# Safety Assessment of *Salix alba* (Willow)-Derived Ingredients as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date [i.e., **November 24, 2025**] to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific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

| | |
|---|---|
| CIR | Cosmetic Ingredient Review |
| Council | Personal Care Products Council |
| *Dictionary* | *International Cosmetic Ingredient Dictionary and Handbook* |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| $EC_{1.5}$ | effective concentration of a test chemical that induces a 1.5-fold increase in luciferase activity |
| ECHA | European Chemicals Agency |
| FDA | Food and Drug Administration |
| GARD | genomic allergen rapid detection |
| GHS | Globally Harmonized System |
| HepG2 | human hepatoma cell line |
| HL-60 | human leukemia-60 |
| Hprt | hypoxanthine-guanine phosphoribosyltransferase |
| $I_{max}$ | mean maximal luciferase activity |
| $LD_{50}$ | median lethal dose |
| l.o. | leave-on |
| log $K_{ow}$ | n-octanol/water partition coefficient |
| MoCRA | Modernization of Cosmetics Regulation Act |
| NA | not applicable |
| ND | not detected |
| NOAEL | no-observed-adverse-effect-level |
| NR | not reported |
| OECD | Organisation for Economic Co-operation and Development |
| Panel | Expert Panel for Cosmetic Ingredient Safety |
| RIFM | Research Institute for Fragrance Materials |
| RLD | Registration and Listing Data |
| RNA | ribonucleic acid |
| r.o. | rinse-off |
| TG | test guideline |
| US | United States |
| USP | United States Pharmacopeia |
| UVA | ultraviolet A |
| Vis | visible light |
| Xprt | xanthine-guanine phosphoribosyltransferase |

## INTRODUCTION

This assessment reviews the safety of the following 6 *Salix alba*-derived ingredients as used in cosmetics formulations:

| | |
|---|---|
| Salix Alba (Willow) Bark Extract | Salix Alba (Willow) Extract |
| Salix Alba (Willow) Bark Powder | Salix Alba (Willow) Flower Extract |
| Salix Alba (Willow) Bark Water | Salix Alba (Willow) Leaf Extract |

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), these ingredients are primarily reported to function as skin-conditioning agents in cosmetics; other functions of these ingredients may be found in Table 1.[1] It should be noted that Salix Alba (Willow) Bark Water is reported to only function as a fragrance ingredient in cosmetics, and the Expert Panel for Cosmetic Ingredient Safety (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, it appears that this ingredient is not included in their review process, and therefore, the Panel is reviewing its safety.

Botanicals, such as the *Salix alba* (willow)-derived ingredients reviewed herein, may contain hundreds of constituents. In this assessment, the Panel is evaluating the potential toxicity of each of the *Salix alba*-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 extensive search of the world's literature; a search was last conducted September 2025. 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.

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics will be followed (i.e., *Salix alba*). Often in the published literature, the general name willow is used. If it is not known whether the substance being discussed is equivalent to the cosmetic ingredient, the test substance will be identified by the name used in the publication that is being cited (e.g., *Salix alba* (willow) bark extract). However, if it is known that the substance is a cosmetic ingredient, the *Dictionary* nomenclature (e.g., Salix Alba (Willow) Bark Extract) will be used.

Furthermore, it should also be noted that the terms "willow" and "willow bark extract" may refer to several different species of willow (e.g., *Salix purpurea*, *Salix fragilis*) in the literature. For the purposes of this report, only studies explicitly using *Salix alba* - derived plant parts were included. However, a few case reports describing allergic reactions to dietary supplements containing "white willow bark" were included, since these products may in fact contain bark derived from *Salix alba*, and these case reports may assist the Panel in evaluating the potential allergenicity of *Salix alba* - derived ingredients.

Much 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**.**

## CHEMISTRY

### Definition and Plant Identification

The definitions of the ingredients included in this review are provided in Table 1. *Salix alba* is a fast-growing deciduous tree native to Europe, Asia, and North Africa, most often occurring in riparian habitats such as riverbanks, wetlands, and other moist soils.[3] These plants are capable of reaching heights up to 30 m with trunks exceeding 1 m in diameter. The leaves are narrow and lanceolate, displaying silver-grey upper surfaces and dense silky white hairs on the underside, while the bark is dark grey and deeply fissured (younger bark may be greenish-yellow).[4] The flowers of the *Salix alba* plant are produced in catkins that emerge in early spring, appearing before or with the leaves.[5] The species is dioecious, meaning male and female catkins are produced on separate trees. Male catkins are typically larger and yellowish due to exposed anthers while female catkins are smaller and greenish.

### Chemical Properties

*Salix alba* (willow) bark extract is a solid brown particulate/powder with a characteristic odor and an n-octanol/water partition coefficient (log $K_{ow}$) of < 0.3.[2] Other chemical properties of this ingredient may be found in Table 2.

### Method of Manufacture

The methods below are general to the processing of *Salix alba* (willow)-derived ingredients. It is unknown if these apply to cosmetic ingredient manufacturing.

Salix Alba (Willow) Bark Extract

In order to prepare a *Salix alba* (willow) bark extract, plant bark was first dried and pulverized into a fine powder.[6] The powder was then extracted in a Soxhlet apparatus using ethanol as the solvent for 7 h. The solution was filtered and evaporated to obtain the bark extract.

Salix Alba (Willow) Leaf Extract

A *Salix alba* (willow) leaf extract was prepared by first collecting, rinsing, and air-drying the leaves.[7] Following drying, the leaves were pulverized via an electric grinder. Extraction was performed via cold maceration of 500 g ethyl acetate with intermittent shaking. The resulting filtrate was concentrated using rotary vapor. To remove chlorophyll, the extract was washed with a non-polar solvent, after which it was concentrated and stored.

### Composition and Impurities

*Salix* species are known for their capacity to concentrate toxic heavy metals.[8] Therefore, the *Salix alba* (willow) plant and plant parts (including the bark and leaves) may contain heavy metals such as cadmium, lead, and zinc.[9]

Salix Alba (Willow) Bark Extract

A cosmetic ingredient supplier states that Salix Alba (Willow) Bark Extract is standardized to contain 53 – 65% salicylates, ensuring consistent levels of the primary bioactive compounds.[10] Data from the scientific literature on *Salix alba* (willow) bark report broader phytochemical compositions. In *Salix alba* (willow) bark extracts, the content of various compounds was measured in both young and mature bark.[11] For young bark, the total salicylate derivative, polyphenol (expressed as gallic acid), flavone (expressed as rutin), and tannin (expressed as pyrograllol) content in extracts of young and mature *Salix alba* (willow) bark were determined to be 15, 55, 4.5, and 16, respectively.[11] In mature bark, the respective values were 19, 65, 3, and 16.6.

The total phenolic content of a hot ethanolic extract of *Salix alba* (willow) bark was determined to be 162 mg/g.[6] The amounts of salicylates, flavonoids, flavan-3-ols, and phenolic acids in a methanolic *Salix alba* (willow) bark extract have been summarized in Table 3.[12] In addition, the phenolic acid, flavanol, and procyanidin content of a hydromethanolic extract of *Salix alba* (willow) bark may be found in Table 4.[13] A chemical analysis of *Salix alba* (willow) bark reported the following structural component contents: 70.18% holocellulose, 40.32% α-cellulose, and 33.81% Klason lignin.[14]

According to the World Health Organization, *Salix alba* (willow) bark used in herbal medicines must conform to the following specifications: not more than 3% of twigs with a diameter greater than 10 mm, and not more than 2% other foreign matter, not more than 10% total ash, not more than 3% acid-insoluble ash, not less than 10% water-soluble extractive, and not more than 11% loss on drying.[15] The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg. In addition, the product must comprise ≥ l.5% of total salicylate derivatives expressed as salicin by high-performance liquid chromatography.

Lastly, an ECHA dossier of *Salix alba* (willow) bark extract lists heavy metal specifications for this ingredient.[2] These specifications indicate that this ingredient should not contain more than 10 ppm heavy metals, 2 ppm lead, 2 ppm arsenic, 2 ppm cadmium, and 2 ppm mercury.

Salix Alba (Willow) Leaf Extract

The total polyphenols (expressed as gallic acid), flavones (expressed as rutin), and tannins (expressed as pyrograllol) content in the extract of young *Salix alba* (willow) leaves was determined to be 55, 8.5, and 12, respectively.[11] In mature leaves, the respective compositions were 70, 8, and 10. The composition of a hydromethanolic extract of *Salix alba* (willow) leaves may be found in Table 4.[13]

The major compounds present in an ethyl acetate *Salix alba* (willow) leaf extract were determined via gas chromatography-mass spectrometry analysis.[7] The detected compounds and their relative abundances (as percentages) were: heptacosan-1-ol (15.59%), tetracosanal (14.93%), n-octacosyl acetate (9.57%), cholesterol (5.11%), octacosylheptafluoro-butyrate (5.09%), octacosyl acetate (4.81%), stearyl aldehyde (4.45%), and cholest-4-en-3-one (4.08%).

## 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 *Salix alba* (willow)-derived ingredients in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products,

injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[16]

According to RLD submitted to CIR in 2024 and 2022 concentration of use data, Salix Alba (Willow) Bark Extract has the highest frequency and concentration of use; it is used in 1328 formulations at up to 0.5% in other suntan preparations (Table 5).[17,18] Concentration of use data on Salix Alba (Willow) Bark Powder, Salix Alba (Willow) Bark Water, Salix Alba (Willow) Extract, and Salix Alba (Willow) Flower Extract have not yet been received; however, a concentration of use survey is currently underway.

These ingredients may be incidentally ingested as they are used in products used in the mouth (e.g., Salix Alba (Willow) Bark Extract is used in mouthwashes and breath fresheners; concentration not reported). In addition, these ingredients may be used near the eye area (e.g., Salix Alba (Willow) Leaf Extract is used in eye makeup removers at 0.0005%) or result in mucous membrane exposure (e.g., Salix Alba (Willow) Bark Extract is used bath soaps and body washes; concentration not reported). Lastly, these ingredients are reported to be used in baby products (e.g., Salix Alba (Willow) Bark Extract is used in other baby products; concentration not reported).

These ingredients may be incidentally inhaled as they are used in spray (Salix Alba (Willow) Bark Extract is used in hair spray; concentration not reported) and powder formulations (Salix Alba (Willow) Bark Extract is used 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 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.

Some products containing *Salix alba* (willow)-derived ingredients may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. Some of the reported product categories for these ingredients as listed in the RLD do require designation if airbrush application is used (e.g., foundations), but no airbrush use was indicated. Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available, when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, 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. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

None of the *Salix alba* (willow)-derived ingredients named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union.[19]

### Non-Cosmetic

*Salix alba* (willow) bark has historically been used to treat various ailments such as pain, fever, inflammation, flu, and headaches; the analgesic, anti-pyretic, and anti-inflammatory properties are primarily attributed to salicin (an analogous precursor to acetylsalicylic acid) content.[6,20] Currently, *Salix alba* (willow) is used in dietary supplements (e.g., weight loss supplements), herbal treatments used for pain management, and fertilizers [8,21-23] These ingredients are also present in acne patches, wart treatments, nail fungal treatments, vitamin C serums, and various homeopathic treatments.[24,25]

According to the European Medicines Agency, willow bark supplements have several contraindications. They should be avoided by individuals with hypersensitivity to salicin, salicylates, or other non-steroidal anti-inflammatory drugs, those with active peptic ulcers, third-trimester pregnancy, glucose-6-phosphate dehydrogenase deficiency, severe liver or kidney dysfunction, coagulation disorders, and children and adolescents under 18 due to the risk of Reye's syndrome.[26] While this guidance specifically refers to willow bark derived from *Salix purpurea*, *Salix daphnoides*, and *Salix fragilis*, it is included herein, as *Salix alba* also contains salicylates and may warrant similar precautions. Similar precautions are required on labels of products containing *Salix alba* (willow) bark according to United States Pharmacopeia (USP) specifications.[4] Labels are required to state that these products should not be used in children, women who are pregnant or nursing, or by persons with known sensitivity to aspirin.

## TOXICOKINETIC STUDIES

No relevant toxicokinetics studies on *Salix alba*-derived ingredients were found in the published literature, and unpublished data were not submitted. In general, toxicokinetics 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

**In Vitro**

Salix Alba (Willow) Bark Extract

In an acute toxicity assay performed according to Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 423, a hydroalcoholic *Salix alba* (willow) bark extract (2000 mg/kg bw; 100% purity; water as vehicle) was given to female Wistar rats (3/group) via gavage.[2] The median lethal dose ($LD_{50}$) was determined to be > 2000 mg/kg bw. [19]

### Short-Term Toxicity Studies

**Animal**

Salix Alba (Willow) Bark Extract

A combined repeated-dose toxicity study with a reproductive/developmental toxicity test was performed in Wistar rats (12/sex/group) according to OECD TG 422.[2] Results regarding the reproductive toxicity parameters evaluated in this study can be found in the Developmental and Reproductive Toxicity section of this report. Animals were treated with 100, 300, or 1000 mg/kg bw/d of a hydroalcoholic *Salix alba (*willow) bark extract (water as vehicle; 100% purity), once a day, via gavage (controls given vehicle only). Males were treated for 28 d and females were treated for approximately 41 d. No test substance-related adverse effects were observed in this assay, and the no-observed-adverse-effect-level (NOAEL) for systemic toxicity was determined to be 1000 mg/kg bw/d.

## DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

**Animal**

Salix Alba (Willow) Bark Extract

As stated previously, a combined repeated-dose toxicity study with a reproductive/developmental toxicity test was performed in Wistar rats (12/sex/group) according to OECD TG 422.[2] Results regarding the systemic toxicity evaluated in this study can be found in the Short-Term Toxicity Studies section of this report. Males were treated for 28 d (14 d pre-mating and 14 d during/post-mating) and females were treated for 14 d pre-mating, for up to 14 d during the mating period and through gestation, and for up to 13 d post-partum. Treatments occurred daily via gavage using a hydroalcoholic *Salix alba* (willow) bark extract (100, 300, and 1000 mg/kg bw/d; water as vehicle; controls were treated with the vehicle only). There were no differences between control- and test item-treated groups with regard to reproductive ability, mating, or gestation indices. The parental NOAEL was determined to be 1000 mg/kg bw/d. In the F1 generation, statistically significantly lower thyroid gland weights were observed in the mid- and high-dosed groups compared to control pups. However, thyroid gland weights were well within the historical range, and no effects on thyroid hormone concentration levels were observed. No developmental or endocrine changes were observed in pups. The NOAEL for reproductive effects and pup development/survival was determined to be 1000 mg/kg bw/d.

## GENOTOXICITY STUDIES

Details regarding the genotoxicity studies summarized herein may be found in Table 6. A hydroalcoholic *Salix alba* (willow) bark extract yielded negative results in a bacterial reverse mutation assay (up to 5000 µg/plate; in water), an in vitro mammalian cell gene mutation test (up to 5000 µg/ml; in water), and in an in vitro mammalian cell micronucleus assay (at up to 2000 µg/ml; in saline).[2] All assays were performed with and without metabolic activation. A statistically significant elevation in deoxyribonucleic acid (DNA) damage was observed in peripheral blood mononuclear cells at concentrations of 50 µg/ml and higher in a comet assay using *Salix alba* (willow) bark extract (use of metabolic activation not stated).[20] However, no genotoxicity was observed in a comet assay performed in human hepatoma cell line (HepG2) cells using *Salix alba* (willow) bark extract (up to 100 µg/ml; use of metabolic activation and vehicle not stated). No genotoxicity was observed in a cytokinesis-block micronucleus assay performed in human peripheral blood leukocytes and HepG2 cells using *Salix alba* (willow) bark extract (up to 100 µg/ml; use of metabolic activation and vehicle not stated). Similarly, no genotoxicity was observed in an in vivo comet assay or an in vivo micronucleus assay. In both in vivo assays, *Salix alba* (willow) bark extract was given to mice at up to 2000 mg/kg bw in dimethyl sulfoxide (DMSO).

## ANTI-CARCINOGENICITY STUDIES

**In Vitro**

Salix Alba (Willow) Bark Extract

The ability of an ethanolic *Salix alba* (willow) bark extract to induce cytotoxicity in human leukemia-60 (HL-60) cells was evaluated.[6] Cells were incubated with 1, 2, 4, 6, 8, or 10 µg of the test substance for up to 24 h. The percent viability of

cells after 24 h treatment with the negative control, 1, 2, 4, 6, 8, and 10 µg of extract was 98, 93, 87, 38, 50, and 16%, respectively.

## DERMAL IRRITATION AND SENSITIZATION STUDIES

Details regarding the following dermal irritation, sensitization, and phototoxicity studies summarized below may be found in Table 7. A hydroalcoholic *Salix alba* (willow) bark extract, tested undiluted, was predicted to be non-irritating in an in vitro reconstructed human epidermis assay.[2] Aqueous *Salix alba* (willow) bark extract in DMSO was predicted to be sensitizing in two KeratinoSens™ assays; in one it was tested at up to 400 µg/ml, but in the other, the test concentration was not stated. Similarly, a hydroalcoholic *Salix alba* (willow) bark extract in DMSO was predicted to be sensitizing in a genomic allergen rapid detection (GARD) assay when tested at up to 500 µg/ml.

### Phototoxicity

A 3T3 neutral red reuptake phototoxicity assay was performed to evaluate the phototoxic potential of 1% Salix Alba (Willow) Bark Extract in ethanol.[28] Balb/c 3T3 cells were irradiated with 5 J/cm$^2$ ultraviolet A (UVA)/visible light (Vis) for 50 min, and the test substance was considered to be non-phototoxic. Similarly, Salix Alba (Willow) Bark Extract (vehicle not stated) was predicted to be non-phototoxic in an EpiDerm™ phototoxicity assay at concentrations up to 10% (vehicle not stated); the cells were irradiated with 6 J/cm$^2$ UVA for 60 min.[29]

## OCULAR IRRITATION STUDIES

### In Vitro

Salix Alba (Willow) Bark Extract

An in vitro ocular irritation assay using isolated chicken eyes (3/treatment with test substance and positive control (imidazole); 1 eye treated with negative control (saline)) was performed according to OECD TG 438.[2] Eyes were treated with the undiluted hydroalcoholic *Salix alba* (willow) bark extract (100% purity; 30 mg). The mean corneal opacity score was 0.5/4. Corneal swelling after 75 min of incubation was 0.5% (values ≤ 5% indicate minimal or no irritation). The fluorescein retention score was 1.67, which falls within the range indicative of severe irritation. Positive and negative controls gave expected results. The test substance was not classified as a severe irritant (Globally Harmonized System (GHS) category 1) and was also not classified as a non-irritant; therefore, it was concluded that further information is required for classification. An EpiOcular™ assay was performed according to OECD TG 492 using reconstructed human cornea-like epithelial tissue (2 replicates/group). Tissues were treated with a hydroalcoholic *Salix alba* (willow) bark extract (undiluted; 100% purity; 50 mg) for a 6-h exposure. Positive and negative controls used were methyl acetate and water, respectively. The test substance was predicted to be an irritant (mean cell viability was 14% compared to the negative control; below 60% is classified as irritating).

## CLINICAL STUDIES

### Case Reports

Salix Alba (Willow) Bark Extract

A 61-yr-old female presented with a sudden onset of shortness of breath and non-productive cough 30 min after taking a white willow bark supplement.[21] Evaluation revealed oxygen desaturation, severe hypoxemia, metabolic acidosis, bilateral interstitial infiltrates which led to a diagnosis of acute hypoxic respiratory failure secondary to severe acute respiratory distress syndrome from reaction to white willow bark. The patient improved following treatment with steroids, antihistamines, and oxygen.

A 25-yr-old woman presented to the emergency department with anaphylaxis requiring epinephrine, antihistamines, steroids, and volume resuscitation.[30] Medication history revealed that the patient ingested 2 capsules of weight loss supplement containing white willow bark. The patient reported a history of allergy to acetylsalicylic acid. No other causes for anaphylaxis were identified.

## SUMMARY

The safety of 6 *Salix alba* (willow)-derived ingredients is reviewed in this safety assessment. According to the *Dictionary*, all of these ingredients are reported to function in skin-conditioning agents in cosmetics, though additional functions are listed for the individual ingredients.

According to 2024 RLD and 2022 concentration of use data, Salix Alba (Willow) Bark Extract has the highest frequency and concentration of use. This ingredient is used in 1328 formulations at up to 0.5% in other suntan preparations.

An acute oral toxicity assay was performed using a hydroalcoholic *Salix alba* (willow) bark extract given to rats via gavage. The $LD_{50}$ in this assay was determined to be > 2000 mg/kg bw. No test substance-related systemic toxicity was observed in a combined repeated-dose and reproductive/developmental toxicity assay in which rats were given up to 1000 mg/kg bw/d of a *Salix alba* (willow) bark extract. The test substance was administered via gavage for 28 d in males (pre- and post-mating) and for 41 d in females (pre-mating, gestation, and post-partum). When reproductive and developmental

toxicity parameters were evaluated in this assay, the NOAEL for reproductive effects and pup development/survival was determined to be 1000 mg/kg bw/d.

No genotoxicity was observed when *Salix alba* (willow) bark extract was evaluated in a bacterial reverse mutation assay (up to 5000 µg/plate), an in vitro mammalian cell gene mutation test (up to 5000 µg/ml), and in an in vitro mammalian cell micronucleus assay (at up to 2000 µg/ml); all assay were performed with and without metabolic activation. A statistically significant elevation in DNA damage was observed in peripheral blood mononuclear cells at concentrations of 50 µg/ml and higher in a comet assay using *Salix alba* (willow) bark extract (use of metabolic activation not stated). However, no genotoxicity was observed in a comet assay performed in human hepatoma cell line (HepG2) cells using *Salix alba* (willow) bark extract (up to 100 µg/ml; use of metabolic activation not stated). Similarly, no genotoxicity was observed in a cytokinesis-block micronucleus assay performed in human peripheral blood leukocytes and HepG2 cells using *Salix alba* (willow) bark extract (up to 100 µg/ml; use of metabolic activation not stated), an in vivo comet assay, and an in vivo micronucleus assay. In both in vivo assays, *Salix alba* (willow) bark extract was given to mice at up to 2000 mg/kg bw.

An ethanolic *Salix alba* (willow) bark extract resulted in a decrease in cell viability of HL-60 cells in a concentration-dependent manner. Cells were incubated with 1 – 10 µg of the test substance.

A hydroalcoholic *Salix alba* (willow) bark extract, tested undiluted, was predicted to be non-irritating in an in vitro reconstructed human epidermis assay. Aqueous *Salix alba* (willow) bark extract was predicted to be sensitizing in a KeratinoSens™ assay when tested at up to 400 µg/ml and in an assay in which the test substance concentration was not stated. Similarly, a hydroalcoholic *Salix alba* (willow) bark extract was predicted to be sensitizing in a GARD assay when tested at up to 500 µg/ml. No phototoxicity was indicated in a 3T3 neutral reuptake assay using a 1% Salix Alba (Willow) Bark Extract or in an EpiDerm™ phototoxicity assay using Salix Alba (Willow) Extract at up to 10%.

An in vitro ocular irritation assay was performed using chicken eyes treated with undiluted hydroalcoholic *Salix alba* (willow) bark extract. The assay showed minimal corneal opacity and swelling, but fluorescein staining retention indicated severe irritation. The same test substance, tested undiluted, was considered an irritant in an EpiOcular™ assay.

A 61-yr-old woman developed acute hypoxic respiratory failure secondary to severe acute respiratory distress syndrome after ingesting a white willow bark supplement. Her condition improved with treatment that included steroids, antihistamines, and oxygen. Additionally, a published case report described a 25-yr-old patient with a known allergy to acetylsalicylic acid who presented to the emergency department with anaphylaxis following ingestion of a supplement containing white willow bark.

## INFORMATION SOUGHT

The following information on these *Salix alba* (willow)-derived ingredients as used in cosmetics is being sought for use in the resulting safety assessment:

- Method of manufacturing data
- Composition and impurities data
- Acute and repeated-dose toxicity data
- Dermal irritation and sensitization data at maximum concentrations of use

# TABLES

**Table 1. Definitions, idealized structures, and reported functions[1]**

| Ingredient/CAS No. | Definition | Function(s) |
|---|---|---|
| Salix Alba (Willow) Bark Extract (84082-82-6) | Salix Alba (Willow) Bark Extract is the extract of the bark of *Salix alba*. | hair conditioning agents<br>skin conditioning agents - occlusive |
| Salix Alba (Willow) Bark Powder | Salix Alba (Willow) Bark Powder is the powder obtained from the dried, ground bark of *Salix alba.* | absorbents<br>exfoliants<br>skin protectants |
| Salix Alba (Willow) Bark Water | Salix Alba (Willow) Bark Water is the aqueous solution of the steam distillate obtained from the bark of *Salix alba*. | fragrance ingredients |
| Salix Alba (Willow) Extract | Salix Alba (Willow) Extract is the extract of the whole plant, *Salix alba*. | antifungal agent<br>skin-conditioning agents – emollient<br>skin-conditioning agents – humectant |
| Salix Alba (Willow) Flower Extract | Salix Alba (Willow) Flower Extract is the extract of the flowers of *Salix alba.* | skin-conditioning agents – miscellaneous |
| Salix Alba (Willow) Leaf Extract (84082-82-6) | Salix Alba (Willow) Leaf Extract is the extract of the leaves of *Salix alba*. | skin conditioning agents - miscellaneous |

**Table 2. Chemical properties[2]**

| Property | Value |
|---|---|
| **Salix alba (willow) bark extract** | |
| Physical Form | solid particulate/powder |
| Color | brown |
| Odor | characteristic |
| Density (g/ml @ 20ºC) | 1.48 |
| Vapor Pressure (Pa @ ≤ 61ºC) | < 0.001 |
| Melting Point (ºC) | ≥ 160 |
| Water Solubility (mg/l @ 20ºC & pH = 7) | 50 |
| log $K_{ow}$ (@ 25ºC) | < 0.3 (measured); - 2.2 (extrapolated) |
| Mass Median Aerodynamic Diameter (µm) | 21 |

**Table 3. Composition of a methanolic Salix alba (willow) bark extract[12]**

| Constituent | Amount (mg/g dry weight) |
|---|---|
| **Salicylates** | |
| salicin | 0.91 |
| salicortin | 0.89 |
| total salicylate content | 1.80 |
| **Flavonoids** | |
| ampelopsin | 0.07 |
| quercetin-hexoside | 0.04 |
| other quercetin-derivatives | 0.02 |
| total flavonoids | 0.13 |
| **Flavan-3-ols** | |
| catechin | 1.26 |
| procyanidin B3 | 0.24 |
| total flavan-3-ols | 1.49 |
| **Phenolic Acid Derivatives** | |
| chlorogenic acid | 0.40 |
| coumaric acid derivative | 0.02 |
| neochlorogenic acid | 0.33 |
| total phenolic acid derivatives | 0.75 |
| **Other Phenolic Compounds** | |
| syringin | 0.30 |
| triadrin | 0.67 |
| total other phenolic compounds | 0.97 |

**Table 4. Composition of hydromethanolic extracts of Salix alba (willow) bark and leaves[13]**

| Constituent | Bark (mg/100 g dry weight) | Leaves (mg/100 g dry weight) |
|---|---|---|
| **Phenolic Acids** | | |
| caffeoylhexose I | 57.71 | 2.98 |
| caffeoylhexose II | 24.71 | ND |
| caffeoxyl hexose-deoxyhexoside I | 140 | ND |
| caffeoyl hexose-deoxyhexoside II | ND | 875.32 |
| 1-*O*-caffeoylquinic acid | ND | 117.43 |
| 3-*O*-caffeoylquinic acid | 41.96 | 386.31 |
| caffeoylhexose III | 240.49 | ND |
| caffeoylquinic acid dimer I | ND | 60.63 |
| caffeoylquinic acid dimer II | ND | 10.11 |
| 5-*O*-caffeoylquinic acid | ND | 37.85 |
| **Flavanols and Procyanidins** | | |
| (epi)catechin-(epi)gallocatechin I | 130.67 | ND |
| (epi)catechin-(epi)gallocatechin II | 10.09 | ND |
| (epi)catechin-(epi)gallocatechin III | 59.79 | ND |
| A-type procyanidin dimer digallate | 48.66 | ND |
| A-type procyanidin dimer I | 224.33 | ND |
| A-type procyanidin dimer II | 22.33 | 241.31 |
| A-type procyanidin dimer III | 9.22 | ND |
| B-type procyanidin trimer I | 22.90 | 241.43 |
| A-type procyanidin trimer I | 25.87 | ND |
| A-type procyanidin dimer IV | 14.27 | ND |
| (+)-catechin | 63.79 | ND |
| (-)-epicatechin | 176.49 | ND |
| epigallocatechin I | ND | 319.52 |
| A-type procyanidin trimer digallate | 99.25 | ND |
| A-type procyanidin trimer II | 15.07 | ND |
| B-type procyanidin trimer II | 40.79 | ND |
| B-type procyanidin trimer III | ND | 124.37 |
| epigallocatechin II | ND | 324.69 |
| B-type procyanidin tetramer I | 25.54 | ND |
| B-type procyanidin trimer IV | ND | 246.46 |
| B-type procyanidin tetramer II | 56.07 | ND |
| A-type procyanidin dimer V | 198.24 | ND |
| B-type procyanidin pentamer | ND | 118.11 |
| B-type procyanidin dimer I | ND | 395.23 |
| (epi)catechin methyl-hexoside I | 68.55 | ND |
| (epi)catechin methyl-hexoside II | 56.78 | ND |
| A-type procyanidin tetramer | 33.45 | ND |
| A-type procyanidin dimer VI | 94.91 | ND |
| A-type procyanidin trimer III | 103.61 | ND |
| (epi)catechin methyl-hexoside III | 96.21 | ND |
| (epi)catechin methyl-hexoside IV | 28.52 | ND |
| (epi)catechin-ethyl trimer | 70.45 | ND |
| **Flavanols** | | |
| quercetin 3-*O*-rutinoside | ND | 92.91 |
| quercetin methyl-pentoside | ND | 9.11 |
| quercetin acylated-deoxylhexoside I | ND | 166.51 |
| quercetin acylated-deoxyhexoside II | ND | 148.93 |
| isorhamnetin 3-O-rutinoside | ND | 459.80 |
| quercetin 3-O-galactoside | ND | 59.27 |
| quercetin 3-O-glucoside | ND | 98.43 |
| quercetin-acylated-hexoside I | ND | 180.03 |
| quercetin-acylated-hexoside II | ND | 413.14 |
| quercetin 3-O-hexoside | 10.47 | ND |
| isorhamnetin-acylated-hexoside I | ND | 4.65 |
| isorhamnetin-3-galactoside | ND | 145.89 |
| kaempferol pentoside | 6.58 | ND |
| isorhamnetin acylated-hexoside II | ND | 32.62 |
| isorhamnetin acylated-hexoside III | ND | 234.36 |
| kaempferol 3-O-galactoside | 12.54 | ND |
| isorhamnetin acylated-hexoside IV | ND | 28.56 |

ND = not detected

**Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[17,18]**

| | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) |
|---|---|---|---|---|---|---|
| | Salix Alba (Willow) Bark Extract | | Salix Alba (Willow) Bark Powder | | Salix Alba (Willow) Bark Water | |
| **Totals*** | **1328** | **0.00003 – 0.5** | **3** | **NS** | **13** | **NS** |
| **summarized by likely duration and exposure**** | | | | | | |
| ***Duration of Use*** | | | | | | |
| *Leave-On* | *913* | *0.00003 – 0.5* | *NR* | *NS* | *7* | *NS* |
| *Rinse-Off* | *390* | *0.0005 – 0.2* | *3* | *NS* | *6* | *NS* |
| *Diluted for (Bath) Use* | *1* | *NR* | *NR* | *NS* | *NR* | *NS* |
| *Permanent Tattoo Ink* | *NR* | *NR* | *NR* | *NS* | *NR* | *NS* |
| *Unknown* | *27* | *NR* | *NR* | *NS* | *NR* | *NS* |
| ***Exposure Type*** | | | | | | |
| Baby Products | 27 | NR | NR | NS | NR | NS |
| Children's Makeup | NR | NR | NR | NS | NR | NS |
| Eye Area | 15 | NR | NR | NS | 2 | NS |
| Incidental Ingestion | 11 | NR | NR | NS | NR | NS |
| Mucous Membrane | 61 | NR | 2 | NS | 1 | NS |
| Incidental Inhalation-Spray | 8; 336[a]; 538[b] | 0.1 – 0.5[a]; 0.00003 – 0.05[b] | 1[a] | NS | 4[a]; 3[b] | NS |
| Incidental Inhalation-Airbrush | NR | NR | NR | NS | NR | NS |
| Incidental Inhalation-Powder | 2; 538[b]; 10[c] | 0.00003 – 0.05[b] | NR | NS | 3[b] | NS |
| Dermal Contact | 1098 | 0.0005 – 0.5 | 3 | NS | 13 | NS |
| Deodorant (underarm) | 6 | 0.0042 | NR | NS | NR | NS |
| Hair - Non-Coloring | 186 | 0.00003 – 0.15 | NR | NS | NR | NS |
| Hair-Coloring | 5 | NR | NR | NS | NR | NS |
| Nail | 2 | NR | NR | NS | NR | NS |
| Tattoo Preparations | NR | NR | NR | NS | NR | NS |
| Other Preparations (Unknown Exposure Type) | 27 | NR | NR | NS | NR | NS |
| **as reported by product category** | | | | | | |
| ***Baby Products*** | | | | | | |
| Baby Shampoos | 2 | NR | | | | |
| Baby Lotions/Oils/Powders/Creams | 10 | NR | | | | |
| Other Baby Products | 10 (l.o.); 5 (r.o.) | NR | | | | |
| ***Bath Preparations (diluted for use)*** | | | | | | |
| Bubble Baths | 1 | NR | | | | |
| ***Eye Makeup Preparations (not children's)*** | | | | | | |
| Eye Shadow | 1 | NR | | | | |
| Eye Lotion | 7 | NR | | | 1 | NS |
| Eye Makeup Remover | 2 | NR | | | | |
| Eyelash and Eyebrow Adhesives/Glues/Sealants | 1 | NR | | | | |
| Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers) | 3 | NR | | | | |
| Other Eye Makeup Preparations | 1 | NR | | | 1 | NS |
| ***Fragrance Preparations*** | | | | | | |
| Perfumes | 1 | NR | | | | |
| Other Fragrance Preparation | 6 | NR | | | | |
| ***Hair Preparations (non-coloring)*** | | | | | | |
| Hair Conditioners | 11 (l.o.); 21 (r.o.) | 0.15 | | | | |
| Hair Sprays (aerosol fixatives) | 1 | NR | | | | |
| Rinses (non-coloring) | 8 | NR | | | | |
| Shampoos (non-coloring) | 41 (r.o.) | 0.15 | | | | |

**Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[17,18]**

| | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) |
|---|---|---|---|---|---|---|
| Tonics, Dressings, Other Hair Grooming Aids | 54 | 0.00003 – 0.008 | | | | |
| Wave Sets | 1 | NR | | | | |
| Other Hair Preparations | 28 (l.o.); 19 (r.o.) | NR | | | | |
| ***Hair Coloring Preparations*** | | | | | | |
| Hair Tints | 1 | NR | | | | |
| Hair Rinses (coloring) | 1 (l.o.); 1 (r.o.) | NR | | | | |
| Hair Shampoos (coloring) | 1 (r.o.) | NR | | | | |
| Other Hair Coloring Preparation | 1 (l.o.); 1 (r.o.) | NR | | | | |
| ***Makeup Preparations (not eye or children's)*** | | | | | | |
| Blushers and Rouges (all types) | 9 | NR | | | | |
| Face Powders | 2 | NR | | | | |
| Foundations | 10 (traditional application) | NR | | | | |
| Lipsticks and Lip Glosses | 9 | NR | | | | |
| Makeup Bases | 5 (traditional application) | NR | | | | |
| Makeup Fixatives | 3 | NR | | | | |
| Other Makeup Preparations | 2 (l.o.) | NR | | | | |
| ***Manicuring Preparations*** | | | | | | |
| Cuticle Softeners | 1 | NR | | | | |
| ***Oral Hygiene Products*** | | | | | | |
| Mouthwashes and Breath Fresheners | 1 | NR | | | | |
| Other Oral Products | 1 | NR | | | | |
| ***Personal Cleanliness*** | | | | | | |
| Bath Soaps and Body Washes | 35 | NR | 2 | NS | | |
| Deodorants (underarm) | 6 | 0.0042 (not spray) | | | | |
| Disposable Wipes | 1 | NR | | | | |
| Other Personal Cleanliness Products | 2 (l.o.); 11 (r.o.) | NR | | | 1 (r.o.) | NS |
| ***Shaving Preparations*** | | | | | | |
| Aftershave Lotions | 8 | 0.001 – 0.4 | | | | |
| Beard Softeners | 12 | NR | | | | |
| Pre-shave Lotions (all types) | 1 | NR | | | | |
| Shaving Cream (aerosol, brushless, lather) | 4 | NR | | | | |
| Other Shaving Preparations | 7 | 0.0005 | | | | |
| ***Skin Care Preparations*** | | | | | | |
| Cleansing | 135 | 0.0012 - 1 | | | | |
| Depilatories | 2 | 0.0005 | | | | |
| Face and Neck (excluding shaving preps) | 365 (l.o.); 71 (r.o.) | NR | | | 2 (l.o.); 1 (r.o.) | NS |
| Body and Hand (excluding shaving preps) | 30 (l.o.); 3 (r.o.) | NR | | | | |
| Moisturizing | 154 | 0.025 – 0.2 (not spray) | | | 2 | NS |
| Night | 12 | NR | | | | |
| Paste Masks (mud packs) | 33 | 0.2 | | | 1 | NS |
| Skin Fresheners | 42 | 0.1 | | | | |
| Other Skin Care Preparations | 54 (l.o.); 21 (r.o.) | 0.05 | 1 (r.o.) | NS | 1 (l.o.); 1 (r.o.) | NS |
| ***Suntan Preparations*** | | | | | | |
| Suntan Gels, Creams, and Liquids | 9 | NR | | | | |
| Indoor Tanning Preparations | NR | 0.0005 | | | | |
| Other Suntan Preparations | NR | 0.5 | | | | |

**Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[17,18]**

| | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) |
|---|---|---|---|---|---|---|
| ***Other Preparations (i.e., those that do not fit another category)*** | 27 | | | | | |
| | **Salix Alba (Willow) Extract** | | **Salix Alba (Willow) Flower Extract** | | **Salix Alba (Willow) Leaf Extract** | |
| **Totals*** | 10 | NS | 6 | NS | 51 | 0.0005 – 0.0053 |
| **summarized by likely duration and exposure**** | | | | | | |
| ***Duration of Use*** | | | | | | |
| *Leave-On* | *10* | *NS* | *6* | *NS* | *48* | *0.0053* |
| *Rinse-Off* | *NR* | *NS* | *NR* | *NS* | ***3*** | *0.0005* |
| *Diluted for (Bath) Use* | *NR* | *NS* | *NR* | *NS* | *NR* | *NR* |
| *Permanent Tattoo Ink* | *NR* | *NS* | *NR* | *NS* | *NR* | *NR* |
| *Unknown* | *NR* | *NS* | *NR* | *NS* | *NR* | *NR* |
| ***Exposure Type*** | | | | | | |
| Baby Products | NR | NS | NR | NS | NR | NR |
| Children's Makeup | NR | NS | NR | NS | NR | NR |
| Eye Area | NR | NS | NR | NS | NR | 0.0005 |
| Incidental Ingestion | NR | NS | 5 | NS | NR | NR |
| Mucous Membrane | NR | NS | 5 | NS | NR | NR |
| Incidental Inhalation-Spray | 4[a]; 6[b] | NS | NR | NS | 8[a]; 21[b] | NR |
| Incidental Inhalation-Airbrush | NR | NS | NR | NS | NR | NR |
| Incidental Inhalation-Powder | 6[b] | NS | NR | NS | 21[b] | 0.0053[c] |
| Dermal Contact | 10 | NS | 1 | NS | 49 | 0.0005 – 0.0053 |
| Deodorant (underarm) | NR | NS | NR | NS | NR | NR |
| Hair - Non-Coloring | NR | NS | NR | NS | 2 | NR |
| Hair-Coloring | NR | NS | NR | NS | NR | NR |
| Nail | NR | NS | NR | NS | NR | NR |
| Tattoo Preparations | NR | NS | NR | NS | NR | NR |
| Other Preparations (Unknown Exposure Type) | NR | NS | NR | NS | NR | NR |
| **as reported by product category** | | | | | | |
| ***Baby Products*** | | | | | | |
| Baby Shampoos | | | | | | |
| Baby Lotions/Oils/Powders/Creams | | | | | | |
| Other Baby Products | | | | | | |
| ***Bath Preparations (diluted for use)*** | | | | | | |
| Bubble Baths | | | | | | |
| ***Eye Makeup Preparations (not children's)*** | | | | | | |
| Eye Shadow | | | | | | |
| Eye Lotion | | | | | | |
| Eye Makeup Remover | | | | | NR | 0.0005 |
| Eyelash and Eyebrow Adhesives/Glues/Sealants | | | | | | |
| Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers) | | | | | | |
| Other Eye Makeup Preparations | | | | | | |
| ***Fragrance Preparations*** | | | | | | |
| Perfumes | | | | | | |
| Other Fragrance Preparation | | | | | | |
| ***Hair Preparations (non-coloring)*** | | | | | | |
| Hair Conditioners | | | | | | |
| Hair Sprays (aerosol fixatives) | | | | | | |

**Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[17,18]**

| | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) |
|---|---|---|---|---|---|---|
| Rinses (non-coloring) | | | | | | |
| Shampoos (non-coloring) | | | | | | |
| Tonics, Dressings, Other Hair Grooming Aids | | | | | | |
| Wave Sets | | | | | | |
| Other Hair Preparations | | | | | 2 (l.o.) | NR |
| ***Hair Coloring Preparations*** | | | | | | |
| Hair Tints | | | | | | |
| Hair Rinses (coloring) | | | | | | |
| Hair Shampoos (coloring) | | | | | | |
| Other Hair Coloring Preparation | | | | | | |
| ***Makeup Preparations (not eye or children's)*** | | | | | | |
| Blushers and Rouges (all types) | | | | | | |
| Face Powders | | | | | | |
| Foundations | | | | | 20 (traditional application) | NR |
| Lipsticks and Lip Glosses | | | 5 | NS | | |
| Makeup Bases | | | | | | |
| Makeup Fixatives | | | 1 | NS | | |
| Other Makeup Preparations | | | | | | |
| ***Manicuring Preparations*** | | | | | | |
| Cuticle Softeners | | | | | | |
| ***Oral Hygiene Products*** | | | | | | |
| Mouthwashes and Breath Fresheners | | | | | | |
| Other Oral Products | | | | | | |
| ***Personal Cleanliness*** | | | | | | |
| Bath Soaps and Body Washes | | | | | | |
| Deodorants (underarm) | | | | | | |
| Disposable Wipes | | | | | | |
| Other Personal Cleanliness Products | | | | | | |
| ***Shaving Preparations*** | | | | | | |
| Aftershave Lotions | | | | | | |
| Beard Softeners | | | | | | |
| Pre-shave Lotions (all types) | | | | | | |
| Shaving Cream (aerosol, brushless, lather) | | | | | | |
| Other Shaving Preparations | | | | | | |
| ***Skin Care Preparations*** | | | | | | |
| Cleansing | | | | | 2 | 0.0005 |
| Depilatories | | | | | | |
| Face and Neck (excluding shaving preps) | 6 (l.o.) | NS | | | 2 (l.o.); 1 (r.o.) | 0.0053 (not spray) |
| Body and Hand (excluding shaving preps) | | | | | 1 (l.o.) | |
| Moisturizing | 4 | NS | | | 2 | |
| Night | | | | | [19] | |
| Paste Masks (mud packs) | | | | | | |
| Skin Fresheners | | | | | | |
| Other Skin Care Preparations | | | | | | |
| ***Suntan Preparations*** | | | | | | |
| Suntan Gels, Creams, and Liquids | | | | | | |
| Indoor Tanning Preparations | | | | | | |

**Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[17,18]**

| | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) | # of Uses RLD (2024) | Max Conc of Use % (2022) |
|---|---|---|---|---|---|---|
| Other Suntan Preparations | | | | | | |
| ***Other Preparations (i.e., those that do not fit another category)*** | | | | | | |

NR – not reported
NS – a concentration of use survey is currently underway, but the results have not yet been received
l.o. – leave-on; r.o. – rinse-off
*The sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple ***exposure*** types.
**Likely duration and exposure are derived from survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
[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.

**Table 6. Genotoxicity studies**

| Test Article | Vehicle | Concentration/Dose | Test System | Protocol | Results | Reference |
|---|---|---|---|---|---|---|
| **IN VITRO** | | | | | | |
| hydroalcoholic *Salix alba* (willow) bark extract | water | 0.5, 1.58, 5, 15.81, 50, 158.1, 500, 1581, and 5000 µg/plate | *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and *Escherichia coli* WP2 | OECD TG 471; bacterial reverse mutation assay; performed with and without metabolic activation; appropriate positive and negative controls used | non-mutagenic; controls gave expected results | [2] |
| hydroalcoholic *Salix alba* (willow) bark extract | water | 62.5, 125, 250, 500, 1000, 2000, and 5000 µg/ml | Chinese hamster ovary cells | OECD TG 476; in vitro mammalian cell gene mutation test using Hprt and Xprt genes; performed with and without metabolic activation; appropriate positive and negative controls used | non-mutagenic; controls gave expected results | [2] |
| hydroalcoholic *Salix alba* (willow) bark extract | saline | without metabolic activation: 125, 250, 500, 750, 1000, 1500 and 2000 µg/ml<br><br>with metabolic activation: 125, 250, 500, 1000, 1500 and 2000 µg/ml | mouse lymphoma L5178Y cells | OECD TG 487; in vitro mammalian cell micronucleus assay; performed with and without metabolic activation; appropriate positive and negative controls used | non-genotoxic; controls gave expected results | [2] |
| *Salix alba* (willow) bark extract | NR | 5, 50, or 100 µg/ml | peripheral blood mononuclear cells | comet assay; 4-h incubation; use of metabolic activation not stated; appropriate positive and negative controls used | a statistically significant elevation in DNA damage was found between the negative control and groups treated with 50 or 100 µg/ml | [20] |
| *Salix alba* (willow) bark extract | NR | 5, 50, or 100 µg/ml | HepG2 cells | comet assay; 4-h incubation; use of metabolic activation not stated; appropriate positive and negative controls used | non-genotoxic; controls gave expected results | [20] |
| *Salix alba* (willow) bark extract | NR | 5, 50, or 100 µg/ml | human peripheral blood leukocytes | cytokinesis-block micronucleus assay; 28-h exposure; use of metabolic activation not stated; micronuclei analysis performed | non-genotoxic; controls gave expected results | [20] |
| *Salix alba* (willow) bark extract | NR | 5, 50, or 100 µg/ml | HepG2 cells | cytokinesis-block micronucleus assay; 24-h exposure; use of metabolic activation not stated; micronuclei analysis performed | non-genotoxic; controls gave expected results | [20] |
| **IN VIVO** | | | | | | |
| *Salix alba* (willow) bark extract | DMSO | 500, 1000, or 2000 mg/kg bw | male Swiss albino mice (6/group) | in vivo assay; gavage administration 1/x for 7 d; appropriate positive and negative controls used; animals killed 4 h after last treatment and cells (bone marrow cells) evaluated; micronucleus assay performed on cells | non-genotoxic; controls gave expected results | [31] |
| *Salix alba* (willow) bark extract | DMSO | 500, 1000, or 2000 mg/kg bw | male Swiss albino mice (6/group) | in vivo assay; gavage administration 1/x for 7 d; appropriate positive and negative controls used; animals killed 4 h after last treatment and cells (peripheral blood, heart and testes cells); comet assay performed on cells | non-genotoxic; controls gave expected results | [31] |

DMSO = dimethyl sulfoxide; DNA = deoxyribonucleic acid; HepG2 = human hepatoma cell line; HPRT = hypoxanthine-guanine phosphoribosyltransferase; NR = not reported; OECD = Oranisation for Economic Co-operation and Development; TG = test guideline; Xprt = xanthine-guanine phosphoribosyltransferase

**Table 7. Dermal irritation and sensitization studies**

| Test Article | Vehicle | Concentration/ Dose | Test Population/ System | Protocol | Results | Reference |
|---|---|---|---|---|---|---|
| **IRRITATION** | | | | | | |
| **IN VITRO** | | | | | | |
| hydroalcoholic *Salix alba* (willow) bark extract (100% purity) | none | 100%; 10 mg | reconstructed human epidermis (n = 3) | OECD TG 439; in vitro irritation reconstructed human epidermis assay; appropriate positive and negative controls used | non-irritating; mean tissue viability was 111.2%; controls gave expected results | 2 |
| **SENSITIZATION** | | | | | | |
| **IN VITRO** | | | | | | |
| aqueous *Salix alba* (willow) bark extract (100% purity) | DMSO | 0.2, 0.39, 0.78. 1.56, 3.1, 6.3, 13, 25, 50, 100, 200, and 400 µg/ml | immortalized human skin keratinocytes | OECD TG 442D; KeratinoSens™ assay; appropriate positive and negative controls used | predicted to be sensitizing<br><br>The $I_{max}$ was determined to be 5.51 and the $EC_{1.5}$ concentration was 152.33 µg/ml. The cell viability at the $EC_{1.5}$ concentration was higher than 70%, indicating a positive prediction for sensitization. Positive and negative controls gave expected results | 2 |
| aqueous *Salix alba* (willow) bark extract (100% purity) | DMSO | NR | immortalized human skin keratinocytes | OECD TG 442D; KeratinoSens™ assay; appropriate positive and negative controls used | predicted to be sensitizing<br><br>The $I_{max}$ values and $EC_{1.5}$ values were determined to be 3.99/7.03 and 118.1/179.55 µg/ml, respectively. At the $EC_{1.5}$, in both repetitions, cell viability was higher than 70%. Positive and negative controls gave expected results. | 2 |
| hydroalcoholic *Salix alba* (willow) bark extract (100% purity) | DMSO | 1, 5 10, 50, 100, 200, 300,400, and 500 µg/ml | dendritic cell line | GARD assay (predicts sensitization by evaluating changes in genomic biomarker expression; positive reactions observed if test substance triggers sensitization-related pathways); 24-h incubation, cell viability measured and RNA extracted and evaluated (RNA expression profiles analyzed); appropriate positive and negative controls used | predicted to be sensitizing<br><br>The mean decision value was 1.76. Values > 0 indicate positive results. Positive and negative controls gave expected results. | 2 |
| **PHOTOTOXICITY** | | | | | | |
| **IN VITRO** | | | | | | |
| Salix Alba (Willow) Bark Extract | ethanol | 1% | Balb/c 3T3 (clone A31) mouse fibroblast cells | OECD TG 432; 3T3 neutral red reuptake phototoxicity assay; cells incubated for 60 min then irradiated or left non-irradiated with UVA/Vis, 5 J/cm$^2$ for 50 min; appropriate positive and negative controls used | non-phototoxic | 28 |
| Salix Alba (Willow) Bark Extract | NR | 0.5, 1.5, 5, and 10% | reconstructed human epidermis | EpiDerm™ model assay; test substance applied to tissues and incubated overnight; appropriate tissues were irradiated with UVA (6 J/cm$^2$) for 60 min; some tissues non-irradiated for use as control; appropriate positive and negative controls used | non-phototoxic | 29 |

DMSO = dimethyl sulfoxide; $EC_{1.5}$ = effective concentration of a test chemical that induces a 1.5-fold increase in luciferase activity; GARD = genomic allergen rapid detection; $I_{max}$ = mean maximal luciferase activity; NR = not reported; OECD = Organisation for Economic Co-operation and Development; RNA = ribonucleic acid; TG = test guideline; UVA = ultraviolet A; Vis = visible light

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