symrise, Inc.



Julisa Valentin
Senior Specialist, Global Regulatory Services & Compliance
Cosmetic Ingredients - Scent & Care Division

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: June 22, 2021

SUBJECT: Hydroxyacetophenone

Symrise. 2021. Certificate of analysis SymSave®H (Hydroxyacetophenone).

Symrise. 2021. Production flow chart of SymSave®H (Hydroxyacetophenone).

Symrise. 2021. Summary dermal irritation study SymSave®H (Hydroxyacetophenone).

Symrise. 2013. Summary of an HRIPT SymSave®H (Hydroxyacetophenone).

Certificate of Analysis 20147850

symrise

SYMRISE INC.
ID No. 22-1682840
300 NORTH STREET
TETERBORO NJ 07608
USA

Date JUN-10-2021 Page 1 / 2
Order 32966385 / 000001
Your Order number 4501387847
Delivery 83246865 / 000001
Partner-No. 10540001
Contact person
Lyndsey Nevin
Corporate Center CCS
Tel. + 1 904 924 2867
Fax
lyndsey.nevin@symrise.com

Material: **979940**
SymSave®H
Batch/Lot: 10301471
Storage: dry, 10 to 30℃
Date produced MAY 2021
Best before APR 2024

	Characteristics	Value		Lower Limit	Upper Limit
	Color / Appearance, as is				
0864	**Visual evaluation in sample vial**	**passed test**			
	Color				
0864	**Visual evaluation in sample vial**	1) **white to beige**			
	Appearance/condition				
0864	**Visual evaluation in sample vial**	1) **crystalline powder**			
	Content				
0467	**GLC**				
	Acetophenone, 4-Hydroxy-	**Area %**	**100.00**	**99.00**	**100.00**
	Content, GC/MS				
0677	**Quantification phenol/1,2dichlorobenzene**				
	Phenol	**mg/kg**	**< 10**	**max.**	**10**
	Water content				
0031	**Karl Fischer, Medium K, 20℃**	**%**	**0.0**	**max.**	**0.5**
	IR spectrum				
0253	**Infrared spectrum as a melt at 160℃**	**passed test**			
		1) **passed test**			

Certificate of Analysis 20147850

symrise

Material: **979940**
Batch/Lot: 10301471

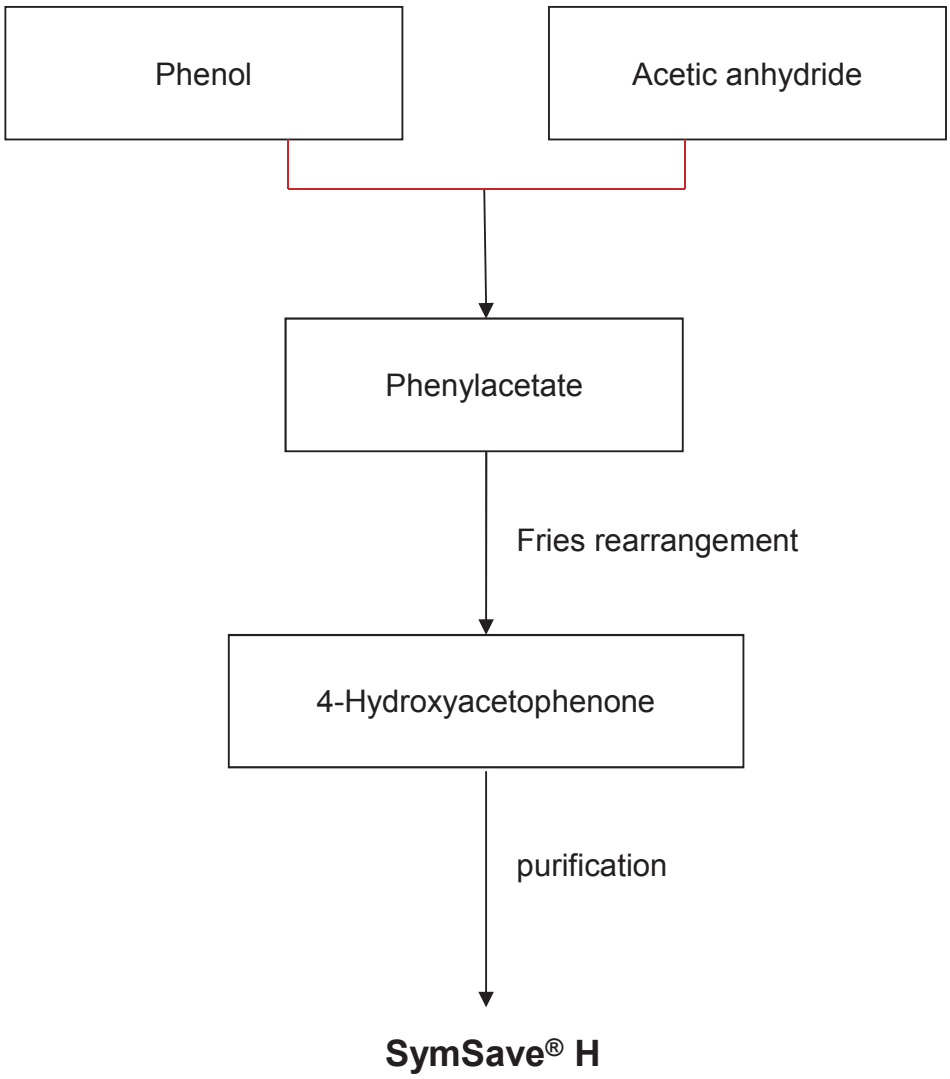
Characteristics	Value	Lower Limit	Upper Limit

Annotation:
1) Target
2) Intermittent tested. This time skipped.

The certificate does not release the user from the responsibility of undertaking his own tests of the characteristics of the product and its suitability in the intended application.
This is a computer generated certificate of analysis and is therefore not signed by hand. The positive release procedure and the stringent workflow of the computerized system ensure the same level of reliability as a handwritten signature.

symrise
always inspiring more…

Production Flow Chart
of
979940 SymSave® H



Summary dermal irritation study - provided June 2021

Product: SymSave® H

The test material was applied for 48 h under occlusive conditions to 54 subjects. 0.2 mL of test item was applied to a 3/4" x 3/4" absorbent pad portion of an adhesive dressing. When secured to the appropriate treatment site (upper back between the scapsula), this dressing formed an occlusive patch. Reading of skin reactions was performed after 48 and 72 h. No dermal reactions occurred in any of the 53 subjects (one woman did not complete the study due to personal reasons), who completed the study. Thus the test substance did not indicate a potential for dermal irritation.

Study Details

Test No. 2013012

Product Name SymSave® H

Cas-No:	EC-No:	Chemical Name:
99-93-4	202-802-8	4'-hydroxyacetophenone

Product code	979940	
Product Name	SymSave® H	
Test code	BIO 2671/3	
Purity	99,0	(if 0,0 then see remarks)
Batch No.	FHBX166	
Study code	C13-1431.01	
Institute Name	Consumer Product Testing Co.	
Description	Human Repeat Insult Patch Test	
Final Report date	20.06.2013	
Results	not sensitizing (0/104)	
Reliability	Rel 1	
GLP	YES	
Remark	HRIPT at 5% in Glycerin; no skin reactions in 104 subjects, except 1 subject with two grade 0.5 skin reactions during induction Rel. 1: test according to standard method and GCP	

Concentration of Use by FDA Product Category – Hydroxyacetophenone

Product Category	Maximum Concentration of Use
Other bath preparations	0.25%
Eye lotions	0.23%
Eye makeup removers	0.23%
Hair conditioners	0.4%
Hair sprays Pump sprays	 0.5%
Shampoos (noncoloring)	0.5%
Other hair preparations (noncoloring)	0.02%
Bath soaps and detergents	0.000099-0.6%
Aftershave lotions	0.6%
Shaving cream Aerosol – bag on valve	 0.5%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.2-0.57%
Face and neck products Not spray	 0.075-0.3%
Body and hand products Not spray	 0.1-0.3%
Moisturizing products Not spray Spray	 0.5% 0.3%
Night products Not spray	 0.25-5%
Paste masks and mud packs	0.35-5%
Skin fresheners	0.5%
Other skin care preparations	0.2-0.72%
Suntan products Not spray	 0.5%

Information collected in 2020

Table prepared January 25, 2021

2022 VCRP Frequency of Use Data – Hydroxyacetophenone

Total Uses: 791

INGREDIENT_NAME	Category Description	CPIS_Count
4-Hydroxyacetophenone	01A- Baby shampoos	1
4-Hydroxyacetophenone	01B - Baby lotions, oils, powders, and creams	3
4-Hydroxyacetophenone	01C - Other baby products	3
4-Hydroxyacetophenone	02B – Bubble baths	1
4-Hydroxyacetophenone	03D - Eye lotion	18
4-Hydroxyacetophenone	03E - Eye makeup remover	2
4-Hydroxyacetophenone	03G - Other eye makeup preparations	27
4-Hydroxyacetophenone	04E - Other fragrance preparation	4
4-Hydroxyacetophenone	05A - Hair conditioner	6
4-Hydroxyacetophenone	05F - Shampoos (non-coloring)	13
4-Hydroxyacetophenone	05G - Tonics, dressings, and other hair grooming aids	6
4-Hydroxyacetophenone	05I - Other hair preparations	7
4-Hydroxyacetophenone	07A- Blushers	3
4-Hydroxyacetophenone	07B - Face powders	3
4-Hydroxyacetophenone	07C - Foundations	17
4-Hydroxyacetophenone	07E - Lipstick	2
4-Hydroxyacetophenone	07F - Makeup bases	5
4-Hydroxyacetophenone	07H - Makeup fixatives	1
4-Hydroxyacetophenone	07I - Other makeup preparations	8
4-Hydroxyacetophenone	08E - Nail polish and enamel	2
4-Hydroxyacetophenone	10A - Bath soaps and detergents	9
4-Hydroxyacetophenone	10B - Deodorants (underarm)	5
4-Hydroxyacetophenone	10D - Feminine deodorants	3
4-Hydroxyacetophenone	10E - Other personal cleanliness products	8
4-Hydroxyacetophenone	11G - Other shaving preparation products	2
4-Hydroxyacetophenone	12A - Cleansing	49
4-Hydroxyacetophenone	12C - Face and neck (exc shave)	202
4-Hydroxyacetophenone	12D - Body and hand (exc shave)	27
4-Hydroxyacetophenone	12F - Moisturizing	236
4-Hydroxyacetophenone	12G - Night	16
4-Hydroxyacetophenone	12H - Paste masks (mud packs)	29
4-Hydroxyacetophenone	12I - Skin fresheners	6
4-Hydroxyacetophenone	12J - Other skin care preps	66
4-Hydroxyacetophenone	13B - Indoor tanning preparations	1