Safety Assessment of Glycolactones as Used in Cosmetics

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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.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Lisa A. Peterson, Ph.D., and Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651
cirinfo@cir-safety.org

ABBREVIATIONS

CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
cGMP	current good manufacturing processes
CPSC	Consumer Product Safety Commission
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 day
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

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 5 glycolactone ingredients. Glucoheptonolactone and Gluconolactone are reported to function in cosmetics as skin-conditioning agents – miscellaneous, and Gluconolactone is also reported to function as a chelating agent. No functions are reported for the other 3 ingredients. The Panel considered the available data and concluded that Gluconolactone is safe in cosmetics in the present practices of use and concentration described in this safety assessment; however, the Panel concluded the available data are insufficient to make a determination that Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This is a safety assessment of the following 5 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 function as an antiacne agent and chelating agent. It should be noted that anti-acne agent is considered a drug function in the United States (US), and therefore, use as such does not fall under the purview of the Expert Panel for Cosmetic Ingredient Safety (Panel). No cosmetic 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), with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration in cosmetics (as described in that safety assessment).[3] The full report 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, CAS numbers, and structures of these ingredients are provided in Table 1.

These polyhydroxy acids are characterized by a tetrahydropyran/furan substituted by a ketone group. The 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; 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).

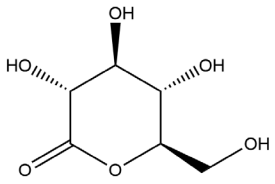


Figure 1. Gluconolactone

In addition, Gluconolactone can be converted into 6-phosphogluconic acid (which is mediated by the enzyme 6-phosphogluconolactonase).

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] The log K_{ow} for Gluconolactone is reported to be -2.2. Other 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

Ribonolactone may be prepared by oxidation of D-ribose with bromine in aqueous solution, followed by crystallization from ethanol.[11]

Impurities

Gluconolactone

According to the *Food Chemicals Codex*, food-grade Gluconolactone is 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, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2022 VCRP and 2019 Council survey data, Gluconolactone is the only ingredient of this group that is reported to be used. According to the VCRP, this ingredient is reported to be used in 312 total formulations (195 leave-on and 117 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 4 ingredients not in use, according to the VCRP and industry survey, are named in Table 4.

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 3 baby product formulations (concentration of use not provided).

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

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 in 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

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

Gluconic Acid (not an ingredient reviewed in this report)

The following study was performed using gluconic acid, which is not an ingredient that is reviewed in this report; however, it has been included herein as Gluconolactone can spontaneously hydrolyze into gluconic acid. Three male subjects were given either 5 g (84 mg/kg) or 10 g (167 mg/kg) gluconic acid, orally.[22] The amounts of gluconic acid recovered in the urine 7 h after administration of 10 g gluconic acid represented 7.7 - 15% of the administered dose. No pathological urine constituents were noted. When 5 g gluconic acid 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 effect 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 of either untreated canned meat or canned meat treated with 1% Gluconolactone.[23] 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 5.

Several developmental 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 STUDIES

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 1 h before mice were killed. 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

In a 29-mo study, SPF-derived Wistar rats (30/sex/group) were fed diets of either untreated canned meat or canned meat treated with 1% Gluconolactone.[23] 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. Tumor incidence was similar in rats given treated meat versus untreated meat. No tumors could be related to the administration of meat treated with Gluconolactone.

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. The base cream alone was applied to each subject to serve as a control. 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

An in vitro skin irritation assay was performed according to OECD TG 439, using EpiSkin™ reconstituted human epidermis.[27] The test substance (a mixture 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 non-treatment 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.

HRIPTs were also performed, according to the same procedure as above ,using a product containing 1.4850% Gluconolactone (0.2 g; occlusive conditions; n = 100)[29] and a product containing 15% Gluconolactone (0.2 ml; occlusive conditions; n = 106).[30] No irritation or sensitization was noted in either study.

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).[31] 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).[32] 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

Of the 5 glycolactone ingredients reviewed in this report, Glucoheptonolactone and Gluconolactone are reported to function in cosmetics as skin-conditioning agents – miscellaneous. Gluconolactone is also reported to function in cosmetics as a chelating agent. No cosmetic functions were reported for the other 3 ingredients. 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 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 2022 FDA VCRP data and 2019 Council survey results, Gluconolactone is reported to be used in 312 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 gluconic acid, orally. The amounts of gluconic acid recovered in the urine 7 h after administration of 10 g gluconic acid represented 7.7 - 15% of the administered dose. No gluconic acid was recovered in the urine after administration of 5 g gluconic acid.

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 either untreated meat or meat treated with 1% Gluconolactone.

Several developmental 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 of either untreated canned meat or canned meat treated with 1% Gluconolactone. No tumors could be related to the administration of meat treated with Gluconolactone.

The effect of Gluconolactone on skin irritation prevention 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. Gluconolactone did not produce irritation or sensitization in HRIPTs performed using various test substances (i.e., cream containing 0.041625% Gluconolactone, product containing 1.4850% Gluconolactone, and a product containing 15% 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

This assessment reviews the safety of 5 glycolactone ingredients as used in cosmetic formulations. The Panel reviewed the available data and concluded that Gluconolactone is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that there is insufficient data to determine the safety of Galactonolactone, Glucarolactone, Glucoheptonolactone, and Ribonolactone.

The Panel determined that the use of Gluconolactone in food and drug products, and the available systemic toxicity data, was sufficient to mitigate any systemic toxicity concerns for this ingredient group. However, although the safety data profile for Gluconolactone was complete, the data profiles for the other 4 ingredients were not. To make a determination of safety for the remaining ingredients (none of which are reported to be in use), the Panel requires impurities data for Galactonolactone, Glucarolactone, Glucoheptonolactone , and Ribonolactone, as well as cosmetic-specific method of manufacturing data for Glucarolactone and Glucoheptonolactone.

The Panel discussed the issue of incidental inhalation exposure that may result with the use of these ingredients (e.g., Gluconolactone is used in tonics, dressings, and other hair grooming aids at up to 0.6%). Inhalation toxicity data were not available; however, the oral toxicity data that were available did not report adverse effects. Additionally, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone, the concentrations at which the ingredients are used (or are expected to be used) in potentially inhaled products, and a lack of systemic toxicity, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Gluconolactone is safe in cosmetics in the present practices of use and concentration described in this safety assessment. Additionally, the Panel concluded the available data are insufficient to make a determination that Galactonolactone,* Glucarolactone,* Glucoheptonolactone,* and Ribonolactone* are safe under the intended conditions of use in cosmetic formulations.

* *There are currently no uses reported for these ingredients.*

TABLES

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

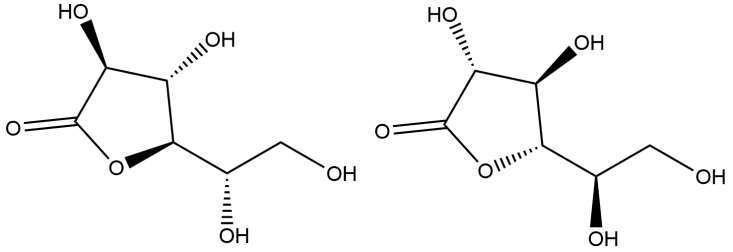
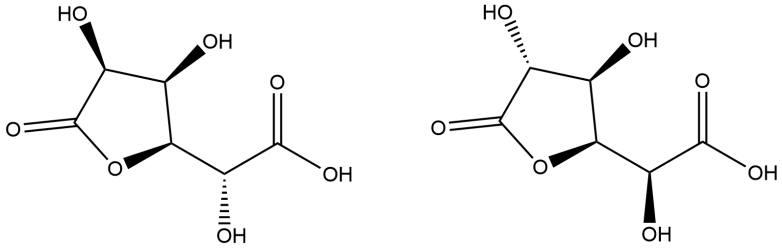
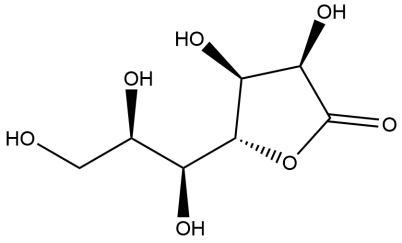
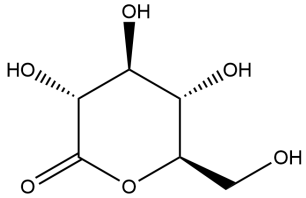
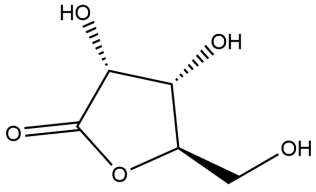
Ingredient	Definition	Function
Galactonolactone (CAS No. 1668-08-2 (L-) 2782-07-2 (D-))	Galactonolactone is the organic compound that conforms to the formula: 	Not Reported
Glucarolactone (CAS No. 2782-04-9; 389-36-6)	Glucarolactone is the organic compound that conforms to the formula: 	Not Reported
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)	[33]
Glucoheptonolactone		
Molecular Weight (g/mol)	208.17	[34]
log K_{ow}	-3.02 (estimated)	[33]
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 (2022) and concentration (2019) of use of Gluconolactone

	# of Uses[13]	Max Conc of Use (%)[14]
Totals*	**312**	**0.0000005 – 15**
Duration of Use		
Leave-On	*195*	*0.00001 – 15*
Rinse-Off	*117*	*0.0000005 – 0.3*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	13	0.075
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	59[a]; 93[b]	0.03 – 0.6[b]
Incidental Inhalation-Powder	59[a]; 2[c]	0.075 – 1.5[c]
Dermal Contact	223	0.0000005 – 15
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	89	0.03 – 0.6
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	14	0.56
Baby Products	3	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. Ingredients not reported to in use according to 2022 FDA VCRP and 2019 concentration of use data[13,14]

Galactonolactone
Glucarolactone
Glucoheptonolactone
Ribonolactone

Table 5. Oral developmental and reproductive toxicity studies on Gluconolactone

Animals/Group	Vehicle	Dose	Procedure	Results	Reference
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]
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]
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]
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]
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]
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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