



Safety Statement

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Product Name & Code:

ABS Willow Bark Extract (10200)
ABS Willow Bark Extract Powder (10224)
ABS White Willow Bark Extract Powder (10229)
ABS White Willow Bark Extract (10230)
ABS Willow Bark Extract 30% (20100)
ACB White Willow Bark Extract 20% (20199)
ACB Willow Bark Extract 20% (20200)

INCI Name: Please refer to individual product specifications.

To continue to be compliant with animal testing restrictions of materials in Europe, Active Concepts, LLC does not test any of our materials on animal subjects. For this reason, a No Observed Adverse Effect Level (NOAEL) has not been determined for any products mentioned in this statement and must instead be estimated.

White willow bark (*Salix alba*) contains a variety of compounds, including glycosides, tannins, flavonoids, saligenin, acids and aldehydes¹. Natural salicylates are present in Active Concepts, LLC's willow bark products from 9.8 to 65.0%. Please refer to product specifications for the individual ranges for each product.

Active Concepts, LLC tests for natural salicylate content using High Performance Liquid Chromatography (HPLC). For this method to accurately measure the percentage of salicylates, it must convert the salicylates back into their acid forms. Therefore many of the specifications for these products will say salicylates (measured as salicylic acid) or something similar, referring to the fact that measuring as salicylic acid is simply an artifact of the test method.

The concept of salicylates vs. salicylic acid is further explored when discussing solubility in water. Salicylic acid has a notoriously low solubility in water (approximately 0.2% at room temperature). All of the aqueous willow bark extracts being discussed contain at least 9.8% salicylates (tested as salicylic acid). Therefore, it is reasonable to conclude that these extracts do in fact contain salicylates, not actual salicylic acid.

The European Medicines Agency completed an *Assessment Report on Salicis Cortex (Willow Bark) and Herbal Preparation (s) Thereof with Well-Established Use and Traditional Use* which outlines a wide variety of pharmacological and toxicological findings when taken orally.

This report classifies all of Active Concepts, LLC's willow bark extracts as quantifiable herbal preparations². Willow bark extracts must contain a minimum 5.0% of total salicylic derivatives to be considered for this type of use as determined by European Pharmacopoeia (04/2008:2312).

¹ Highfield, Ellen S. and Kathi J. Kemper, MD, MPH. The Longwood Herbal Task Force. <http://www.longwoodherbal.org/willowbark/willow.pdf>

² European Medicines Agency: Evaluation of Medicines for Human Use. *Assessment report on Salicis Cortex (Willow Bark) and Herbal Preparations Thereof with Well Established use and Traditional Use*. London, 26, September 2009. Doc Ref: EMEA/HMPC/295337/2007

³ European Commission: Health and Consumers. Cosmetics: CosIng. <http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=29470>

⁴ TOXNET Hazardous Substances Database: Salix alba. "Selenium Compounds". <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?/temp/~S7vGzO:2>

⁵ WHO Monographs on Selected Medicinal Plants: Volume 4. World Health Organization. <http://www.who.int/medicines/areas/traditional/SelectMonoVol4.pdf>

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The European Scientific Cooperative on Phytotherapy has approved the use of aqueous extracts of willow bark to contain 120 – 240 mg of total salicin per day when taken orally. Similarly, this was also accepted in Germany as a marketing authorization that grants the use of willow bark extract with a maximal daily dose range of 120 mg to 240 mg of salicin.³ Allergic skin reactions have been noted when willow bark dry extracts (daily doses of 120 – 240mg) where administered during studies as reported by the European Medicines Agency.

There may be concern regarding selenium content in extracts of *Salix alba*⁴, but the manufacturing processes employed by Active Concepts, LLC tightly control heavy metal content. These processes make the selenium content non-detectable.

The World Health Organization published a compilation of data related to several plant groups, one being Cortex Salicis, which consists of bark from young branches of *Salix alba*, *Salix daphnoides*, *Salix fragilis*, *Salix purpurea*, and other *Salix* species. Toxicology of bark extracts was addressed, naming a study where 40% of an ethanolic extract was delivered intragastrically to rats at a dose of 1.6 mL/kg for 13 weeks. This extract had no effect on kidney or liver function, cholesterol, or hematological parameters. The animals were evaluated after death, and these analyses showed no pathological changes in the brain, heart, lungs, bones, kidneys, liver, reproductive organs, mammary tissue, stomach, or intestines.⁵

Active Concepts, LLC’s willow bark extracts are intended for topical applications. A Human Subject Repeat Insult Patch Test evaluation was completed to determine if a spray dried white willow bark extract (ABS White Willow Bark Extract Powder) would be classified as an irritant or sensitizing agent. The powder was diluted to a 5% solution in water and 0.2ml (or 0.2g) was applied to an area of 1cm². The procedure is repeated until a series of nine consecutive ‘open patch’ applications have been made every Monday, Wednesday, and Friday for three consecutive weeks. Under the reported testing conditions, results indicated that the powdered white willow bark extract was not a primary sensitizer and a non-irritating material. Please find attached a copy of these results.

Overall, the daily exposure to salicylates when using ABS White Willow Bark Extract Powder topically is 4.3g/kg/day assuming the reasonable reservoir represented by the skin under the 1cm² patch given salicylates partition coefficient can be represented at a mass of 1 g. This is calculated using the following formula.

Dose tested	0.2g
Dilution	5%
Total application during study	9
Length of study (days)	21

$$\text{Weighted Dose: } \frac{0.2 \times 9 \times .05}{21} = 0.0043\text{g/day}$$

$$0.0043\text{g/day} \times 1,000 \text{ g/kg} = 4.3\text{g/kg/day}$$

¹ Highfield, Ellen S. and Kathi J. Kemper, MD, MPH. The Longwood Herbal Task Force. <http://www.longwoodherbal.org/willowbark/willow.pdf>

² European Medicines Agency: Evaluation of Medicines for Human Use. *Assessment report on Salicis Cortex (Willow Bark) and Herbal Preparations Thereof with Well Established use and Traditional Use*. London, 26, September 2009. Doc Ref: EMEA/HMPC/295337/2007

³ European Commission: Health and Consumers. Cosmetics: CosIng. <http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=29470>

⁴ TOXNET Hazardous Substances Database: Salix alba. “Selenium Compounds”. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?/temp/~S7vGzO:2>

⁵ WHO Monographs on Selected Medicinal Plants: Volume 4. World Health Organization. <http://www.who.int/medicines/areas/traditional/SelectMonoVol4.pdf>

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Dermal and ocular irritation studies have been conducted for the following products and are attached for reference. All products were determined to be non-irritants at the appropriate use levels.

10200 ABS Willow Bark Extract
10229 ABS White Willow Bark Extract Powder
10230 ABS White Willow Bark Extract
20199 ACB White Willow Bark Extract 20%
20200 ACB Willow Bark Extract 20%

Also, a Bacterial Reverse Mutation (AMES) test was performed on 10200 ABS Willow Bark Extract. As seen in the attached report, ABS Willow Bark Extract did not cause a mutagenic response in any strains.

Global regulations for salicylic acid and its salts are as follows:

- Europe
 - Maximum authorized concentration up to 3.00% (0.50% as acid) when used other than a preservative, depending on the application:
 - Rinse-off Products: Up to 3.00
 - Other Products: Up to 2.00%
 - Labeling Requirements: Not be used in preparations for children under 3 years of age
 - Restrictions: Not to be used for children under 3 years of age, except for shampoos
- USA
 - Safe when formulated to avoid irritation and to avoid increasing sun sensitivity
- Japan
 - Maximum authorized concentration:
 - Salicylic Acid Salts: 1.00 as total (per 100 grams)
 - Salicylic Acid: 0.20 (per 100 grams)
- Canada
 - Maximum concentration 2.00%
- China, Brazil, Phillipines (ASEAN), Mercosur Countries
 - Maximum authorized concentration 0.50% (as acid)
 - Labeling Requirements: Not be used in preparations for children under 3 years of age
 - Restrictions: Not to be used for children under 3 years of age, except for shampoos
- Mexico
 - Maximum authorized concentration 0.50% (as acid)
 - Limitations: Not to be used in preparations for children under 3 years of age

Please note that the maximum suggested use level for Active Concepts, LLC's willow bark extracts is 6.5% salicylates (when using the powdered extract at 10%). The aqueous extracts generally have a maximum salicylate content of 3.2% when used at recommended use levels. For specific use concentrations, please refer to the individual products' Technical Data Sheets. No further testing is required.

¹ Highfield, Ellen S. and Kathi J. Kemper, MD, MPH. The Longwood Herbal Task Force. <http://www.longwoodherbal.org/willowbark/willow.pdf>

² European Medicines Agency: Evaluation of Medicines for Human Use. *Assessment report on Salicis Cortex (Willow Bark) and Herbal Preparations Thereof with Well Established use and Traditional Use*. London, 26, September 2009. Doc Ref: EMEA/HMPC/295337/2007

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