Safety Assessment of Glycolactones as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	August 20, 2021
Panel Meeting Date:	September 13 - 14, 2021

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.; Lisa A. Peterson, 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 Priya Cherian, Scientific Analyst/Writer, CIR.

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Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer, CIR
Date: August 20, 2021
Subject: Safety Assessment of Glycolactones as Used in Cosmetics

Enclosed is the Draft Report of the Safety Assessment of Glycolactones in Cosmetics (*glycol092021rep*). The ingredients reviewed in this report include Galactonolactone, Glucarolactone, Glucoheptonolactone, Gluconolactone, and Ribonolactone. This is the first time the Expert Panel is reviewing this ingredient group. The Scientific Literature Review (SLR) was announced on October 13, 2020. Since the issuing of the SLR, the following unpublished data were received

- Summary in vitro dermal irritation assay data on a product containing 70 - 80% Gluconolactone (*glycol092021data2*)
- An HRIPT performed on 105 subjects using a cream containing 0.041625% Gluconolactone (*glycol092021data3*)
- An HRIPT performed on 100 subjects using a product containing 1.4850% Gluconolactone (*glycol092021data4*)
- Summary in vitro ocular irritation assay data on a test substance containing 10% Gluconolactone (*glycol092021data2*)

Included in this packet are concentration of use data (*glycol092021data1*), 2021 VCRP frequency of use data (*glycol092021FDA*), report history (*glycol092021hist*), data profile (*glycol092021prof*), search strategy (*glycol092021strat*), and flow chart (*glycol092021flow*). In addition, comments on the SLR were provided from Council (*glycol092021pcpc*), and have been addressed.

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.

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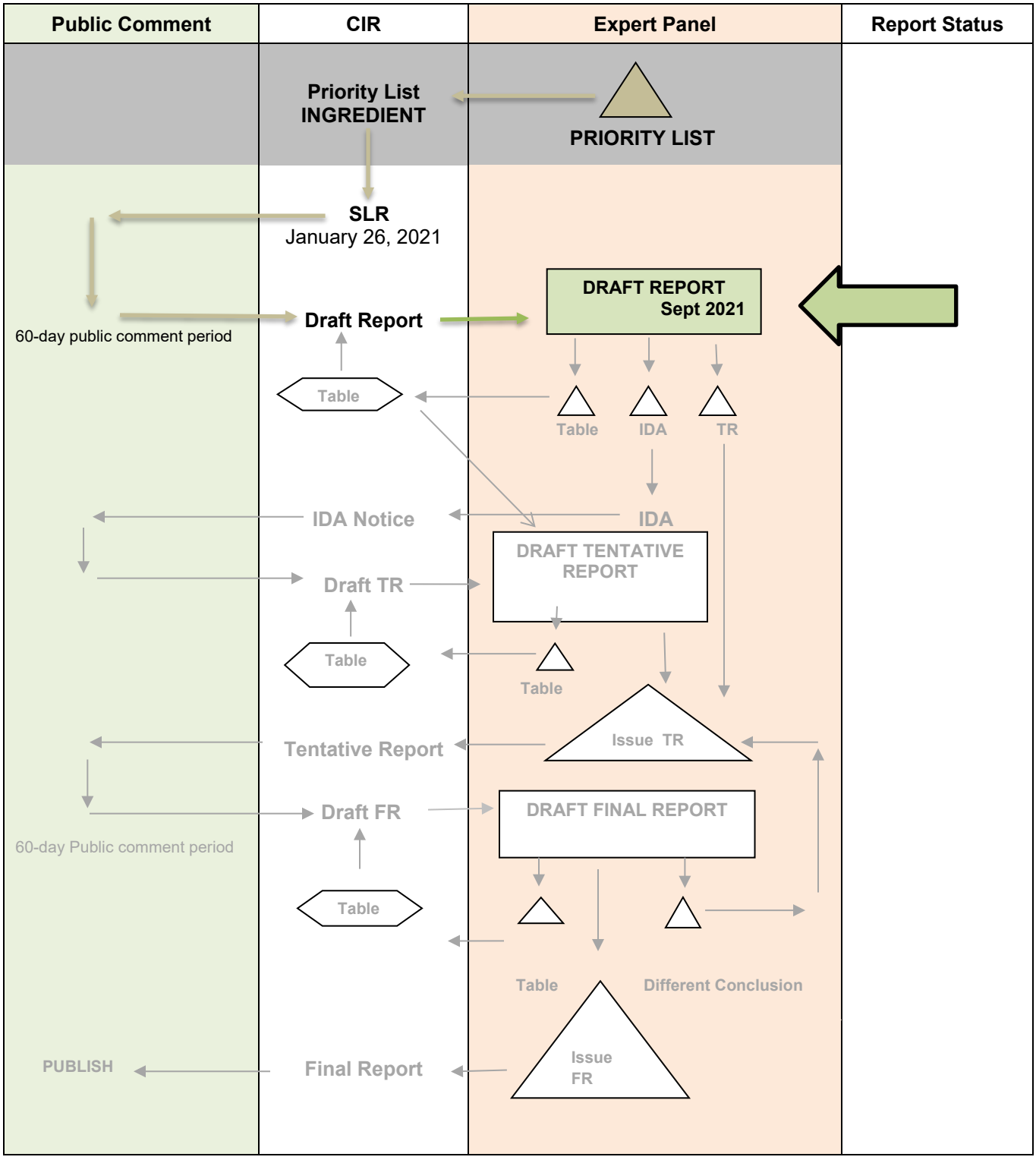
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Glycolactones

MEETING September 2021



Glycolactones – History

February 2020
-2020 VCRP data received for Gluconolactone

April 2020
-concentration data received from Council for Gluconolactone

October 2020
-SLR issued

January 2021
-updated 2021 VCRP data received for Gluconolactone

February 2021
-comments on SLR received
-unpublished data received: HRIPT on product containing 1.4850% Gluconolactone
-unpublished data received: HRIPT on product containing 0.041625% Gluconolactone

June 2021
-unpublished data received: in vitro ocular and dermal irritation summary data on Gluconolactone

September 2021
-Expert Panel reviews Draft Report

Glycolactones Data Profile – September 2021 – Priya Cherian																															
				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
Galactonolactone		X		X																									
Glucarolactone				X																									
Glucoheptonolactone				X																									
Gluconolactone	X	X	X	X		X		X			X			X	X	X		X			X			X		X		X	
Ribonolactone		X		X																									

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

[Glycolactones – September 2021 - Priya Cherian]

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Gluconolactone	90-80-2	Y	Y	N	Y	Y	Y	N	Y	N	N	N	Y	N	N	N	N	N	Y
Galactonolactone	1668-08-2 (L-); 2782-07-2 (D-)	Y	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y
Glucarolactone	2782-04-9; 389-36-6	Y	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y
Glucoheptanolactone	60046-25-5	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y
Ribonolactone	5336-08-3	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y

Y = yes/data found; N = no/data not found

Search Strategy

- All search terms were used in PubMed and ToxNet
- INCI names and CAS numbers were searched in the “Pertinent Websites” listed below

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- Search terms:
  - Allergy
  - Sensitization
  - Irritation
  - Metabolism
  - Manufacturing
  - Production
  - Synthesis
  - Clinical
  - Reproduction
  - Inhalation
  - Maternal
  - Ocular
  - Eye
  - Dermal
  - Cosmetic
  - Respiratory
  - Dermal Penetration
  - Absorption
  - Toxicity
  - Carcinogenicity
  - Mutagenicity

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

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;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- 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
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- 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/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- 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
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.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

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

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ABBREVIATIONS

CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
DART	developmental and reproductive toxicity
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
ECHA	European Chemicals Agency
EU	European Union
FDA	Food and Drug Administration
GD	gestation days
GRAS	generally recognized as safe
HRIPT	human repeat insult patch test
K_{ow}	n-octanol/water partition coefficient
NOAEL	no-observable-adverse-effect-level
NR	not reported
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
SIDS	screening information dataset
SLS	sodium lauryl sulfate
TEWL	transepidermal water loss
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This is a safety assessment of the following glycolactones as used in cosmetics:

Galactonolactone	Gluconolactone
Glucarolactone	Ribonolactone
Glucoheptonolactone	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Glucoheptonolactone and Gluconolactone are reported to be used as a skin-conditioning agent – miscellaneous (Table 1).[1] In addition, Gluconolactone is reported to be used as an antiacne agent and chelating agent. Because antiacne agents are considered a drug function in the United States (US), the Expert Panel for Cosmetic Ingredient Safety (Panel) will not be evaluating these ingredients for this particular function. No functions were reported for Galactonolactone, Glucarolactone, or Ribonolactone.

These ingredients are being reviewed together as they are all oxidized monosaccharides that readily equilibrate, via hydrolysis, to the retrospective organic acids. For example, Gluconolactone is soluble in water and hydrolyzes into gluconic acid spontaneously.[2] In 2019, the Panel published a safety assessment reviewing gluconic acid and its salts (calcium gluconate, potassium gluconate, and sodium gluconate).[3] These ingredients were considered safe as used in in cosmetics in the present practices of use and concentration (as described in that safety assessment). The full reports on these ingredients can be accessed on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

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

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) database[4] or was available from the Organisation for Economic Cooperation and Development (OECD) screening information dataset (SIDS) reports.[5] Information from these sources is cited throughout this assessment. Please note that the ECHA website and OECD SIDS documents provide summaries of information generated by industry, and when cited herein, it is those summary data that are incorporated into this safety assessment.

CHEMISTRY

Definition and Structure

All ingredients reviewed in this report are oxidized derivatives of glucose or other monosaccharides.[6] The definitions and structures of these ingredients are provided in Table 1.

These polyhydroxy acids are characterized by a tetrahydropyran/furan substituted by a ketone group. These glycolactones are, typically, weakly basic and exist in many living organisms, ranging from bacteria to humans. For instance, within humans, Gluconolactone (CAS No. 90-80-2; molecular weight = 178.14 g/mol; log K_{ow} = -2.2; Figure 1) participates in a number of enzymatic reactions, starting with biosynthesis from β-D-glucose 6-phosphate (which is mediated by the enzyme glucose-6-phosphate 1-dehydrogenase).

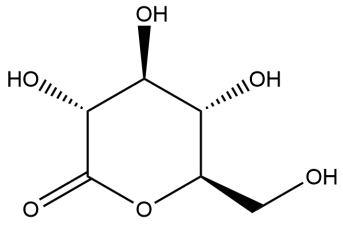


Figure 1. Gluconolactone

In addition, Gluconolactone can be converted into 6-phosphogluconic acid (which is mediated by the enzyme 6-phosphogluconolactonase). Gluconolactone is also involved in the metabolic disorder called the glucose-6-phosphate dehydrogenase deficiency pathway.

Chemical Properties

The glycolactones reviewed in this report are water-soluble and have molecular weights that range from 148 g/mol to 208 g/mol.[6-9] Chemical properties of the ingredients reviewed in this report are provided in Table 2.

Method of Manufacture

The methods below are general to the processing of glycolactones. No methods specific to cosmetic ingredient manufacture were found in the literature or submitted as unpublished data.

Galactonolactone

Galactonolactone can be prepared by the reduction of D-galacturonic acid by borohydride as follows. Via this method, D-galacturonic acid (10 g) is dissolved in 40 ml of water and neutralized with sodium hydroxide (pH between 8.5 and 9.0).[10] Next, borohydride is gradually added, constantly stirring, at room temperature. Samples are removed and acidified with acetic acid to remove excess borohydride, and boiled with a chemical reagent. After completion of the reduction, the solution is acidified with acetic acid, barium acetate is added, and the precipitate filtered off. Ethanol is added to the solution and the precipitate is collected. After the precipitate is washed with 60% ethanol, barium is removed with an ion exchange resin. One to 2 drops of n-butanol are then added to the precipitate, and the solution is concentrated to a syrup and dried. The lactone is recrystallized from absolute ethanol.

Gluconolactone

Gluconolactone may be prepared by direct crystallization from the aqueous solution of gluconic acid [21CFR184.1318]. Gluconic acid for food use in the US may be produced in any of three different ways: by the oxidation of D-glucose with bromide water, by the oxidization of D-glucose by microorganisms that are nonpathogenic and non-toxicogenic to man or other animals, and by the oxidation of D-glucose with enzymes derived from these organisms.

Ribonolactone

Via one potential method to prepare D-Ribonolactone, a flask is fitted with a mechanical stirrer and a 100-ml pressure-equalizing addition funnel, and an internal thermometer is charged with D-ribose (100 g), sodium bicarbonate (112 g), and water (600 ml).[11] The mixture is stirred at room temperature for 15 min, and the flask is then immerged in an ice water bath. The addition funnel is then filled with bromine (112 g), and the bromine is added to the vigorously stirred aqueous solution. When the addition is complete, the funnel is replaced with a stopper and the resulting solution is stirred for 50 min. Sodium bisulfate (6.5 g) is added in order to change the color of the solution (from orange to translucent). The solution is then transferred to a 2-l flask and evaporated until a wet slurry remains. Absolute ethanol (400 ml) and toluene (100 ml) are added, and the solvent is removed by rotary evaporation to provide a damp solid. Absolute ethanol is again added and the mixture is heated on a steam bath for 30 min. The hot ethanolic suspension is filtered, and the solids are rinsed with hot absolute ethanol. Following cooling, the filtrate is refrigerated for 16 h. The crystalline product is filtered, rinsed first with cold absolute ethanol and then with diethyl ether, and dried under vacuum to yield 125 g of crude product.

Impurities

Gluconolactone

According to the *Food Chemicals Codex*, food-grade Gluconolactone is usually sold as pure material, and is required to be no less than 99% and no more than 100.5% D-gluconolactone.[12] In addition, Gluconolactone should not contain more than 4 mg/kg lead, and may not contain more than 0.5% reducing substances (D-glucose).

USE

Cosmetic

The safety of the cosmetic ingredients 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 these ingredients 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 2021 VCRP and 2019 Council survey data, Gluconolactone is the only ingredient of this group that is reported to be used. In the VCRP, this ingredient is reported to be used in 262 total formulations (173 leave-on and 89 rinse-off; Table 3).[13] The results of the concentration of use survey conducted by the Council indicate Gluconolactone is used at up to 15%, with the highest maximum concentration of use reported for other skin care preparations.[14] The ingredients not in use, according to the VCRP and industry survey include, Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone.

Cosmetic products containing Gluconolactone may be applied near the eyes, as it is reported to be used in eye lotions (concentration not reported), eye makeup removers (concentration not reported), and other eye makeup preparations (up to 0.075%). In addition, mucous membrane exposure may occur, as Gluconolactone is reported to be used in feminine wipes at concentrations up to 0.56%. Gluconolactone is also reported to be used in 2 baby product formulations (concentration of use not provided).

The glycolactone ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[15]

Non-Cosmetic

According to the US FDA, Gluconolactone is a direct food substance affirmed as generally recognized as safe (GRAS), with no other limitations other that current good manufacturing practices (cGMP) [21CFR1318]. Gluconolactone is allowed for use in human food as a curing, pickling, leavening, and pH control agent [21CFR184.1318]. It is also used as a coagulant, acidulant [21CFR133.129, 21CFR155.120], and sequestrant in food processing.[16] In meat-packaging, Gluconolactone is used for color retention enhancement and as an emulsifying agent.[17] The use of Gluconolactone in meat products treated with nitrites provides a bacteriostatic effect. Gluconolactone is a natural constituent is several foods such as honey, fruit juices, wine, and many fermented products.[18] Glucarolactone can be found in kombucha teas.[19] Kombucha prepared from black tea contained approximately 5.23 g/l Glucarolactone.

In the US, Gluconolactone is an FDA-approved active ingredient that is used in conjunction with citric acid and magnesium carbonate to aid in the dissolution of bladder calculi.[20] Gluconolactone is also listed as an inactive ingredient in several intramuscular, intravenous, oral, and topical FDA-approved drug products.[21]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Gluconolactone

Radioactivity was measured in the blood of normal and alloxan diabetic rats (strain not reported) after oral administration of [U-^{14}C] Gluconolactone (9 - 10 animals tested).[5] Animals were dosed with approximately 0.8 g/kg bw of the test substance via gavage. Radioactivity was also measured in the intestinal contents and feces 5 h after ingestion of the test materials. Intestinal absorption was rapid following oral administration of Gluconolactone. Initial oxidation occurred 4 h after administration of Gluconolactone and the oxidative turnover of Gluconolactone was significantly enhanced in diabetic animals.

Human

Oral

Gluconolactone

Three male subjects were given either 5 g (84 mg/kg) or 10 g (167 mg/kg) Gluconolactone orally.[22] The amounts of Gluconolactone recovered in the urine 7 h after administration of 10 g Gluconolactone represented 7.7 - 15% of the administered dose. No pathological urine constituents were noted. When 5 g Gluconolactone were given orally, none of the administered dose was recovered in the urine. No other details regarding this study were provided.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

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

Chronic Toxicity Studies

Oral

Gluconolactone

Gluconolactone (99% purity) in water was given via gavage to Sprague-Dawley rats (10/sex/group) at doses of 250, 500, 1000, 2000, or 4000 mg/kg bw, for 6 mo.[4,5] Significant hematological changes were sporadic, not dose-dependent, and occurred in one sex only. Increased albumin levels and decreased cholesterol levels were noted in the 1000, 2000, and 4000 mg/kg bw groups. Significantly decreased blood urea nitrogen levels were also observed in males dosed with 4000 mg/kg bw Gluconolactone. No other dose-dependent clinical effects were noted. In all treated groups, thickening of the stratified squamous epithelium was detected in the anterior stomach, particularly the transitional area continuous with the pyloric stomach. Frequency and severity of this effects increased with dose. Submucosal inflammatory cell infiltration was detected in high dose groups; however, this effect was not observed in a statistically significant manner. No deaths or other abnormalities were detected.

Chronic oral toxicity of Gluconolactone was also evaluated in a 24-mo study involving Wistar rats (30/sex/group).[5] Animals were fed a diet containing 2.5% or 10% Gluconolactone (total intake of the test substance was 1240 - 1350 mg/kg bw in the 2.5% treated group, and 4920 - 5760 mg/kg bw in the 10% treated group). Weight gain was slightly reduced 2 - 3 mo after the initiation of administration of the test substance in the 10% Gluconolactone-treated group. Histopathological effects and number of deaths were similar among the control and treated groups.

In a 29-mo study, SPF-derived Wistar rats (30/sex/group) were fed diets containing meat treated with either 1% Gluconolactone, 0.5% sodium nitrite, 1% Gluconolactone and 0.5% sodium nitrite, or 1% Gluconolactone and 0.02% sodium nitrite.[17,23] A control group was given meat without Gluconolactone treatment. Blood samples for hematological investigations were taken from 10 animals in each group after 12, 24, 37, 51, 66, 78, and 91 wk. Bromosulphthalein determinations of serum glutamic-pyruvic transaminase activity were carried out at week 13 in 5 males/group and at week 26 in 5 females/group. Mortality rates, hematology, clinical biochemistry, liver function tests, and histopathology revealed no differences between treated animals and controls. No other details regarding this study were provided. Results regarding carcinogenicity can be found in the Carcinogenicity section of this report.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Details regarding the DART studies summarized below are provided in Table 4.

Several reproductive toxicity study summaries were available evaluating Gluconolactone.[5,24] The test substance was considered a non-teratogen in multiple species when administered orally (mice and rats at up to 4000 mg/kg bw (GD 6 - 15); hamsters at up to 560 mg/kg bw (GD 6 - 10); rabbits at up to 780 mg/kg bw (GD 6 - 18)).

GENOTOXICITY

In Vitro

Gluconolactone

An Ames assay was performed on Gluconolactone according to OECD Test Guideline (TG) 471.[25] The test substance (Gluconolactone) was evaluated in *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 at concentrations of 2.5 and 5 µg/ml. Tests were performed with and without metabolic activation. No signs of genotoxicity were observed. Gluconolactone was also evaluated in a different Ames assay according to the same testing procedures as above on *Saccharomyces cerevisiae* strain D4. The test substance was tested at concentrations of 12.5 and 25 µg/ml, with and without metabolic activation. No genotoxicity was observed.

In Vivo

Gluconolactone

The potential genotoxicity of Gluconolactone was evaluated in a chromosomal aberration assay using male C57BL mice (2/group).[5] Mice were fed a single dose of either 2, 4, or 8 g/kg Gluconolactone, or a dose of 2 or 4 g/kg Gluconolactone, each day, for 4 d. Animals were killed after the last administration of the test substance. Approximately 0.3 ml of 500 µg/ml colchicine was intraperitoneally injected to each mouse 1 h before sacrifice. At least 200 metaphase cells per mouse were examined. The test substance did not show mutagenic properties in the cells of mice administered single doses of Gluconolactone or in the cells of mice administered repeated doses of Gluconolactone.

CARCINOGENICITY STUDIES

Oral

Gluconolactone

As described above, in a 29-mo study, SPF-derived Wistar rats (30/sex/group) were fed diets containing meat treated with either 1% Gluconolactone, 0.5% sodium nitrite, 1% Gluconolactone and 0.5% sodium nitrite, or 1% Gluconolactone and 0.02% sodium nitrite.[17,23] A control group was given meat without Gluconolactone or sodium nitrite. Throughout the experiment, the animals were inspected regularly for tumors. After 29 mo of treatment, the study was terminated and the remaining animals were killed and evaluated. Pronounced hyperplasia of the parathyroid glands was observed in all treated groups. In addition, nitrosamine carcinogenesis was noted in the lungs, esophagus, gastrointestinal tract, liver, kidney, bladder, and central nervous system of all treated groups. No tumors could be related to the administration of meat treated with Gluconolactone. Results regarding other toxicity parameters measured during this study can be seen in the Chronic Toxicity section of this report.

OTHER RELEVANT STUDIES

Effect on Skin Barrier Function and Irritation

Gluconolactone

The effect of Gluconolactone on skin irritation prevention and skin barrier function was evaluated in 11 healthy subjects.[26] Gluconolactone (8%) in a base cream was applied to the skin of the subjects over an 8 cm x 5 cm test area, twice a day, for 4 wk. Control applications of the base cream alone was also applied on each subject. At week 4, a 5% sodium lauryl sulfate (SLS) challenge patch test was performed, under occlusion, for 6 h. Barrier function and skin irritation were evaluated by means of evaporimetry and chromametry weekly, and at 0, 24, and 48 h after SLS patch removal. After SLS challenge, Gluconolactone-treated sites resulted in significantly lower transepidermal water loss (TEWL) compared to the

control sites. Similarly, erythema values were significantly reduced after irritation with SLS in Gluconolactone-treated sites compared to control sites.

DERMAL IRRITATION AND SENSITIZATION

Irritation

In Vitro

Gluconolactone

According to summary data, an in vitro skin irritation assay was performed according to OECD TG 439, using EpiSkin™ reconstituted human epidermis.[27] The test substance (a product containing 70 - 80% Gluconolactone) was considered to be non-irritating. No other details regarding this study were provided.

Sensitization

Human

Gluconolactone

A human repeated insult patch test (HRIPT) was performed on 105 subjects, using a test substance consisting of a white cream containing 0.041625% Gluconolactone.[28] The test article (0.1 - 0.15 g) was applied under an occlusive patch, to the back of each subject, 3 times a week, for 3 wk. After a 2-wk rest period, a challenge patch was applied to a previously untreated site, and the site evaluated 24 and 72 h after application. The test substance was considered non-irritating and non-sensitizing. A different HRIPT was performed on 100 subjects, using a product containing 1.4850% Gluconolactone (0.2 g; under occlusive conditions), according to a similar procedure as above.[29] No irritation or sensitization was noted.

OCULAR IRRITATION STUDIES

In Vitro

Gluconolactone

An EpiOcular™ eye irritation assay was performed according to OECD TG 492.[27] The test substance (10% Gluconolactone) was not considered to be an irritant. No other details regarding this study were provided.

CLINICAL STUDIES

Clinical Trials with Gluconolactone-Containing Products

Gluconolactone

A 28-d, double-blind, within-person, study was performed in order to evaluate the effect of a product containing Gluconolactone in acne vulgaris patients (n = 25).[30] All subjects were asked to place the product (7% glycolic acid, 1% salicylic acid, 2% Gluconolactone, 0.05% licochalcone A, and adapalene (0.1%)) on each side of the face (0.25 g), once nightly, for 28 d. Patients were assessed on day 0, 7, 14, and 28. At each study visit, the safety profile, defined as the average score of erythema and scaling, was evaluated. Most patients reported an erythema and scaling score of ≤ 2 (no severe symptoms were reported). Results were similar at each evaluation period.

A double-blind clinical trial was performed on acne patients to evaluate the skin tolerance of an aqueous lotion containing 14% Gluconolactone (n = 50) in the treatment of mild to moderate acne when compared with its vehicle alone (base lotion; placebo; n = 50), or 5% benzoyl peroxide alone (n = 50).[31] Details regarding application were not provided. An initial baseline assessment was carried out, and patients were re-assessed at 2, 4, 8, and 12 wk. An assessment of skin tolerance was conducted at each review with respect to burning, stinging, erythema, scaling, pruritus, and dryness. There were no significant differences between the treatment groups for the clinical assessment of skin erythema, pruritis, burning, or stinging during treatment. Approximately 24% of the Gluconolactone-treated patients reported unwanted effects during the trial. Patients in the Gluconolactone-treated group reported more erythema, burning, stinging, pruritis, and scaling than those in the placebo group, however, these differences were not statistically significant.

SUMMARY

The glycolactones reviewed in this report are reported to function in cosmetics as skin-conditioning agents and chelating agents. These ingredients may readily equilibrate into their corresponding organic acids. For example, Gluconolactone is capable of spontaneously hydrolyzing into gluconic acid in aqueous solutions. In the US, food grade Gluconolactone is usually sold as pure material, and is required to be no less than 99% and no more than 100.5% D-gluconolactone. Food grade Gluconolactone may not exceed 20 mg/kg in heavy metals or 10 mg/kg lead, and may not contain more than 0.5% reducing substances (D-glucose).

According to 2021 FDA VCRP data and 2019 Council survey results, Gluconolactone is reported to be used in 262 total formulations, with a maximum leave-on concentration of 15% in other skin care preparations. It is reported to be used near the eyes (up to 0.075%), in baby formulations (concentration of use not provided), and in formulations that may result in

mucous membrane exposure (up to 0.56% in feminine wipes). No cosmetic uses were reported for Galactonolactone, Glucarolactone, Glucoheptonolactone, or Ribonolactone.

According to the US FDA, Gluconolactone is GRAS as a direct human food ingredient, with no limitations, other than cGMP. In addition to being a curing, pickling, leavening, and pH control agent in various foods, Gluconolactone is a natural constituent is foods such as honey, fruit juices, wine, and many fermented products. Glucarolactone has been reported to be found in kombucha teas.

Radioactivity was measured in the blood of normal and alloxan diabetic rats after animals were given 0.8 g/kg bw of [U-^{14}C] Gluconolactone via gavage. Initial oxidation occurred 4 h after administration of Gluconolactone. The oxidative turnover of Gluconolactone was significantly enhanced in diabetic animals. In a human study, 3 males were given either 5 g or 10 g Gluconolactone, orally. The amounts of Gluconolactone recovered in the urine 7 h after administration of 10 g Gluconolactone represented 7.7 - 15% of the administered dose. No Gluconolactone was recovered in the urine after administration of 5 g Gluconolactone.

In a 6-mo study, Sprague-Dawley rats (10/sex/group) were given up to 4000 mg/kg bw Gluconolactone via gavage. No deaths, signs of clinical abnormalities, or dose-dependent hematological abnormalities were noted. Significantly decreased, dose-dependent, blood urea nitrogen levels were observed in males dosed with 4000 mg/kg bw Gluconolactone. Dose-dependent thickening of the stratified squamous epithelium was detected in the anterior stomach of treated animals. In a 24-mo study, Wistar rats (30/sex/group) were fed diets containing up to 5760 mg/kg bw Gluconolactone. Histopathological effects and number of deaths was similar among control and treated groups. Similarly, no differences were noted between control and treated groups in a 29-mo study involving SPF-derived Wistar rats (30/sex/group); rats were fed diets containing meat treated with either 1% Gluconolactone, 0.5% sodium nitrite, 1% Gluconolactone and 0.5% sodium nitrite, or 1% Gluconolactone and 0.02% sodium nitrite.

Several reproductive toxicity study summaries were available evaluating Gluconolactone. The test substance was considered a non-teratogen in multiple species when administered orally (mice and rats at up to 4000 mg/kg bw (GD 6 - 15); hamsters at up to 560 mg/kg bw (GD 6 - 10); rabbits at up to 780 mg/kg bw (GD 6 - 18)).

Gluconolactone was not genotoxic in Ames assays involving *S. typhimurium* strains TA1535, TA1537, TA1538 (at concentrations of up to 5 µg/ml) and *Saccharomyces cerevisiae* strain D4 (at concentrations up to 25 µg/ml). Assays were performed with and without metabolic activation. An in vivo chromosomal aberration assay was performed in C57BL mice (2/group). Mice were fed a single dose of either 2, 4, or 8 g/kg Gluconolactone, or a dose of 2 or 4 g/kg Gluconolactone, each day, for 4 d. After observation of metaphase cells of the mice, no signs of mutagenicity were observed in any test group.

In a 29-mo study, SPF-derived Wistar rats (30/sex/group) were fed diets containing meat treated with either 1% Gluconolactone, 0.5% sodium nitrite, 1% Gluconolactone and 0.5% sodium nitrite, or 1% Gluconolactone and 0.02% sodium nitrite. Pronounced hyperplasia of the parathyroid glands was observed, and nitrosamine carcinogenesis was noted in the lungs, esophagus, gastrointestinal tract, liver, kidney, bladder, and central nervous system of all treated groups. No tumors could be related to the administration of meat treated with Gluconolactone.

The effect of Gluconolactone on skin irritation was evaluated in 11 healthy subjects. Gluconolactone (8%) in a base cream was applied to the skin of the subjects over an 8 cm x 5 cm test area, twice a day, for 4 wk. After 4 wk of administration, test sites were subjected to an SLS challenge patch test. Erythema values were significantly reduced after irritation with SLS in Gluconolactone-treated sites compared to control sites.

An in vitro skin irritation assay was performed according to OECD TG 439, using a test substance containing 70 - 80% Gluconolactone. The test substance was considered to be non-irritating. No irritation or sensitization was noted in an HRIPT performed in 105 subjects using a cream containing 0.41625% Gluconolactone. Similarly, no irritation or sensitization was observed in an HRIPT performed on 100 subjects using a test substance containing 1.4850% Gluconolactone.

A test substance consisting of 10% Gluconolactone was not considered to be an ocular irritant in an EpiOcular™ in vitro eye irritation assay.

Acne vulgaris patients (n = 25) applied a product containing 2% Gluconolactone on each side of the face (0.25 g), once nightly, for 28 d. No severe symptoms were reported in any of the subjects after administration of the test substance. In a different study, the skin tolerance of an aqueous lotion containing 14% Gluconolactone was assessed in 150 patients (50 patients/group) with mild to moderate acne. A control group was treated with the vehicle (base lotion) alone and another group was treated with 5% benzoyl peroxide only. Applications occurred for 12 wk. There were no significant differences between the treatment and control groups for the clinical assessment of skin erythema, pruritis, burning, or stinging during treatment.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. INCI names, definitions, structures, and functions of the glycolactone ingredients in this safety assessment[1], CIR Staff

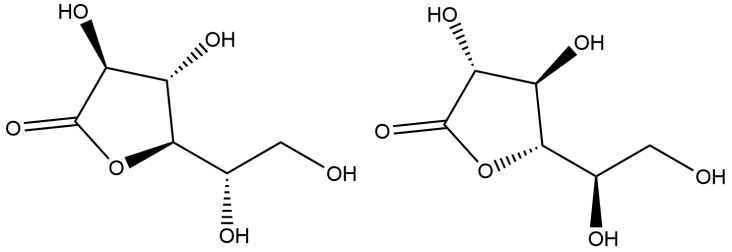
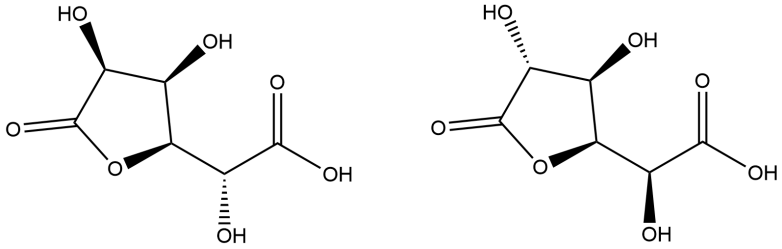
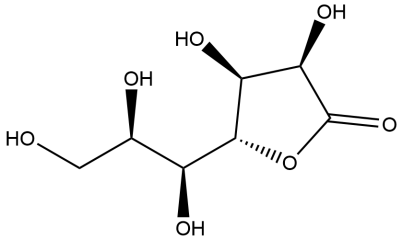
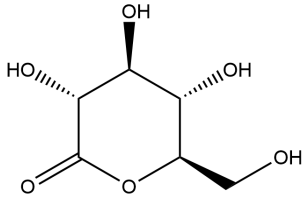
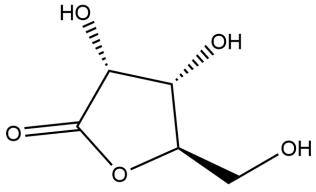
Ingredient	Definition	Function
Galactonolactone (CAS No. 1668-08-2 (L-) 2782-07-2 (D-))	Galactonolactone is the organic compound that conforms to the formula: 	Not Reported
Glucarolactone (CAS No. 2782-04-9; 389-36-6)	Glucarolactone is the organic compound that conforms to the formula: 	Not Reported
Glucoheptonolactone (CAS No. 60046-25-5)	Glucoheptonolactone is the organic compound that conforms to the formula: 	Skin-Conditioning Agents - Miscellaneous
Gluconolactone (CAS No. 90-80-2)	Gluconolactone is the lactone that conforms to the formula: 	Antiacne Agents; Chelating Agents; Skin-Conditioning Agents – Miscellaneous
Ribonolactone (CAS No. 5336-08-3)	Ribonolactone is the organic compound that conforms to the formula: 	Not Reported

Table 2. Chemical properties

Property	Value	Reference
Galactonolactone		
Physical Form	Solid, crystalline powder	7
Color	White	16
Odor	Odorless	16
Molecular Weight (g/mol)	178.14	7
Water Solubility (g/l)	583	7
log K_{ow}	-2.3	7
Glucarolactone		
Molecular Weight (g/mol)	192.12	9
log K_{ow}	-2.03 (estimated)	32
Glucoheptonolactone		
Molecular Weight (g/mol)	208.17	33
log K_{ow}	-3.02 (estimated)	32
Gluconolactone		
Physical Form	Solid	6
Color	White	5
Molecular Weight (g/mol)	178.14	6
Density/Specific Gravity (@ 20 ºC)	1.68	5
Melting Point (ºC)	153	5
Boiling Point (ºC)	398.5	5
Water Solubility (g/l)	586	6
log K_{ow}	-2.2	6
Disassociation constants (pKa)	3.70	5
Ribonolactone		
Physical Form	Solid	8
Molecular Weight (g/mol)	148.11	8
Water Solubility (g/l)	847	8
log K_{ow}	-2	8

Table 3. Frequency (2021) and concentration (2019) of use of Gluconolactone

	# of Uses[13]	Max Conc of Use (%)[14]
Totals*	**262**	**0.0000005 – 15**
Duration of Use		
Leave-On	*173*	*0.00001 – 15*
Rinse-Off	*89*	*0.0000005 – 0.3*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	13	0.075
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	57[a]; 77[b]	0.03 – 0.6[b]
Incidental Inhalation-Powder	57[a]; 1[c]	0.075 – 1.5[c]
Dermal Contact	189	0.0000005 – 15
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	73	0.03 – 0.6
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	6	0.56
Baby Products	2	NR

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

[a] 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

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

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

Table 4. Oral developmental and reproductive toxicity studies

Test Article	Animals/Group	Vehicle	Dose	Procedure	Results	Reference
Gluconolactone	CD-1 mouse (25 females/group)	Water	0, 6.95, 32.5, 150, 695 mg/kg bw	Animals were treated daily on days 6-15 of gestation; administration via gavage. Animals were observed daily for abnormalities. On day 17, all dams were subjected to caesarean section, and the number of implantation sites, resorption sites, and live and dead fetuses were recorded. External, visceral, and skeletal evaluations were performed on fetuses.	Parameters evaluated were similar among treated and control groups. Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 695 mg/kg bw	[24]
Gluconolactone	ICR mice (number of animals not reported)	Not reported	1000 and 4000 mg/kg bw	Animals were treated daily on days 6 to 15 of gestation; method of oral administration not stated	Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 4000 mg/kg bw	[5]
Gluconolactone	Wistar rat (25 females/group)	Water	0, 5.94, 27.6, 128, 594 mg/kg bw	Animals were treated daily on days 6-15 of gestation; administration via gavage. Animals were observed daily for abnormalities. On day 20, all animals were subjected to caesarean section, and the number of implantation sites, resorption sites, and live and dead fetuses were recorded. External, visceral, and skeletal evaluations were performed on fetuses.	Parameters evaluated were similar among treated and control groups. Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 594 mg/kg bw	[24]
Gluconolactone	Sprague-Dawley rat (number of animals not reported)	Not reported	1000 and 4000 mg/kg bw	Animals were treated daily on days 6-15 of gestation; method of oral administration not reported	Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 4000 mg/kg bw	[5]
Gluconolactone	Golden Hamster (22-27 females/ group)	Water	0, 5.6, 26, 121, 560 mg/kg bw	Animals were treated daily on days 6-10 of gestation; administration via gavage. Animals were observed daily for abnormalities. On day 14, all animals were subjected to caesarean section, and the number of implantation sites, resorption sites, and live and dead fetuses were recorded. External, visceral, and skeletal evaluations were performed on fetuses.	Parameters evaluated were similar among treated and control groups. Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 560 mg/kg bw	[24]
Gluconolactone	Dutch rabbit (14-17 animals/ group)	Water	0, 7.8, 36.2, 168.5, 780 mg/kg bw	Animals were treated daily on days 6-18 of gestation; administration via gavage. Animals were observed daily for abnormalities. On day 29, all animals were subjected to caesarean section, and the number of implantation sites, resorption sites, and live and dead fetuses were recorded. External, visceral, and skeletal evaluations were performed on fetuses.	Parameters evaluated were similar among treated and control groups. Non-teratogen; NOAEL maternal toxicity and NOAEL teratogenicity > 780 mg/kg bw	[24]

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2021 FDA VCRP Data – Glycolactones

Gluconolactone – Total: 262

Baby Lotions, Oils, Powders, and Creams	1
Other Baby Products	1
Eye Lotion	6
Eye Makeup Remover	2
Other Eye Makeup Preparations	5
Hair Conditioner	24
Hair Straighteners	1
Rinses (non-coloring)	1
Shampoos (non-coloring)	29
Tonics, Dressings, and Other Hair Grooming Aids	10
Other Hair Preparations	8
Leg and Body Paints	1
Other Makeup Preparations	1
Bath Soaps and Detergents	3
Other Personal Cleanliness Products	3
Aftershave Lotion	1
Cleansing	22
Face and Neck (exc shave)	49
Body and Hand (exc shave)	8
Moisturizing	46
Night	12
Paste Masks (mud packs)	4
Skin Fresheners	6
Other Skin Care Preps	15
Indoor Tanning Preparations	3

No reported VCRP uses for Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone

Concentration of Use by FDA Product Category – Glycolactones*

Gluconolactone
Galactonolactone
Glucarolactone
Glucoheptonolactone
Ribonolactone

Ingredient	Product Category	Maximum Concentration of Use
Gluconolactone	Other eye makeup preparations	0.075%
Gluconolactone	Hair conditioners	0.1%
Gluconolactone	Shampoos (noncoloring)	0.4-0.6%
Gluconolactone	Tonics, dressings and other hair grooming aids	0.03-0.6%
Gluconolactone	Leg and body paints	0.045%
Gluconolactone	Other personal cleanliness products Feminine wipe	0.56%
Gluconolactone	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0000005-0.005%
Gluconolactone	Face and neck products Not spray	0.075-1.3%
Gluconolactone	Body and hand products Not spray	1.5%
Gluconolactone	Moisturizing products Not spray	0.00003-0.93%
Gluconolactone	Other skin care preparations	0.000001-15%
Gluconolactone	Suntan products Not spray	1.2%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported

Information collected in 2019
Table prepared: July 23, 2019

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 11, 2021

SUBJECT: Gluconolactone

Anonymous. 2021. Summaries of in vitro studies on Gluconolactone.

June 2021

Summaries of In Vitro Studies on Gluconolactone

- In an *in vitro* skin irritation test (2011) using EpiSkinTM reconstituted human epidermis, a product containing 70%-80% Gluconolactone was found to be not irritating. This study was performed in the spirit of Good Laboratory Practice and was in compliance with OECD TG 439.

- In an EpiOcular™ Eye Irritation test (2016), 10% of Gluconolactone was not an irritant. This study was performed in accordance with Good Laboratory Practice regulations and was in compliance with OECD TG 492.

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: February 26, 2021

SUBJECT: Gluconolactone

Anonymous. 2016. Repeated insult patch test (product contains 0.041625% Gluconolactone).

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

product contains 0.041625% Gluconolactone

Sponsor

[redacted]

Sponsor Representative

[redacted]

Clinical Testing Facility

[redacted]

Date of Final Report

12-7-16

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted]

Board-Certified Dermatologist
Medical Investigator

[redacted]

QUALITY ASSURANCE STATEMENT

This study ([redacted] was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in 21 CFR Part 50 (Protection of Human Subjects – Informed Consent) and the Standard Operating Procedures of [redacted].

For purposes of this clinical study:

_X_	Informed Consent was obtained.
____	Informed Consent was not obtained.
_X_	An IRB review was not required.
____	An IRB review was conducted and approval to conduct the proposed clinical research was granted.

To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the applicable study records and report. This report is considered a true and accurate reflection of the testing methods and source data.

[redacted]
Manager, Quality Assurance

3 Dec 2016
Date

[redacted]

[redacted]

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[redacted]

[redacted]

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the irritation and/or sensitization potential of the test article after repeated application under occlusive patch test conditions to the skin of human subjects (non-exclusive panel).

2.0 SPONSOR

[redacted]

2.1 Sponsor Representative

[redacted]

3.0 CLINICAL TESTING FACILITY

The study was conducted by:

[redacted]

4.0 CLINICAL INVESTIGATORS

Study Director: [redacted]
Principal Investigator: [redacted] PhD, DABT, BCFE
Medical Investigator: [redacted] MD, Board-Certified Dermatologist

5.0 STUDY DATES

Study initiation: October 12, 2016 [redacted]

Final evaluation: November 18, 2016 [redacted]

[redacted]

6.0 ETHICS

6.1 Ethical Conduct of the Study

This study was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in Title 21 of the U.S. Code of Federal Regulations (CFR), the Declaration of Helsinki and/or Essex Testing Clinic (ETC) Standard Operating Procedures.

6.2 Subject Information and Consent

This study was conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed Consent was obtained from each subject in the study and documented in writing before participation in the study. A copy of the Informed Consent was provided to each subject.

7.0 TEST MATERIAL

The test article used in this study was provided by:

[redacted]

It was received on September 28, 2016 and identified as follows:

	Description
[redacted]	White Cream

8.0 TEST SUBJECTS

At least 100 male and female subjects ranging in age from 18 to 79 years were to be empanelled for this test.

The subjects chosen were to be dependable and able to read and understand instructions. The subjects were not to exhibit any physical or dermatologic condition that would have precluded application of the test article or determination of potential effects of the test article.

[redacted]

9.0 TEST PROCEDURE

The 9 Repeated Insult (occlusive) Patch Test (9-RIPT)[1] was conducted as follows:

9.1 Induction Phase

A sufficient amount of the test article (approximately 0.1 g – 0.15 g) was placed onto a Parke-Davis Readi-Bandage® occlusive patch (approximately 25 - 38 mg/cm^2 of test material) and applied to the back of each subject between the scapulae and waist, adjacent to the spinal mid-line. This procedure was performed by a trained technician/examiner and repeated every Monday, Wednesday and Friday until 9 applications of the test article had been made.

The subjects were instructed to remove the patch 24 hours after application. Twenty-four hour rest periods followed the Tuesday and Thursday removals and 48-hour rest periods followed each Saturday removal. Subjects returned to the Testing Facility and the site was scored by a trained examiner just prior to the next patch application.

If a subject developed a positive reaction of a level 2 erythema or greater during the Induction phase or if, at the discretion of the Study Director, the skin response warranted a change in site, the patch was applied to a previously unpatched, adjacent site for the next application. If a level 2 reaction or greater occurred at the new site, no further applications were made. However, any reactive subjects were subsequently Challenge patch tested.

9.2 Challenge Phase

After a rest period of approximately 2 weeks (no applications of the test article), the Challenge patch was applied to a previously unpatched (virgin) test site. The site was scored 24 and 72 hours after application. All subjects were instructed to report any delayed skin reactivity that occurred after the final Challenge patch reading. When warranted, selected test subjects were called back to the Clinic for additional examinations and scoring to determine possible increases or decreases in Challenge patch reactivity.

Dermal responses for both the Induction and Challenge phases of the study were scored according to the following 6-point scale:

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 uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

All other observed dermal sequelae (eg, edema, dryness, hypo- or hyperpigmentation) were appropriately recorded on the data sheet and described as mild, moderate or severe.

[1] Marzulli FN, Maibach HI. (1976) Contact allergy: predictive testing in man. *Contact Dermatitis*. 2, 1-17.

[redacted]

[redacted]

9.0 TEST PROCEDURE (CONT'D)

9.3 Data Interpretation

Edema, vesicles, papules and/or erythema that persist or increase in intensity either during the Induction and/or Challenge phase may be indicative of allergic contact dermatitis. Allergic responses normally do not resolve or improve markedly at 72-96 hours.

Exceptions to typical skin reactions may occur. These may include, but not be limited to, symptoms of allergic contact sensitivity early in the Induction period to one or more test products. When this occurs in one subject, such a reaction usually suggests either an idiosyncratic response or that the subject had a pre-exposure/sensitization to the test material or component(s) of the test material or a cross-reactivity with a similar product/component. Data for such reactions will be included in the study report but will not be included in the final study analysis/conclusion of sensitization.

10.0 RESULTS AND DISCUSSION

(See Table 1 for Individual Scores)

A total of 113 subjects (11 males and 102 females ranging in age from 19 to 79 years) were empanelled for the test procedure. One hundred five (105/113) subjects satisfactorily completed the test procedure on Test Article: [redacted]. Six (6/113) subjects discontinued for personal reasons unrelated to the conduct of the study. Two (2/113) subjects (Subject Nos. 35 and 36 [redacted] were discontinued due to violation of the protocol; the subjects were concurrently testing at another facility. Discontinued subject data are shown up to the point of discontinuation, but are not used in the Conclusions section of this final report.

Induction Phase Summary

Test Article	Induction Scores (Number of Responses)						Evidence of Irritation
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

Challenge Phase Summary

Test Article	Challenge Scores (Number of Responses)						Evidence of Sensitization
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

There was no skin reactivity observed at any time during the course of the study.

11.0 CONCLUSIONS

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in 105 subjects, Test Article: [redacted] was "Dermatologist-Tested" and was not associated with skin irritation or allergic contact dermatitis in human subjects.

[redacted]

TABLE 1

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj.	Induction Evaluation Number									Challenge Virgin Site	
No.	1	2	3	4	5	6	7	8	9	24hr	72hr
1	0	0	0	Discontinued							
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0

Scale: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 uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	24hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0
35	0	Discontinued									
36	0	Discontinued									
37	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0

Scale: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 uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	24hr	72hr
1	0	0	Discontinued								
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	Discontinued							
22	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0
24	Discontinued										
25	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0

Scale: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 uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

TABLE 1 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	24hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	Discontinued			
53	0	0	0	0	0	0	0	0	0	0	0
54	Discontinued										
55	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0

Scale: 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 uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

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: February 22, 2021

SUBJECT: Gluconolactone

Anonymous. 2017. Repeated insult patch test (product contains 1.4850% Gluconolactone).

[redacted]

REPEATED INSULT PATCH STUDY

product contains 1.4850% Gluconolactone

[redacted]

CONDUCTED FOR:

[redacted]

DATE OF ISSUE:

February 24, 2017

[redacted] [redacted]

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APPENDICES

[redacted]

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and [redacted]'s Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

[redacted]

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

[redacted] [redacted] [redacted]

TITLE OF STUDY

Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIAL

Body Milk, F# [redacted]

DATE STUDY INITIATED

December 7, 2016

DATE STUDY COMPLETED

January 20, 2017

DATE OF ISSUE

February 24, 2017

INVESTIGATIVE PERSONNEL

[redacted]

[redacted]

CLINICAL SITE

[redacted]

[redacted] [redacted] [redacted]

SUMMARY

One product, F# [redacted], was evaluated as supplied to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. One hundred (100) subjects completed the study. The Dermatologist was present and made evaluations at both the initial and final study visits.

Under the conditions employed in this study, there was no evidence of sensitization to product, F# [redacted].

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 100 completed subjects. In the absence of any sensitization reactions in this sample size (100 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 3.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 years of age or older, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;
2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;

3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

INDUCTION

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to initial patch application, the Board Certified Dermatologist conducted baseline readings of the test sites. Patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks and were removed by the subjects approximately 24 hours after application. Subject returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patched applied on Friday were removed on Saturday and the site evaluated on Monday, 72 hours after application.

A strong positive reaction of redness, vesicles, papules, infiltration (2) or extreme in nature of intense redness, infiltration, blister formation possible (3) or extreme positive reaction (4) observed at the first or second evaluation were to be considered evidence of possible pre-sensitization and application of the product was to be discontinued on the affected subject for the remainder of the study. Product application would have continued on all other subjects.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last Induction Visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading). Subjects who missed the 9th evaluation (N9G) but have had 9 patch applications were considered to have completed the Induction Phase.

REST PERIOD

The rest period consisted of approximately 10-15 days. During this time, subjects did not have the study material applied.

CHALLENGE

At Challenge, subjects who had completed the Induction Phase and the rest period had identical patches applied to sites previously unexposed to the study material. The patches were removed 24 hours after application. The sites were graded 24 and 48 hours following patch removal (i.e. 48 and 72 hours after patch application). Following a negative induction, a 48/72-hour sequence of "0/1" or "1/1" would have resulted in an additional reading to be performed at the 96-hour interval.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

At the conclusion of the Challenge Phase, the Board Certified Dermatologist conducted the final skin evaluations.

RECHALLENGE
There was no requirement for a Rechallenge Phase.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1[3]	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

1-6	Same as Week 2

WEEK 4

1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU induction patches
3	Staff graded MU induction sites at MU visit
2-7	Rest Period

WEEK 5

1-7	Rest Period

[3] Study flow starting with Week 1, Day 1, will be altered when enrollment occurs other than on Monday. Study flow could be altered when a holiday occurs during the study.

[redacted] [redacted] [redacted]

WEEK 6

1 Staff applied patches
2 Subject removed patches
3 Staff graded sites
4 Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

(E)-ERYTHEMA

Grade	Response
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

(A)-ALLERGY

Grade	Significance	Reaction Type
0	no adverse effect	Negative
1	redness, infiltration, papules may be present	positive reaction (+, weak)
2	redness, vesicles, papules, infiltration	positive reaction (++, strong)
3	intense redness, infiltration, blister formation possible	positive reaction (+++, extreme)

(M)- MISCELLANEOUS EFFECTS

Incidence of Miscellaneous Effects:

Notation	Description
E	edema
P	papules
V	vesicles
S	spreading

SV	soap effect
F	fissuring
D	desquamation
Dr	dryness
C	↑pigmentation
Fr	folliculitis
T	tape reaction
Cr	crusting
I	itching
X	subject absent
PD	patch dislodged
NA	not applied
NP	not patched (due to reaction achieved)
N9G	no ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting [redacted]'s strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 Study Material Specifications

Identification : Body Milk, F#[redacted]
Amount Applied : 0.2 g

4.2 Storage, Handling, and Documentation of Study Material

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by [redacted]. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 Application of Study Material

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline. Sodium lauryl sulfate, 0.2% aqueous solution, supplied by [redacted] served

as an irritant control for dermal irritation during Induction. Unless otherwise directed by the Sponsor, the study material was discarded upon completion of the study. A sample was to be retained for a period of 6 months.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. [redacted]'s preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a [redacted] facility in a secured room accessible only to [redacted] employees, or at an offsite location which provided a

secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of .

7.0 RESULTS AND DISCUSSION

One hundred nineteen (119) subjects between the ages of 20 and 75 were enrolled and 100 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition:

Number enrolled:		119
Number discontinued:		19
Lost to follow-up:	15	
Voluntary withdrawal:	3	
Protocol violation: (108: history of Hepatitis C)	1	
Number completed:		100

Source: Table 1, Appendix I

There were no AEs reported during the study.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to product, F#

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

Draize JH, Woodward G, Calvary HO. Methods for the study of irritation and toxicology of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 82: 377-390.

Lanman BM, Elvers WB, Howard CS. The role of human patch testing in a product development program. Joint Conf Cosmet Sci Toilet Goods Assoc 1968; 135-145.

Marzulli FN, Maibach HI. Contact allergy: predictive testing in man. Contact Dermatitis 1976; 2:1.

Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

APPENDIX I

SUMMARY TABLES

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	119
Subjects completed induction phase	102 (85.7)
Subjects completed all phases	100 (84.0)
Total subjects discontinued	19 (16.0)
Lost to follow-up	15 (12.6)
Voluntary withdrawal	3 (2.5)
Protocol violation	1 (0.8)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

[redacted]

[redacted]

Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	32 (26 9)
N (%) 45 to 59	35 (29.4)
N (%) 60 to 65	22 (18 5)
N (%) 66 and up	30 (25 2)
Mean (SD)	54.1 (14.0)
Median	55.1
Range	20.8 to 75.5
Gender	
N (%) Male	22 (18 5)
N (%) Female	97 (81 5)
Race	
Asian	1 (0.8)
Black	45 (37.8)
Caucasian	73 (61 3)
Ethnicity	
Hispanic/Latino	13 (10 9)
Not Hispanic/Not Latino	106 (89.1)

See data listing 2 for further detail.

[redacted]

[redacted]

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = F#[redacted]

	Induction Reading										Challenge Phase		
Response (EAM)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Make Up**	**48hr**	**72hr**	**96hr***
00	112	107	107	103	102	101	96	102	63	10	101	100	
10	0	1	0	0	0	0	0	0	0	0	0	0	
Total evaluable	112	108	107	103	102	101	96	102	63	10	101	100	
Number absent	0	1	1	1	1	1	6	0	39	.	0	0	
Number discontinued	7	10	11	15	16	17	17	17	17	.	18	19	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=102)

Response	n(%) Subjects
00	101 (99.0%)
10	1 (1.0%)

All 119 subjects were present at Day 1 and received a baseline reading prior to initial patch application. All baseline readings were evaluated with a grade of 0.

See Table 3.1 for key to symbols and scores

[redacted]

[redacted]

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction

(E)-ERYTHEMA

Grade	Response
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

(A)-ALLERGY

Grade	Significance	Reaction Type
0	no adverse effect	Negative
1	redness, infiltration, papules may be present	positive reaction (+, weak)
2	redness, vesicles, papules, infiltration	positive reaction (++, strong)
3	intense redness, infiltration, blister formation possible	positive reaction (+++, extreme)

(M)- MISCELLANEOUS EFFECTS

Incidence of Miscellaneous Effects:

Notation	Description
E	edema
P	papules
V	vesicles
S	spreading
SV	soap effect
F	fissuring
D	desquamation
Dr	dryness
C	↑pigmentation
Fr	folliculitis
T	tape reaction
Cr	crusting
I	itching
X	subject absent
PD	patch dislodged
NA	not applied
NP	not patched (due to reaction achieved)
N9G	no ninth grading

APPENDIX II

DATA LISTINGS

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
002	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
003	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
004	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
005	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
006	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
007	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
008	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
009	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
010	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
011	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
012	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
013	12/07/16	12/07/16	01/10/17	01/12/17	I9	L	37
014	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
015	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
016	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
017	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
018	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
019	12/07/16	12/07/16	--	12/12/16	I0	S	6
020	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
021	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
022	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
023	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
024	12/07/16	12/07/16	--	12/07/16	I0	L	1
025	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
026	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
027	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
028	12/07/16	12/07/16	--	12/23/16	I5	L	17
029	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
030	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
031	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
032	12/07/16	12/07/16	--	12/16/16	I2	L	10
033	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
034	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
035	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
036	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
037	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
038	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
039	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
040	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
041	12/07/16	12/07/16	01/10/17	01/13/17	C1	L	38
042	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
043	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
044	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
045	12/07/16	12/07/16	--	12/07/16	I0	L	1
046	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
047	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
048	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
049	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
050	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
051	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
052	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
053	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
054	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
055	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
056	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
057	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
058	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
059	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
060	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
061	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
062	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
063	12/07/16	12/07/16	--	12/12/16	I0	L	6
064	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
065	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
066	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
067	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
068	12/07/16	12/07/16	--	12/21/16	I4	L	15
069	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
070	12/07/16	12/07/16	--	12/07/16	I0	S	1
071	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
072	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
073	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38
074	12/07/16	12/07/16	01/10/17	01/13/17	C	C	38

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	**Screened**	**1st Applic**	**Chall Applic**	**Ended**	**Last Reading #**	**Completion Status**	**Days in Study**
075	12/07/16	12/07/16	--	12/06/16	I3	L	0
076	12/07/16	12/07/16	--	12/19/16	I3	L	13
077	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
078	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
079	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
080	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
081	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
082	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
083	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
084	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
085	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
086	12/09/16	12/09/16	--	12/12/16	I0	S	4
087	12/09/16	12/09/16	--	12/19/16	I3	L	11
088	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
089	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
090	12/09/16	12/09/16	01/10/17	01/13/17	C	C	36
091	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
092	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
093	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
094	12/14/16	12/14/16	01/17/17	01/20/17	I1	L	38
095	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
096	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
097	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
098	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
099	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
100	12/14/16	12/14/16	--	12/23/16	I3	L	10
101	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
102	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
103	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
104	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
105	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
106	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
107	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
108	12/14/16	12/14/16	--	12/16/16	I1	V	3
109	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
110	12/14/16	12/14/16	01/17/17	01/20/17	I0	L	38
111	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38

Key:
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[redacted]

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	**Screened**	**1st Applic**	**Chall Applic**	**Ended**	**Last Reading #**	**Completion Status**	**Days in Study**
112	12/14/16	12/14/16	--	12/19/16	I1	L	6
113	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
114	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
115	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
116	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
117	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
118	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38
119	12/14/16	12/14/16	01/17/17	01/20/17	C	C	38

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

[redacted]

[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
001	67.7	Female	Not Hispanic/Not Latino	Caucasian
002	69.5	Female	Not Hispanic/Not Latino	Caucasian
003	35.7	Female	Not Hispanic/Not Latino	Black
004	62.3	Female	Not Hispanic/Not Latino	Caucasian
005	66.6	Female	Not Hispanic/Not Latino	Black
006	54.1	Female	Not Hispanic/Not Latino	Caucasian
007	60.0	Female	Hispanic/Latino	Caucasian
008	63.7	Male	Not Hispanic/Not Latino	Caucasian
009	33.8	Female	Hispanic/Latino	Caucasian
010	46.5	Female	Not Hispanic/Not Latino	Caucasian
011	64.4	Female	Not Hispanic/Not Latino	Caucasian
012	66.7	Female	Not Hispanic/Not Latino	Caucasian
013	44.5	Female	Not Hispanic/Not Latino	Caucasian
014	52.0	Female	Hispanic/Latino	Caucasian
015	62.5	Female	Not Hispanic/Not Latino	Caucasian
016	72.4	Male	Not Hispanic/Not Latino	Caucasian
017	67.2	Female	Not Hispanic/Not Latino	Black
018	32.1	Female	Not Hispanic/Not Latino	Black
019	47.6	Female	Not Hispanic/Not Latino	Black
020	70.3	Female	Not Hispanic/Not Latino	Caucasian
021	69.9	Female	Not Hispanic/Not Latino	Black
022	73.6	Female	Not Hispanic/Not Latino	Caucasian
023	23.3	Female	Not Hispanic/Not Latino	Black
024	61.8	Female	Not Hispanic/Not Latino	Black
025	54.5	Female	Not Hispanic/Not Latino	Black
026	68.2	Female	Not Hispanic/Not Latino	Caucasian
027	30.5	Male	Not Hispanic/Not Latino	Black
028	42.2	Female	Not Hispanic/Not Latino	Caucasian
029	64.5	Female	Not Hispanic/Not Latino	Caucasian
030	68.3	Male	Not Hispanic/Not Latino	Caucasian
031	73.0	Female	Not Hispanic/Not Latino	Black
032	50.5	Female	Not Hispanic/Not Latino	Caucasian
033	68.4	Male	Not Hispanic/Not Latino	Caucasian
034	39.4	Female	Not Hispanic/Not Latino	Black
035	44.2	Female	Not Hispanic/Not Latino	Caucasian
036	33.4	Female	Not Hispanic/Not Latino	Black
037	70.0	Male	Hispanic/Latino	Caucasian

[redacted]

[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
038	44.8	Female	Hispanic/Latino	Caucasian
039	53.8	Female	Not Hispanic/Not Latino	Caucasian
040	60.9	Female	Not Hispanic/Not Latino	Black
041	29.0	Male	Not Hispanic/Not Latino	Black
042	31.3	Female	Not Hispanic/Not Latino	Caucasian
043	67.9	Male	Not Hispanic/Not Latino	Caucasian
044	60.9	Female	Not Hispanic/Not Latino	Caucasian
045	60.0	Female	Not Hispanic/Not Latino	Caucasian
046	66.1	Female	Not Hispanic/Not Latino	Black
047	58.3	Male	Not Hispanic/Not Latino	Black
048	68.9	Female	Not Hispanic/Not Latino	Caucasian
049	52.7	Male	Not Hispanic/Not Latino	Caucasian
050	30.5	Female	Not Hispanic/Not Latino	Black
051	31.8	Male	Not Hispanic/Not Latino	Black
052	43.9	Female	Not Hispanic/Not Latino	Black
053	69.0	Male	Not Hispanic/Not Latino	Black
054	69.0	Female	Not Hispanic/Not Latino	Caucasian
055	46.1	Female	Not Hispanic/Not Latino	Black
056	45.2	Female	Not Hispanic/Not Latino	Caucasian
057	42.8	Female	Hispanic/Latino	Caucasian
058	67.6	Female	Not Hispanic/Not Latino	Caucasian
059	64.8	Male	Not Hispanic/Not Latino	Caucasian
060	58.8	Female	Not Hispanic/Not Latino	Caucasian
061	61.8	Female	Not Hispanic/Not Latino	Caucasian
062	54.6	Female	Not Hispanic/Not Latino	Caucasian
063	37.6	Female	Hispanic/Latino	Caucasian
064	44.9	Female	Not Hispanic/Not Latino	Black
065	65.6	Female	Not Hispanic/Not Latino	Caucasian
066	49.9	Female	Not Hispanic/Not Latino	Caucasian
067	20.8	Female	Not Hispanic/Not Latino	Caucasian
068	50.4	Female	Not Hispanic/Not Latino	Caucasian
069	52.2	Male	Not Hispanic/Not Latino	Black
070	63.1	Female	Not Hispanic/Not Latino	Caucasian
071	71.2	Female	Not Hispanic/Not Latino	Caucasian
072	49.1	Female	Not Hispanic/Not Latino	Caucasian
073	54.2	Female	Not Hispanic/Not Latino	Caucasian
074	65.7	Female	Not Hispanic/Not Latino	Caucasian

[redacted]

[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
075	47.3	Female	Not Hispanic/Not Latino	Caucasian
076	36.0	Female	Not Hispanic/Not Latino	Black
077	53.9	Female	Not Hispanic/Not Latino	Caucasian
078	50.9	Male	Not Hispanic/Not Latino	Black
079	41.7	Female	Not Hispanic/Not Latino	Black
080	43.4	Female	Hispanic/Latino	Caucasian
081	37.4	Female	Hispanic/Latino	Caucasian
082	64.3	Female	Not Hispanic/Not Latino	Caucasian
083	70.9	Male	Not Hispanic/Not Latino	Caucasian
084	55.4	Male	Not Hispanic/Not Latino	Black
085	61.6	Female	Not Hispanic/Not Latino	Caucasian
086	49.3	Female	Not Hispanic/Not Latino	Black
087	55.1	Female	Hispanic/Latino	Caucasian
088	72.9	Female	Not Hispanic/Not Latino	Caucasian
089	37.1	Female	Not Hispanic/Not Latino	Caucasian
090	75.5	Male	Not Hispanic/Not Latino	Caucasian
091	75.4	Female	Not Hispanic/Not Latino	Caucasian
092	52.5	Female	Not Hispanic/Not Latino	Caucasian
093	33.8	Female	Not Hispanic/Not Latino	Black
094	25.3	Female	Not Hispanic/Not Latino	Black
095	67.7	Female	Not Hispanic/Not Latino	Caucasian
096	50.8	Female	Not Hispanic/Not Latino	Black
097	54.7	Female	Not Hispanic/Not Latino	Black
098	26.1	Female	Not Hispanic/Not Latino	Black
099	69.9	Female	Not Hispanic/Not Latino	Caucasian
100	39.7	Female	Hispanic/Latino	Caucasian
101	68.2	Female	Not Hispanic/Not Latino	Asian
102	74.3	Female	Not Hispanic/Not Latino	Caucasian
103	58.1	Male	Hispanic/Latino	Caucasian
104	65.9	Female	Not Hispanic/Not Latino	Black
105	63.7	Male	Not Hispanic/Not Latino	Black
106	24.3	Female	Not Hispanic/Not Latino	Black
107	56.8	Female	Not Hispanic/Not Latino	Black
108	60.8	Female	Not Hispanic/Not Latino	Black
109	25.7	Female	Hispanic/Latino	Black
110	51.3	Female	Not Hispanic/Not Latino	Black
111	53.5	Female	Not Hispanic/Not Latino	Caucasian
112	45.2	Female	Not Hispanic/Not Latino	Black
113	61.1	Male	Not Hispanic/Not Latino	Black
114	58.7	Female	Not Hispanic/Not Latino	Black
115	64.2	Female	Not Hispanic/Not Latino	Caucasian
116	59.5	Female	Not Hispanic/Not Latino	Caucasian
117	38.6	Male	Not Hispanic/Not Latino	Caucasian
118	66.4	Female	Not Hispanic/Not Latino	Caucasian
119	52.9	Female	Not Hispanic/Not Latino	Black

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading 1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	Challenge Phase MU	48hr	72hr	96hr(*)
001	00	00	00	00	00	00	00	00	00		00	00	
002	00	00	00	00	00	00	00	00	00		00	00	
003	00	00	00	00	00	00	00	00	00		00	00	
004	00	00	00	00	00	00	00	00	N9G		00	00	
005	00	00	00	00	00	00	00	00	00		00	00	
006	00	00	00	00	00	00	00	00	00		00	00	
007	00	00	00	00	00	00	00	00	00		00	00	
008	00	00	00	00	00	00	00	00	00		00	00	
009	00	00	00	00	00	00	X	00	00	00	00	00	
010	00	00	X	00	00	00	00	00	00	00	00	00	
011	00	00	00	00	00	00	00	00	00		00	00	
012	00	00	00	00	00	00	00	00	00		00	00	
013	00	00	00	00	00	X	00	00	00	00	X	X	
014	00	00	00	00	00	00	00	00	00		00	00	
015	00	00	00	00	00	00	00	00	00		00	00	
016	00	00	00	00	00	00	00	00	00		00	00	
017	00	00	00	00	00	00	00	00	00		00	00	
018	00	00	00	00	00	00	00	00	00		00	00	
019	X	X	X	X	X	X	X	X	X		X	X	

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading 1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	Challenge Phase MU	48hr	72hr	96hr(*)
020	00	00	00	00	00	00	X	00	00	00	00	00	
021	00	00	00	00	00	00	00	00	00		00	00	
022	00	00	00	00	00	00	00	00	00		00	00	
023	00	00	00	00	00	00	00	00	N9G		00	00	
024	X	X	X	X	X	X	X	X	X		X	X	
025	00	00	00	00	00	00	00	00	00		00	00	
026	00	00	00	00	00	00	00	00	00		00	00	
027	00	00	00	00	00	00	00	00	00		00	00	
028	00	00	00	00	00	X	X	X	X		X	X	
029	00	00	00	00	00	00	00	00	00		00	00	
030	00	00	00	00	00	00	00	00	00		00	00	
031	00	00	00	00	00	00	00	00	00		00	00	
032	00	00	X	X	X	X	X	X	X		X	X	
033	00	00	00	00	00	00	00	00	00		00	00	
034	00	00	00	00	00	00	00	00	00		00	00	
035	00	00	00	00	00	00	X	00	00	00	00	00	
036	00	00	00	00	00	00	00	00	00		00	00	
037	00	00	00	00	00	00	00	00	00		00	00	
038	00	00	00	00	00	00	00	00	N9G		00	00	

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading 1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	Challenge Phase MU	48hr	72hr	96hr(*)
039	00	00	00	00	00	00	X	00	00	00	00	00	
040	00	00	00	00	00	00	00	00	00		00	00	
041	00	00	00	00	00	00	00	00	00		00	X	
042	00	00	00	00	00	00	00	00	00		00	00	
043	00	00	00	00	00	00	00	00	00		00	00	
044	00	00	00	00	00	00	00	00	00		00	00	
045	X	X	X	X	X	X	X	X	X		X	X	
046	00	00	00	00	00	00	00	00	00		00	00	
047	00	00	00	00	00	00	00	00	00		00	00	
048	00	00	00	00	00	00	00	00	00		00	00	
049	00	00	00	00	00	00	00	00	00		00	00	
050	00	00	00	00	00	00	00	00	00		00	00	
051	00	00	00	00	00	00	00	00	00		00	00	
052	00	00	00	00	X	00	00	00	00	00	00	00	
053	00	00	00	00	00	00	00	00	00		00	00	
054	00	00	00	00	00	00	00	00	00		00	00	
055	00	00	00	00	00	00	X	00	00	00	00	00	
056	00	10	00	00	00	00	00	00	00		00	00	
057	00	00	00	X	00	00	00	00	00	00	00	00	

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading 1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	Challenge Phase MU	48hr	72hr	96hr(*)
058	00	00	00	00	00	00	00	00	00		00	00	
059	00	00	00	00	00	00	00	00	00		00	00	
060	00	00	00	00	00	00	00	00	00		00	00	
061	00	00	00	00	00	00	00	00	00		00	00	
062	00	00	00	00	00	00	00	00	00		00	00	
063	X	X	X	X	X	X	X	X	X		X	X	
064	00	00	00	00	00	00	00	00	00		00	00	
065	00	00	00	00	00	00	00	00	00		00	00	
066	00	00	00	00	00	00	00	00	00		00	00	
067	00	00	00	00	00	00	00	00	00		00	00	
068	00	00	00	00	X	X	X	X	X		X	X	
069	00	00	00	00	00	00	00	00	00		00	00	
070	X	X	X	X	X	X	X	X	X		X	X	
071	00	00	00	00	00	00	00	00	00		00	00	
072	00	00	00	00	00	00	00	00	00		00	00	
073	00	00	00	00	00	00	00	00	00		00	00	
074	00	00	00	00	00	00	X	00	00	00	00	00	
075	00	X	00	X	X	X	X	X	X		X	X	
076	00	00	00	X	X	X	X	X	X		X	X	X

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores

[redacted]

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F#[redacted]

Subject No.	Induction Reading 1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	MU	Challenge Phase 48hr	72hr	96hr(*)
077	00	00	00	00	00	00	00	00	N9G		00	00	
078	00	00	00	00	00	00	00	00	N9G		00	00	
079	00	00	00	00	00	00	00	00	N9G		00	00	
080	00	00	00	00	00	00	00	00	N9G		00	00	
081	00	00	00	00	00	00	00	00	N9G		00	00	
082	00	00	00	00	00	00	00	00	N9G		00	00	
083	00	00	00	00	00	00	00	00	N9G		00	00	
084	00	00	00	00	00	00	00	00	N9G		00	00	
085	00	00	00	00	00	00	00	00	N9G		00	00	
086	X	X	X	X	X	X	X	X	X		X	X	
087	00	00	00	X	X	X	X	X	X		X	X	
088	00	00	00	00	00	00	00	00	N9G		00	00	
089	00	00	00	00	00	00	00	00	N9G		00	00	
090	00	00	00	00	00	00	00	00	N9G		00	00	
091	00	00	00	00	00	00	00	00	N9G		00	00	
092	00	00	00	00	00	00	00	00	N9G		00	00	
093	00	00	00	00	00	00	00	00	N9G		00	00	
094	00	X	X	X	X	X	X	X	X		X	X	
095	00	00	00	00	00	00	00	00	N9G		00	00	

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores

[redacted]

[redacted]
TKL Study No. DS108916

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F# [redacted]

Subject No.	Induction Reading 1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	MU	Challenge Phase 48hr	72hr	96hr(*)
096	00	00	00	00	00	00	00	00	N9G		00	00	
097	00	00	00	00	00	00	00	00	N9G		00	00	
098	00	00	00	00	00	00	00	00	N9G		00	00	
099	00	00	00	00	00	00	00	00	N9G		00	00	
100	00	00	00	X	X	X	X	X	X		X	X	
101	00	00	00	00	00	00	00	00	N9G		00	00	
102	00	00	00	00	00	00	00	00	N9G		00	00	
103	00	00	00	00	00	00	00	00	N9G		00	00	
104	00	00	00	00	00	00	00	00	N9G		00	00	
105	00	00	00	00	00	00	00	00	N9G		00	00	
106	00	00	00	00	00	00	00	00	N9G		00	00	
107	00	00	00	00	00	00	00	00	N9G		00	00	
108	00	X	X	X	X	X	X	X	X		X	X	
109	00	00	00	00	00	00	00	00	N9G		00	00	
110	X	X	X	X	X	X	X	X	X		X	X	
111	00	00	00	00	00	00	00	00	N9G		00	00	
112	00	X	X	X	X	X	X	X	X		X	X	
113	00	00	00	00	00	00	00	00	N9G		00	00	
114	00	00	00	00	00	00	00	00	N9G		00	00	
115	00	00	00	00	00	00	00	00	N9G		00	00	
116	00	00	00	00	00	00	00	00	N9G		00	00	
117	00	00	00	00	00	00	00	00	N9G		00	00	
118	00	00	00	00	00	00	00	00	N9G		00	00	
119	00	00	00	00	00	00	00	00	N9G		00	00	

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores

[redacted]

APPENDIX III

INFORMED CONSENT DOCUMENT

[redacted] [redacted] [redacted]

INFORMED CONSENT
REPEATED INSULT PATCH TEST

STUDY NO.: [redacted]

PURPOSE

You are invited to participate in this Repeated Insult Patch Test (RIPT), which is a research study to determine if these products can be applied to human skin without causing an allergic reaction. The study will involve a minimum of 100 participants.

STUDY PRODUCT

The study product include or may be components of cosmetics, moisturizers, lipsticks, skin care products, shampoos, shower gel/body wash, antiperspirants/deodorants, disinfectants, antibacterial, fragrances, soaps, sunscreens, fibers, adhesives, antimicrobials (an ingredient used as a preservative), and/or any other products which are intended for and/or may come into contact with human skin. Included is sodium lauryl sulfate (SLS) which is a caustic soap solution used as a control for comparison.

STUDY DURATION

This study consists of 13 visits (14 visits, if required) over 6 weeks, most visits lasting approximately 10 minutes. You will receive a schedule of visit dates and instructions.

PROCEDURE

Before you can start the study, the study staff will explain the study and answer any questions you may have. You will be asked to read and sign this form stating that you understand the study procedures. The study staff will begin screening you to see if you meet all study entrance requirements. This study consists of three phases, which include Induction, Rest and Challenge which are explained below.

Each patch received during this study will contain one cosmetic study product. However, more than one patch will be applied with several different cosmetic study products. The dose of the study product will be about 0.2mL, covering a 2cm by 2cm area. You will wear the study product and patch(s) on your back.

Induction: The first three weeks of the study are called the induction phase. During the induction phase you will report to [redacted] on Mondays, Wednesdays and Fridays. At each visit study staff will apply a set of patches to your back. Each patch will be removed 24 hours after application and new patch(s) will be applied at each visit. Your skin will be examined before any study product is applied. The patch(s) applied on Monday and Wednesday and Friday will remain on your back for 24 hours. At each of these induction visits, a clinical evaluator will examine your back to see if you are reacting to any of the products. If you have a strong reaction at the study site (where the study product is applied), the study product will not be applied to that site, but may be applied to another site. The induction period consists of 10 visits.

Rest: During week four of the study, you will begin a rest period during which study product will not be applied to your back and you will not have to report to [redacted]. This rest period will last through weeks four and five.

Challenge: After the rest period is over and week six begins (the final week of the study), you will receive the same products applied on a new area of the back. The study products (with patches) will be put on the part of your back that has not received study product before. During this phase of the study, you will have to return to [redacted] for three more visits. The first visit during the challenge phase you will have your back evaluated and identical patches re-applied. You will return to [redacted] 48 hours after initial challenge patch application for patch removal and skin evaluation. Finally you will return to [redacted] L for your final visit, 72 hour after initial challenge patch application, for your final evaluation. If the study doctor/staff determines that it is necessary to make additional evaluations, due to reactions, you will be asked to come back for an additional visit.

[redacted] [redacted] [redacted]

INFORMED CONSENT
REPEATED INSULT PATCH TEST

STUDY NO.: [redacted]

If you are a female of childbearing potential (i.e., not surgically sterile or have not experienced menopause), you must agree to prevent pregnancy throughout this study by using at least one form of accepted birth control [e.g., oral/ injectable/transdermal contraceptive pill, IUD, condom/diaphragm with spermicide, abstinence (no sexual intercourse)].

If you are breastfeeding a child, you will not be permitted to participate in this study. Pregnancy and breastfeeding are prohibited to prevent any unforeseen risk to an unborn child or breast-feeding child.

SUBJECT REQUIREMENTS

You must agree to make all your scheduled visits to [redacted]. You must not apply products such as creams, lotions and moisturizers on or near the test sites. You must avoid sun exposure or the use of tanning beds on your back (including the rest period). You must agree to refrain from swimming during the course of the study. You must agree to minimize water exposure on the patch area while showering or bathing by taking a low tub bath or frontal shower. You will receive written instructions for this study.

POTENTIAL RISKS

Some of the study products may be irritating under certain conditions but the degree of irritation is not expected to be greater than that described below. Individuals participating in this study may experience side effects such as redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. Reactions usually occur only where the study products or patch products (such as the patch tape adhesive) touch the skin. On rare occasions, the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist in an occasional individual. Reactions may be due to either skin irritation or allergy to either study products or patch products (e.g., patch tape adhesive). This study may include taking photographs of part(s) of your back that received study product.

It may be necessary to do additional application (rechallenge) to determine if an allergic reaction has occurred. If you should prove to be allergic, you can expect to react to this product if you encounter it at a later date. Whenever possible, you will be informed as to the identity of the product in order that you may avoid contact with it in the future.

For any significant reactions that may occur as a direct result of your participation in this study, appropriate and reasonable medical treatment will be provided by [redacted]. at no cost to you to resolve the immediate problem. Provision of such medical care is not an admission of legal liability or responsibility for the condition being treated. If such reactions occur, [redacted] personnel should be contacted immediately at [redacted] during business hours and at [redacted] at, night or weekends. Extended medical care will not be provided.

POTENTIAL BENEFITS

You may receive no direct benefit from being in this study. However, taking part in this study may benefit society by gaining new knowledge

SIGNIFICANT NEW FINDINGS

You will be informed of any significant new findings that may affect your willingness to continue your participation.

ALTERNATIVE TREATMENT

Since this study is for research only, the only alternative is for you not to participate.

WITHDRAWAL FROM STUDY

Participation in the study is voluntary and you may refuse to participate or may withdraw at any time. Voluntary withdrawal from the study for reasons unrelated to the study or failure to follow test procedures

[redacted] [redacted] [redacted]

INFORMED CONSENT
REPEATED INSULT PATCH TEST

STUDY NO.: [redacted]

will result in some loss of payment based on the number of visits completed. Subjects will be paid $5.00 per visit for early withdrawal. Your participation may also be discontinued at any time without your consent by the study doctor, or the study sponsor(s) (the company(s) that makes the product(s) being evaluated). If you fail to comply with study procedures, your participation may be terminated.

COST
Your participation in the study will not incur any cost to you.

FINANCIAL INCENTIVE
Your participation is voluntary. You may discontinue participation at any time without prejudice. You will be compensated for you participation. A payment of $160.00 will be made only upon completion of all phases of the study. If in the judgment of the investigating personnel, it is best to discontinue your participation in this study due to an adverse experience or severe reaction you will be paid in full for your participation. Voluntary withdrawal from the study for reasons unrelated to the study or failure to follow test procedures will result in some loss of payment based on the number of visits completed. Subjects will be paid $5.00 per visit. Other than the compensation described above, you will not directly benefit from this study. This study is for scientific information. Not participating in the study would be your alternative.

CONFIDENTIALITY AND AUTHORIZATION
[redacted] will protect information about you and your taking part in this research study to the best of our ability. If information about this study is published, your identity will remain confidential. Reports prepared by [redacted] will utilize statistical information only and at no time will your name be used. However, the U.S. Food and Drug Administration (FDA), the sponsor and [redacted] may sometimes inspect the research record and study information of those who take part in this study. By signing this consent form, you are authorizing such access. A court of law could also order research records shown to other people, but that is unlikely. Therefore, absolute confidentiality cannot be guaranteed.

WHO TO CALL
Additional information regarding this research is available either before or during the course of this study. If you have any questions or research related side effect or injury, you may contact the study coordinator, [redacted] during business hours. After business hours the emergency phone number is [redacted].

A copy of this consent form will be given to you.
****
I have read and understand the information given in this consent form. I have had an opportunity to ask questions and my questions have been answered. I voluntarily consent to participate. By signing this form I have not given up any of my legal rights which I would otherwise have as a research subject.

Entry Number	Print Name	Signature	Date

Signature of Person Explaining the Consent Form _____ Date _____

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: February 9, 2021

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

The Personal Care Products Council has no suppliers listed for Galactonolactone, Glucarolactone Glucoheptonolactone and Ribonolactone.

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

Key Issue
In Scientific Literature Reviews, it would be helpful to state when other references used read across to support a safety endpoint. For example, to address dermal sensitization for Gluconolactone, the ECHA dossier relied on data for gluconic acid. The Expert Panel for Cosmetic Ingredient Safety can then determine if they agree with the read across for the specific endpoint and the additional data can be added to the report.

Definition and Structure – The following sentence is not correct as Ribonolactone is not a derivative of glucose. "All ingredients in this report are oxidized derivatives of glucose." If this statement is left in the report, it should not be cited to reference 6 which just concerns Gluconolactone.

Subchronic – Please review the ECHA dossier description of the "90-day" study again. The dossier states that this is a 6-month study. The ECHA dossier indicates that the reference is a partial English translation of a 1978 Japanese study. It appears to be the same study presented in the Chronic section that is cited in reference 5 where the reference is given as Fukuhara (1978). The ECHA dossier indicates that the material studied was 99.0% pure (it conformed to Japan's specifications and standards for food additives) and that there was a distilled water control group (this information should be included in the CIR report). Although a NOAEL was not identified

in this study, the only effect observed in the low dose group was an effect on the forestomach which is not considered relevant to humans. It should be made clear that the hematological effects were not considered compound related.

Additional Considerations

Definition and Structure – The description of the "conversion" of Gluconolactone should be in the ADME section.

Method of Manufacture – The method of manufacture information for Gluconolactone should be cited to 21CFR184.1318 which is the primary reference, not reference 11 which is a secondary reference.

Impurities – As Gluconolactone is used in food and drugs, the specifications listed in the *Food Chemical Codex* and the USP/NF should be added to the Impurities section.

ADME, Animal, Oral, Gluconolactone – Was the test substance used in reference 5 really gluconate as stated in the CIR report, or was it Gluconolactone?

As it states that the study was completed in "alloxan diabetic rats", "species not reported" should be corrected to "strain not reported".

Chronic, Oral – Please correct "Bromosulphtalein" (missing an "h")

DART – This section should state whether maternal effects were observed in any of the studies.

Carcinogenicity – Did the study with treated meat include a control in which rats were treated with meat not containing either sodium nitrite or Gluconolactone?

Clinical Studies – The studies in this section are clinical studies, but they are neither retrospective nor multicenter studies. The subheading Retrospective and Multicenter Studies needs to be deleted.

Was a control product used in the study described in reference 26? The title of the reference suggests that it was a product containing only adapalene which is a retinoid drug.

Summary – It should be made clear that the PCPC concentration of use information was provided in 2019.

Please correct "good manufacturing processes" to "good manufacturing practices".

The study in rats was 6-months in duration rather than 90 days.

Table 3 – It should be indicated in this table that the mucous membrane product with a reported use concentration of 0.56% was a feminine wipe product.

Table 4 – Since all the values in the third column are doses, "/Concentration" should be deleted from the column heading.

Reference 13 – Please correct "recveid"

Reference 14 – The use concentrations were not submitted to PCPC on July 23, 2019. The date is when the information was summarized (July 24, 2019 was when the information was provided to CIR).