Safety Assessment of *Rosa damascena*-Derived Ingredients as Used in Cosmetics

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ABBREVIATIONS

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Cyt B	cytochalasin B
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMEM	Dulbecco's modified Eagle's medium
DMSO	dimethyl sulfoxide
EC	maximal effective concentration
ECHA	European Chemicals Agency
FBS	fetal bovine serum
FDA	Food and Drug Administration
GAE	gallic acid equivalents
GC-MS	gas chromatography – mass spectroscopy
GRAS	generally recognized as safe
HCA	hydroxycitric acid
h-CLAT	human cell line activation test assay
HeLa	human cervical cancer cell line
HDL	high-density lipoprotein
HRIPT	human repeat insult patch test
IFRA	International Fragrance Association
LD	lethal dose
LDL	low-density lipoprotein
MIT	minimum induction threshold
MMC	mitomycin C
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
N/A	not applicable
NR	not reported/none reported
NS	not specified
OECD	Organisation for Economic Co-operation and Development
OTC	over-the-counter
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PHA	phytohemagglutinin
RIFM	Research Institute for Fragrance Materials
RPMI	Roswell Park Memorial Institute
SCCS	Scientific Committee on Consumer Safety
SLS	sodium lauryl sulfate
TG	test guideline
TG	triglyceride
THP-1	human monocytic leukemia cell lines
TNBS	trinitrobenzenesulfonic acid
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 10 *Rosa damascena*- derived ingredients as used in cosmetic formulations, which are reported to function in cosmetics mostly as skin conditioning agents and fragrance ingredients. Because final product formulations may contain multiple botanicals, each containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. With *Rosa damascena* – derived ingredients, the Panel was concerned about the presence of benzyl alcohol, eugenol, methyl eugenol, geraniol, citronellol, limonene, linalool, and farnesol as potential allergens in cosmetics. Industry should use good manufacturing practices to minimize impurities that could be present in botanical ingredients. The Panel considered all the data and concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing.

INTRODUCTION

This assessment reviews the safety for the following 10 *Rosa damascena*-derived ingredients, as used in cosmetic formulations:

Hydrolyzed Rosa Damascena Flower Extract
Rosa Damascena Bud Extract
Rosa Damascena Extract
Rosa Damascena Flower
Rosa Damascena Flower Extract
Rosa Damascena Flower Oil
Rosa Damascena Flower Powder
Rosa Damascena Flower Water
Rosa Damascena Flower Water Extract
Rosa Damascena Flower Wax

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), some *Rosa damascena*-derived ingredients are reported to function as skin conditioning agents and fragrance ingredients in cosmetic products (Table 1).[1] Additionally, these ingredients are sometimes reported to function as antioxidants and cosmetic astringents. Common names for *Rosa damascena* include damask rose, pink rose, Turkish rose, and Bulgarian rose.[2]

The Expert Panel for Cosmetic Ingredient Safety (Panel) does not review ingredients that function only as fragrance ingredients because, as fragrances, the safety of these ingredients is evaluated by the Research Institute for Fragrance Materials (RIFM). Rosa Damascena Extract, Rosa Damascena Flower Extract, Rosa Damascena Flower Powder, and Rosa Damascena Flower Wax are reported to function only as fragrance ingredients, according to the wINCI *Dictionary*. However, according to personal communications with RIFM in May-June 2020, these ingredients are not currently scheduled for review by RIFM; thus, the Panel is reviewing the safety of these 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.

Botanicals, such as *Rosa damascena*-derived ingredients, often contain hundreds of constituents, some of which have the potential to cause adverse effects. For example, geraniol, citronellol, and linalool are known potential dermal sensitizers. In this assessment, the Panel is evaluating the potential toxicity of each of these *Rosa damascena* – derived ingredients as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical ingredients.

Also, with botanicals, it is often not known how the substance being tested in a study compares to the cosmetic ingredient. In the report text, if it is known that the material being tested is a cosmetic ingredient, the INCI naming convention is used (i.e., the names of cosmetic ingredients are capitalized, without italics (e.g., Rosa Damascena Extract)). If it is not known that the test substance is the same as the cosmetic ingredient, the taxonomic naming conventions (i.e. with genus and species name italicized (e.g., a *Rosa damascena* extract)) is used.

CHEMISTRY

Definition and Plant Identification

Definitions of the 10 *Rosa damascena*-derived ingredients reviewed in this safety assessment are presented in Table 1.[1] Generically, the bud is defined as a not yet developed shoot in the axil of a leaf, often covered with scales, or a young flower that has not bloomed. The flower is defined as the reproductive shoot in flowering plants, usually with sepals, petals, stamens, and pistil(s).

Rosa damascena is an ornamental, old garden rose hybrid, belonging to the Rosaceae family, with more than 200 species and 18,000 cultivars around the world.[3] Thought to originate in the Mediterranean or Asia, *Rosa damascena* is mainly grown in Turkey, Bulgaria, Morocco, Iran, Egypt, France, China, and India, with Turkey and Bulgaria reported to be the largest producers.[2] Commonly known as the damask rose, *Rosa damascena* is one of the few rose species which possesses the

characteristic rose fragrance, owing to its highly valuable aromatic oil.[2] The total world production of *Rosa damascena* oil and *Rosa damascena* concrete (flower wax) is estimated to be 15 - 20 tons.

Rosa damascena is a thorny shrub, up to 2.5 m in height, that blooms in the spring.[4] The stem has numerous stout and hooked prickles, occasionally mixed with glandular bristles, while the leaves are pinnate and compound with 5 - 7 leaflets that are 2.5 - 6.3 cm long, ovate-oblong, and have serrated edges.[5] Flowers have an average of 33 petals, which are arranged in a corymb, and can range in color from white to light red; most *Rosa damascena* flowers are light pink or magenta in hue.[4,5]

Chemical Properties

A summary of chemical properties described for *Rosa damascena*-derived ingredients are provided in Table 2.

Rosa Damascena Flower Oil and Rosa Damascena Flower Water

A supplier described a trade mixture, comprising 0.1 - 1 % Rosa Damascena Flower Oil and 0.1 - 1% Rosa Damascena Flower Water formulated in pentylene glycol, as a transparent, colorless liquid with a characteristic odor.[6] At 20 °C, the refractive index of this trade mixture is 1.434 - 1.444.

Method of Manufacture

Most of the methods below are general to the processing of *Rosa damascena*-derived materials, and it is unknown if these 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.[1]

Rosa Damascena Bud Extract

In a method of preparing a *Rosa damascena* bud extract, 1700 g of air-dried, whole buds of *Rosa damascena* were coarsely powdered and extracted with distilled water at 100 °C for 2 h.[7] Upon removal of the water under vacuum, 720 g of a *Rosa damascena* bud extract were obtained, suspended in distilled water, and sequentially partitioned with n-hexane, chloroform, ethyl acetate, and n-butanol to create multiple fractions.

Rosa Damascena Flower Extract

In a pharmacological analysis of *Rosa damascena* petals, 100 g of dried *Rosa damascena* flower powder was passed through a sieve and macerated, separately, with water, ethanol, chloroform, ethyl acetate, and petroleum ether for 7 d, with occasional agitation.[8] The extracts were filtered through muslin cloth, and the filtrates were evaporated under reduced pressure, vacuum dried, and stored.

Rosa Damascena Flower Oil

A large quantity of *Rosa damascena* flowers yields a relatively small amount of a *Rosa damascena* flower oil (e.g., 4000 kg of flowers yields 1 kg of oil).[9] Optimal yield and higher quality *Rosa damascena* flower oil is produced from roses freshly picked in either the early morning hours or colder temperatures, compared to roses subject to heat or fermentation, due to minimal evaporation.[2,10]

A *Rosa damascena* flower oil has been manufactured traditionally for centuries, using copper stills, loosely connected to a condensing apparatus.[11] In the present-day, a *Rosa damascena* flower oil is often produced industrially in well-sealed, steel stills, producing oils with a richer constituent profile, which are of higher quality.[12]

Rosa Damascena Flower Oil and Rosa Damascena Flower Water

A *Rosa damascena* flower water is often a by-product of the hydrodistillation process to produce a *Rosa damascena* flower oil.[2] Both fresh and dried *Rosa damascena* flowers can be utilized in the manufacture of a *Rosa damascena* flower oil and water.[13,14] In a study using fresh *Rosa damascena* flowers, 400 g of fresh flower petals were hydrodistilled with 2 l of water for 4 h in a Clevenger apparatus, to yield 800 ml of a *Rosa damascena* flower water.[13] In a study using shade-dried *Rosa damascena* petals, 60 g of rose petals (with 79.3% moisture removed) were hydrodistilled with 1.5 l of water for 4 h to prepare 800 ml of a *Rosa damascena* flower water.[14]

Rosa damascena flower oil, and consequently *Rosa damascena* flower water, are often produced by the hydrodistillation of *Rosa damascena* flowers in a Clevenger apparatus, or via an analogous steam distillation procedure.[14] In a method of preparing a *Rosa damascena* flower oil, a cauldron was filled with 200 kg of fresh *Rosa damascena* flowers and water, and boiled for approximately an hour.[9] After boiling, steam transported through an attached condensing pipe to a refrigerator yielded a distillation product of a *Rosa damascena* flower water. This *Rosa damascena* flower water moved from the first Floridian container, where a very small quantity of oil (~15%) was segregated, and the water was boiled for about 2.5 h, twice, before condensing in a separate refrigerated pipe, where it passed through a second Floridian container, and separated from the remaining oil. After repeated distillations, rose oil from both Floridian containers was combined and passed through a clean filter; a final yield of 50 - 60 g of a *Rosa damascena* flower oil was obtained.

Rosa Damascena Flower Powder

Rosa damascena flower petals were separated from the sepals and shade-dried.[8] The dried petals were then ground into a fine powder, resulting in a *Rosa damascena* flower powder.

Rosa Damascena Flower Water

A supplier has reported that Rosa Damascena Flower Water is also produced from dried raw material.[15] The water phase of dried *Rosa damascena* flowers processed via steam distillation is further concentrated and added to a 80%, 1,3-butylene glycolic solution.

Rosa Damascena Flower Water Extract

Fresh *Rosa damascena* flowers (2.0 kg) were soaked in 12.5 l water overnight to yield 1.0 l of a *Rosa damascena* flower water.[16] Well-stirred *Rosa damascena* flower water (500 ml) was extracted with dichloromethane (250 ml x 5) and dried over fused calcium chloride/anhydrous sodium sulfate. After the solvent was removed by distillation, a *Rosa damascena* flower water extract (dichloromethane) was stored at -5 °C.

Rosa Damascena Flower Wax

Volatile, hydrocarbon solvents, such as ethyl alcohol, hexane, petroleum ether, and benzene, are often used to extract *Rosa damascena* absolute and concrete, a semisolid, waxy substance from *Rosa damascena* flowers.[11,17] During the industrial production of this *Rosa damascena* flower wax, 600 - 750 kg of *Rosa damascena* flowers were added to a 3000 l extraction vessel, filled half-way with n-hexane, and extracted in two cycles for 20 min at 60 - 65 °C.[17] The resulting extracts were combined in an evaporator, and traces of the solvent were removed in a vacuum evaporator, to yield > 1 kg of a *Rosa damascena* flower wax.

Composition and Impurities

Solid residues, containing mainly straight-chain saturated hydrocarbons and the esters of carboxylic acids, were identified in a gas chromatography-mass spectrometry (GC-MS) analysis of *Rosa damascena* flower extracts (absolute), produced from a *Rosa damascena* flower wax (concrete).[18]

Of the 26 fragrance allergens defined by the European Union Cosmetic Directive, benzyl alcohol, eugenol, geraniol, citronellol, limonene, linalool, and farnesol are present in *Rosa damascena*-derived ingredients.[2,13,14,16,17,19-22] The components identified in *Rosa damascena*-derived ingredients can vary greatly, depending upon extraction solvent and method,[14] part of the plant,[7] or growth and harvest conditions.[23,24] A percent-composition profile of constituents found in a *Rosa damascena* flower oil, a flower water, a flower water extract, and a flower wax, produced from dried and fresh flowers, is presented in Table 3.

Rosa Damascena Bud Extract

A *Rosa damascena* bud extract (720 g), obtained via hydrodistillation, was used to create concentrated fractions with n-hexane (0.5 g), chloroform (2.8 g), ethyl acetate (124.7 g), n-butanol (274.4 g), and water (317.6 g).[7] Repeated silica gel, octadecyl silane, and Sephadex LH-20 column chromatography of the ethyl acetate fraction yielded five main flavonoids, including: isoquercitrin, afzelin, cyanidin-3-*O*-β-glucoside, quercetin gentiobioside, and kaempferol-3-*O*-β-D-glucopyranosyl(1→4)-β-D-xylopyranoside.

Rosa Damascena Extract

Flavonoids, such as kaempferol, quercetin, and pectolinargenin, were identified as the major components in hydroalcoholic, ethyl acetate: ethanol, and ether extracts of dried and powdered *Rosa damascena* flowers.[25]

In an compositional analysis of *Rosa damascena* fruit extracts, a 5 g sample of *Rosa damascena* fruit yielded 332 mg/100 g ascorbic acid, while a 2 g sample of *Rosa damascena* fruit yielded 7.10 µg/g α- tocopherol, and 3.70 µg/g β- carotene.[26] The fatty acid content was determined to be 93.18% in *Rosa damascena* fruit seed oil.

Rosa Damascena Flower

In a reversed phase high performance liquid chromatography test of fresh *Rosa damascena* flowers, the following components were identified, in µg/ml: gallic acid (125.41), rutin (84.98), quercitrin (360.87), myricetin (170.43), quercetin (81.35), and kaempferol (2.36).[27] Trace amounts of catechin were also identified.

Rosa Damascena Flower Extract

The total phenolic content of fresh and spent *Rosa damascena* flowers, used in the hydrodistillation process, was measured in gallic acid equivalents (GAE/g).[28] The GAE of these *Rosa damascena* flowers, extracted with methanol, were measured at 276.02 ± 2.93 mg GAE for fresh flowers, and 248.97 ± 2.96 mg GAE, for spent flowers. A *Rosa damascena* extract, produced from rose blossoms spent in the hydrodistillation process, produced sufficient amounts of citronellol, nerol, geraniol, and β-phenethyl alcohol, suggesting the utility of rose waste in obtaining valuable extracts.[18]

According to International Fragrance Research Association (IFRA) standards, typical concentrations of components found in *Rosa damascena* absolute can comprise 0.1% benzyl alcohol, 0.5% methyl eugenol, 2.3% eugenol, 5% geraniol, and 6% citronellol.[29-33]

Rosa Damascena Flower Oil

Rosa damascena flower oil is characterized by high percentages of monoterpene alcohols, including citronellol (35.1%), geraniol (17.9%), nerol (8.4%), phenethyl alcohol (2.5%), and linalool (1%).[2] Additionally, various hydrocarbons, oxides, ethers, esters, aldehydes, and phenols are found in *Rosa damascena* flower oil. Citronellol is the major component which determines rose oil quality. Methyl eugenol levels may be over 2.5%, especially in the oils distilled from rose flowers subject to excess or long-term fermentation.[2]

According to IFRA standards, *Rosa damascena* oil is reported to contain 0.02% benzyl alcohol, 1% farnesol, 1.2% eugenol, 2% methyl eugenol, 20% geraniol, and 34% citronellol.[29-34]

Rosa Damascena Flower Oil and Rosa Damascena Flower Water

Specifications provided by a supplier indicate that a trade mixture containing 0.1 - 1% Rosa Damascena Flower Oil and 0.1 - 1% Rosa Damascena Flower Water, formulated in pentylene glycol, should contain 0.15 – 0.35 % phenethyl alcohol and < 10 ppm methyl eugenol.[35] In this trade mixture, most of the 26 allergens defined by the European Union Cosmetic Directive are below the level of detection (< 1ppm), with the following exceptions: benzyl alcohol (41 ppm), citral (16 ppm), citronellol (1080 ppm), farnesol (6 ppm), geraniol (365 ppm), and linalool (33 ppm).[36]

This supplier measured the mean concentration of several constituents in the *Rosa damascena* fraction mixture, using 3 batches of the same trade mixture.[37] It was determined that the *Rosa damascena* fraction mixture could contain 1 ppm of benzaldehyde, 2 ppm of pinene, 36 ppm of isobutenyl methyltetrahydropyran, 40 ppm of terpineols, 48 ppm of β-caryo-phyllene, 50 ppm of citronellal, 150 ppm of 1-nonadecene, 350 ppm of nonadecane, and 400 ppm of nerol.

Rosa Damascena Flower Water

Due to an increased solubility in water, phenethyl alcohol is the major component collected in a *Rosa damascena* flower water, during the hydrodistillation of roses to produce *Rosa damascena* flower oil.[2] In a GC-MS analysis of *Rosa damascena* flower water samples, phenethyl alcohol was present at up to 39.53%, geraniol at up to 24.01%, and β-citronellol at up to 10.26%.[20]

Methanol and ethanol, produced via plant fiber fermentation, were measured in 90 commercial herbal distillates, including 9 *Rosa damascena* water samples, by GC-MS.[38] The methanol content in *Rosa damascena* flower water samples was 9.04 mg/dl. Two *Rosa damascena* flower water samples were found to have the highest average ethanol content (56.77 mg/dl and 38.97 mg/dl).

A supplier reported that Rosa Damascena Flower Water, formulated in a trade mixture with butylene glycol, contained no more than 20 ppm heavy metals and 2 ppm arsenic.[15] No further details were provided.

Rosa Damascena Flower Water Extract

Dichloromethane extracts of a *Rosa damascena* flower water produced from fresh flowers contained up to 50% more *Rosa damascena* flower oil than flower water produced from dried flowers.[16] These fresh flower dichloromethane extracts also contained mostly phenethyl alcohol (69.7 - 81.6%), linalool (1.5 - 3.3%), citronellol (1.8 - 7.2%), nerol (0.2 - 4.2%), and geraniol (0.9 - 7.0%).

Rosa Damascena Flower Wax

Phenethyl alcohol is present at over 50% in a *Rosa damascena* flower wax.[2] Although citronellol, geraniol, and nerol contents are relatively lower, the phenethyl alcohol content is higher in a *Rosa damascena* flower wax than in a *Rosa damascena* flower oil. As per IFRA standards, typical concentrations of components found in *Rosa damascena* concrete can comprise 0.5% methyl eugenol, 1% eugenol, 2.7% geraniol, and 4.7% citronellol.[30-33]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. The cosmetic product categories named in the VCRP database indicate the intended uses of cosmetic ingredients, and are identified in 21 CFR Part 720. Data are submitted by the cosmetic industry in response to a survey conducted by the Personal Care Products Council (Council) of maximum reported use concentrations, also by product category. Neither the categories provided by the VCRP, nor those provided by the Council survey, include a designation for use via airbrush application. Airbrush devices, alone, are within the purview of the US

Consumer Product Safety Commission (CPSC), while ingredients used in airbrush devices are within the jurisdiction of the FDA. As airbrush technology use for cosmetics has neither been evaluated by the CPSC, nor the use of cosmetic ingredients in airbrush technology by the FDA, no US regulatory authority has evaluated the safety of this delivery methodology for cosmetic ingredients. Moreover, no consumer habits and practices data are available to evaluate the risks associated with this use type.

According to 2022 VCRP survey data, Rosa Damascena Flower Water is reported to be used in 302 formulations, Rosa Damascena Flower Extract is reported to be used in 293 formulations, and Rosa Damascena Flower Oil is reported to be used in 229 formulations (Table 4).[39] Rosa Damascena Flower Oil is reported to be used at up to 10.8% in other skincare preparations, and according to a manufacturer, is sold with instructions to dilute the product before use, hence, resulting in much lower use concentrations when applied.[40,41] Otherwise, the highest reported leave-on use concentration for Rosa Damascena Flower Oil is at up to 0.16% in non-spray face and neck products. Results from the concentration of use surveys, conducted in 2019 by the Council, indicate that the highest reported leave-on, use concentration for Rosa Damascena Flower Water is at up to 1.9% in foundations. Hydrolyzed Rosa Damascena Flower Extract and Rosa Damascena Bud Extract are not in reported to be in use, according to the VCRP and industry survey.

These ingredients have been reported to be used in products that may lead to incidental ingestion and exposure to mucous membranes, such as in lipstick; for example, Rosa Damascena Flower Oil and Rosa Damascena Flower Wax are reported to be used at up to 0.01% and 1.1% in lipsticks, respectively. Additionally, some of these ingredients are reported to be used in products applied near the eye (e.g., up to 0.13% Rosa Damascena Flower Wax in eyeliners).

Several of these ingredients are used in cosmetic products that could possibly be inhaled; for example, Rosa Damascena Flower Oil is reported to be used at up to 0.0003% in aerosol hair spray, Rosa Damascena Extract is reported to be used at up to 0.00007% in aerosol spray deodorant formulations, and Rosa Damascena Flower Extract is reported to be used in face powder formulations (concentration of use 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. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. 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.

Additionally, although products containing some of these ingredients may be marketed for use with airbrush technology, 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 related to this use technology), the data are insufficient to evaluate the safety thereof in airbrush applications.

The *Rosa damascena*-derived ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[42] However, according to Regulation EC No 1223/2009, restrictions for methyl eugenol, a minor component of *Rosa damascena*, include a maximum concentration of 0.0002% in other leave-on and oral products that are ready for use, 0.001% in rinse-off products, 0.002% in fragrance cream, 0.004% in eau de toilette products, and 0.01% in fine fragrances.[43] Additionally, the same regulation states that citronellol, eugenol, farnesol, geraniol, limonene, and linalool (fragrance allergens) are required to be included in cosmetic labelling when use concentrations for these individual constituents in a formulation exceed 0.001% for leave-on products, 0.01% for rinse-off products.

Non-Cosmetic

According to the US FDA, the essential oils, oleoresins (solvent-free), and natural extractives/distillates of *Rosa damascena* rose absolute, rose otto, rose buds, rose flowers, and rose fruit are generally recognized as safe (GRAS) for their intended use in foods [21CFR182.20].

Traditionally, *Rosa damascena* flowers and derived products have a wide range of uses in religious ceremonies, pharmaceuticals, and food, especially in the Middle East and Southeast Asia.[4,14,20] Dried *Rosa damascena* flower petals and flower water are added to flavor and embellish food, and are consumed in Iran as a digestive aide.[4,14] In traditional medicine, *Rosa damascena* flower oil and flower water are considered to possess antibacterial, analgesic, antioxidant, and anti-inflammatory properties.[44] Consequently, these ingredients have been used in aromatherapy,[45,46] and for the treatment of many conditions, including skin, eye, and oral ailments,[44] arthritis,[47] dysmennorhea,[48] pediatric seizures,[49] depression, and cognitive decline.[50]

TOXICOKINETIC STUDIES

No relevant toxicokinetic studies on *Rosa damascena*-derived ingredients were found in the published literature, and unpublished data were not submitted. In general, toxicokinetic data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute dermal and oral toxicity studies summarized below are described in Table 5.

The acute dermal LD_{50} of *Rosa damascena* flower oil was determined to be > 2500 mg/kg in rabbits.[51-53] No toxic effects were observed and the acute oral LD_{50} of a *Rosa damascena* flower extract, prepared in 0.7% carboxymethylcellulose, was > 2000 mg/kg in male and female Swiss albino mice.[54] In one study, the acute oral LD_{50} of *Rosa damascena* flower oil was determined to be > 5000 mg/kg in rats.[51-53] In subsequent oral toxicity studies, the acute oral LD_{50} of *Rosa damascena* flower oil was determined to be 5525 mg/kg in male rats, and 2975 mg/kg and 3972 mg/kg, in mature and immature female rats, respectively.[52] Swiss albino mice dosed orally with up to 6000 mg/kg of a *Rosa damascena* flower water extract did not die during the 24-h post-treatment observation period, and the acute LD_{50} was determined to be > 6000 mg/kg.[55]

Short-Term and Subchronic Toxicity Studies

Details of the short-term and subchronic oral toxicity studies summarized below are provided in Table 6.

Groups of 10 Wistar rats were administered 0, 2.5, 5, 25, or 50 mg/kg/d aqueous *Rosa damascena* flower extract, via gavage, for 30 d.[56] Body weight gain was greater in all test groups compared to controls, but the percent weight gains were not statistically significant. Blood samples were collected on days 0 and 30 to assess hematological parameters and biochemical changes; increased triglyceride (TG) levels were statistically significant in only the 50 mg/kg/d group, while the cholesterol/high-density lipoprotein (HDL) ratio and low-density lipoprotein (LDL)/HDL ratios were significantly decreased in the 2.5, 5, and 25 mg/kg/d groups. A methanolic, *Rosa damascena* flower extract was administered at 1.5 g, via diet, to rabbits (number not specified) for 45 d.[57] TG levels were significantly higher than controls at the end of the experiment; no other significant differences in lipid profiles, pulse, or cardiac indices were observed. Groups of 5 dogs were administered distilled water or lactulose (controls), or, 90, 180, 360, 720, or 1440 mg/kg/d aqueous *Rosa damascena* flower extract, in the diet, for 10 d.[58] No significant differences were observed between groups for respiration, temperature, or cardiac response. A dose-dependent increase of diarrhea was observed, starting with the lowest dose of 90 mg/kg/d. Animals in the 720 and 1440 mg/kg/d groups exhibited slight weight loss after day 7, which was attributed to possible diarrhea-induced malabsorption, or dehydration. In another study, groups of 5 dogs were administered distilled water or lactulose (controls), or, 90, 180, 360, 720, or 1440 mg/kg/d aqueous *Rosa damascena* flower extract, in food, for 10 d.[59] Except for a significant increase in bilirubin levels on day 3 and alanine aminotransferase on day 10 in animals in the 1440 mg/kg bw/d group, there were no statistically significant differences from controls. Groups of 10 male albino rabbits were orally dosed with 250 or 500 mg/kg bw/d *Rosa damascena* flower water for 60 d.[60] No significant differences were observed between hemoglobin, white blood cells, red blood cells, and platelets after 30 and 60 days of dosing. A significant increase in the red blood cell and platelet count was observed for both doses at day 60, compared to 30. Fifteen Swiss albino mice (compared to 10 controls) were orally administered 300 mg/kg/d *Rosa damascena* flower water extract for 28 d.[55] No significant differences from controls in body or organ (liver, intestine, heart, lungs, kidneys and spleen) weights, tissue, mortality, or hematological biomarkers were observed upon sacrifice. Groups of 25 Swiss albino mice were orally dosed with 0 or 300 mg/kg/d *Rosa damascena* flower water extract for 90 d.[55] Two control and 2 treated mice died in the first month, one control mouse and 2 treated mice died in the second month, and no mortality occurred in the third month of observation. Mice killed after the first, second, and third month (number not specified), progressively exhibited mild hydropic degeneration in the liver, congestion in coronary blood vessels, and peribronchiolar aggregation of round cells in the lungs. No significant differences were observed in body and organ weights, and various hematological markers, compared to the control group.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

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

GENOTOXICITY

In Vitro

Rosa Damascena Flower Oil

In a micronucleus assay, concentrations of 1, 10, 50, 100, 150, or 200 µg/ml *Rosa damascena* flower oil were added to whole blood samples treated with Roswell Park Memorial Institute (RPMI) culture medium supplemented with fetal bovine serum (FBS) containing L-glutamine, antibiotics, and phytohemagglutinin (PHA).[61] Cytochalasin B (Cyt B) was added at a concentration of 6 µg/ml 44 h after PHA stimulation. The frequency of micronuclei in binucleated lymphocytes was significantly greater ($p < 0.05$) in samples treated with > 50 µg/ml *Rosa damascena* flower oil, compared to negative and 1% dimethyl sulfoxide (DMSO)-treated controls.

No inhibition of mitotic activity was observed when a *Rosa damascena* flower oil (absolute) and a *Rosa damascena* flower oil (extracted from fresh flowers) were tested on cultures of normal human blood lymphocytes at concentrations of 10

µg/ml.[62] *Rosa damascena* flower absolute oil showed significant antimutagenic activity ($p < 0.001$) when added at a concentration of 10 µg/ml to a blood lymphocyte culture treated with 300 ng/ml mitomycin C (MMC).

Rosa Damascena Flower Oil and Rosa Damascena Flower Water

A trade mixture of 0.1 - 1% Rosa Damascena Flower Oil and 0.1 - 1% Rosa Damascena Flower Water, in pentylene glycol, was tested in an Ames test using *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1537, at up to 5000 µg/plate, with and without metabolic activation.[63] No signs of precipitate or dose responses were found at any concentration. The test material was not deemed genotoxic.

CARCINOGENICITY STUDIES

Carcinogenicity studies on the *Rosa damascena* - derived ingredients were not found in the published literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Cytotoxicity

Rosa Damascena Flower Extract

A methanolic extract of dried *Rosa damascena* flowers was used in an 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay to evaluate in vitro activity against human cervical cancer (HeLa) and African green monkey kidney epithelial (Vero) cell lines.[64] Studies examining the effect of increasing doses of the extract upon cytotoxicity exhibited IC_{50} values at 265 µg/ml and > 1000 µg/ml *Rosa damascena* flower extract on the HeLa and Vero cells, respectively. Additionally, a selectivity index (SI), of > 3.8 for the *Rosa damascena* flower extract indicated minimal concerns for concurrent cytotoxic effects in normal cells.

Rosa Damascena Flower Oil and Rosa Damascena Flower Water

The cytotoxicity of a trade mixture of 0.1 - 1.0% Rosa Damascena Flower Water and 0.1 - 1.0% Rosa Damascena Flower Oil formulated in pentylene glycol was estimated by measuring the intake of neutral red dye by murine fibroblast cells treated with either 1.4 - 50 mg/ml of the test article or 10 - 100 µg/ml sodium lauryl sulfate (SLS), for 48 h, in an vitro cytotoxicity assay, in accordance with the Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 129.[63] A mean IC_{50} value of 6.68 mg/ml was determined.

In Vitro Cell Transformation

Rosa Damascena Flower Oil

Human colon carcinoma SW742 cell lines and human fibroblast cell lines were prepared for an MTT assay with RPMI-1640 medium, combined with FBS (10% v/v), streptomycin (100 µg/ml), and penicillin (100 µg/ml).[65] Doses of 0, 1, 2, 3, 4, 5, or 10 µl of a *Rosa damascena* flower oil were introduced, in triplicate, to cells for 48 h. Outer and inner controls were used, in which cells not exposed to the flower oil were cultured in separate, or the same, dishes as cell lines treated with flower oil. Both morphology and cell survival rates of cancer and fibroblast cells were affected by *Rosa damascena* flower oil exposure. The evaporated (non-soluble) phase of the oil was shown to have an inhibitory effect on cell growth, especially in the inner controls, while the water-soluble phase of the oil significantly increased cell growth by nine-fold, compared to the inner controls. Both SW742 cells and fibroblasts showed cell growth induction when exposed to 10 µl of *Rosa damascena* flower oil, while at lower concentrations a potent induction effect was only seen in fibroblasts.

DERMAL IRRITATION AND SENSITIZATION

The dermal irritation and sensitization studies summarized below are described in Table 7.

In an in vitro study, 30 µl of a trade mixture containing 0.1 - 1% Rosa Damascena Flower Oil and 0.1 - 1% Rosa Damascena Flower Water, in pentylene glycol, was predicted to be non-irritating and non-sensitizing when applied neat to an EpiSkin™ model.[63] Human monocytic leukemia cell lines (THP-1) exposed to up to 5000 µg/ml of the same trade mixture, undiluted, in a human cell line activation test (h-CLAT) in vitro assay were considered to be sensitized (minimum induction threshold of 923 µg/ml).[63] The trade mixture of 0.1 - 1% Rosa Damascena Flower Oil and 0.1 - 1% Rosa Damascena Flower Water was not considered sensitizing when evaluated in a luciferase assay (KeratinoSens™ model), undiluted, at up to 400 µg/ml.[63]

Undiluted *Rosa damascena* flower oil was not irritating to the skin of mice and pigs, but was moderately irritating when applied to the intact or abraded skin of rabbits for 24 h; no further details were provided.[51,53] A trade mixture of 0.1-1% Rosa Damascena Flower Oil and 0.1-1% Rosa Flower Water, in pentylene glycol, was not irritating when applied as a single, semi-occlusive application of 160 µl, at a concentration of 20% in distilled water, to 11 subjects.[63] *Rosa damascena* flower oil, 2% in petrolatum, was not irritating in a single, occlusive, 48-h patch test (number of subjects not specified) and was also not sensitizing in a maximization test using 25 subjects (additional details not provided).[51,53] Two fragrance products, one

containing 0.7794% Rosa Damascena Flower Extract and one containing 0.1068% Rosa Damascena Flower Water, both in 100 subjects, and one mask formulation containing 0.1260% Rosa Damascena Flower Oil, in 107 subjects, were not sensitizing in 3 separate HRIPTs.[66-68]

Photosensitization/Phototoxicity

In Vitro

Rosa Damascena Flower Oil and Rosa Damascena Flower Water

In an ultraviolet-visible spectrophotometric analysis of a trade mixture of 0.1 - 1% Rosa Damascena Flower Oil and 0.1 - 1% Rosa Damascena Flower Water, formulated in pentylene glycol, diluted to 10% in water, a very low UV absorption was observed between 290 - 400 nm.[63] The test article was not considered to have phototoxic potential.

Animal

Rosa Damascena Flower Oil

No phototoxic effects were reported when undiluted *Rosa damascena* flower oil was applied on hairless mice and swine.[51,53] No further details were provided.

OCULAR IRRITATION STUDIES

In Vitro

Rosa Damascena Flower Oil and Rosa Damascena Flower Water

The potential of a trade mixture comprising 0.1 - 1.0% Rosa Damascena Flower Oil and 0.1 - 1.0% Rosa Damascena Flower Water formulated in pentylene glycol to cause ocular irritation was investigated in a neutral red release assay.[63] Rabbit cornea fibroblast cells (SIRC cell line) were preloaded with neutral red dye (amount not specified) for 3 h at 37 °C. The dyed cells were then treated with either 500 µl of the test article diluted at 0, 25, or 50% (in water), sodium dodecyl sulfate diluted at 0.2%, 0.05%, or 0.01% in saline solution (positive control), or saline solution (negative control), for 60 s. Upon removal of the test article and controls, the amount of dye, released solely by surviving cells, was measured at an optical density of 540 nm. The resulting cell death percentages were plotted against the corresponding test article concentrations to determine IC_{50} values. Under these experimental conditions, the trade mixture exhibited negligible cytotoxicity (≤ 20% cell death at 50% dilution), with the positive controls producing expected results. The test article was not considered an ocular irritant.

CLINICAL STUDIES

Dermatological Patch Test Studies

Rosa Damascena Flower Oil

Patients in Japan (n= 1483), suspected of having contact dermatitis, were enrolled in an 8-yr study (1990-1998), in which they were annually patch tested with a series of essential oils.[69] A *Rosa damascena* flower oil (2% pet.) was one of the 10 fragrance oils applied on the upper back of patients, in a 2-d closed patch test, using Finn Chambers and Scanpor tape. Readings were taken at 1 h and 1 d after removal, according to International Contact Dermatitis Group recommendations. The average patch test positivity rate for this *Rosa damascena* flower oil, over 8 yr, was 0.4%.

Case Reports

A 48-yr old woman with a history of allergy to imitation jewelry reported experiencing an intense scalp itch in response to a hair dye application.[70] The subject was treated with oral antihistamines and topical corticosteroids, and symptoms resolved within 2 d. Three months later, itching and erythema occurred at sites which came in contact with a cologne containing *Rosa damascena* flower oil; itchy papules appeared as much on untouched areas as on those in contact with the cologne. Standard and additional patch tests (Chemotechnique fragrance series), scored on day 2 and day 4, revealed a + reaction to the fragrance mix at 8% in petrolatum, a ++reaction to nickel sulfate at 5% in petrolatum and to *Rosa damascena flower* oil at 2% in petrolatum, and a +++ reaction to geraniol at 2% in petrolatum. Since this was the first patient with suspected contact dermatitis from perfumes to show a positive reaction to *Rosa damascena* flower oil following patch-testing with this series (a total of 326 had been tested), a chromatographic analysis of the oil was conducted. Citronellol, geraniol, and neral were identified as the main components (33.4%, 18.5%, and 5.9%, respectively). *Rosa damascena* flower oil contains approximately 20% geraniol, which led the researchers to surmise that the woman's reaction was possibly attributed to this component in the cologne.

A 71-yr old woman reported painful, pruritic, palmar eruptions, lasting 3 mo, shortly after a first-time exposure to a household cleaner.[71] The patient presented with hyperkeratotic plaques and bilateral fissures on her palms and fingers. The differential diagnosis included irritant, as opposed to allergic contact, dermatitis. Treatment with over-the-counter (OTC) products and the use of a fragrance-free soap did not alleviate the condition. Patch test results, graded according to the North American Contact Dermatitis Group, revealed numerous positive reactions to fragrance chemicals at 48 and 72 h, including a

1+ reaction to *Rosa damascena* flower oil and a 1+ reaction to geraniol. It was determined that the fragrance-free soap contained rose oil. The observed dermatitis only partly diminished after discontinued use of the fragrance-free soap and other recommendations based on test results and case history.

SUMMARY

The safety of 10 *Rosa damascena*-derived ingredients as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, some of these ingredients are reported to function as skin-conditioning and fragrance ingredients, while a few are reported to function as antioxidants and cosmetic astringents, in cosmetic products. Some constituents of concern, such as the fragrance allergens eugenol, geraniol, citronellol, limonene, linalool, and farnesol, are found in *Rosa damascena*-derived ingredients, with amounts varying based on time of harvest, as well as the timing and method of extraction.

According to 2022 VCRP survey data, Rosa Damascena Flower Water is reported to be used in 302 formulations, at a maximum concentration of 1.9% in foundations, Rosa Damascena Flower Extract is reported to be used in 293 formulations, and Rosa Damascena Flower Oil is reported to be used in 229 formulations. (Rosa Damascena Flower Oil is reported to be used at up to 10.8% in other skincare preparations, with instructions to dilute before use, resulting in much lower use concentrations when applied.) Incidental ingestion and mucous membrane exposure are possible; for example, Rosa Damascena Flower Wax is reported to be used at a maximum of up to 1.1% in lipsticks. Additionally, these ingredients are used in cosmetic sprays and powders, and could possibly be inhaled. For example, Rosa Damascena Flower Extract is reported to be used at up to 0.00007% in aerosol spray deodorant formulations, and Rosa Damascena Flower Oil is reported to be used at up to 0.0003% in hair spray. Rosa Damascena Flower Extract is reported to be used in face powder formulations (concentration of use not reported)

The acute dermal LD_{50} of *Rosa damascena* flower oil was determined to be ≥ 2500 mg/kg in rabbits. A single oral dose of 2000 mg/kg ethyl acetate *Rosa damascena* flower extract did not cause toxic effects in groups of 3 male and 3 female Swiss albino mice. The acute oral LD_{50} of *Rosa damascena* flower oil was determined to be > 5000 mg/kg in rats, and in another study, was determined to be up to 5525 mg/kg in male rats and 2975 mg/kg in mature, and 3972 mg/kg in immature, female rats, respectively. No deaths were observed in groups of 6 Swiss albino mice orally dosed with up to 6000 mg/kg *Rosa damascena* flower water extract, and the acute LD_{50} in mice was determined to be > 6000 mg/kg.

Groups of 10 Wistar rats administered 0, 2.5, 5, 25, or 50 mg/kg/d aqueous *Rosa damascena* flower extract, via gavage, for 30 d, exhibited greater body weight gain in all test groups compared to controls, but the percent weight gain was not statistically significant. Significant decreases in the cholesterol/HDL and LDL/HDL ratios were observed in the 2.5 and 50 mg/kg/d groups, as well as a significant TG increase in the 50 mg/kg/d group. A methanolic, *Rosa damascena* flower extract was administered at 1.5 g, via diet, to rabbits (number not specified) for 45 d. Comparison of fasting blood samples on day 1 and 1 d after the experiment revealed significantly higher TG levels in treated animals compared to the controls. No other significant differences in lipid profiles, pulse, or cardiac indices were observed. Groups of 5 dogs administered 0, 90, 180, 720, or 1440 mg/kg/d aqueous *Rosa damascena* flower extract, in the diet, for 10 d exhibited a dose dependent increase of diarrhea, and animals in the 720 and 1440 mg/kg/d groups exhibited slight, but not significant, weight loss after day 7. In another study, groups of 5 dogs were administered 90, 180, 360, 720, or 1440 mg/kg/d, in the diet, for 10 d; except for a significant increase in bilirubin levels on day 3 and ALT on day 10 in animals in the 1440 mg/kg bw/d group, there were no statistically significant differences from controls. Blood samples collected from groups of 10 male albino rabbits orally dosed with either 250 or 500 mg/kg bw/d *Rosa damascena* flower water for 60 d only showed a statistically significant increase in red blood cell counts for the 250 mg/kg group, and an increase in platelet counts for both groups, at day 60, compared to day 30 of dosing. No significant differences in body or organ (liver, intestine, heart, lungs, kidneys and spleen) weights, organ tissue, mortality, or hematological biomarkers were observed in 15 Swiss albino mice orally administered 300 mg/kg/d *Rosa damascena* flower water extract for 28 d (compared to 10 controls). Groups of 25 Swiss albino mice were orally dosed with 0 or 300 mg/kg/d *Rosa damascena* flower water extract for 90 d. Two control mice and 2 treated mice died in the first month, 1 control mouse and 2 treated mice died in the second month, and no mortality occurred during the third month of observation. Mice killed after the first, second, and third month (number not specified), progressively exhibited mild hydropic degeneration in the liver, congestion in coronary blood vessels, and peribronchiolar aggregation of round cells in the lungs. No significant differences were observed in body and weights, and various hematological markers, compared to the control group.

Whole blood samples exposed to up to 200 µg/ml of a *Rosa damascena* flower oil, followed by PHA stimulation and the addition of Cyt B, exhibited a significantly greater frequency of micronuclei at concentrations > 50 µg/ml, compared to controls. Concentrations of 10 µg/ml of a *Rosa damascena* flower oil (absolute) and a *Rosa damascena* flower oil (extracted from whole flowers) did not inhibit mitotic activity in normal human blood lymphocytes. *Rosa damascena* flower oil (absolute) exhibited significant ($p < 0.001$) antimutagenic activity when added to a blood lymphocyte culture treated with 300 ng/ml MMC. A trade mixture of 0.1 - 1% Rosa Damascena Flower Oil and 0.1 - 1% Rosa Damascena Flower Water, in pentylene glycol was not considered genotoxic when tested in an Ames test using *S. typhimurium* strains TA 98, TA100, TA 102, TA 1535, TA 1537, at up to 5000 µg/plate.

In two separate MTT assays, a methanolic *Rosa damascena* flower extract exhibited IC_{50} values of 265 µg/ml and > 1000 µg/ml on HeLa and Vero cell lines, respectively. Murine fibroblast cell lines treated with up to 50 mg/ml of a trade mixture comprising 0.1 – 1% Rosa Damascena Flower Oil and 0.1 – 1% Rosa Damascena Flower Water formulated in pentylene glycol, yielded a mean IC_{50} value of 6.68 mg/ml. Human colon carcinoma cell lines dosed with up to 10 µl of a *Rosa damascena* flower oil in an MTT assay exhibited a significant cell growth induction at the highest dose, while an induction effect was observed at lower concentrations in human fibroblast cells.

In an in vitro study, 30 µl of a trade mixture of 0.1-1% Rosa Damascena Flower Oil and 0.1-1% Rosa Damascena Flower Water, formulated in pentylene glycol did not cause irritation or sensitization when applied to an EpiSkin™ model. Human monocytic leukemia cell lines (THP-1) exposed to up to 5000 µg/ml of the same trade mixture, undiluted, in an h-CLAT in vitro assay were sensitized, with a minimum induction threshold of 923 µg/ml. The aforementioned trade mixture was not considered sensitizing when evaluated in a luciferase assay (KeratinoSens™ model), undiluted, at up to 400 µg/ml. No dermal irritation or phototoxic effects were observed when *Rosa damascena* flower oil was applied to the backs of hairless mice and swine. Rabbits with intact or abraded skin exposed to undiluted *Rosa damascena* flower oil for 24 h under occlusion showed signs of moderate irritation. The same trade mixture of Rosa Damascena Flower Oil and Rosa Damascena Flower Water, in pentylene glycol was not irritating when applied, at a concentration of 20% in distilled water, at160 µl in a single, semi-occlusive patch test of 11 subjects. *Rosa damascena* flower oil, 2% in petrolatum, did not produce irritation in a 48-h closed patch test, or, sensitization reactions in a maximization test using 25 human subjects. Sensitization was not observed in 3 separate HRIPTs testing the sensitizing potential of two fragrance products containing 0.7794% Rosa Damascena Flower Extract, 0.1068% Rosa Damascena Flower Water, and a mask formulation containing 0.1260% Rosa Damascena Flower Oil, in either 100 or 107 subjects.

A trade mixture of 0.1 - 1% Rosa Damascena Flower Oil and 0.1 - 1% Rosa Damascena Flower Water, in pentylene glycol, diluted to 10% in water, had very low UV absorption between 290 - 400 nm, and was considered not phototoxic. Undiluted *Rosa damascena* flower oil was not considered phototoxic to mice and swine skin. The same trade mixture, applied at a dose of 500 µl, neat or 25 or 50%, in water, to neutral red dye treated-rabbit cornea fibroblast cells for 60 s did not exhibit cytotoxicity and was not considered an ocular irritant.

In an 8-yr, annual essential oil patch study of 1483 patients susceptible to contact dermatitis, among the 10 fragrance oils used, the average patch test positivity rate for *Rosa damascena* flower oil (2% pet.) was 0.4%. A 48-yr old woman, with prior allergic reactions to imitation jewelry and hair dye experienced itching and erythema from exposure to a cologne containing *Rosa damascena* flower oil; in subsequent patch-testing, the woman had a ++ reaction to *Rosa damascena flower* oil (2% pet.), a +++ reaction to geraniol. Pruritic, palmar eruptions experienced by a 71-yr old woman, after exposure to a household cleaner did not diminish with use of treatment with OTC products or the use of a fragrance-free soap. Discontinued use of the soap, which was determined to contain *Rosa damascena* flower oil (for which the subject patch tested positive, +1), led to only partial diminishing of the symptoms.

DISCUSSION

This assessment reviews the safety of 10 *Rosa damascena*-derived ingredients as used in cosmetic formulations. The Panel concluded that that these 10 *Rosa damascena*-ingredients are safe in the present practices of use and concentrations described in this safety assessment when formulated to be non-sensitizing.

The need for systemic toxicity data was mitigated, as all of the ingredients described in this report are composed from plant parts that are used in foods or are considered GRAS for intended food use, according to the US FDA. Since systemic exposure from food is expected to be far greater than exposure via cosmetics, the Panel considered the toxicity data in this review sufficient.

The Panel expressed concern regarding pesticide residues. heavy metals, and other plant species that may be present in botanical ingredients. The Panel stressed that the cosmetics industry should continue to use current good manufacturing practices to limit these impurities.

Additionally, because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For *Rosa damascena*-derived ingredients, examples of the constituents the Panel was concerned about include benzyl alcohol, eugenol, methyl eugenol, geraniol, citronellol, limonene, and linalool, which are possible sensitizers. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization.

The Panel discussed the issue of incidental inhalation exposure that could result with the use of some of these ingredients (e.g., up to 0.0003% Rosa Damascena Flower Oil in aerosol hair spray). Inhalation toxicity data were not available. However, 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 concentrations at which the ingredients are used, 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.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 10 *Rosa damascena*- 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.

Hydrolyzed Rosa Damascena Flower Extract*
Rosa Damascena Bud Extract*
Rosa Damascena Extract
Rosa Damascena Flower
Rosa Damascena Flower Extract
Rosa Damascena Flower Oil
Rosa Damascena Flower Powder
Rosa Damascena Flower Water
Rosa Damascena Flower Water Extract
Rosa Damascena Flower Wax

* 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.

TABLES

Table 1. Definitions and reported functions of *Rosa damascena* ingredients [1]

Ingredient/CAS No.	Definition	Function
Hydrolyzed Rosa Damascena Flower Extract	Hydrolyzed Rosa Damascena Flower Extract is the hydrolysate of Rosa Damascena Flower Extract derived by acid, enzyme, or other method of hydrolysis.*	Antioxidants
Rosa Damascena Bud Extract 90106-38-0	Rosa Damascena Bud Extract is the extract of the buds of *Rosa damascena*.*	Skin-conditioning agents - miscellaneous
Rosa Damascena Extract 90106-38-0	Rosa Damascena Extract is the extract of the rose, *Rosa damascena*.*	Fragrance ingredients
Rosa Damascena Flower 90106-38-0	Rosa Damascena Flower are the flowers of *Rosa damascena.**	Skin-conditioning agents - miscellaneous
Rosa Damascena Flower Extract 906106-38-0	Rosa Damascena Flower Extract is the extract of the flowers of *Rosa damascena*.*	Fragrance ingredients
Rosa Damascena Flower Oil 8007-01-0 90106-38-0	Rosa Damascena Flower Oil is the volatile oil obtained from the flowers of *Rosa damascena.**	Fragrance ingredients; Skin-conditioning agents – miscellaneous
Rosa Damascena Flower Powder 90106-38-0	Rosa Damascena Flower Powder is the powder obtained from the dried, ground flowers of *Rosa damascena.**	Fragrance ingredients
Rosa Damascena Flower Water 90106-38-0	Rosa Damascena Flower Water is an aqueous solution of the steam distillate obtained from the flowers of *Rosa damascena.**	Fragrance ingredients; Skin-conditioning agents - miscellaneous
Rosa Damascena Flower Water Extract 90106-38-0	Rosa Damascena Flower Water Extract is the extract of Rosa Damascena Flower Water.*	Antioxidants; Cosmetic astringents
Rosa Damascena Flower Wax 90106-38-0	Rosa Damascena Flower Wax is a wax obtained from the flower of *Rosa damascena.**	Fragrance ingredients

* The accepted scientific name for *Rosa damascena* is *Rosa* x *damascena.*

Table 2. Chemical properties of *Rosa damascena*-derived ingredients

Property	Value	Reference
	Rosa Damascena Extract	
Physical Form (@ 20°C and 1013 hPa)	Viscous liquid; can contain crystallized product	[72]
Color	Orange-red	[72]
Density (g/ml)	0.9804	[72]
Vapor pressure (mmHg @ 20 ºC; 25°C)	3.053; 3.960	[72]
Boiling Point	Decomposed before boiling	[72]
	Rosa Damascena Flower	
Physical Form (fresh petal width and length, in cm)	Heart/pear shape, soft and smooth petals; 0.9-3.8; 1.8-4.2	[8]
Color	Magenta on base, light yellow near apex pink	[2,8]
Odor	Aromatic distinct	[8]
Density (g/ml)	0.202	[8]
pH	6.56	[8]
Ash (% w/w upon burning); Total Acid insoluble; Water soluble	6.34 1.51; 2.48	[8] [8]
	Rosa Damascena Flower Extract	
UV Wavelengths and Absorbance (nm; AU)* (UVA (315-400 nm), UVB (280-315 nm), UVC (100-280 nm)) Hydroalcoholic extract Ether extract Ethyl acetate:ethanol 	 228; 2.57 (λ_{max}) 226; 2.42 355; 0.9 269; 1.59 (λ_{max}) 238; 1.35 350; 0.85 270; 1.16 (λ_{max}) 354; 0.64	[25]
	Rosa Damascena Flower Oil	
Physical Form	Liquid or crystallized	[73]
Color	Colorless, light yellow to yellow-green	[2,73,74]
Odor	Floral, rose	[73]
Density (g/ml @ 20 ºC)	0.848-0.880	[73]
	Rosa Damascena Flower Water	
Density (g/ml @ 20 ºC)	0.9916; 0.9927	[4,9]
Viscosity (cm^2/s) @ 25 ºC)	104	[9]

Table 2. Chemical properties of *Rosa damascena*-derived ingredients

Melting Point (ºC)	93	[9]
pH	7.2; 6.55	[4,9]
Rosa Damascena Flower Wax		
Melting Point (ºC)		[17]
Turkish rose wax	42	
Bulgarian rose wax	41.0-46.5	

Table 3. Percent composition of constituents found in *Rosa damascena*-derived ingredients[2,13,14,16,17,20-22]

	Shade-dried petals of *Rosa damascena*		**Fresh flowers of *Rosa damascena***			
Constituent	**Hydrodistilled Essential Oil**	**Hexane Extract of Rose Water**	**Hydrodistilled Essential Oil**	**Rose Water**	**Rose Water Extract***	**Rose Wax****
α-bulnesene	0.4%	0.1%	NR	NR	NR	NR
α-guaiene	NF	0.1%	2.0%	NR	NR	NR
α-humulene	0.3%	0.2%	0.6%	NR	NR	NR
α-pinene	0.1%	0.3%	2.8%	0.71%[20]	NR	NR
α-selinene	trace	trace	NR	NR	NR	NR
α-terpinene	trace	trace	NR	NR	NR	NR
α-terpineol	0.1%	0.2%	1.6%	0.12%	NR	NR
β-caryophyllene	trace	-	trace	NR	NR	NR
β-citronellol	NR	NR	NR	28.70%	NR	NR
β-copaene	0.1%	0.2%	2.0%	NR	NR	NR
β-damascenone	NR	NR	0.5%	NR	NR	NR
β-elemene	0.1%	-	NR	NR	NR	NR
β-myrcene	0.2%	0.2%	2.4%	NR	NR	NR
β-pinene	NR	0.1%	0.3%	NR	NR	NR
β-selinene	0.1	-	NR	NR	NR	NR
δ-cadinene	-	0.1%	NR	NR	NR	NR
δ-elemene	0.1%	trace	NR	NR	NR	NR
(2*e*,6*e*)-farnesol	0.4%	0.3%	0.6%	NR	NR	NR
e-β-ocimene	0.3	-	0.8%	1.06%	NR	NR
(*e*)-rose oxide	NR	NR	0.7%	NR	trace	NR
(z)-rose oxide	NR	NR	0.2%	NR	trace	NR
z-β-farnesene	0.3%	0.1%	NR	NR	NR	NR
z-β-ocimene	trace	-	0.3%	0.18%	NR	NR
(z)-9-nonadecene	NR	NR	0.6%	NR	NR	NR
1-eicosene	0.1%	0.1%	NR	NR	NR	NR
1-nonadecene	1.6%	0.8%	10.2%[2]	NR	NR	NR
10-*epi*-γ-eudesmol	0.1%	0.1%	NR	NR	NR	NR
benzaldehyde	trace	0.1%	NR	NR	NR	NR
benzyl alcohol	NR	NR	NR	0.85%	NR	NR
caryophyllene oxide	0.1%	0.1%	NR	NR	NR	NR
cis-geraniol	NR	NR	NR	10.81%	NR	NR
citronellal	0.1%	0.2%	NR	NR	NR	NR
citronellol	7.1%	2.2%	35.3%	29.44%[22]	1.8-7.2%	17%
citronellyl acetate	0.1%	0.3%	0.5%	NR	NR	NR
citronellyl butyrate	0.1 %	-	NR	NR	NR	NR
citronellyl formate	0.2%	0.3%	NR	NR	NR	NR
docasane	1.1%	1.4%	0.6%	0.4%[20]	NR	NR
eicosane	2.5%	2.4%	0.5%	0.45%	0.2%	NR
ethanol	NR	NR	2.1%[2]	NR	NR	NR
eugenol	NR	NR	1.6%[2]	2.26-17.75%[20]	0.4%	1%
farnesol	NR	NR	NR	0.89%	NR	NR
geranial	0.1%	trace	0.7%	NR	NR	NR
geraniol	4.1%	2.5%	18.7%	30.74%[22]	0.9-7.0%	5%
geranyl acetate	0.8%	0.1%	1.7%	7.33%	NR	NR
geranyl formate	0.5%	1.5%	1.0%	NR	NR	NR
geranyl propionate	trace	-	NR	NR	NR	NR
germacrene-d	trace	-	NR	NR	NR	NR
heneicosane	19.7%	15.7%	2.6%	0.56%	1.4%	NR
heptadecane	0.6%	0.5%	0.3%	1.08%[20]	NR	NR
hexadecane	0.1%	0.4%	NR	2.14%	NR	NR
isomenthone	0.2%	0.3%	NR	NR	NR	NR
limonene	NR	NR	0.8%	NR	NR	NR

Table 3. Percent composition of constituents found in *Rosa damascena*-derived ingredients[2,13,14,16,17,20-22]

	Shade-dried petals of *Rosa damascena*		Fresh flowers of *Rosa damascena*			
Constituent	**Hydrodistilled Essential Oil**	**Hexane Extract of Rose Water**	**Hydrodistilled Essential Oil**	**Rose Water**	**Rose Water Extract***	**Rose Wax****
linalool	0.5%	0.7%	2.6%	0.65-8.99%[20]	1.5-3.3%*	NR
linalyl acetate	trace	trace	NR	NR	NR	NR
methyl eugenol	trace	0.1%	1.3%	1.83%	0.4%	2%
methyl geranate	trace	-	NR	NR	NR	NR
n-decanal	NR	NR	trace	NR	NR	NR
neral	trace	0.1%	0.3%	NR	NR	NR
nerol	0.1%	-	7.2%	16.12%[22]	0.2-4.2%	4%
nerol oxide	0.2%	0.1%	NR	NR	NR	NR
neryl acetate	0.4%	-	NR	NR	NR	NR
nonane	NR	NR	NR	0.31%[20]	NR	NR
n-nonanal	0.4%	0.4%	0.2%	NR	NR	NR
nonadecane	13.0%	8.4%	4.5%	2.05%	0.9%	0.1%
nonadecene	NR	NR	NR	NR	0.7%	-
octadecane	0.2%	0.9%	NR	NR	NR	NR
p-cymene	0.6%	0.6%	NR	NR	NR	NR
pentacosane	5.3%	5.1%	0.5%	NR	NR	NR
pentadecane	-	0.2%	NR	0.73%	NR	NR
phenethyl alcohol	0.4%	7.1%	2.9%	4.95%[21]; 23.70%[22]	69.7-81.6%	43%
terpinen-4-ol	0.1%	0.2%	0.5%	NR	NR	NR
terpinolene	0.1%	0.1%	NR	NR	NR	NR
tetracosane	0.9%	1.1%	trace	NR	NR	NR
tetradecanol	0.1%	-	NR	NR	NR	NR
trans-geraniol	NR	NR	NR	16.44%	NR	NR
tricosane	11.3%	9.3%	0.6%	NR	NR	NR

* *Rosa damascena* flower extracts prepared with listed solvents (20 mg%)

Abbreviations: - (not found); NR- not reported; *dichloromethane extract; ** solid phase microextraction (SPME) analysis

Table 4. Frequency (2022)[39] and concentration (2019)[40,41] of use of *Rosa damascena*-derived ingredients

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Rosa Damascena Extract		**Rosa Damascena Flower**		**Rosa Damascena Flower Extract**	
Totals*	**59**	**0.000005-0.05**	**6**	**NR**	**293**	**0.0012-0.0018**
Duration of Use						
Leave-On	*40*	*0.00001-0.014*	*5*	*NR*	*261*	*NR*
Rinse-Off	*19*	*0.000005-0.05*	*1*	*NR*	*30*	*0.0012-0.0018*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*2*	*NR*
Exposure Type						
Eye Area	3	NR	NR	NR	70	NR
Incidental Ingestion	NR	NR	NR	NR	74	NR
Incidental Inhalation-Spray	5; 18[a]; 10[b]	0.00001-0.00027; 0.00013-0.0065[a]	2; 1[a]; 1[b]	NR	19[a]; 22[b]	NR
Incidental Inhalation-Powder	10[b]; 2[c]	0.00077-0.014[c]	1[b]	NR	8; 22[b]	NR
Dermal Contact	56	0.000005-0.05	6	NR	184	0.0018
Deodorant (underarm)	1[a]	aerosol: 0.00007; 0.00007 (not spray)	NR	NR	2[a]	NR
Hair - Non-Coloring	3	0.00001-0.0065	NR	NR	12	0.0012
Hair-Coloring	NR	0.0023	NR	NR	NR	NR
Nail	NR	NR	NR	NR	19	NR
Mucous Membrane	5	0.000005-0.05	NR	NR	86	NR
Baby Products	2	NR	NR	NR	NR	NR
	Rosa Damascena Flower Oil		**Rosa Damascena Flower Powder**		**Rosa Damascena Flower Water**	
Totals*	**229**	**0.000059-0.31; 10.8****	**1**	**NR**	**302**	**0.009-1.9**
Duration of Use						
Leave-On	*184*	*0.00013-0.16; 10.8***	*1*	*NR*	*246*	*0.09-1.9*
Rinse Off	*36*	*0.000059-0.31*	*NR*	*NR*	*56*	*0.009-0.99*
Diluted for (Bath) Use	*9*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	6	0.0095	NR	NR	22	NR
Incidental Ingestion	2	0.0002-0.01	NR	NR	10	NR
Incidental Inhalation-Spray	48; 61[a]; 46[b]	0.00013-0.0003; 0.0012[a]	NR	NR	4; 80[a]; 95[b]	NR
Incidental Inhalation-Powder	46[b]; 2[c]	0.005-0.16[c]	NR	NR	95[b]	0.94[c]
Dermal Contact	217	0.00014-0.16; 10.8**	1	NR	282	0.09-1.9
Deodorant (underarm)	2[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	8	0.00013-0.0017	NR	NR	10	0.009
Hair-Coloring	NR	0.000059	NR	NR	NR	0.03-0.09
Nail	NR	0.005	NR	NR	NR	NR
Mucous Membrane	21	0.00014-0.01	NR	NR	16	0.09
Baby Products	2	NR	NR	NR	NR	NR

	Rosa Damascena Flower Water Extract		**Rosa Damascena Flower Wax**	
Totals*	**1**	**NR**	**7**	**0.015-1.1**
Duration of Use				
Leave-On	*NR*	*NR*	*6*	*0.015-1.1*
Rinse-Off	*1*	*NR*	*1*	*0.05*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	1	0.13
Incidental Ingestion	NR	NR	2	1.1
Incidental Inhalation-Spray	NR	NR	1[b]	NR
Incidental Inhalation-Powder	NR	NR	1[b]	0.05[c]
Dermal Contact	1	NR	4	0.015-0.13
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	3	1.1
Baby Products	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.

**According to a supplier, this product is an essential oil that is sold with instructions to dilute the product before use.[41]

[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 5. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/ Results	Reference
DERMAL						
Rosa damascena flower oil	Rabbits	NR	NR	NR	LD_{50} > 2500 mg/kg	[51-53]
ORAL						
Rosa damascena flower extract	Male and female Swiss albino mice	3/sex	0.7% carboxy-methylcellulose	2000 mg/kg ethyl acetate extract	LD_{50} > 2000 mg/kg	[54]
Rosa damascena flower oil	rats	NR	NR	NR	LD_{50} > 5000 mg/kg	[51-53]
Rosa damascena flower oil	Male and female rats	NR	NR	NR	LD_{50} was determined to be 5525 mg/kg in male rats, and 2975 mg/kg and 3972 mg/kg in mature and immature female rats, respectively.	[52]
Rosa damascena flower water extract	Swiss albino mice	6/group	NR	500, 1000, 2000, 3000, 4000, 5000, or 6000 mg/kg	LD_{50} > 6000 mg/kg	[55]

NR – not reported

Table 6. Short-term and subchronic oral toxicity studies

Ingredient	Animals/Group	Study Duration	Vehicle/Control	Dose/Concentration	Protocol/Results	Reference
Rosa damascena flower extract Aqueous extract	Wistar rats; 10/group	30 d	0.9 % saline	0, 2.5, 5, 25, or 50 mg/kg/d, via gavage	Body weight increased more in test groups than in controls, but the percent weight gains were not statistically significant. Blood samples were collected on days 0 and 30 to assess hematological parameters and biochemical changes. Significant decreases in total white blood cell count was noted in the 2.5 and 50 mg/kg/d groups, while platelet counts were significantly increased in all test groups. Fasting glucose, AST, and ALT levels were significantly decreased and ALP levels were significantly increased in all test groups. Increased TG levels were statistically significant in only the 50 mg/kg/d group, while the cholesterol/HDL ratio and LDL/HDL ratios were significantly decreased in the 2.5, 5, and 25 mg/kg/d groups.	[56]
Rosa damascena flower extract Methanolic extract	Rabbits; (number not specified)	45 d	NS	1.5 g, in the diet	Animals were anesthetized at the end of the experiment, and under intubation, had pressure transducer cannulae inserted into the left carotid artery and left ventricle, to record heart rate, arterial blood pressure, and left ventricular pressure, respectively. A fasting blood sample was taken on days 1 and 46 to measure the total cholesterol, TG, LDL, and HDL levels. TG levels were significantly higher than controls at the end of the experiment. No other significant differences in lipid profiles, pulse, or cardiac indices were observed.	[57]

Table 6. Short-term and subchronic oral toxicity studies

Ingredient	Animals/Group	Study Duration	Vehicle/Control	Dose/Concentration	Protocol/Results	Reference
Rosa damascena flower extract Aqueous extract	Dogs (strain not specified); 5/group (test substance) 4/group (controls)	10 d	Distilled water; Negative control: distilled water Positive control: lactulose	0, 90, 180, 360, 720, or 1440 mg/kg/d, in the diet	Animals were monitored for changes in gastrointestinal performance, weight, electrocardiogram, temperature, respiration, and heart rates. No significant differences were observed between groups for respiration, temperature, or cardiac response. A dose-dependent increase of soft feces and diarrhea was observed, starting from the 90 mg/kg/d group. The animals in the 1440 mg/kg/d group showed sedation, and animals in the 720 and 1440 mg/kg/d groups exhibited slight weight loss, especially after day 7, which was statistically significant. However, animals treated with lactulose also experienced slight weight loss, and this effect was, therefore, attributed to possible diarrhea-induced malabsorption, or dehydration. No further changes or adverse effects were observed.	[58]
Rosa damascena flower extract Aqueous extract	Dogs (strain not specified); 5/group (test substance) 4/group (controls)	10 d	Distilled water; Negative control: distilled water Positive control: lactulose	0, 90, 180, 360, 720, 1440 mg/kg, in the diet	Serum levels of urea, creatinine, ALP, ALT, bilirubin, albumin, and protein were measured in all experimental groups at day 0, 1, 3, 7, and 10. Except for a significant increase in bilirubin levels on day 3 and ALT on day 10 in animals in the 1440 mg/kg bw/d group, there were no statistically significant differences with controls.	[59]
Rosa damascena flower water	Male albino rabbits; 10/group	60 d	NS	250 or 500 mg/kg bw/d, via gavage	Blood samples were collected for hematological testing on day 31 and day 61; compared to controls, no significant differences were observed between hemoglobin, white blood cells, red blood cells, and platelets after 30 and 60 days of dosing. The 250 mg/kg/d group had a significant increase in red blood cell count, and a higher platelet count was observed for both doses, at day 60 compared to day 30.	[60]
Rosa damascena flower water extract	Swiss albino mice; control: 10; treated: 15	28 d	NS	0, 300 mg/kg/d, via gavage	Animal body weights were recorded prior to, and during, treatment. Animals were sacrificed 24 h after the end of treatment and vital organs were weighed and examined for histopathological changes. No significant differences in body or organ weights, organ tissue, or mortality were observed in treated mice. ALT, ALP, AST, urea, and creatinine levels were not significantly different from controls.	[55]
Rosa damascena flower water extract	Swiss albino mice; 25/group	90 d	NS	0, 300 mg/kg/d, via gavage	Mortality rates were recorded, and every month a group of mice (# not specified) was sacrificed. Total body and organ weights, and histopathological changes in the kidney and liver were assessed. Two control and 2 treated mice died in the first month (8%, both groups), one control and 2 treated mice in the second month (12.5% treated mice vs. 6.25% control mice), and no mortality occurred in the third month of observation. In the mice killed after the first month, the liver of treated mice showed mild hydropic degeneration and the heart showed slight congestion in coronary blood vessels with mild perivascular edema. In mice killed after the second month, the liver showed mild hydropic degeneration, and slight congestion of hepatic blood vessels, the kidneys had mild vacuolations and hydropic degeneration in the tubular epithelia, the heart showed granular eosinophilic sarcoplasm and slightly congested coronary blood vessels, and the lung had peribronchiolar aggregations of round cells with thickening of the adjacent interalveolar septa. In addition to the aforementioned effects, mice killed after the third month had focal hyaline degeneration in cardiac muscle fibers, the intestine showed an increase in the numbers of goblet cells and slight activation of Paneth cells, and the spleen exhibited sub capsular edema. No significant differences were observed in body and organ weights, or ALT, ALP, AST, urea, and creatinine levels in treated mice compared to the control group. (statistical significance not provided).	[55]

ALT- alanine aminotransferase, ALP- alkaline phosphatase, AST- aspartate aminotransferase; HDL- high-density lipoprotein; LDL – low-density lipoprotein; NS- not specified; TG – triglyceride

Table 7. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO STUDIES		
0.1-1% Rosa Damascena Flower Oil and 0.1-1% Rosa Damascena Flower Water, in pentylene glycol	Undiluted; 10%, or 50% v/v in DMSO; 10% v/v in PBS 30 µl of each dilution	EpiSkin™, Sens-IS	Test articles were applied to the model for 15 min, rinsed with PBS, and then incubated at 37 °C for 6 h. After incubation, the epidermis was collected, and RNA was extracted to analyze the expression of irritation and sensitization biomarker genes. Overexpression of at least 15 of 23 genes associated with irritation would classify the substance as an irritant.	Not sensitizing. Three negative controls (PBS, olive oil, and DMSO - treated skins), a positive irritation control (5% SLS), and two positive sensitization controls (50% HCA and 1% TNBS) were used for each experiment.	63
0.1-1% Rosa Damascena Flower Oil and 0.1-1% Rosa Damascena Flower Water, in pentylene glycol	Undiluted; up to 5000 µg/ml	Human monocytic leukemia cell line (THP-1)	OECD TG 442E. In an h-CLAT in vitro assay, THP-1 cell lines were exposed to 8 concentrations of the test article ranging from 19.5 to 5000 µg/ml for 24 h. Post-exposure, the expression of two cell surface antigens, CD86 and CD54, was measured by flow cytometry. Vehicle control (RPMI), negative control (lactic acid), and positive controls (2,4-dinitrochlorobenzene or nickel sulfate) were also run in parallel.	Sensitizing; Based on linear regression, the median concentrations to induce a 150/200% expression of CD86/CD54 relative fluorescence intensity, were an EC_{200} of 923 µg/ml and an EC_{150} of 2125 µg/ml. The MIT was calculated as 923 µg/ml, from these EC_{200} and EC_{150} values.	63
0.1-1% Rosa Damascena Flower Oil and 0.1-1% Rosa Damascena Flower Water, in pentylene glycol	Undiluted, 0.2 µg/ml – 400 µg/ml (12 concentrations)	KeratinoSens™, transformed keratinocytes	OECD TG 442D. Luciferase induction was measured in keratinocytes transformed with the AKR1C2 gene (a gene which identifies skin sensitizers). Cinnamaldehyde and 1% DMSO were run in parallel as positive and negative controls, respectively. The experiment was repeated twice to calculate average values for luciferase induction, i.e., test article concentrations at which the luciferase activity was 1.5-fold higher than basal luciferase activity ($EC_{1.5}$), and cell viability (IC_{70}).	Not sensitizing. Luciferase induction was lower than 1.5-fold of base values, and $EC_{1.5}$ values were not determined.	63
			ANIMAL		
Rosa damascena flower oil	NR	Mice and pigs (# and strain not stated)	NR	Not irritating	51,53
Rosa damascena flower oil	NR	Rabbits (# and strain not stated)	Intact or abraded rabbit skin was exposed to undiluted test article for 24 h, under occlusion. No further details provided.	Moderately irritating	51,53
			HUMAN		
0.1-1% Rosa Damascena Flower Oil and 0.1-1% Rosa Damascena Flower Water, in pentylene glycol	20%, diluted in distilled water/ 160 µl	11 subjects	A single, semi-occlusive application of the test article was made for 48 h. Readings were taken 30-40 min after removal of the patches.	Not irritating	63
Rosa damascena flower oil	NR; 2%, in petrolatum	NR	A one-time, occlusive application of the test article, was made for 48 h. No further details provided.	Not irritating	51,53
Rosa damascena flower oil	NR; 2% in petrolatum	25 subjects	NR	Not sensitizing	51,53
Fragrance; 0.7794% Rosa Damascena Flower Extract	0.2 ml	100 subjects	In an HRIPT, 9 occlusive induction applications were applied for 24 h using 2 cm^2 patches, over 3 wk. Prior to each patch application, the test article was evaporated for 30 min. Test sites were scored and retested every 48 - 72 h. After a rest period of 10-15 d, a previously unexposed site was challenged with the test substance for 24 h. Challenge sites were scored 48 and 72 h after application.	Not sensitizing; 1 adverse event, which was not test article related, was reported.	66
Mask; 0.1260% Rosa Damascena Flower Oil	0.2 ml	107 subjects	In an HRIPT, 9 occlusive induction applications were applied for 24 h using 2 cm^2 patches, over 3 wk. Test sites were scored and retested every 48 h. After a rest period of 10-15 d, a previously unexposed site was challenged with the test substance for 24 h. Challenge sites were scored 48 and 72 h after application.	Not sensitizing	68

Table 7. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Fragrance; 0.1068% Rosa Damascena Flower Water	0.2 ml	100 subjects	In an HRIPT, 9 occlusive induction applications were applied for 24 h using 2 cm^2 patches , over 3 wk. Prior to each patch application, the test article was evaporated for 30 min. Test sites were scored and retested every 48 h. After a rest period of 10-15 d, a previously unexposed site was challenged with the test substance for 24 h. Challenge sites were scored 48 and 72 h after application.	Not sensitizing	[67]

DMSO – dimethyl sulfoxide; EC - maximal effective concentration ; HCA- hydroxycitric acid; HRIPT – human repeated insult patch test; MIT – minimum induction threshold; NR – not reported; PBS- phosphate-buffered saline; RPMI – Roswell Park Memorial Institute; SLS – sodium lauryl sulfate; TNBS – trinitrobenzenesulfonic acid

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