Safety Assessment of *Zingiber officinale* (Ginger) – Derived Ingredients as Used in Cosmetics

Status:	Tentative Report for Public Comment
Release Date:	June 28, 2022
Panel Meeting Date:	September 26 – 27, 2022

All interested persons are provided 60 days from the above release date (i.e., August 27,2022) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to the Cosmetic Ingredient Review (CIR) will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth

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ABBREVIATIONS

ALP	alkaline phosphatase
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BUN	blood urea nitrogen
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
cGMPs	current good manufacturing practices
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
DART	developmental and reproductive toxicity
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DNFB	dinitrofluorobenzene
DPPH	1,1-diphenyl-2-picryl-hydrazyl
DPRA	direct peptide reactivity assay
ECHA	European Chemicals Agency
FDA	Food and Drug Administration
GC	gas chromatography
GD	gestation day
GRAS	generally recognized as safe
HaCaT	human epidermal keratinocyte line
HDM	house dust mite
HeLa	human cervical cancer cells
HPLC	high performance liquid chromatography
HRIPT	human repeated insult patch test
IC_{50}	half-maximal inhibitory concentration
IgE	immunoglobulin E
IL	interleukin
kDa	kilodaltons
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LD_{50}	median lethal dose
MDA-MD-231	human breast cancer cells
MS	mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCE	normochromatic erythrocytes
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	no-observable-adverse-effect-level
NR	not reported
OECD	Organisation for Economic Cooperation and Development
OVA	ovalbumin
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PII	primary irritation index
RAST	radioallergosorbent
RIFM	Research Institute for Fragrance Materials
SDS-PAGE	sodium dodecyl sulphate-polyacrylamide gel electrophoresis
SIDS	screening information dataset
SPME	solid phase microextraction
$T_{1/2}$	elimination half life
TG	test guidelines
T_{max}	time to reach serum concentration
TNF-α	tumor necrosis factor alpha
US	United States
UV	ultraviolet
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 9 *Zingiber officinale* (ginger)-derived ingredients. The majority of these ingredients are reported to function in cosmetics as skin-conditioning agents. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. With *Zingiber officinale* (ginger)-derived ingredients, the Panel was concerned about the presence of potential sensitizers (e.g., citronellol) in cosmetics. Industry should continue to use good manufacturing practices to minimize impurities that could be present in botanical ingredients. The Panel reviewed the available data to determine the safety of these ingredients, and concluded that the 7 *Zingiber officinale* (ginger) root- and rhizome-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. In addition, the Panel concluded that the available data are insufficient data to make a determination that Zingiber Officinale (Ginger) Extract and Zingiber Officinale (Ginger) Leaf Cell Extract are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This is a safety assessment of the following 9 *Zingiber officinale* (ginger)-derived ingredients as used in cosmetic formulations:

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Leaf Cell Extract
Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the majority of these ingredients are reported to function in cosmetics as skin-conditioning agents – miscellaneous (Table 1).[1] Other reported functions include antioxidants, skin protectants, antimicrobial agents, fragrance ingredients, and flavoring agents. It should be noted that skin protectant and antimicrobial functions are considered drug, not cosmetic, functions in the United States (US), and therefore, use as such does not fall under the purview of the Panel.

Zingiber Officinale (Ginger) Water is reported to function only as fragrance ingredient. The Panel does not typically review ingredients that function only as fragrance ingredients, because, as fragrances, the evaluation of the safety of these ingredients is the purview of the Research Institute for Fragrance Materials (RIFM). However, according to personal communications with RIFM, it is unknown when the safety assessment of this ingredient will be prepared; therefore, it will be reviewed herein.

The United States (US) Food and Drug Administration (FDA) has affirmed that *Zingiber officinale* is generally recognized as safe (GRAS) as a spice, natural seasoning agent, and flavoring agent [21CFR182.10]. In addition, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are considered GRAS for human consumption [21CFR182.2]. For the ingredients that are affirmed GRAS, systemic toxicity via the oral route will not be the focus of this safety assessment. Although oral exposure data are included in this report, the primary focus of this safety assessment is topical exposure and local effects.

Zingiber officinale contains many constituents. In this assessment, the Panel is evaluating the potential toxicity of each of the *Zingiber officinale* (ginger)-derived ingredients as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical 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 Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Some of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[2] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited**.** The CAS No. used to identify the test material in the ECHA data (84696-15-1) is generic, and the ingredient that is being tested is not clearly identified; it could possibly correspond to several of the ingredients in this report, with the exception of Zingiber Officinale (Ginger) Root Oil (which has a different CAS No.). Therefore, it should be noted that when ECHA summary data are presented, it is possible that it may refer to any ginger-derived ingredient in which the CAS number 84696-15-1 is used.

Confusion exists between the distinction of ginger root versus ginger rhizome in both the *Dictionary* and published literature, and many times, it is possible that these plant names are used synonymously. Therefore, for the purposes of this report, research on the ginger rhizome juice, oil, and powder is placed under the closest root ingredient. For example, data regarding a *Zingiber officinale* (ginger) rhizome oil is placed under the name Zingiber Officinale (Ginger) Root Oil, as this name is included in the *Dictionary*.

CHEMISTRY

Definition and Plant Identification

All ingredients reviewed in this report are derived from the *Zingiber officinale* (ginger) plant. The definitions of the ginger-derived ingredients included in this review are provided in Table 1; the generic CAS number for the majority of these ingredients is 84696-15-1.[1]

Ginger is a tropical, flowering, 2 - 4 ft long perennial plant, with grass-like leaves that grow up to a foot in length.[3] The shoots and leaves grow directly from thick, underground, branched rhizomes, which have a corky, brown to golden outer skin.[4] The interior of the rhizomes are juicy, fleshy, and pale yellow in color.

Chemical Properties

According to ECHA data, a *Zingiber officinale* (ginger) extract (may refer to other ginger-derived ingredients reviewed in this report) is reported to be a liquid substance with a water solubility and log k_{ow} of 0.0004 g/l and 6.9, respectively.[2] Other chemical properties evaluated for this test substance and other ginger-derived ingredient mixtures can be found in Table 2.

Method of Manufacture

It is unknown if the methods found in the published literature apply to cosmetic ingredient manufacturing; however, data provided by suppliers do apply to cosmetic ingredient manufacturing. In some cases, the definition of the ingredients, as given in the *Dictionary*, provides insight as to the method of manufacture.

Zingiber Officinale (Ginger) Extract

Air-dried Zingiber Officinale (ginger) was pulverized and percolated in 95% methanol, multiple times, until extraction completion.[5] The extracts were concentrated under reduced pressure using a rotary vapor. Concentrated extracts were kept at -20° C until use.

Zingiber Officinale (Ginger) Rhizome Extract

Ginger rhizome extracts were prepared by weighing 300 g of fresh rhizomes, and combining with a solvent (*n*-hexane or methanol) in a flask.[6] These samples were shaken for 48 h, and filtered with filter paper. The filtrate was subjected to rotary evaporation for removal of the solvent. The solvent was further removed under a purified nitrogen stream. A different *Zingiber officinale* (ginger) rhizome extract was prepared by first cleaning, peeling, chopping, and drying the rhizomes.[7] After drying, rhizomes were ground into a fine powder, and soaked in distilled water for 24 h. This aqueous extract was then filtered by double gauze and concentrated under reduced pressure.

Zingiber Officinale (Ginger) Root Extract

According to a supplier, Zingiber Officinale (Ginger) Root Extract is produced via maceration of the ginger root, followed by sterilizing filtration and evaporation.[8] Typical solvents include water, glycerin 50/50, glycerin 20/80, and refined sunflower oil. Another supplier reported that a Zingiber Officinale (Ginger) Root Extract is manufactured via extraction using a mixture of propylene glycol (68.5%) and water (30%), followed by filtration.[9,10]

Data were also submitted by a supplier regarding the manufacturing process of a trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)).[11] This mixture is created via the grinding/milling of the plant roots, followed by aqueous extraction, solvent dilution (with hexylene glycol and caprylyl glycol), and filtration.

An aqueous ginger root extract was prepared by first peeling ginger roots.[12] Peeled ginger root (50 g) was then cut into small pieces and homogenized in 75 ml of 0.9% sodium chloride, in the presence of crushed ice. Homogenization was performed using a blender for a total of 12 min. This mixture was then filtered through cheesecloth, and the filtrate was centrifuged for 10 min. The clear supernatant was made up to 100 ml with saline.

Zingiber Officinale (Ginger) Root Juice

Fresh rhizomes of ginger (1 kg) were obtained and crushed.[13] Crushed ginger rhizomes were then squeezed in muslin cloth to obtain juice, and stored in a refrigerator until use.

Zingiber Officinale (Ginger) Root Oil

In order to create a ginger root fixed oil (non-volatile), approximately 4023 g fresh ginger were reduced to a paste using a laboratory mortar, and macerated in n-hexane, for 72 h.[14] This solution was shaken for 15 min and filtrated with filter paper. The vehicle (n-hexane) was evaporated via a rotary evaporator, leaving an oily extract. This extract was cooled and stored in a tight-capped fitted container. In order to produce a ginger root essential oil, 1000 g of fresh ginger were ground using an electric blender. The sample was placed in a conical flask and connected to a Clevenger apparatus. Distilled water was added to the flask and heated. The steam in combination with the essential oils was distilled into a graduated cylinder for 5 h, and separated from the aqueous layer. The extracted oil was kept in a refrigerator until further use.

Zingiber Officinale (Ginger) Root Powder

Fresh ginger rhizomes were washed in water to remove dirt, and chopped into small pieces.[15] Pieces were allowed to dry for 5 d. Dried samples were milled into fine particles, and sieved. The powder was stored in an air-tight container until further use. Other methods of drying include oven drying, microwave drying, and solar drying.[16]

Zingiber Officinale (Ginger) Water

According to a supplier, Zingiber Officinale (Ginger) Water is produced by steam distillation of the roots of *Zingiber officinale*.[17] The distillate is then filtrated to produce the final product.

Composition and Impurities

Zingiber Officinale (Ginger) Extract

The main components of a *Zingiber officinale* (ginger) extract (solvent not stated) were determined by a solid phase microextraction (SPME) assay.[18] Identified components included camphene (7.27%), geranial (8.37%), α-zingiberene (14.50%), α-farnesene (9.14%), β-bisabolene (6.52%), and β-sesquiphellandrene (9.92%).

The total phenolic and flavonoid content of methanolic *Zingiber officinale* (ginger) leaf and stem extracts was evaluated via a 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay.[19] Two varieties of ginger in the *Zingiber officinale* family were evaluated (Halia Bentong and Halia Bara). The average phenolic content in the leaves of the Halia Bentong and Halia Bara varieties was 33.0 ± 1.13 and 39.1 ± 9.2 mg gallic acid/g dry plant material, respectively. The average flavonoid content in the leaves of the Halia Bentong and Halia Bara varieties was 5.54 ± 1.83 and 7.05 ± 7.4 mg quercetin/g dry plant material, respectively. In addition, the average phenolic content in the stems of the Halia Bentong and Halia Bara varieties was 7.8 ± 0.65 and 8.5 ± 0.81 mg gallic acid/g dry plant material, respectively. The average flavonoid content in the stems of the Halia Bentong and Halia Bara varieties was 1.36 ± 0.85 and 1.77 ± 0.75 mg quercetin/g dry plant material, respectively.

Zingiber Officinale (Ginger) Rhizome Extract

The major constituents of ginger rhizomes include carbohydrates (50-70%), lipids (3-8%), terpenes (zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene), and phenolic compounds (gingerol, paradols, and shogaol).[20] Maximum phenolic content in a methanolic and hexane extract of fresh ginger rhizomes was reported to be 95.2 mg/g dry extract and 87.5 mg/g dry extract, respectively.[6]

The levels of various metals in ginger rhizome samples in four different regions of Ethiopia were evaluated via flame atomic absorption spectrometry.[21] The mean metal concentration ranges (μg/g dry weight basis) in the ginger samples were: Ca (2000 - 2540), Mg (2700 - 4090), Fe (41.8 - 89.0), Zn (38.5 - 55.2), Cu (1.1 - 4.8), Co (2.0 - 7.6), Cr (6.0 - 10.8), Mn (184 - 401), Ni (5.6 - 8.4) and Cd (0.38 - 0.97). In a different study, an aqueous *Zingiber officinale* (ginger) rhizome extract was reported to contain 5.52% gingerol and 11.7% shogaol.[22]

Zingiber Officinale (Ginger) Root

Ginger root contains a lipophilic oleoresin, including essential oil with mainly sesquiterpenes.[23] Furthermore, the oleoresin contains different phenylpropanoids and gingerols, mainly 6-gingerol; further, there are homologues with longer side chain, e.g., 8- and 10-gingerol.

Zingiber Officinale (Ginger) Root Extract

According to a supplier, a mixture consisting of Zingiber Officinale (Ginger) Root Extract (1 - 5%) and helianthus annus (sunflower) seed oil (> 50%) contained potential allergens at concentrations less than 0.4%.[24] These potential allergens include citral (< 0.4%), citronellol (< 0.2%), geraniol (< 0.01%), limonene (< 0.03%), linalool (< 0.05%), and α-pinene (< 0.06%). A trade name mixture consisting of Zingiber Officinale (Ginger) Root Extract (≤ 1.5%), propylene glycol (68.5%), and water (30%) was reported to be free from diethylene glycol, dioxin, formaldehyde, formol, gluten, glycol ether, and phthalate.[25]

Another supplier reported that a trade name mixture containing Zingiber Officinale (Ginger) Root Extract (12 – 17%) also comprised hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%).[26] According to this supplier, this trade name mixture did not contain the following heavy metals in levels exceeding their specifications: total heavy metals (< 20 ppm), chromium (< 20 ppm), lead (< 10 ppm), nickel (< 10 ppm), cobalt (< 10 ppm), antimony (< 5 ppm), arsenic (< 2 ppm), mercury (< 1 ppm), and cadmium (< 1 ppm). In addition, fragrance allergens listed in Annex III of EU Cosmetic Regulation (EC) No. 1223/2009 and pesticides were not known to be present in this trade name mixture.

The chemical composition of *Zingiber officinale* (ginger) root extract in various solvents (water at 100°C and 30°C, ethanol, methanol, acetone, 80% methanol, 80% ethanol) was evaluated.[27] Total polyphenols, flavonoids, and tannins were highest in the aqueous extract (0.84 mg/g, 2.98 g/100 g, and 1.51 g/100 g, respectively). Antioxidant components and total antioxidant activity of each ginger extract can be found in Table 3. The average total amounts of protein, fat carbohydrate, vitamin C, and carotenoids from all samples were 5.09, 3.72, 38.35, 9.33, and 29 g/100g, respectively. Phosphorous, calcium, manganese, and iron were present in all samples in average amounts of 1.74, 0.88, 0.09, and 0.008 g/100g, respectively.

Zingiber Officinale (Ginger) Root Oil

A *Zingiber officinale* (ginger) oil, prepared from ginger rhizomes using hydrodistillation and extracted with pentane, was evaluated via gas chromatography (GC) and GC-mass spectrometry (MS).[28] The oil, for which the yield was 2.52%, contained 64.4% sesquiterpene hydrocarbons, 6.6% carbonyl compounds, 5.6% alcohols, 2.4% monoterpene hydrocarbons, and 1.6% esters. The main compounds were zingiberene (29.5%) and sesquiphellandrene (18.4%). Specific amounts of hydrocarbons and oxygenated constituents identified in the ginger rhizome oil are provided in Table 4.

Zingiber Officinale (Ginger) Root Powder

The compositions of *Zingiber officinale* (ginger) powders prepared by various drying methods are summarized in Table 5.[16] Polyphenol contents were similar among all samples (average amount of 12.3 mg/100 g powder). The phytochemical and mineral composition of a *Zingiber officinale* (ginger) rhizome powder was evaluated.[15] Phytins, tannins, saponins, oxalates, and glycosides were present in amounts of 0.28, 0.02, 4.01, 0.26, 0.81 mg/100 g, respectively. The following minerals were present in the ginger rhizome powder: Zn (4.19 µg/g), Mn (18.9 µg/g), Cu (0.86 µg/g), Ca (34.55 µg/g), P (26.70 µg/g), Fe (1.59 µg/g), Na (38.96 µg/g), and K (36.34 µg/g).

Zingiber Officinale (Ginger) Water

According to a supplier, a trade name mixture containing Zingiber Officinale (Ginger) Water consisted of 98.5% Zingiber Officinale (Ginger) Water and phenoxyethanol (1.5%).[29] This mixture was reported to be free from diethylene glycol, dioxin, formaldehyde, formol, gluten, glycol ether, and phthalate.[30]

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 survey data, Zingiber Officinale (Ginger) Root Extract is reported to be used in 244 formulations (154 leave-on formulations; 84 rinse-off formulations; 2 formulation diluted for bath use) and Zingiber Officinale (Ginger) Root Oil is reported to be used in 135 formulations (95 leave-on formulations; 36 rinse-off formulations; 7 formulations diluted for bath use; Table 6).[31] All other in-use ingredients are reported to be used in 7 formulations or less. The results of the concentration of use survey conducted by the Council in 2020 indicate Zingiber Officinale (Root) Extract also has the highest concentration of use in a leave-on formulation; it is used at up to 0.2% in face and neck formulations.[32] The 3 ingredients not in use according to the VCRP and industry survey can be found in Table 7.

Incidental ingestion and mucous membrane exposure of these ginger-derived ingredients may occur due to use in lipstick, dentifrices, and other oral hygiene product formulations (e.g. Zingiber Officinale (Ginger) Root Extract is used at up to 0.02% in lipsticks). In addition, Zingiber Officinale (Ginger) Root Extract is reported to be used in one eye lotion formulation (concentration for this formulation type was not provided).

Some of these ginger-derived ingredients are used in cosmetic sprays and powders, and could possibly be inhaled; for example, Zingiber Officinale (Ginger) Root Extract is reported to be used in other fragrance preparations (up to 0.1%), and Zingiber Officinale (Ginger) Root Oil is reportedly used pump spray body and hand formulations (up to 0.001%), and in face powders (concentration not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

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.

All of the ginger-derived ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[33]

Non-Cosmetic

Zingiber officinale (ginger) has been used worldwide as a food and flavoring agent.[34] Ginger rhizomes may be consumed fresh, dried, pulverized into a spice, candied, or pickled. Ginger may also be incorporated into baked goods, or steeped in boiling water to make ginger tea. According to the US FDA (21CFR182.10), *Zingiber officinale* is GRAS as a spice, natural seasoning agent, and flavoring. Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are GRAS for human consumption (21CFR182.20), and in animal drugs, feeds, and related products (21CFR582.20). According to 2020 concentration of use data provided by the Council, Zingiber Officinale (Ginger) Root Oil is reported to be sold at a concentration of 100% in "other fragrance preparations" as an essential oil, in which a few drops are used per teaspoon of carrier oil. It is unlikely that essential oils at concentrations of 100% would be used in cosmetic products; therefore, the Panel considered this use to be a non-cosmetic use.[32]

Ginger is commonly consumed as an over-the-counter remedy for nausea and dyspepsia, and has been listed as an inactive ingredient in two orally-ingested, FDA-approved drug products.[34,35] In Asian cultures, ginger is used as a traditional medicine to treat various ailments such as arthritis, hypercholesterolemia, baldness, toothache, and respiratory conditions. Historically, ginger has been used to improve appetite, reduce nausea, and as a topical counter-irritant.

TOXICOKINETIC STUDIES

Penetration Enhancement

In Vitro

Zingiber Officinale (Ginger) Root Extract

The influence of an aqueous *Zingiber officinale* (ginger) root extract on the transdermal absorption of hydrophilic ([^{14}C]caffeine) and hydrophobic ([^{14}C]salicylic acid) penetrants was evaluated via a flow-through in vitro porcine skin system.[36] Skin samples were placed into a two-compartment diffusion cell, and the dermal side of the skin sections were perfused using the receptor fluid consisting of a buffer solution, dextrose, and bis(trimethyl)acetamide. The flow rate of the flow-through receptor solution was 4 ml/h. A 10% solution of the ginger root extract prepared in ethanol was applied to the porcine skin, with either caffeine or salicylic acid, to an area of 1 cm^2. Control samples were exposed to ethanol combined with either caffeine or salicylic acid. All doses were occluded following topical application. Receptor fluid was collected 0, 15, 30, 45, 60, 75, 90, 105, and 230 min after application, and then 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24 h after application. Flux and permeability of caffeine with ginger root extract (flux: 1.67 ± 0.28 μg/cm^2/h; permeability: 0.78 ± 0.13 cm/h*10^3) was compared to the flux and permeability of caffeine with ethanol (flux: 0.58 ± 0.08 μg/cm^2/h; permeability: 0.29 ± 0.04 cm/h*10^3). No significant differences were observed in the absorption of [^{14}C]salicylic acid with the ginger root extract compared to the control.

Absorption, Distribution, Metabolism, and Excretion

Human

Oral

Zingiber Officinale (Ginger) Root Extract

The pharmacokinetics of active constituents found in a *Zingiber officinale* (ginger) root extract (6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol) were evaluated in humans.[37] Nine healthy volunteers received a 2 g oral dose of the ginger root extract.[37] Blood was drawn from participants at baseline, and at 0.25, 0.75, 1, 2, 4, 6, 10, 24, 48, and 72 h after ingestion. Plasma was separated from blood and evaluated via a liquid chromatography-mass spectrometry (LC-MS) analysis. Free 10-gingerol was detected in plasma with a peak concentration of 9.5 ± 2.2 ng/ml at 1 h, but was undetectable after 2 h post-dosing. Free 6-shogaol was detected in plasma at a peak concentration of 13.6 ± 6.9 ng/ml at 1 h, and was undetectable after 4 h post-dosing. No free 6-gingerol or 8-gingerol was detected in the plasma samples from 0 to 24 h post-dosing. In a multiple-dose assay, 23 healthy human subjects received either placebo (n = 11) or ginger root extracts (2.0 g/d; n = 12), for 24 d. Blood samples were drawn within 24 h of the last dose. No free 6-, 8-, or 10-gingerol and no 6-shogaol was detected in the plasma of all the subjects 24 h after the last dosing, suggesting that there was no accumulation of free 6-, 8-, or 10-gingerol or 6-shogaol in plasma after multiple daily dosing. Low levels of 6-gingerol glucuronide, 6-gingerol sulfate, and 10-gingerol glucuronide were observed in 4 subjects.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Zingiber Officinale (Ginger) Extract

No toxicity was observed in male Wistar rats (5/group) given a single oral dose of a *Zingiber officinale* (ginger) extract (concentrations ranging from 100 – 1000 mg/kg).[38] In a different study, Sprague-Dawley rats (5 rats/sex/group) were given a single oral dose of up to 5000 mg/kg steamed and dried ginger extract via gavage.[39] No mortalities or adverse effects were reported.

Zingiber Officinale (Ginger) Rhizome Extract

Five Syrian golden hamsters (5/sex/group) were given an ethanolic *Zingiber officinale* (ginger) rhizome extract via gavage in doses of 1000, 3000, or 5000 mg/kg bw.[40] Control hamsters were fed a mixture of distilled water and a polysorbate surfactant. No deaths were observed throughout the study. Reversible stomach irritation was noted directly after administration. No other toxic effects were observed.

Zingiber Officinale (Ginger) Root Powder

Sprague-Dawley rats (5/sex/group) were given either 5000 mg/kg bw *Zingiber officinale* (ginger) rhizome powder, or distilled water, via gavage.[41] No signs of acute toxicity were observed.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

An acute toxicity assay on a *Zingiber officinale* (ginger) extract in an olive oil vehicle was performed according to Organisation for Economic Cooperation and Development (OECD) test guidelines (TG) 423.[2] Three female Wistar rats were given a single administration of the test substance (2000 mg/kw bw ginger extract in olive oil) via drinking water. Animals were inspected daily for the next 14 d. The LD_{50} was determined to be greater than 2000 mg/kg bw.

Short-Term Toxicity Studies

Animal

Oral

Zingiber Officinale (Ginger) Rhizome Extract

Syrian golden hamsters (5/sex/group) were given an ethanolic *Zingiber officinale* (ginger) rhizome extract via gavage in doses of 1000, 3000, or 5000 mg/kg bw, for 30 d.[40] Control hamsters were fed a mixture of distilled water and a polysorbate surfactant. At the end of the treatment period, animals were sacrificed and vital organs were examined. Body weights and water and food intake were similar among control and treated groups. No abnormal histopathology was observed.

Zingiber Officinale (Ginger) Root Extract

Female Sprague-Dawley rats (6/group) were given 0.5 ml of saline or a *Zingiber officinale* (ginger) root extract (50 or 500 mg/kg), daily, via gavage, for 4 wk.[12] Mortality, hematological parameters and systemic toxicity was evaluated. No mortalities were reported throughout the study period. Total lactate dehydrogenase levels in serum was statistically significantly higher in rats treated with 500 mg/kg ginger root extract compared to controls. Histopathological examinations revealed similar results in the lungs and liver in control and treated rats.

Zingiber Officinale (Ginger) Root Oil

Male Wistar rats (10/group) were given either 0.02 or 0.002 ml/kg bw of a *Zingiber officinale* (ginger) root fixed oil, or 0.04 ml/kg bw *Zingiber officinale* (ginger) root essential oil, via gavage, for 60 d.[14] (The production of the essential and fixed oils are provided in the Method of Manufacture section of this report.) A control group received 0.5 ml/kg bw corn oil over the same time period. Behavioral, morphological, macroscopic, hematological, and histomorphological parameters were evaluated. A statistically significant ($p < 0.05$) increase in weights of the kidneys, lungs, liver, and spleen was observed in animals treated with the fixed ginger root oil, at both doses, compared to controls. A statistically significant decrease in alkaline phosphatase (ALP; $p < 0.05$) and increase in alanine transaminase was recorded in animals treated with 0.002 ml/kg bw ginger root fixed oil. Some forms of pathologies in the liver and spleen were observed in rats treated with ginger root fixed oil; however, these effects were not observed in animals treated with ginger root essential oil. No significant organ weight differences were observed in animals treated with ginger root essential oil, compared to controls. Aspartate aminotransferase (AST) values were significantly reduced in animals treated with 0.04 ml/kg bw ginger root essential oil, compared to controls. No observable differences in the histology of the heart, lung, and kidney, were observed, in either ginger-treated group, compared to the control group. Test effects were reversed after study termination.

Zingiber Officinale (Ginger) Root Powder

Sprague-Dawley rats (5/sex/group) were given either 500, 1000, or 2000 mg/kg bw *Zingiber officinale* (ginger) rhizome powder, via gavage, each day, for 28 d.[41] A control group received distilled water. Results were similar among ginger-treated and control rats regarding body weight, behavior, histopathology, and laboratory parameters. Statistically significant increased numbers of white blood cells, neutrophils, and lymphocytes were noted in all ginger-treated groups, compared to controls.

A *Zingiber officinale* (ginger) root powder (5 ml/kg) in 5% gum arabic was given to Sprague-Dawley rats (5 rats/sex/group) at doses of 500, 1000, and 2000 mg/kg bw, via gavage, for 35 d.[42] Five males and 5 females were given the vehicle (5% gum arabic), only. Mortality, behavior, growth, food and water consumption, hematological parameters, and histopathological parameters were evaluated. All parameters evaluated were similar between control and treated groups, however, a dose-related decrease in serum lactate dehydrogenase activity in males was observed. Treatment with 2000 mg/kg of the ginger powder led to slightly reduced absolute and relative weights of the testes.

Human

Oral

Zingiber Officinale (Ginger) Extract

The potential toxic effects of a steamed ethanolic *Zingiber officinale* (ginger) extract was evaluated in a 12-wk, randomized, double-blind, placebo-controlled trial.[43] Seventy healthy obese participants were given an oral dose of either steamed ginger extract (200 mg in capsule form; n = 36), or a placebo (n = 34), daily. Blood pressure, pulse, and hematological and biochemical parameters (white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet, ALP, gamma-glutamyl transferase, total bilirubin, total protein, albumin, blood urea nitrogen, creatinine, glucose, creatinine kinase, lactate dehydrogenase) were evaluated. All clinical test results were normal, and all participants completed the study. No extract-related adverse effects were observed.

Subchronic Toxicity Studies

Oral

Zingiber Officinale (Ginger) Root Oil

A 13-wk oral toxicity assay was performed in Wistar rats (5 rats/sex/group).[44] Animals were either left untreated, treated with the vehicle control (paraffin oil), or treated with 100, 250, or 500 mg/kg *Zingiber officinale* (ginger) oil. Administrations occurred via gavage once per day. Mortality, body weight, food consumption, hematological parameters, and histopathological parameters were similar in control and treated groups. The no-observed-adverse-effect level (NOAEL) was determined to be greater than 500 mg/kg/d.

Chronic Toxicity Studies

Oral

Zingiber Officinale (Ginger) Root Powder

The potential chronic toxicity of a *Zingiber officinale* (ginger) rhizome powder was evaluated in Sprague-Dawley rats (20 rats/sex/group).[41] Animals were given the powder, via gavage, in doses of either 250, 500, or 1000 mg/kg bw, for 12 mo. Control animals were given distilled water. On day 366, animals were euthanized, and histopathological and hematological parameters were evaluated. No treatment-related, serious, adverse clinical effects were noted during the treatment period. Body weights and food and water consumption were similar amongst all dose levels. The NOAEL was considered to be 1000 mg/kg bw. Hematological and biochemical parameters were generally similar among control and treated groups. However, statistically significant differences were observed in hemoglobin, white blood cell, neutrophil, lymphocyte, cholesterol, triglyceride, and glucose numbers, in rats treated with 500 and 1000 mg/kg bw ginger rhizome powder, compared to controls (further details were not provided). Histopathological examination revealed no apparent adverse effects after ginger rhizome treatment (at any dose) compared to controls.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Zingiber Officinale (Ginger) Rhizome Extract

Reproductive effects of an aqueous *Zingiber officinale* (ginger) rhizome extract were evaluated in female ICR mice, at different dosing intervals.[7] At each dosing interval, mice were given either 250, 500, 1000, or 2000 mg/kg bw of the test article via gavage. A control group was treated with distilled water. For the main study, female mice (25/group) were dosed with the test substance for 90 d, and throughout mating and gestation. On gestation day (GD) 20, mice were killed and fetuses were evaluated. For estrous cycle evaluation, mice (10/group) were treated for 2 wk before evaluating vaginal cytology, and throughout a 20-d evaluation period (35 d total). During the evaluation period, estrous cycle phases were screened daily, and vaginal cytology was assessed. Pre-implantation loss (anti-fertility effects) was evaluated in 10 mice/group treated for 20 d throughout gestation. Post-implantation loss (abortifacient effects) were evaluated in mice (10/group) treated 20 d before, and throughout gestation. All pregnant females survived until necropsy, except for one female treated with 1000 mg of the extract in the pre-implantation loss group, and in 2 females treated with 2000 mg of the extract in the post-implantation loss group. High doses of the ginger rhizome extract significantly reduced the number of live fetuses, and increased fetal death and resorption, compared to controls ($p \leq 0.05$). Mice treated with 2000 mg/kg bw in the post-implantation loss group displayed significant decreases in implantation sites, compared to control animals ($p \leq 0.05$). At the highest dose level, estrous cycles were prolonged, with a significant decrease in the duration of the luteal phase, compared to control animals. The NOAEL was determined to be 500 mg/kg bw.

Zingiber Officinale (Ginger) Root Powder

The effect of prenatal exposure to a *Zingiber officinale* (ginger) rhizome powder on pregnancy outcome and postnatal development of Sprague Dawley rats was evaluated.[45] Pregnant rats were given dry powder extracts (500 mg/kg/d ; n = 4 or 1000 mg/kg/d; n = 5) of ginger rhizomes via gavage on GD 5-15. A negative, untreated control group consisted of 6 rats. Daily food and water intake, and total weight gain was significantly reduced in ginger-fed rats compared to controls ($p < 0.05$). Significant embryonic loss was observed in ginger-treated rats ($p < 0.05$), however, growth and physical maturation parameters of offspring (pup body weight and length) exposed to ginger were unaffected. No external congenital anomalies were found in either treated or control groups.

The effect of *Zingiber officinale* (ginger) rhizome powder (50 or 100 mg/kg/d) on spermatogenesis and sperm parameters were evaluated in male Wistar rats (10 rats/group).[46] Animals were treated orally for 20 d. The method of oral administration was not stated. A control group consisting of 10 rats received treatment with distilled water, only. Serum total testosterone levels was significantly increased in the group treated with 100 mg/kg/d ginger rhizome extract, compared to the control group ($p < 0.05$). Sperm viability and motility were significantly increased in the ginger-treated groups compared to controls ($p < 0.05$). Luteinizing hormone levels, follicle stimulating hormone levels, sperm concentration, morphology, and testes weights were similar in both ginger-treated and control groups.

ANTI-REPRODUCTIVE TOXICITY STUDIES

Treatment with *Zingiber officinale* (ginger) in rats resulted in an ameliorating effect against several reproductive toxicants.[47-51] Toxicants evaluated in these studies included aluminum chloride, ethanol, cisplatin, sodium arsenite, and cadmium chloride.

GENOTOXICITY STUDIES

In Vitro

Zingiber Officinale (Ginger) Root Oil

A *Zingiber officinale* (ginger) essential oil prepared from the rhizomes of ginger was tested for the induction of reverse mutations in *Salmonella typhimurium* strains TA1535, TA98, TA100, and TA102, with and without metabolic activation.[52] The oil was tested at concentrations of 10, 50, 100, 1000, and 3000 µg/plate. No indication of mutagenic activity was observed.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

An Ames assay was performed on a *Zingiber officinale* (ginger) extract (up to 5 µl/plate) using *S. typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102, with and without metabolic activation.[2] This assay was performed according to OECD TG 471. The test substance was considered to be non-genotoxic.

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

In Vitro

Zingiber Officinale (Ginger) Rhizome Extract

The anticancer activity of a *Zingiber officinale* (ginger) rhizome extract (12.5, 25, 50, 100, 200, and 400 µg/ml) against human cervical cancer (HeLa) cells and breast cancer (MDA-MD-231) cells was evaluated via a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) and colony formation assay.[53] The rhizome extract inhibited proliferation in both cell lines in a dose- and time-dependent manner. The effect of a *Zingiber officinale* (ginger) rhizome extract (0, 10, 50, 100, 200, 500, 800, 1000, and 1500 µg/ml) on the proliferation and apoptosis of colon cancer cell lines (HCT 116 and HT 29) was also evaluated via an MTT assay.[54] The ginger extract inhibited proliferation of HCT 116 and HT 29 cells with an half-maximal inhibitory concentration (IC_{50}) of 496 ± 34.2 µg/ml and 455 ± 18.6 µg/ml, respectively. Ginger extract also caused an increase in apoptosis of the cancer cell lines in a dose-dependent manner.

Animal

Zingiber Officinale (Ginger) Extract

Potential anti-prostate cancer activity of a whole *Zingiber officinale* (ginger) extract was evaluated in male Balb/c nude mice (6 mice/group).[55] Human prostate (PC-3) xenografts were subcutaneously implanted in all test mice. Animals were fed 100 mg/kg/d ginger extract in phosphate buffered saline for 8 wk. A control group received the vehicle only. Tumors in vehicle-treated control animals showed unrestricted progression, while ginger extract treatment resulted in a time-dependent inhibition of tumor growth over the 8-wk study period. A reduction in tumor burden by 56% was observed after 8 wk of ginger extract treatment. The mean final tumor volume was significantly less in ginger extract treated mice compared to control mice ($p < 0.05$).

The effect of an ethanolic *Zingiber officinale (*ginger) extract on ethionine-induced hepatoma was evaluated in male Wistar rats (6 rats/group).[56] Rats were randomly divided into 5 groups based on diet: i) control (given normal rat chow), ii) olive oil, iii) ginger extract (100 mg/kg body weight), iv) choline-deficient diet + 0.1% ethionine to induce liver cancer (positive control) and v) choline-deficient diet + ginger extract (100mg/kg body weight). A significant reduction in positive staining of tumor necrosis factor (TNF)-α and expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) was observed in rats treated with ginger ($p < 0.05$), compared to rats in the positive control group. In addition, treatment with ginger lowered liver nodule incidence by 17%, compared to the positive control group.

OTHER RELEVANT STUDIES

Ultraviolet (UV)-Protective Effects of Ginger

Zingiber Officinale (Ginger) Rhizome Extract

The following study is included in this report as it may be helpful in addressing cosmetic safety concerns regarding phototoxicity. Male C57BL/6 mice (5 mice/group) were subjected to mid-wavelength ultraviolet light (UVB) exposure (200 mJ/cm^2) every alternate day for 2 wk, and then given different oral doses of an aqueous *Zingiber officinale* (ginger) rhizome extract (1% and 2.5%), following each UVB exposure.[22] A control group received UVB radiation followed by distilled water. The method of oral administration was not stated. Mice were killed 24 h after the last irradiation, and blood was collected. The dorsal skin was removed and measured for cytokines and hematoxylin and eosin staining. Treatment with the ginger rhizome extract reduced the effects of UVB-induced hyperplasia, infiltration of leukocytes, and dilation of blood vessels in the dermis of mice, in a dose-dependent manner. The protective effects of *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol, were also evaluated in human epidermal keratinocyte (HaCaT) cells. HaCaT cells were UVB-irradiated (100 mJ/cm^2) and cultured with test substances. Treatment with *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol at concentrations up to 10 µg/ml or 10 µM had an insignificant effect on the toxicity of irradiation. However, all test substances inhibited production of cytokines in UVB-irradiated HaCaT cells.

Immunomodulatory Effects

The following studies were included as they may be helpful in addressing cosmetic safety concerns regarding allergenicity/ hypersensitivity of the ginger-derived ingredients evaluated in this report.

Zingiber Officinale (Ginger) Extract

Anti-inflammatory effects of a whole *Zingiber officinale* (ginger) extract were evaluated in a murine asthma model.[57] Lung inflammation was induced in C57/B16 mice, via house dust mite (HDM) sensitization (intranasally), for 10 d. Throughout this period, mice also received a ginger extract (40 mg/kg) via gavage in 2% hydroxypropyl methylcellulose and 2.5% polyethylene glycol, twice daily. Control mice received the vehicle only. Bronchoalveolar lavages (BAL) and histologic analyses were performed following study completion. In addition, lung homogenate interleukin-4 (IL-4) concentrations were evaluated. Significant lung inflammation and increases in BAL total cell counts were evaluated after HDM administration. Co-administration of ginger extracts significantly decreased BAL cell counts compared with control mice ($p < 0.05$). The ginger extract also decreased lung concentration of IL-4 ($p < 0.05$), by 59%, compared to control animals.

Zingiber Officinale (Ginger) Powder

The anti-allergic effects of *Zingiber officinale* (ginger) powder was evaluated using a mouse allergy model.[58] Female Balb/c mice (8-10/group) were sensitized via an injection of ovalbumin (OVA), twice, in a 2-wk interval. Mice were fed diets containing 2% *Zingiber officinale* (ginger) powder, or a control diet, from 2 wk before the first injection of OVA until the end of the experiment. Two wk after the second injection, sensitization was followed by intranasal challenges, daily, for 6 d, with OVA, in all groups. Mice with OVA-induced allergic rhinitis and treatment with ginger displayed a reduction in the severity of sneezing and nasal rubbing by nasal sensitization of OVA and suppressed infiltration of mast cells in nasal mucosa and secretion of OVA-specific IgE in serum, compared to control animals.

Zingiber Officinale (Ginger) Rhizome Extract

Four patients with IgE-mediated allergy to *Zingiber officinale* (ginger) were evaluated in a study to analyze specific allergens of the ginger rhizome.[59] Two patients reported previous dyspnea and gastrointestinal symptoms following ingestion of ginger. One patient reported palpitations, hyperhidrosis, and loss of consciousness after consumption of raw ginger. Another patient reported facial angioedema and conjunctival irritation after handling ginger powder, but no symptoms after ingestion of ginger. Skin prick tests with a raw ginger extract were positive in all patients. Three healthy control subjects had negative skin prick tests to raw ginger. The ginger extract showed protein bands ranging from 90 kilodaltons (kDa) to 8 kDa. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) IgE immunoblotting assays were performed using individual patient sera. IgE-reactivity bands with molecular weights of approximately 30 and 32 kDa were observed in all patient sera. Serum from one patient revealed bands of 8-10 kDa, and serum for another patient revealed a band of 8 kDa. The 8-, 10-, 30-, and 32-kDa protein bands of the raw ginger extract were excised and analyzed. The analysis of the peptides by mass spectrometry corresponded to the cysteine protease GP-1, for the 30- and 32-kDa band. No matches were found for the 8- and 10-kDa bands.

Zingiber Officinale (Ginger) Root Oil

The anti-hypersensitivity effect of a volatile oil of *Zingiber officinale* (ginger) was evaluated in female ICR mice (12/group).[60] Mice were sensitized with 0.5% dinitrofluorobenzene (DNFB) in absolute acetone and olive oil, onto shaved abdominal skin, at the beginning of the experiment. Five days after initial sensitization, animals were challenged with 10 µl DNFB on both sides of the left ears. The right ear was treated with the vehicle (acetone and olive oil). Mice were then treated with the vehicle, ginger oil (0.125, 0.25, and 0.5 g/kg bw), or dexamethasone sodium phosphate (0.005 g/kg), via gavage, daily, for 5 d. Following the 5-d test substance administration, a DNFB challenge was performed, and mice were sacrificed. Ear swelling, thymus, and spleen weights were noted. The ginger oil, at all doses, weakened the delayed type of hypersensitivity response to DNFB in sensitized mice ($p < 0.05$), in a dose-dependent manner.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details on the dermal irritation and sensitization studies summarized below can be found in Table 8.

In vitro dermal irritation assays performed using reconstructed human epidermis on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded negative results.[2,61] An acute dermal toxicity assay on steamed and dried *Zingiber officinale* (ginger) extract (0.5 ml) was performed in 6 New Zealand White rabbits.[39] No erythema or edema was observed 24 and 72 h after treatment on intact or abraded skin. Similarly, no irritation was noted in a 48-h patch test performed on 10 subjects, using a product containing 0.0995% Zingiber Officinale (Ginger) Root. [62]

A KeratinoSens™ ARE-Nrf2 luciferase assay and direct reactivity peptide assay (DPRA) performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract yielded negative results. [63,64] A DPRA performed using a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded positive results.[2] Assays performed in humans yielded negative results (human repeated insults patch tests (HRIPTs) performed using a moisturizer containing 0.1% Zingiber Officinale (Ginger) Rhizome Extract (n = 54), a serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract (n = 104), and a product containing 0.2% Zingiber Officinale (Ginger) Root Extract (n = 53).[65-67]

OCULAR IRRITATION STUDIES

In Vitro

Zingiber Officinale (Ginger) Root Extract

An EpiOcular™ was performed on a trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%).[61] Two tissue inserts (corneal epithelial models) were incubated with the test material for 30 min. The test article was considered to be non-irritating.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

Potential ocular irritancy of a *Zingiber officinale* (ginger) extract was evaluated in an in vitro assay performed according to OECD TG 437.[2] Bovine corneas (3/group) were incubated with the test substance (ginger extract) for 10 minutes, and evaluated. Negative controls were incubated with a balanced salt solution, and positive controls were incubated with dimethylformamide. The concentrations of the test agents used were not reported. Corneal opacity values were similar among the negative control and treated groups.

CLINICAL STUDIES

Case Reports

In 2013, a woman took an herbal medicine containing ginger for motion sickness and felt full-body pruritus soon after ingestion.[68] The woman reported use of this herbal medicine for 20 yr prior, with no symptoms. Several hours after ingestion, the woman lost consciousness and was taken to the emergency department. The patient was diagnosed with anaphylactic shock. A year later, the woman reported dyspnea and itchy rash following ingestion of a different herbal medication, also containing ginger. A skin prick test was performed using powdered zedoary, powdered ginger, powdered turmeric, powdered Japanese kelp, and microcrystalline cellulose, in order determine the causative agent. Reactions were apparent after zedoary, turmeric, and ginger skin pricks. The patient was diagnosed with immediate-type allergy to zedoary/turmeric/ginger-containing drugs and foods.

A 43-yr-old man reported interrupted urinary stream associated with dysuria, perineal, and flank pain, for 4 yr.[69] The patient also reported a feeling of warmness, chest heaviness, and palpitations. History analysis revealed that the patient had been consuming ginger tea (2 - 3 tsp dry ginger) each day, for 15 yr. One week after eliminating ginger from the diet, symptoms began to recede. All symptoms were completely cleared after 8 wk without ginger consumption.

Four subjects with reported occupational allergic contact dermatitis from spices were evaluated using patch testing and prick testing.[70] Eleven spices (including powdered ginger), were put on a filter paper in a test chamber, moistened with a drop of water, and placed on the back, under occlusion. Each spice was tested in different chambers. Patches stayed in placed for 2 d. One patient elicited a strong (2+) reaction to the ginger powder spice. No patients displayed reactions to skin prick testing.

A 26-yr-old man employed at a spice factory reported shortness of breath and rhinitis approximately 2 yr after starting the job.[71] By the third year, the patient reported serious attacks of dyspnea with wheezing. When assigned a different job that did not require exposure to spices, all symptoms of atopic disease diminished. Total IgE, and allergen-specific IgE, radioallergosorbent (RAST) inhibition were evaluated using various powdered spices. Specific IgE antibodies against all evaluated spices were observed in patient sera. Percent IgE binding to coriander, curry, mace, paprika, ginger, white pepper, and mugwort were reported to be 45, 44, 26, 30, 27, 13, and 5%, respectively. IgE-binding components from coriander did not cross-react with the IgE-binding components from ginger and paprika.

Forty-five female spice-factory workers were recruited to evaluate possible allergenicity to various spices (chili pepper, paprika, pepper, parsley, garlic, onion, parsnip, ginger, turmeric, salt, and dextrose). Forty-five women without

constant exposure to spices were also recruited as controls. Intradermal skin tests were performed with an aqueous extract of the individual spices, in exposed and control workers. Skin reactions were read after 20 min. The most frequent positive dermal reactions occurred with chili pepper (13.3%), followed by paprika and parsnip (11.1%), pepper and turmeric (6.7%), and onion and ginger (2.2%). Among control workers, only 1 of 45 reacted to individual allergens, specifically with the chili pepper extract.

Spice Allergy in Spice-Sensitive Patients

Scratch tests with powdered commercial spices were performed in 70 atopic subjects with positive skin tests to birch and/or mugwort pollens and celery.[72] Scratch tests were also performed on 12 healthy controls. Anise seed, fennel, coriander, and cumin caused the highest number of positive reactions (46, 28, 26, and 24 patients, respectively). Ginger caused a positive scratch test in 3 of 70 patients.

SUMMARY

The safety of 9 *Zingiber officinale* (ginger)-derived ingredients as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, the majority of these ingredients are reported to function in cosmetics as skin-conditioning agents – miscellaneous; additional functions were also reported. *Zingiber officinale* is GRAS in the US as a spice, natural seasoning, and flavoring agent. In addition, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are considered GRAS for human and animal consumption.

According to 2022 VCRP survey data, Zingiber Officinale (Ginger) Root Extract is reported to be used in 244 cosmetic formulations (154 leave-on formulations; 84 rinse-off formulations; 2 formulations diluted for bath use). Zingiber Officinale (Ginger) Root Oil is reported to be used in 135 total formulations. All other in-use ingredients are reported to be used in 7 formulations or less. The results of the concentration of use survey conducted by the Council indicate Zingiber Officinale (Root) Extract also has the highest concentration of use in a leave-on formulation; it is used at up to 0.2% in face and neck formulations.

The influence of a *Zingiber officinale* (ginger) root extract on the transdermal absorption of [^{14}C]caffeine and [^{14}C]salicylic acid was evaluated in porcine skin. The dermal absorption of [^{14}C]caffeine was significantly higher with the ginger root extract compared to the control (ethanol). No significant differences were observed in the absorption of [^{14}C]salicylic acid with the ginger root compared to the control.

Nine healthy volunteers were given a 2 g dose of *Zingiber officinale* (ginger) root extract in order to evaluate metabolism. Plasma was evaluated at various intervals following ingestion. Metabolites found in the plasma included 10-gingerol and 6-shogaol. In a multiple-dose assay, 23 healthy volunteers received a placebo or 2 g *Zingiber officinale* (ginger) root extract, once a day, for 24 d. No free 6-, 8-, and 10-gingerol or 6-shogaol were detected in the plasma of any the subjects 24 h after the last dosing, suggesting that there was no accumulation of free 6-, 8-, and 10-gingerol or 6-shogaol in plasma after multiple daily dosing.

No adverse effects were reported in oral toxicity assays on *Zingiber officinale* (ginger) extracts performed in rats at up to 5000 mg/kg. Similarly, no adverse effects were reported in an acute oral toxicity assay involving Sprague-Dawley rats given up to 5000 mg/kg *Zingiber officinale* (ginger) rhizome powder. Reversible stomach irritation was observed in an acute oral toxicity assay performed in Syrian golden hamsters given *Zingiber officinale* (ginger) root powder. No other toxic effects were observed.

In a short-term oral toxicity assay, Syrian golden hamsters were given an ethanolic *Zingiber officinale* (ginger) rhizome extract, via gavage, at up to 5000 mg/kg bw/d, for 30 d. No signs of toxicity were observed. Female Sprague-Dawley rats were given up to 500 mg/kg of a *Zingiber officinale* (ginger) root extract, daily, via gavage, for 4 wk. Elevated total lactate dehydrogenase levels in the serums of high-dosed animals were observed; however, no other adverse effects were reported. In a 60-d study, male Wistar rats were given either 0.02 or 0.002 ml/kg bw of a *Zingiber officinale* (ginger) root fixed oil, or 0.04 ml/kg bw *Zingiber officinale* (ginger) root essential oil, via gavage, daily. Reversible, statistically significant increases in kidney, lung, liver, and spleen weights, and pathologies in the liver and spleen, were observed in animals treated with fixed ginger oil. These effects were not observed in animals treated with ginger root essential oil. In a 28-d study, Sprague-Dawley rats were given up to 2000 mg/kg bw of a *Zingiber officinale* (ginger) rhizome powder, daily, via gavage. Statistically significant increased numbers of white blood cells, neutrophils, and lymphocytes were noted in all ginger-treated groups, compared to controls. No other adverse effects were reported. In a different study, a *Zingiber officinale* (ginger) root powder was orally administered to Sprague-Dawley rats at doses of up to 2000 mg/kg bw/d, via gavage, for 35 d. All parameters evaluated were similar between control and treated groups, however, a dose-related decrease in serum lactate dehydrogenase activity in males, was observed. In a 13-wk oral toxicity assay, a *Zingiber officinale* (ginger) root oil was administered to Wistar rats, each day, via gavage, at doses up to 500 mg/kg/d. The NOAEL was determined to be greater than 500 mg/kg/d. The potential chronic toxicity of a *Zingiber officinale* (ginger) rhizome powder was evaluated in Sprague-Dawley rats. Animals were treated via gavage in doses up to 1000 mg/kg bw, for 12 mo. No treatment-related, serious, adverse clinical effects were noted during the 12 mo.

In a human assay, an ethanolic *Zingiber officinale* (ginger) extract (200 mg) was given to 36 healthy, obese participants via a capsule, each day, for 12 wk. No extract-related adverse effects were observed.

The reproductive effect of an aqueous Zingiber officinale (ginger) rhizome extract (up to 2000 mg/kg bw/d; gavage administration) was evaluated in ICR mice. Estrous cycles, pre-implantation loss, and post-implantation loss were

evaluated. High doses of the ginger rhizome extract significantly reduced the number of live fetuses, and increased fetal death and resorption, compared to controls ($p \leq 0.05$). Mice in the post-implantation loss group, treated with 2000 mg/kg bw, displayed significant decreases in implantation sites, compared to control animals ($p \leq 0.05$). The NOAEL was determined to be 500 mg/kg bw. The effect of prenatal exposure to a *Zingiber officinale* (ginger) rhizome powder on pregnancy outcome and postnatal development of Sprague Dawley rats was evaluated. Pregnant rats were given dry powder extracts (500 mg/kg/d ; n = 4 or 1000 mg/kg/d; n = 5) of ginger rhizomes via gavage on GD 5-15. Significant embryonic loss was observed in ginger-treated rats ($p < 0.05$); however, growth and physical maturation parameters of offspring (pup body weight and length) exposed to ginger were unaffected. The effect of a *Zingiber officinale* (ginger) rhizome powder (up to 100 mg/kg/d; 20 d oral administration) on sperm parameters were evaluated in male Wistar rats. Serum total testosterone levels, sperm viability, and sperm motility were statistically increased in ginger-treated rats compared to controls ($p < 0.05$). Treatment with *Zingiber officinale* (ginger) resulted in an ameliorating affect against several reproductive toxicants (aluminum chloride, ethanol, cisplatin, sodium arsenite, and cadmium chloride) in several anti-reproductive toxicity assays.

No mutagenicity was observed in an Ames assay performed using a *Zingiber officinale* essential oil (up to 3000 µg/plate; with and without metabolic activation), on *S. typhimurium* strains TA1535, TA98, TA100, and TA102. An Ames assay was performed using a *Zingiber officinale* (ginger) extract (may refer to other ginger-derived ingredients; up to 5 µl/plate; with and without metabolic activation) on *S. typhimurium* strains TA1535, TA1537, TA98, TA100, TA102. The test substance was considered to be non-mutagenic.

The anti-cancer effect of a *Zingiber officinale* (ginger) rhizome extract (up to 400 µg/ml) on human cervical and breast cancer cells was evaluated in vitro. The rhizome extract inhibited proliferation in both cell lines in a dose- and time-dependent manner. A similar assay was performed in order to evaluate the effect of *Zingiber officinale* (ginger) rhizome extract (up to 1500 µg/ml) in colon cancer cell lines. The ginger rhizome extract inhibited proliferation and increased apoptosis in the human colon cancer cell lines, in a dose-dependent manner. In a mouse assay, the potential anti-prostate cancer effect of a whole *Zingiber officinale* (ginger) extract (100 mg/kg/d; 8-wk oral administration) was evaluated in male Balb/c nude mice with subcutaneously implanted human prostate xenografts. A reduction in tumor burden by 56% was observed after 8 wk of ginger extract treatment. The effect of an ethanolic *Zingiber officinale (*ginger) extract (100 mg/kg bw) on ethionine-induced hepatoma was evaluated in male Wistar rats. Treatment with ginger lowered liver nodule incidence by 17%, compared to the positive control group.

The potential UV-protective effects of an aqueous *Zingiber officinale* (ginger) rhizome extract (1 and 2.5%) was evaluated in male C57BL/6 mice. Treatment with the ginger rhizome extract reduced the effects of UVB-induced hyperplasia, infiltration of leukocytes, and dilation of blood vessels in the dermis of mice, in a dose-dependent manner. An in vitro assay was also performed using UVB-irradiated HaCaT cells to evaluate the potential protective effects of *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol. All test substances inhibited production of cytokines in UVB-irradiated HaCaT cells.

The anti-inflammatory effects of a whole *Zingiber officinale* (ginger) extract was evaluated in C57/B16 mice. Lung inflammation was induced via intranasal HDM sensitization, for 10 d. Mice also received the ginger extract (40 mg/kg/d) via gavage, twice daily. Ginger extracts resulted in a statistically significant decrease in BAL cell counts and lung concentrations of IL-4, compared to controls ($p < 0.05$).

The anti-allergic effects of a *Zingiber officinale* (ginger) powder was evaluated in female Balb/c mice. Mice were sensitized via OVA injection, and fed diets containing 2% *Zingiber officinale* (ginger) powder. Mice with OVA-induced allergic rhinitis and treatment with ginger displayed a reduction in the severity of sneezing and nasal rubbing by nasal sensitization of OVA and suppressed infiltration of mast cells in nasal mucosa and secretion of OVA-specific IgE in serum, compared to control animals.

The anti-hypersensitivity effect of a volatile oil of *Zingiber officinale* (ginger) was evaluated in female ICR mice. Mice were initially dermally sensitized with DNFB in acetone and olive oil. Treated mice were given ginger oil (up to 0.5 g/kg bw), via gavage, daily, for 5 d. Following the 5-d test substance administration, a DNFB challenge was performed, and mice were sacrificed. The ginger oil, at all doses, weakened the delayed type of hypersensitivity response to DNFB in sensitized mice ($p < 0.05$), in a dose-dependent manner.

Four patients with IgE-mediated allergy to *Zingiber officinale* (ginger) were evaluated to analyze the specific allergens of the ginger rhizomes via IgE immunoblotting assays. IgE-reactivity bands with molecular weights of approximately 30 and 32 kDa were observed in all patient sera. The analysis of the peptides by mass spectrometry corresponded to the cysteine protease GP-1, for the 30- and 32-kDa band.

In vitro dermal irritation assays performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded negative results. An acute dermal toxicity assay on steamed and dried *Zingiber officinale* (ginger) extract (0.5 ml) was performed in 6 New Zealand White rabbits. No erythema or edema was observed 24 and 72 h after treatment on intact or abraded skin. Similarly, no irritation was noted in a 48-h patch test performed on 10 subjects, using a product containing 0.0995% Zingiber Officinale (Ginger) Root. A KeratinoSens™ ARE-Nrf2 luciferase assay and direct reactivity peptide assay (DPRA) performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract yielded negative results. A DPRA performed using a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived

ingredients) yielded positive results. Assays performed in humans yielded negative results (HRIPTs performed using a moisturizer containing 0.1% Zingiber Officinale (Ginger) Rhizome Extract, a serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract, and a product containing 0.2% Zingiber Officinale (Ginger) Root Extract).

In vitro ocular irritation assays performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract yielded negative results.

Full-body pruritus and loss of consciousness was reported in a woman after consumption of an herbal medication containing ginger. The patient reported prior 20-yr use of this medication with no adverse effects. One yr after the initial incident, the patient reported dyspnea and an itchy rash following a different herbal preparation containing ginger. Skin prick tests confirmed allergy to zedoary, turmeric, and ginger. A 43-yr-old man reported dysuria, perineal and flank pain, for 4 yr. History analysis revealed that the patient had been ingesting ginger tea, each day, for 15 yr. The patient's symptoms resolved after eliminating ginger from the diet.

Four subjects with reported occupational allergic contact dermatitis from spices were evaluated using patch testing and prick testing. One patient elicited a strong (2+) reaction to the ginger powder spice. No patients displayed reactions to skin prick testing. A 26-yr-old spice factory-worker reported increasingly exacerbated dyspnea and wheezing 2 yr after starting the job. Total IgE, and allergen-specific IgE, RAST inhibition were evaluated using various powdered spices. Percent IgE binding to coriander, curry, mace, paprika, ginger, white pepper, and mug wort were reported to be 45, 44, 26, 30, 27, 13, and 5%, respectively. Forty-five female spice-factory workers were recruited to evaluate possible allergenicity to various spices (chili pepper, paprika, pepper, parsley, garlic, onion, parsnip, ginger, turmeric, salt, and dextrose) via intradermal skin tests. Only 2.2% of patients reported a positive reaction to ginger. In a different study, scratch tests with powdered commercial spices were performed in 70 atopic patients with positive skin tests to birch and/or mugwort pollens and celery. Ginger caused a positive scratch test in 3 of 70 patients.

DISCUSSION

This assessment reviews the safety of 9 *Zingiber officinale* (ginger)-derived ingredients as used in cosmetic formulations. The Panel reviewed the available data and concluded that the 7 *Zingiber officinale* (ginger) root- and rhizome-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. It should be noted that the Panel found the available data to be sufficient to conclude safety for Zingiber Officinale (Ginger) Water, as this ingredient, according to manufacturers, is reported to be prepared via the distillation of ginger roots.

The Panel also concluded the available data are insufficient to make a determination that Zingiber Officinale (Ginger) Extract and Zingiber Officinale (Ginger) Leaf Cell Extract are safe under the intended conditions of use in cosmetic formulations. In order to determine safety for Zingiber Officinale (Ginger) Leaf Cell Extract, the Panel requires method of manufacturing, composition, and impurities data. If the composition of Zingiber Officinale (Ginger) Leaf Cell Extract notably differs from the root-derived ginger ingredients, systemic toxicity data (e.g., 28-d dermal toxicity, genotoxicity, developmental/reproductive toxicity, and carcinogenicity data) would also be required. Insufficiencies for Zingiber Officinale (Ginger) Extract are irritation and sensitization data at the maximum use concentration.

The Panel expressed concern about pesticide residues, heavy metals, and other plant species that may be present in these *Zingiber officinale*-derived ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

Because final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For the *Zingiber officinale*-derived ingredients, the Panel was concerned about the presence of potential sensitizers (e.g., citronellol) in cosmetics. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., Zingiber Officinale (Ginger) Root Extract is reported to be used in other fragrance preparations at up to 0.1%). Inhalation toxicity data were not available; however, inhalation toxicity concerns were mitigated due to low concentrations of use, high NOAELs in subchronic, chronic, and reproductive oral toxicity assays, and the use of these ingredients in foods. In addition, 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 tracheobronchial 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 and the low concentrations at which the ingredients are used in potentially inhaled products, 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 the following 7 *Zingiber officinale* (ginger)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root*
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice*
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

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

Additionally, the Panel concluded the available data are insufficient to make a determination that the following 2 ingredients are safe under the intended conditions of use in cosmetic formulations:

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Leaf Cell Extract**

* *There are currently no reported uses for this ingredient.*

TABLES

Table 1. INCI names, definitions, and functions of the *Zingiber officinale* (ginger)-derived ingredients in this safety assessment[1]

Ingredient (CAS No.)	Definition	Function
Zingiber Officinale (Ginger) Extract [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Extract is the extract of the whole plant, *Zingiber officinale*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Leaf Cell Extract	Zingiber Officinale (Ginger) Leaf Cell Extract is the extract of a culture of the leaf cells of *Zingiber officinale*	Antioxidants, Skin Protectants
Zingiber Officinale (Ginger) Rhizome Extract	Zingiber Officinale (Ginger) Rhizome Extract is the extract of the rhizomes of *Zingiber officinale.*	Antimicrobial Agents
Zingiber Officinale (Ginger) Root	Zingiber Officinale (Ginger) Root is the root of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Extract [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Root Extract is the extract of the roots of the ginger, *Zingiber officinale.*	Fragrance Ingredients; Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Juice [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Root Juice is the juice expressed from the roots of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Oil [CAS No. 8007-08-7]	Zingiber Officinale (Ginger) Root Oil is obtained from the dried rhizomes of *Zingiber officinale*. (The chemical class for this ingredient is essential oils and waters.)	Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Powder	Zingiber Officinale (Ginger) Root Powder is the powder obtained from the dried, ground roots of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Water [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Water is an aqueous solution of the steam distillate obtained from *Zingiber officinale.*	Fragrance Ingredients

Table 2. Physical and chemical properties of a *Zingiber officinale* (ginger)-derived ingredients and trade name mixtures

Property	Value	Reference
Zingiber officinale (ginger) extract		
Physical Form	liquid	2
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.878	2
Vapor pressure (mmHg@ 20 ºC)	63.76	2
Boiling Point (ºC)	229.9	2
Water Solubility (g/L)	0.0004	2
log K_{ow}	6.9	2
Zingiber Officinale (Ginger) Water (98.5%), phenoxyethanol (1.5%)		
Physical Form	transparent solution	73
Color	colorless	73
Odor	characteristic	73
Refraction Index (@ 20 ºC)	0.332 – 1.339	73
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.999 – 1.002	73
Water Solubility	miscible	73
Alcohol Solubility	miscible	73
Mineral/Vegetable Oil Solubility	non-miscible	73
Zingiber Officinale (Ginger) Root Extract (1-5%) and helianthus annuus hybrid oil (> 50%)		
Physical Form	clear – slightly turbid liquid	24
Color	yellow – brown	24
Odor	characteristic	24
Refraction Index (@ 20 ºC)	1.445 – 1.489	24
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.891 – 0.924	24
Water Solubility	10%; not soluble	24
Alcohol Solubility	10%; not soluble	24
Zingiber Officinale (Ginger) Root Extract (1.5%), propylene glycol (68.5%), and water (30%)		
Physical Form	translucent liquid with slight precipitate	74
Color	orange yellow to orange	74
Odor	characteristic	74
Refraction Index (@ 20 ºC)	1.410 – 1.420	74
Density/Specific Gravity (g/cm^3 @ 20 ºC)	1.045 – 1.055	74
Water Solubility	miscible	74
Alcohol Solubility	miscible	74
Mineral/Vegetable Oil Solubility	non-miscible	74
Zingiber Officinale (Ginger) Water (98.5%) and phenoxyethanol (1.5%)		
Physical Form	transparent solution	73
Color	colorless	73
Odor	characteristic	73
Refraction Index (@ 20 ºC)	0.332 – 1.339	73
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.999 – 1.002	73
Water Solubility	miscible	73
Alcohol Solubility	miscible	73
Mineral/Vegetable Oil Solubility	non-miscible	73

Table 3. Antioxidant components and antioxidant activity of various ginger extracts[27]

Solvent	Total Polyphenols (mg/100 g)	Tannins mg/100 g	Flavonoids (mg/100 g)	Total antioxidant activity (µmol/g of sample)
Water (100 °C)	840	1510	2980	73,529.4
Water (30 °C)	838	1340	1371	79,400
Methanol	510	1120	685	98,822.5
Ethanol	565	980	278	91,176.25
Methanol (80%)	780	1280	404	85,294
Ethanol (80%)	800	1150	352	80,000
Acetone	325	670	249	32,056

Table 4. Hydrocarbons and oxygenated compounds in a *Zingiber officinale* (ginger) rhizome essential oil[28]

Constituent	Amount (%)	Constituent	Amount (%)
(*E*)-farnesene	0.73	pinanol	amount undermined
(*E,E*) α-farnesene	1.92	sabinene	trace
(*Z*)-β-Farnesene	amount undermined	santalene	trace
2,6-dimethylhepen-1-ol	0.01	terpinolene	0.09
2-ethyl hexanol	amount undermined	toluene	0.03
2-methyl butanal	amount undermined	*t*-muurolene	amount undermined
2-methyl-2-hepten-6-one	0.09	*t*-muurolol	0.14
2-pentanone	amount undermined	*trans*-2-octanol	trace
acetic acid	0.03	*trans*-isouegenol	0.60
acetone	0.02	vetivinene	0.57
allaromadendrene	trace*	zingiberene	29.54
bergametene	0.23	α-bisabolol	amount undermined
borneol	1.27	α-copaene	amount undermined
cadinol	amount undermined	α-cubebene	0.11
calamenene	amount undermined	α-eudesmol	0.11
camphene	0.61	*α*-eugenol	trace
camphor	0.06	α-gurjumene	0.01
cintronellal	0.14	α-himachallene	amount undermined
cintronellol	0.60	α-humulene	0.22
elemol	0.36	α-phellandrene	0.03
eremophyllene	0.09	α-pinene	0.21
eudesmol	0.36	α-terpineol	0.61
farnesene	6.46	α-ylangene	0.55
geranial	3.46	β-caryophyllene	0.35
geraniol	0.77	β-phellandrene	0.95
geranoic acid	0.24	β-pinene	0.61
geranylacetone	amount undermined	β-selinene	0.16
germacrene D	3.58	β-sesquiphellandrene	18.42
hexanal	0.02	β-sesquiphellandrol	0.34
ionone	amount undermined	γ-elemene	0.12
isovaleraldehyde	amount undermined	δ-elemene	1.14
lauric acid	amount undermined	δ-terpinene	0.01
limonen-10-ol	0.02	*ρ*-cymene	0.03
limonene	0.34	geranic acid	amount undermined
linalool	0.40	isobornyl acetate	0.03
methyl-*n*-heptylketone	0.03	citronelly acetate	0.39
methyl-*n*-undecylketone	0.09	geranyl acetate	amount undermined
Myrene	0.11	neryl acetate	1.22
n-butylaldehyde	Trace	1,8-cineole	0.41
neral	2.50	linalool oxide	amount undermined
nerolidol	0.54	caryophyllene oxide	0.18
n-heptanol-2-ol	0.02	acetyl furan	amount undermined
perillene	amount undermined	methyl pyrrole	amount undermined

*trace - < 0.01%

Table 5. Composition of *Zingiber officinale* (ginger) powders dried via different methods (mg/100 g ginger powder)[16]

Ginger Powder	Shade dried	Solar dried	Oven dried	Microwave dried
Moisture	3.7±0.08	3.5±0.08	3.6±0.07	3.7±0.09
Protein	5.8±0.09	5.5±0.10	5.0±0.05	5.7±0.09
Crude Fiber	5.4±0.08	4.9±0.07	5.4±0.09	5.6±0.10
Fat	0.90±0.02	0.76±0.04	0.78±0.02	0.80±0.02
Ash	3.5±0.04	3.4±0.07	3.3±0.04	3.6±0.05
β-carotene	0.81±0.01	0.68±0.02	0.71±0.05	0.78±0.07
Ascorbic acid	3.8±0.07	2.2±0.08	2.3±0.09	3.5±0.10
Polyphenols	12.5±0.13	11.8±0.15	12.4±0.10	12.4±0.12
Calcium	69.2±1.02	65.3±1.04	64.4±1.02	67.6±1.03
Iron	1.8±0.05	1.6±0.06	1.5±0.03	1.6±0.02
Copper	0.75±0.03	0.46±0.06	0.68±0.03	0.70±0.02

Table 6. 2022 Frequency[31] and 2020 concentration[32] of use according to duration and exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Zingiber Officinale (Ginger) Extract		**Zingiber Officinale (Ginger) Rhizome Extract**		**Zingiber Officinale (Ginger) Root Extract**	
Totals*	**7**	**0.000042 – 0.0009**	**2**	**NR**	**244**	**0.0000033 – 0.22**
Duration of Use						
Leave-On	*3*	*0.000042*	*2*	*NR*	158	*0.0001 – 0.2*
Rinse-Off	*4*	*0.0009*	*NR*	*NR*	84	*0.0001 – 0.22*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	2	*0.0000033 – 0.001*
Exposure Type						
Eye Area	NR	NR	NR	NR	4	NR
Incidental Ingestion	NR	NR	NR	NR	13	0.0072 – 0.02
Incidental Inhalation-Spray	1[a]; 1[b]	0.000042[a]	2[a]	NR	1; 57[a];42[b]	0.001 – 0.1; 0.009[a]
Incidental Inhalation-Powder	1[b]	NR	NR	NR	42[b]	0.0001 – 0.2[c]
Dermal Contact	5	NR	2	NR	151	0.0000033 – 0.22
Deodorant (underarm)	1[a]	NR	NR	NR	1[a]	NR
Hair - Non-Coloring	NR	0.000042 – 0.0009	NR	NR	80	0.0001 – 0.018
Hair-Coloring	NR	NR	NR	NR	NR	0.0016
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	22	0.0000033 – 0.02
Baby Products	NR	NR	NR	NR	NR	NR
	Zingiber Officinale (Ginger) Root Oil		**Zingiber Officinale (Ginger) Root Powder**		**Zingiber Officinale (Ginger) Water**	
Totals*	**135**	**0.000046 – 0.004**	**5**	**NR**	**2**	**NR**
Duration of Use						
Leave-On	*95*	*0.000046 – 0.003*	1	*NR*	NR	*NR*
Rinse Off	*36*	*0.001 – 0.004*	4	*NR*	1	*NR*
Diluted for (Bath) Use	*4*	*0.001*	NR	*NR*	1	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	2	NR	1	NR	NR	NR
Incidental Inhalation-Spray	16; 28[a]; 21[b]	0.00032 – 0.001; 100**	1[b]	NR	NR	NR
Incidental Inhalation-Powder	1; 21[b]	0.001 – 0.003[c]	1[b]	NR	NR	NR
Dermal Contact	109	0.000046; 100**	4	NR	1	NR
Deodorant (underarm)	5[a]	0.000046 – 0.0021	NR	NR	NR	NR
Hair - Non-Coloring	22	0.004	NR	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	19	0.001	3	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
**Essential oil: diluted for use; a few drops used per tsp of carrier oil
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – not reported

Table 7. Ingredients not reported to be in use according to 2022 FDA VCRP and 2020 concentration of use data[31,32]

Zingiber Officinale (Ginger) Leaf Cell Extract
Zingiber Officinale (Ginger) Root
Zingiber Officinale (Ginger) Root Juice

Table 8. Dermal irritation and sensitization studies

Ingredient	Test Article	Dose/Concentration	Test Population	Procedure	Results	Reference
IRRITATION						
In Vitro						
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	100	3 tissue inserts	EpiDermTM assay; reconstructed human epidermis; tissue inserts incubated for 60 min	Non-irritating	[61]
Zingiber Officinale (Ginger) Extract*	*Zingiber officinale* (ginger) extract*	NR	3 tissue inserts	OECD TG 439; reconstructed human epidermis	Non-irritating	[2]
Animal						
Zingiber Officinale (Ginger) Extract	*Zingiber officinale* (ginger) extract (dried)	0.5 ml; concentration not reported	6 New Zealand white rabbits	The test substance was applied to intact and abraded skin (level of occlusion not reported), and kept in place for 24 h	Non-irritating; PII = 0	[39]
Human						
Zingiber Officinale (Ginger) Root Extract	Product containing 0.0995% Zingiber Officinale (Ginger) Root Extract	0.02 ml; 100%	10 subjects	48-h application; occlusive conditions; evaluations made 30 min after patch removal	Non-irritating	[62]
SENSITIZATION						
In Vitro						
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	0.00098 - 2 mM	HaCaT cells	KeratinoSens^{TM} ARE-Nrf2 luciferase test; OECD TG 442D	Non-sensitizing; IC_{50} > 1000 µm	[63]
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	100 mM	cysteine- and lysine-containing peptides (3 replicates)	DPRA; OECD TG 442C	Non-sensitizing; mean percent depletion of 1.89% (minimal reactivity)	[64]
Zingiber Officinale (Ginger) Extract*	*Zingiber officinale* (ginger) extract*	100%	cysteine- and lysine-containing peptides (3 replicates)	DPRA; OECD TG 442C	Sensitizing; mean percent depletion pf 27.81% (moderate reactivity)	[2]
Human						
Zingiber Officinale (Ginger) Rhizome Extract	Moisturizer containing 0.1% Zingiber Officinale (Ginger) Rhizome Extract	concentration and application area not reported; 0.1 – 0.15 g	54 subjects	HRIPT; occlusive conditions; test article was volatized for 30-90 min prior to application	Non-sensitizing	[67]
Zingiber Officinale (Ginger) Root Extract	Serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract	100%; dose and application area not reported	104 subjects	HRIPT; occlusive conditions	Non-irritating and Non-sensitizing	[65]
Zingiber Officinale (Ginger) Root Extract	Product containing 0.2% Zingiber Officinale (Ginger) Root Extract	100%; 2 cm x 2 cm application area	53 subjects	HRIPT; semi-occlusive conditions	Non-irritating and Non-sensitizing	[66]

*potential inference source for one or more ginger-derived ingredients

DPRA = direct peptide reactivity assay; HaCaT = immortalized human keratinocytes; HRIPT = human repeat insult patch test; IC_{50} = half-maximal inhibitory concentration; OECD TG = Organisation for Economic Cooperation and Development test guidelines; PII = primary irritation index

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