Safety Assessment of *Scutellaria baicalensis*-Derived Ingredients as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: August 22, 2019
Panel Date: September 16-17, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Date: August 22, 2019

Subject: Draft Report on *Scutellaria baicalensis*-Derived Ingredients

Enclosed is a draft report on 4 *Scutellaria baicalensis*-derived ingredients. This is the first time the Panel is seeing a safety assessment of cosmetic ingredients derived from the herb, *Scutellaria baicalensis*. A Scientific Literature Review (SLR) was announced on June 20, 2019.

In addition to data found in the published literature, the attached report (*scutel092019rep*) contains the following unpublished data that were received from the Council:

(1) Use concentration data on all *Scutellaria baicalensis*-derived ingredients (*scutel092019data1 and scutel092019data2* files)
(2) Use concentration data on Scutellaria Baicalensis Sprout Extract (*scutel092019data3 and scutel092019data4* files)
(3) Method of manufacture data on Scutellaria Baicalensis Root Extract (different extractants) (*scutel092019data5* file)
(4) Chemical characterization data on Scutellaria Baicalensis Root Extract trade name materials (*scutel092019data5* file)
(5) Impurities data on a Scutellaria Baicalensis Root Extract trade name material (*scutel092019data5* file)
(6) Human skin irritation and sensitization data on Scutellaria Baicalensis Root Extract trade name materials (*scutel092019data5* file)

Additionally, the attached comments on the SLR (*scutel092019pcpc*) that were received from the Council have been addressed. Also included in this package for your review are the CIR report history (*scutel092019hist*), flow chart (scutel*092019flow*), literature search strategy (*scutel092019strat*), ingredient data profile (*scutel092019prof*), and 2019 FDA VCRP data (*scutel092019fda*).

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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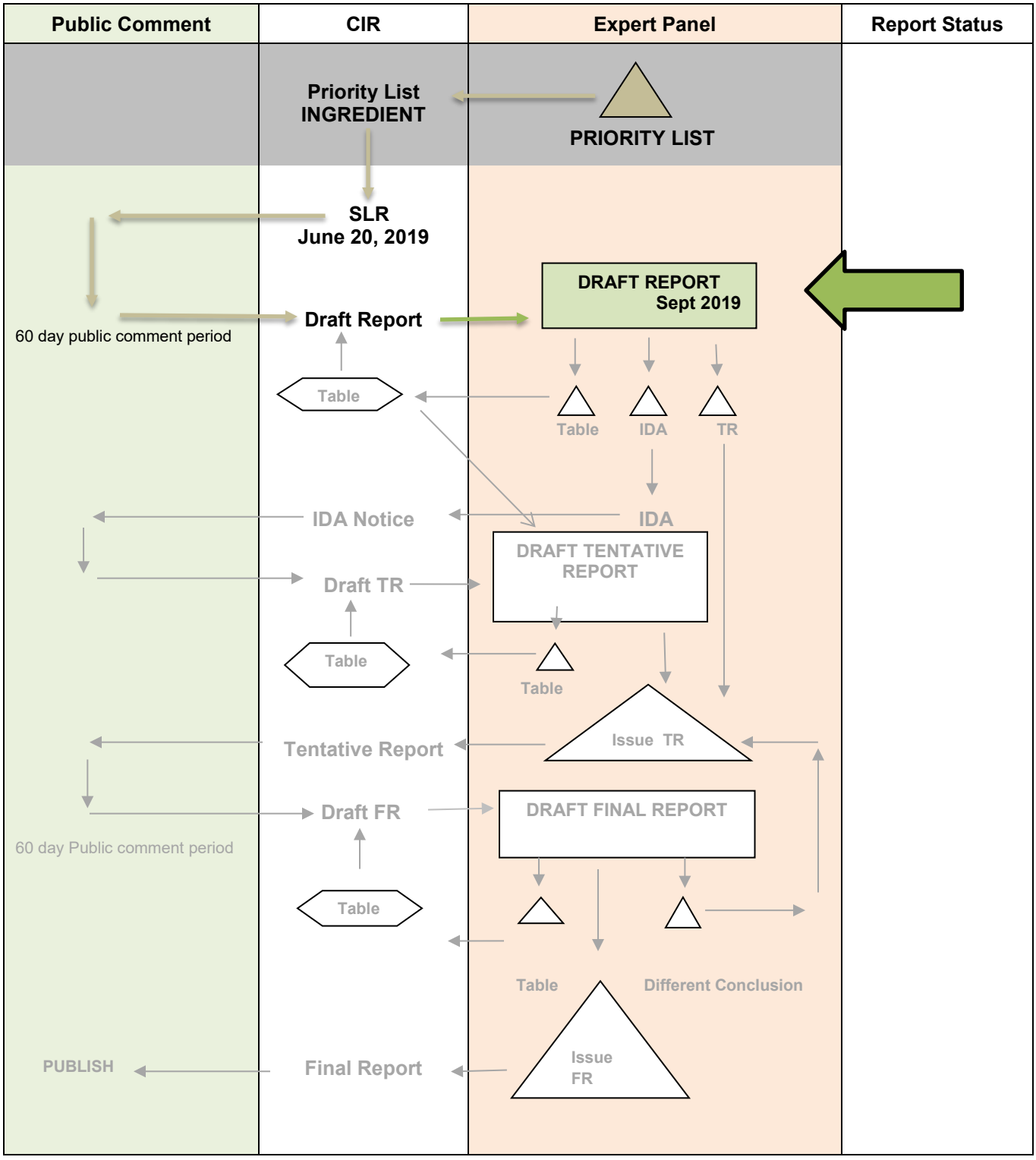
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Scutellaria baicalensis*-derived Ingredients

MEETING September 2019



CIR History of:

Scutellaria baicalensis-derived Ingredients

A Scientific Literature Review (SLR) on *Scutellaria baicalensis* -Derived Ingredients was issued on June 20, 2019. Comments and unpublished data were received from the Council before/after announcement of the SLR.

Draft Report, Teams/Panel: September 16-17, 2019

The draft report has been revised to include the following unpublished data that were received from the Council:

(1) Use concentration data on all *Scutellaria baicalensis*-derived Ingredients
(2) Use concentration data on Scutellaria Baicalensis Sprout Extract
(3) Method of manufacture data on Scutellaria Baicalensis Root Extract (different extractants)
(4) Chemical characterization data on Scutellaria Baicalensis Root Extract trade name materials
(5) Impurities data on a Scutellaria Baicalensis Root Extract trade name material
(6) Human skin irritation and sensitization data on Scutellaria Baicalensis Root Extract trade name materials

Comments on the safety assessment that were received from the Council have been addressed, and the report has been updated to include unpublished data (stated above) that were received from the Council.

Scutellaria baicalensis-derived Ingredients Data Profile* –September 16-17, 2019 – Wilbur Johnson, Jr.																														
						Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents	Impurities	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Scutellaria Baicalensis Extract	X			X	X		X																							X
Scutellaria Baicalensis Root Extract	X		X	X	X		X								X	X					X	X			X	X				
Scutellaria Baicalensis Root Powder																															
Scutellaria Baicalensis Sprout Extract	X																													

* “X” indicates that data were available in a category for the ingredient

[

Scutellaria Baicalensis-Derived Ingredients – 5/10/2019; 7/29/19]

Ingredient	CAS #	InfoBase	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Scutellaria Baicalensis Root Extract	94279-99-9	Yes	6/3	92/3	No	Yes	No	No	No	No	No	No	No	No	No	No	
Scutellaria Baicalensis Extract	94279-99-9	Yes	191/14	293/11	No	Yes	REACH PreReg. – No Dossier	No	No	No	No	No	No	No	No	No	
Scutellaria Baicalensis Root Powder	94279-99-9	Yes	0	7/0	No	Yes	No	No	No	No	No	No	No	No	No	No	
Scutellaria Baicalensis Sprout Extract	94279-99-9	Yes	0	2/0	No	No	No	No	No	No	No	No	No	No	No	No	
94279-99		Yes	0	717/14	No	Yes	REACH PreReg. – No Dossier	No	No	No	No	No	No	No	No	No	

Search Strategy

[*document search strategy used for PubMed and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

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INTRODUCTION

The safety of the following 4 *Scutellaria baicalensis*-derived ingredients, as used in cosmetics, is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment.

Scutellaria Baicalensis Extract
Scutellaria Baicalensis Root Extract
Scutellaria Baicalensis Root Powder
Scutellaria Baicalensis Sprout Extract

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients, collectively, are of the same genus and species and have the following reported functions in cosmetics: antimicrobial agent, skin conditioning agent, abrasives, fragrance ingredients, skin protectants, and antioxidants (See Table 1).[1] However, these ingredients do not have any functions in common.

Botanicals, such as *Scutellaria baicalensis*-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, CIR is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex mixture. CIR is not reviewing the potential toxicity of the individual constituents.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

In many of the published studies, it is not known how the substance being tested compares to the cosmetic ingredient. Therefore, if it is not known whether the substance being discussed is a cosmetic ingredient, the test substance will be identified by genus and species (e.g., "a *Scutellaria baicalensis* extract"). If it is known that the substance is a cosmetic ingredient, INCI nomenclature (e.g., "Scutellaria Baicalensis Extract") will be used; italics are not used in INCI names.

CHEMISTRY

Definition

The definitions and functions in cosmetics of the 4 *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment are presented in Table 1.[1] All of these ingredients are derived from the same genus and species, and from either the root or the sprout plant parts. The root is defined as an organ of the plant that absorbs and transports water and nutrients, lacks leaves and nodules, and is usually underground. The sprout is defined as a seedling, germinating seed, and any new growth of a plant from a stem such as a new branch or a bud.

Plant Identification

Scutellaria baicalensis Georgi is an herb of the Lamiaceae family (i.e., mint family) and Scutellarioideae subfamily.[2,3] Baikal skullcap and Chinese skullcap are common names for this herb, which is native to the Asia-Temperate geographical region that includes Siberia, Mongolia, Russian (far east), China, and Korea. *Scutellaria radix* is defined as the root of *Scutellaria baicalensis* Georgi.[4]

Physical and Chemicals Properties

Scutellaria Baicalensis Root Extract

In an ultraviolet (UV) spectral analysis of a *Scutellaria baicalensis* root extract (aqueous ethanol extract), an absorption peak between 200 and 250 nm (within the mid-wavelength UV (UVB)) and an absorption peak between 250 and 300 nm (crossing both UVB and short-wavelength (UVC)) were observed.[4]

Method of Manufacture

Scutellaria Baicalensis Root Extract

Cosmetic Ingredient

Data on the methods of manufacture of Scutellaria Baicalensis Root Extract (using different extractants) were provided by the Personal Care Products Council.[7]

Scutellaria Baicalensis Root Extract (90% ethanol extract)

Dried raw material → extract with 90 vol% ethanolic solution → filtrate → concentration → concentration adjustment (50 vol% ethanolic solution) → sedimentation → filtrate → packaging

Scutellaria Baicalensis Root Extract (30% ethanol extract)

Dried raw material → extract with 30 vol% ethanolic solution → filtrate → concentration → add squalene → sedimentation → filtrate → packaging

Scutellaria Baicalensis Root Extract (butylene glycol extract)

Dried raw material → extract with 50 vol% 1,3-butylene glycolic solution → filtrate → sedimentation → filtrate → packaging

General Information

A method of preparation of a *Scutellaria baicalensis* root extract from a published study is summarized as follows.[5] Briefly, the dried roots of *Scutellaria baicalensis* are ground into powder (60-mesh) and 250 g are extracted twice with 10 volumes of boiling purified water for 1 h. The supernatants are then combined, filtered, and lyophilized. The extract (powder) is then stored at 4 ºC until use.

In a method of preparation from another study, *Scutellaria baicalensis* roots were chopped into pieces, immersed in distilled water for 1 h, and then extracted under thermal reflux for 1 h, twice.[6] The extract was filtrated using analytical filter paper and evaporated to dryness using a rotary evaporator at 60 ºC under reduced pressure. The dried residue was dissolved in distilled water to yield a final concentration of 0.3 g/L.

Composition

Scutellaria Baicalensis Extract

Phytochemical analyses have detected and quantified the flavonoids baicalin, baicalein, scutellarin, wogonin, and the human neurohormones, melatonin and serotonin, in leaf and stem tissues from *Scutellaria baicalensis*.[8] The extraction of dried slices of *Scutellaria baicalensis* with ethanol has yielded a number of chemical constituents, including various glucuronides and flavones (See Table 2).[9]

Scutellaria Baicalensis Root Extract

The content of major flavonoids in a *Scutellaria baicalensis* root extract (250 g) have been determined to be: baicalin (406 mg/g extract), wogonoside (155 mg/g extract), 7-O-β-D-glucuronide (53.8 mg/g extract), baicalein (31.7 mg/g extract), wogonin (30.5 mg/g extract), and oroxylin A (7.24 mg/g extract).[5] The total content of these 6 main flavonoids accounted for 68.5% of the extract.

A Scutellaria Baicalensis Root Extract trade name mixture (30% ethanol extract) is reported to contain flavonoid compounds.[7] Another Scutellaria Baicalensis Root Extract trade name mixture (90% ethanol and butylene glycol extracts) contains tannin and flavonoid compounds.

Scutellaria Baicalensis Root Powder

A *Scutellaria baicalensis* root (dried root) contains a variety of flavones, phenylethanoids, amino acids, sterols, and essential oils.[5] The major flavonoid glycosides of this material include baicalin, wogonoside, oroxylin A 7-O-β-D-glucuronide, and their aglycones baicalein, wogonin and oroxylin A.[5,10] Baicalin is the most abundant flavonoid constituent of this *Scutellaria baicalensis* root. Minor flavonoids that have been identified in this *Scutellaria baicalensis* root include: viscidulin III-2-O-β-D-glucoside; 5,7,2,5-tetrahydroxyflavone; (-)-eriodictyol; rivularin; chrysin 8-C-β-D-glucopyranoside; and 5,2'-dihydroxy-6,7,8,3'-tetramethoxyflavone.[11]

Impurities

Scutellaria Baicalensis Extract

The results of a high-performance thin-layer chromatographic analysis of a *Scutellaria baicalensis* extract have indicated the absence of *Teucrium chamaedrys* (Gemander), which has been reported as an adulterant of *Scutellaria lateriflora* (American skullcap) herbal preparations.[12] *Teucrium chamaedrys* is a species of ornamental plant native to Mediterranean region of Europe and North Africa, and to the Middle East as far east as Iran.

Scutellaria Baicalensis Root Extract

A Scutellaria Baicalensis Root Extract trade name mixture (ethanol and butylene glycol extracts) is reported to contain no more than 20 ppm heavy metals and no more than 2 ppm arsenic.[7]

USE

Cosmetic

The safety of *Scutellaria baicalensis*-derived ingredients is evaluated based on data received from the United States Food and Drug Administration (US 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 FDA's Voluntary Cosmetic Registration Program (VCRP) database.[13] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Council, of maximum reported use concentrations by product category.[14,15]

According to 2019 VCRP data, Scutellaria Baicalensis Root Extract is reported to be used in 419 cosmetic products (338 leave-on products, 81 rinse-off products).[13] Of the *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency. The results of concentration of use surveys conducted by the Council in 2018 and 2019 indicate that Scutellaria Baicalensis Root Extract is used at maximum use concentrations up to 0.5% in leave-on products (moisturizing products).[14,15] This is the highest use concentrations in leave-on products that is being reported for the *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment. Further use data are presented in Table 3.

According to VCRP and Council survey data, Scutellaria Baicalensis Root Powder is not currently in use in cosmetic products.

Cosmetic products containing *Scutellaria baicalensis*-derived ingredients may be applied to the skin or, incidentally, may come in contact with the eyes (e.g., Scutellaria Baicalensis Root Extract at concentrations up to 0.07% in eye shadows). Scutellaria Baicalensis Root Extract and Scutellaria Baicalensis Sprout Extract are used in products that come in contact with mucous membranes during product use (maximum ingredient use concentrations of 0.0045% (lipstick) and 0.0002% (bath soaps and detergents), respectively). Additionally, Scutellaria Baicalensis Root Extract could be incidentally ingested (maximum use concentrations up to 0.0045% (lipstick)). Products containing *Scutellaria baicalensis*-derived ingredients may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Non-Cosmetic

Scutellaria Baicalensis Root Extract and Scutellaria Baicalensis Root Powder

Scutellaria Radix, known as Huangqin in Chinese, is the dried root of *Scutellaria baicalensis* Georgi. It is a well-known traditional herbal medicine that is used to treat inflammation, cardiovascular diseases, and respiratory and gastrointestinal infections.[5] *Scutellaria baicalensis* Georgi is one of the 50 fundamental herbs of traditional Chinese medicine, and pharmacological effects of *Scutellaria baicalensis* have been described.[5,11,16]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Scutellaria Baicalensis Extract

The toxicokinetics of *Scutellaria baicalensis* extract (ethanol extract) was studied using groups of Sprague-Dawley rats.[17] *Scutellaria baicalensis* herb (plant part not stated) was extracted in this study. In an oral absorption experiment, a *Scutellaria baicalensis* extract (single dose of 2.5 mL/kg) was administered (method not stated) to 6 Sprague-Dawley rats, after which blood samples were collected. The blood concentration of baicalin (a flavone component of the extract) quickly reached its peak, suggesting that it was absorbed rapidly and eliminated slowly. In the distribution experiment, the extract (2.5 mL/kg) was administered orally to 30 Sprague-Dawley rats. The animals were killed and tissue samples from the following organs were collected at various intervals (15, 30, 60, 120, 360, and 600 min): heart, liver, lung, kidney, stomach, spleen, brain, and intestines. Baicalin was detected in all of the tissues that were collected. The amount of baicalin that was

found in the brain indicated that this flavone could pass the blood-brain barrier. Baicalein (another flavone component) was also detected in the liver, heart, lung, kidney, stomach, and intestine. Another experiment that was performed involved 6 rats that were dosed orally (method not stated) with the extract (2.5 mL/kg). Urine and feces were collected at different time points (0 - 4 h, 4 - 8 h, 8 - 12 h, 12 - 24 h post-dosing). Baicalin and baicalein were detected in the urine and feces after dosing. The urinary cumulative excretion of baicalin was 0.12% and the fecal cumulative excretion of baicalin was 0.48% of the dose up to 24 h post-administration. The urinary cumulative excretion of baicalein was 0.05% and the fecal cumulative excretion of baicalein was 0.04% of the dose up to 24 h post-administration.

Scutellaria Baicalensis Root Extract

Metabolism and excretion of an orally (gavage)-administered *Scutellaria baicalensis* root extract (aqueous extract) were evaluated using groups of male Sprague-Dawley rats.[6] The first experiment involved 2 groups of 6 fasted rats (test and control groups). The aqueous extract (dissolved in distilled water prior to dosing) was administered by gavage at a dose of 4.5 g/kg bw. Control animals received distilled water (5 mL). Urine and feces samples were collected at 12 h post-dosing. In the second experiment, another group of 6 fasted rats was dosed by gavage with the test substance, and bile samples were collected from the cannulated bile duct within 12 h. Four parent components (from *Scutellaria baicalensis* root) and a total of 15 metabolites (sulfate and glucuronide conjugates, and hydroxylated, methylated, acetylated, and deoxygenated products) were detected, with most present in the urine. The metabolites identified are presented in Table 4.

A *Scutellaria baicalensis* root extract (suspended in an aqueous 0.5% carboxymethyl cellulose sodium salt solution, to a concentration of 100 mg/mL) was administered orally (method not stated) to fasted male Sprague-Dawley rats (number not stated) at a dose of 800 mg/kg (equivalent to baicalin (324.80 mg/kg), wogonoside (124.00 mg/kg), oroxylin A 7-O-β-D-glucuronide (43.04 mg/kg), baicalein (25.36 mg/kg), wogonin (24.40 mg/kg), and oroxylin A (5.79 mg/kg)).[5] Blood samples (250 µl) were obtained from the jugular veins and collected at the following times after dosing: 0.083 h, 0.167 h, 0.25 h, 0.33 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 18 h, 24 h, 36 h, and 48 h. The peak plasma concentration (C_{max}) and the time reaching C_{max} (T_{max}) were obtained directly from the experimental data. The three tested flavonoid glucuronides (baicalin, wogonoside, and oroxylin A 7-O-β-D-glucuronide) and their aglycones (baicalein, wogonin and oroxylin A) exhibited rapid absorption ($T_{max} < 12$ min) and exhibited a multiple-peak phenomenon. Focusing on the dose in the extract, because the dose of baicalein is much higher than that of andoroxylin A, one would expect that the systemic exposure of baicalein would have been greater, but it was comparable to that of andoroxylin A. Therefore, the potential for systemic exposure per unit time would be greater for andoroxylin A (when compared to baicalein). Because the doses of baicalein and wogonin in the extract are comparable, the expectation is that the systemic exposure would have been comparable, but the systemic exposure of baicalein was much less than that of wogonin. Therefore, the potential for systemic exposure per unit time would be greater for wogonin (when compared to baicalein). These data indicate that the systemic absorption, over time, of baicalein would be less when compared to the other 2 constituents.

Human

Oral

Scutellaria Baicalensis Root Powder

A study was performed to investigate the urinary pharmacokinetics of flavone constituents of a *Scutellaria baicalensis* root powder (contains baicalin, baicalein, wogonoside and wogonin flavones).[18] Quantitation (using high performance liquid chromatography) of the commercial powder indicated that baicalin and wogonoside were the major flavone constituents, and that their aglycones, baicalein and wogonin, were less abundant. The powder (5.2 g) and 200 mL water were administered orally to 10 subjects after an overnight fast. Urine samples were collected before and after dosing. The glucuronides and sulfates of baicalein and wogonin in urine were hydrolyzed with ß-glucuronidase and sulfatase, respectively. Study results indicated that the mean cumulated renal excretion of baicalein glucuronides and sulfates were 43.1 ± 4.5 µmol (2.9% of dose) and 64.8 ± 6.3 µmol (4.3% of dose), respectively. Wogonin glucuronides and sulfates were 21.6± 2.0 µmol (5.9% of dose) and 20.7 ± 1.7 µmol (5.7% of dose), respectively. The renal excretion of conjugated metabolites of wogonin (11.6% of dose; number of µmols not stated) were higher than that of baicalein (7.2% of dose; number of µmols not stated). The baicalein sulfates predominated when compared to the corresponding glucuronides; whereas, the presence of wogonin sulfates was comparable to the corresponding glucuronides.

TOXICOLOGICAL STUDIES

General toxicity studies of *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Scutellaria Baicalensis Root Extract

The teratogenicity of a *Scutellaria baicalensis* root extract (aqueous extract) was evaluated using groups of 30 pregnant, Sprague-Dawley female rats.[20] The test substance was administered by gavage to 3 groups, at doses of 0.25, 12.49, and 24.98 g/kg/day, on gestation days 7 to 17 (11 days). Control rats were administered distilled water. Two-thirds of pregnant females in each group were killed on day 20 of gestation, and their fetuses were examined. The remaining dams were allowed to litter naturally, and postnatal development of the offspring was evaluated. A statistically significant ($p < 0.05$), dose-dependent increase in the incidence of skeletal variations (presence of lumbar ribs) was observed. A dose-dependent increase in the frequency of dilatation of the ureter was also reported. However, the incidence of this abnormality was comparable between the 12.49 and 24.98 g/kg/day dose groups. Dilatation was observed along the entire length of the ureter, not in localized segments. Various minor abnormalities were also observed in the 24.98 g/kg/day dose group, and hydrocephaly was observed in one of the control litters. There were no statistically significant differences in the following between control and treated groups: maternal body weight, intake of diet and water, efficiency of diet, hematologic values, resorbed and dead fetuses, corpora lutea, separation of eyelids, emergence of abdominal hair and incisors, traction test values, sex organ function in fetuses, and the growth of fetuses.

A *Scutellaria baicalensis* root extract (aqueous extract) was administered by gavage to 20 pregnant rats.[21] The extract, in saline (15 g in 750 mL), was administered slowly (186 mg/kg bw) daily, from day 7 to day 17 of gestation. The authors noted that the administered dose was equivalent to 25 g/kg of *Scutellaria baicalensis* root (starting material), representing a 100-fold increase over the typical human intake level. The control group (20 pregnant rats) was administered equal volumes of saline. Ten maternal animals in each group were killed on gestation day 20, and the fetuses were delivered by cesarean section. The following were then determined: number of dead fetuses, live fetuses, resorption sites, and corpora lutea; fetal sex; and fetal body weights. Skeletal examinations of fetuses were also performed after the animals were killed on day 20. Skeletons of offspring obtained by natural delivery were evaluated at postnatal day 50 by necropsy. The remaining animals were allowed to naturally deliver their offspring, and all of the weanlings were maintained to postnatal day 50 for the reversibility study. In fetuses obtained by cesarean section on gestational day 20, the incidence of fetal lumbar rib was increased in the treated group ($11.54 \pm 0.15\%$) when compared to the vehicle control group. However, in the groups obtained by natural delivery, the fetal lumbar rib incidence of the treated group ($0.81 \pm 0.01\%$) was decreased on postnatal day 50 when compared to the fetuses that were delivered by cesarean section on day 20. This means that the lumbar rib had been recovered by postnatal day 50. The weights of fetuses in the treated group tended to be less when compared to those in the control group. Alkaline phosphatase in treated dams was increased on gestation day 20, but was decreased on postnatal day 50. There were no significant differences between the control and treated group with respect to the following: maternal body weight, or embryological, histopathological, hematological, or serum biochemical changes. The authors stated that the results of this study suggest that the appearance of lumbar rib induced by the test material is a transient fetal variation rather than teratogenicity or maternal toxicity.

The effect of a *Scutellaria baicalensis* root extract (aqueous extract) on embryonic development was studied using groups of 18 pregnant ICR mice that received oral (gavage) doses of 2 g/kg/day, 8 g/kg/day, or 32 g/kg/day.[19] The doses (dose volume = 0.5 mL/30 g bw) were administered from gestation day 6 to 15. The control group (18 pregnant mice) was administered water. The animals were killed on gestation day 18, and the following parameters were evaluated: live and dead fetuses, resorptions, external and skeletal malformed fetuses, maternal body weights, and maternal liver, kidney, and heart weights. When compared to the negative control group, no statistically significant differences in fetal parameters were observed. Maternal absolute liver and kidney weights in the 32 g/kg/day group were significantly higher ($p < 0.05$) when compared to the control group. Additionally, increases in relative liver and kidney weight values in this group were statistically significant ($p < 0.05$). The authors concluded that the oral administration of this extract at or below a dose of 32 g/kg/day during organogenesis did not cause statistically significant fetal external or skeletal malformations. However, dosing with 32 g/kg/day presented potential maternal toxicity.

GENOTOXICITY STUDIES

In Vitro

Scutellaria Baicalensis Root Extract

The genotoxicity of *Scutellaria baicalensis* root extracts (methanol extract and aqueous extract) was evaluated in the *Bacillus subtilis* rec-assay using strains H17 Rec^+ and M45 Rec^- without metabolic activation.[22] A filter-paper disk containing the extract (100 mg/mL; 60 µl) and a bacterial strain was incubated overnight. The diameter of inhibition zones formed around the disk was measured, and Rec^+ and Rec^- spore plates were compared. Mitomycin C and furylfuramide (AF-2) served as positive controls. Results were positive for the methanol extract and negative for the aqueous extract.

The Ames test was also used to evaluate the genotoxicity of *Scutellaria baicalensis* root extracts (methanol extract and aqueous extract), using *Salmonella typhimurium* strains TA98 and TA100, with and without metabolic activation.[22] The

bacterial suspension + extract (0.1 mL) was incubated for 2 days, and the revertant colonies formed were scored. AF-2 and benzo[a]pyrene served as positive controls. Results for the aqueous extract were positive in strain TA100 with, but not without, metabolic activation. All strain TA98 results for the aqueous extract were negative. Results were also negative for the methanol extract, with or without metabolic activation, in both strains.

In Vivo

Data on the in vivo genotoxicity of *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

OTHER RELEVANT STUDIES

Effect on Melanogenesis

Scutellaria Baicalensis Root Extract

The effect of a *Scutellaria baicalensis* root extract (powder, ethanol extract) on melanogenesis was studied using B16F10 mouse melanoma cells.[23] B16F10 cells were cultured for 24 h with a *Scutellaria baicalensis* root extract at concentrations of 7 μg/mL, 35 μg/mL, and 70 μg/mL. Linoleic acid (100 μM) served as the positive control. Incubation with a *Scutellaria baicalensis* root extract for 24 h resulted in a statistically significant ($p < 0.01$) decrease in melanin levels in a dose-dependent manner as the dose was increased from 35 μg/mL to 70 μg/mL. At a concentration of 70 μg/mL, the extract inhibited melanin formation more effectively than did the positive control (100 μM linoleic acid). It should be noted that results also indicated that 2 flavone components of *Scutellaria baicalensis* root (wogonin and wogonoside) consistently inhibited melanogenesis in both B16F10 melanoma cells and melanocytes. In order to determine the most efficient extraction of *Scutellaria baicalensis* root, the inhibition of melanogenesis by each extract generated from the following 4 organic solvents was evaluated: n-hexane, ethyl acetate, methanol, and water. The solvents n-hexane, ethyl acetate, methanol and water resulted in 83.2, 109.2, 177.6, and 84.4 mg of the crude extract (a *Scutellaria baicalensis* root extract) from the ratio of powder/solvent (20.3 g/100 mL, 10.1 g/50 mL, 1.0 g/5 mL, and 1.0 g/30 mL), respectively. Melanin content was assessed after treatment of B16F10 cells with each extract for 24 h. The methanol extract caused a statistically significant ($p < 0.05$) decrease in melanin content, whereas no decrease was observed after treatment with the other three extracts. The extract eluted by ethyl acetate tended to increase melanin content and produced toxicity. These results suggest that this *Scutellaria baicalensis* root extract is capable of inhibiting melanogenesis (strong inhibitory effect, without cytotoxicity), and its active components can be efficiently extracted. The authors stated that the difference in results depending on the extractant used is that certain flavonoids in a *Scutellaria baicalensis* root extract (present in one extract versus the other) were responsible for the inhibition of melanogenesis.

Antiallergic Effects

Scutellaria Baicalensis Extract

Antiallergic effects of a *Scutellaria baicalensis* extract (ethanol extract, plant part not stated) were evaluated using the following groups of 6 Sprague–Dawley rats: rats sensitized with anti-dinitrophenyl (anti-DNP) immunoglobulin E (IgE); rats sensitized with anti-DNP IgE and treated with a *Scutellaria baicalensis* extract; normal control group; and negative control group.[24] The rats received intradermal injections of anti-DNP IgE at each of three dorsal skin sites. At 48 h post-injection, each rat received an intravenous injection of DNP-HSA in saline containing 4% Evans blue. A *Scutellaria baicalensis* Extract (28 mg/100 g body weight) was administered orally prior to this injection. The rats were then killed, dorsal skin was removed, and the pigment area was measured. Additionally, rat peritoneal mast cells (RPMCs) were cultured and purified to investigate histamine release. RPMC's were incubated for 10 min with a *Scutellaria baicalensis* extract at concentrations of 1, 10, and 100 μg/mL. Histamine release was evoked by adding compound 48/80. Also, in vitro, human mast cells (HMC-1) were pretreated with a *Scutellaria baicalensis* extract (1, 10, and 100 μg/mL) for 1 h before stimulation with phorbol 12-myristate 13-acetate (PMA) plus A23187 (a calcium ionophore). The effects on pro-inflammatory cytokine expression and mitogen activated protein (MAP) kinase expression were investigated using tumor necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8) assays, and Western blotting analysis of HMC-1 cells. Treatment with a *Scutellaria baicalensis* extract inhibited the passive cutaneous anaphylaxis reaction, when compared to the control group. Following treatment of RPMCs with a *Scutellaria baicalensis* extract (both concentrations), histamine release decreased significantly. In HMC-1 cells, a *Scutellaria baicalensis* extract restored IL-8 and TNF-α expression and inhibited MAP kinase expression in compound 48/80-induced HMC-1 cells. The authors noted that these data suggest that a *Scutellaria baicalensis* extract may prove to be a useful anti-inflammatory agent through its downregulation of the expression of various inflammatory mediators.

Scutellaria Baicalensis Root Extract

The antiallergic effect of topically applied a *Scutellaria baicalensis* root extract (aqueous extract) in suppressing 2,4-dinitrochlorobenzene (DNCB)-induced allergic contact dermatitis was studied.[25] A *Scutellaria baicalensis* root extract (aqueous extract) was evaluated using the following 6 groups (5 mice per group) of female BALB/c mice: negative control group (cream base alone); positive group (dinitrochlorobenzene (DNCB) + cream base); dexamethasone group (DNCB + 0.1% dexamethasone cream); 0.1% *Scutellaria baicalensis* root extract (aqueous extract) group (DNCB + 0.1% *Scutellaria baicalensis* root extract (aqueous extract) cream); and 0.5% *Scutellaria baicalensis* root extract (aqueous extract) (DNCB + 0.5% *Scutellaria baicalensis* root extract (aqueous extract) cream). Each gram of creams contained (w/w) 1 mg of dexamethasone and a *Scutellaria baicalensis* root extract (aqueous extract) (1 and 5 mg) in an emollient cream base consisting of the following components: propylene glycol, stearyl alcohol, acetyl alcohol, sorbitan monostearate, polysorbate 60, mineral oil and purified water. A *Scutellaria baicalensis* root extract (aqueous extract) was defined as a spray dried extract with the following components: baicalin (6.45%), wogonoside (3.37%), baicalein (2.07%), and wogonin (0.48%). The mice received topical applications (on dorsal skin) of ~20 mg dexamethasone cream, a *Scutellaria baicalensis* root extract (aqueous extract) creams, or emollient cream base alone daily on days 1 to 14. Allergic sensitization was induced according to the following procedure: A 1-cm^2 gauze patch containing 0.1 mL of 1% DNCB in acetone/olive oil (3:1) was applied for 4 h (on days 1 and 4) to the back. After a 4-day non-treatment period, the mice were challenged (dorsal skin) with a patch containing 0.2% DNCB on days 8 and 11. On day 14, the mice were killed and blood samples were collected. Dorsal skin samples from each mouse were subjected to histopathological and biochemical examination.

Topical application of a *Scutellaria baicalensis* root extract (aqueous extract) attenuated the epidermal thickness and mast cell infiltration into the skin in DNCB-induced contact dermatitis. Additionally, a *Scutellaria baicalensis* root extract (aqueous extract) suppressed DNCB-induced production of serum IgE as well as IL-4, IFN-γ, and TNF-α in the skin. Topical application of a *Scutellaria baicalensis* root extract (aqueous extract) also ameliorated the significant decrease in dermal glutathione and superoxide dismutase levels. The researchers stated that these results indicated that the topical application of *Scutellaria baicalensis* suppressed DNCB-induced contact dermatitis.

Cytotoxicity

Scutellaria Baicalensis Root Extract

A *Scutellaria baicalensis* root extract (aqueous extract) was tested in apoptosis experiments involving the following cell types from 26 children with acute lymphoblastic leukemia: the NALM-6 cell line (human peripheral blood leukemia pre-B cells), peripheral blood leukocytes, and bone marrow cells.[26] The 3 cell types were incubated for 48 h with a *Scutellaria baicalensis* root extract (aqueous extract) at concentrations up to 200 µg/mL/ 2 x 10^6 cells. Peripheral blood (from 16 healthy children) tested with the same concentrations served as the control. The percentage of living peripheral blood leukocytes and bone marrow cells after 24 h of incubation oscillated around 90% (test and control cells). However, on day 2, the number of living bone marrow cells from patients with acute lymphoblastic leukemia decreased to only 65%. A *Scutellaria baicalensis* root extract (aqueous extract) enhanced the apoptosis of peripheral blood leukocytes in bone marrow cells of leukemic children. The percentage of peripheral blood leukocytes that underwent apoptosis increased from 11% in the control to 17% and 24% for the doses of 100 µg/mL and 200 µg/mL, respectively. At a dose of 200 µg/mL, apoptosis in bone marrow cells and peripheral blood leukocytes from patients with acute lymphoblastic leukemia was statistically significantly increased ($p < 0.05$), when compared to peripheral blood leukocytes from healthy controls. A *Scutellaria baicalensis* root extract (aqueous extract) did not induce apoptosis of control peripheral blood leukocytes. Pro-apoptotic activity of a *Scutellaria baicalensis* root extract (aqueous extract) in the NALM-6 cell line was also reported (details relating to results not included). The authors noted that the observation of a *Scutellaria baicalensis* root extract (aqueous extract)-induced apoptosis in peripheral blood leukocytes from leukemia patients, but not from healthy controls may be related to the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). They stated that TRAIL induces apoptosis in various cancer cells in vitro and in vivo, with little or no toxicity in normal cells.

The cytotoxicity of a *Scutellaria baicalensis* root extract (aqueous ethanol extract) was evaluated using human keratinocytes (HaCaT) that were cultured with the extract for 24 h.[4] The extract tested was nontoxic at concentrations up to 30 µg/mL. However, statistically significant ($p < 0.05$) cytotoxicity was observed at concentrations of 100 µg/mL and 1000 µg/mL.

Estrogenic Activity

Scutellaria Baicalensis Root Extract

A *Scutellaria baicalensis* root extract (ethanol extract) was assayed for estrogenic activity in vitro using a recombinant yeast system with both a human estrogen receptor expression plasmid and a reporter plasmid.[27] The extract (in dimethyl sulfoxide) was added to the culture, reaching final concentrations between 0.1 and 1000 µg/mL, and incubated for 2 h. ß-Galactosidase activity, which is dependent on binding of the ligand to the estrogen receptor, was then assayed. The activity of ß-galactosidase resulted in a color reaction, which was measured absorbance at 420 nm. 17ß-Estradiol served as the positive control. EC_{50} (concentration of test material at half-maximum ß-galactosidase activity) values were determined.

The estrogenic relative potency (RP) of the test material was computed by dividing the EC_{50} of 17ß-estradiol by the EC_{50} of the test material, and then multiplying this value by 100. The EC_{50} for 17ß-estradiol was 0.205 ± 0.025 ng/mL (RP = 100). The EC_{50} for this *Scutellaria baicalensis* root extract was 262.3 µg/mL (RP = 8.77 x 10^{-5}). This *Scutellaria baicalensis* root extract was classified as negative for estrogenic activity.

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation

Animal

Scutellaria Baicalensis Root Extract

The skin irritation/corrosion potential of a *Scutellaria baicalensis* root extract (aqueous extract) was evaluated in accordance with Organization for Economic Co-operation and Development (OECD) test guideline (TG) 404, using 6 New Zealand white rabbits.[28] The dried powder (spray dried extract) test article comprised in part: baicalin (6.45%), wogonoside (3.37%), baicalein (2.07%), and wogonin (0.48%). Distilled water (negative control) was also applied to the 6 rabbits. Reactions were scored using the Draize scale, and the primary irritation index (PII) was calculated using the mean score at 24 h, 48 h, and 72 h. There were no significant body weight changes, clinical signs, or mortality following topical application of the test substance. Slight erythema with edema (score of 1) was observed in 1 of 6 rabbits at 1 h after patch removal. By 24 h post-application, the reactions had resolved. The extract was classified as a non-irritant (PII = 0). The distilled water control also produced negative results.

Human

Scutellaria Baicalensis Root Extract

Results from a human patch test on a 10% Scutellaria Baicalensis Root Extract trade name mixture (butylene glycol extract; dose per cm^2 not stated) involving 12 subjects were negative for skin irritation.[7] Details relating to the test protocol and results were not included.

Sensitization

Animal

Scutellaria Baicalensis Root Extract

The skin sensitization potential of a *Scutellaria baicalensis* root extract (aqueous extract) was evaluated in accordance with OECD TG 404 (Buehler method) using the following groups of Hartley guinea pigs: 10 test animals, 20 negative control animals, and 10 positive control animals.[28] The dried powder (spray dried extract) applied to the skin was defined as Scutellaria Baicalensis Root Extract (aqueous extract) with the following components: baicalin (6.45%), wogonoside (3.37%), baicalein (2.07%), and wogonin (0.48%). DNCB (1%) and distilled water served as positive and negative controls, respectively. Skin reactions were scored at 24 h and 48 h after patch removal according to the Magnusson and Kligman grading scale. Results were expressed as mean ± standard error of the mean. There were no significant body weight changes, clinical signs, or mortality following topical application of the test substance. Treatment with the test substance was not associated with any changes on the skin surface, including erythema and edema at 24 and 48 h following patch removal. The test material was classified as a non-sensitizer (Buehler score = 0). Skin sensitization was observed in the positive control group. The average skin response scores in the DNCB-treated group were 0.6 and 0.4 at 24 and 48 h, respectively. Reactions were not observed in the distilled water, negative control group.

Human

Scutellaria Baicalensis Root Extract

Results from a human repeated insult patch test (HRIPT) on a 10% Scutellaria Baicalensis Root Extract trade name mixture (butylene glycol extract; dose per cm^2 not stated) involving 49 subjects were negative for skin sensitization.[7] Details relating to the test protocol and results were not included. In another HRIPT involving 54 subjects patch tested with an undiluted Scutellaria Baicalensis Root Extract trade name mixture (30% ethanol extract; dose per cm^2 not stated), test results were also negative for skin sensitization. Details relating to the test protocol and results were not included.

OCULAR IRRITATION STUDIES

Data on the ocular irritation potential of *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

CLINICAL STUDIES

Case Report

Scutellaria Baicalensis Extract

A normal female developed facial eczema after using a resveratrol skin cream containing Scutellaria Baicalensis Extract (concentration not stated) for several weeks.[29] Repeated open application testing of the product twice daily on the antecubital flexures yielded a positive reaction within 2 days. Patch testing of the undiluted cream yielded a 1+ reaction on days 1 and 2. In other patch tests 0.5% aqueous Scutellaria Baicalensis Extract yielded a 1+ reaction on days 2 and 3, and weaker 1+ reactions to resveratrol (1% in petrolatum) on days 2 and 3 were also observed. Positive reactions were not observed when 15 control patients were patch tested with Scutellaria Baicalensis Extract or resveratrol. The case authors concluded that the patient was sensitized to Scutellaria Baicalensis Extract, with possible co-sensitization to resveratrol.

SUMMARY

The safety of the following 4 *Scutellaria baicalensis*-derived ingredients, as used in cosmetics, is reviewed in this CIR safety assessment: Scutellaria Baicalensis Extract, Scutellaria Baicalensis Root Extract, Scutellaria Baicalensis Root Powder, and Scutellaria Baicalensis Sprout Extract. These ingredients, collectively, have the following functions in cosmetics, although none of the ingredients has the same reported functions: antimicrobial agent, skin conditioning agent, abrasive, fragrance ingredient, skin protectant, and antioxidant.

Method of manufacture data on Scutellaria Baicalensis Root Extract (ethanol extracts and a butylene glycol extract) were received from the Council. The extractants used in 2 methods of manufacture are 90% ethanol (one method) and 30% ethanol (another method). In both methods, the starting material is dried raw material that is subsequently concentrated and then filtered prior to packaging. The only real difference between these 2 methods is the addition of squalene after the concentration step in the method involving extraction with 30% ethanol. The only real difference between the method using butylene glycol as the extractant and the other 2 methods (ethanol extraction) is the use of a different extractant.

A Scutellaria Baicalensis Root Extract trade name mixture (30% ethanol extract) contains flavonoid compounds. Another Scutellaria Baicalensis Root Extract trade name mixture (90% ethanol and butylene glycol extracts) contains tannin and flavonoid compounds. A Scutellaria Baicalensis Root Extract trade name mixture (ethanol and butylene glycol extracts) is reported to contain not more than 20 ppm heavy metals and not more than 2 ppm arsenic.

According to 2019 VCRP data, Scutellaria Baicalensis Root Extract is reported to be used in 419 cosmetic products (338 leave-on products, 81 rinse-off products). Of the *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency. The results of concentration of use surveys conducted by the Council in 2018 and 2019 indicate that the maximum leave-on use concentration in this ingredient group is 0.5% Scutellaria Baicalensis Root Extract is in moisturizing products (not spray). According to VCRP and Council survey data, Scutellaria Baicalensis Root Powder is not currently in use in cosmetic products.

Scutellaria baicalensis Georgi is one of the 50 fundamental herbs of traditional Chinese medicine.

After a *Scutellaria baicalensis* extract (ethanol extract) was administered orally to rats, the tissue distribution and excretion (in urine and feces) of 2 major flavone constituents was reported. A *Scutellaria baicalensis* root extract (aqueous extract) was also administered orally to rats. After dosing, components of the extract, as well as their metabolites, were detected in the urine, feces, or bile: sulfate and glucuronide conjugates and hydroxylated, methylated, acetylated, and deoxygenated products. When a *Scutellaria baicalensis* root extract, aqueous extract (suspended in carboxymethyl cellulose sodium salt solution) was administered orally to rats, the 6 major flavonoid components detected in the plasma were rapidly absorbed. A human study was performed to investigate the urinary pharmacokinetics of flavone constituents of a commercial *Scutellaria baicalensis* root powder. The renal excretion of sulfate and glucuronide conjugates was reported.

The teratogenicity of a *Scutellaria baicalensis* root extract (aqueous extract) was evaluated using groups of 30 pregnant Sprague-Dawley female rats. The test substance was administered by gavage to 3 groups, at doses of 0.25, 12.49, and 24.98 g/kg/day, on gestation days 7 to 17. A statistically significant ($p < 0.05$), dose-dependent increase in the incidence of skeletal variations (presence of lumbar ribs) was observed. A dose-dependent increase in the frequency of dilatation of the ureter was also reported. In another study, the effect of a *Scutellaria baicalensis* root extract (aqueous extract) on embryonic development was studied using groups of 18 pregnant ICR mice that received oral doses of 2 g/kg/day, 8 g/kg/day, or 32 g/kg/day on gestation days 6 to 15. Oral administration of a *Scutellaria baicalensis* root extract (aqueous extract) at or below a dose of 32 g/kg/day during organogenesis did not cause statistically significant fetal external or skeletal malformations. A *Scutellaria baicalensis* root extract (aqueous extract) was also administered orally to 20 pregnant rats. The aqueous extract, in saline (15 g in 750 mL), was administered slowly (186 mg/kg body weight) from day 7 to day 17 of gestation. Fetal lumbar rib incidence was increased on gestational day 20, and then decreased on postnatal day 50. The results of this study suggest that the appearance of lumbar rib is a transient fetal variation rather than teratogenicity or maternal toxicity.

The genotoxicity of a *Scutellaria baicalensis* root extract (methanol extract and aqueous extract, 100 mg/mL (60 µl)) was evaluated in the *B. subtilis* rec-assay using strains H17 Rec^+ and M45 Rec^- without metabolic activation. Results for the methanol extract and aqueous extract were positive and negative, respectively. The genotoxicity of a *Scutellaria baicalensis* root extract (methanol extract and aqueous extract, 0.1 mL) was also evaluated in the Ames test using *S. typhimurium* strains TA98 and TA 100 with and without metabolic activation. Results for the aqueous extract were positive in strain TA100 with, but not without, metabolic activation. All strain TA98 results for the aqueous extract were negative. Results were negative for the methanol extract, with or without metabolic activation, in both bacterial strains.

A *Scutellaria baicalensis* root extract (ethanol extract) had a strong inhibitory effect on melanogenesis in B16F10 melanoma cells. Incubation with a *Scutellaria baicalensis* root extract (ethanol extract) for 24 h resulted in a statistically significant ($p < 0.01$) decrease in melanin levels in a dose-dependent manner at concentrations between 35 µg/mL and 70 µg/mL.

In a study evaluating the antiallergic effects of a *Scutellaria baicalensis* extract (ethanol extract), groups of 6 Sprague-Dawley (SD) rats included rats sensitized with anti-DNP IgE and rats sensitized with anti-DNP IgE and treated with a *Scutellaria baicalensis* extract (28 mg/100 g body weight). Treatment with a *Scutellaria baicalensis* extract inhibited the passive cutaneous anaphylaxis reaction, when compared to the control group. In a study involving groups of 5 female BALB/c mice, a topically applied *Scutellaria baicalensis* root extract (aqueous extract, 0.1%) attenuated the epidermal thickness and mast cell infiltration into the skin in DNCB-induced contact dermatitis.

A *Scutellaria baicalensis* root extract (aqueous extract, 100 and 200 µg/mL) induced apoptosis in peripheral blood leukocytes from leukemia patients, but not from healthy controls. The cytotoxicity of a *Scutellaria baicalensis* root extract (aqueous ethanol extract) was evaluated using HaCaT human keratinocytes. The extract was nontoxic at concentrations up to 30 µg/mL, but statistically significant ($p < 0.05$) cytotoxicity was observed at concentrations of 100 µg/mL and 1000 µg/mL.

A *Scutellaria baicalensis* root extract (ethanol extract) was assayed for estrogenic activity in vitro using a recombinant yeast system with both a human estrogen receptor expression plasmid and a reporter plasmid. The extract was classified as negative for estrogenic activity at concentrations between 0.1 and 1000 µg/mL.

A *Scutellaria baicalensis* root extract (aqueous extract) (comprised in part of baicalin (6.45%), wogonoside (3.37%), baicalein (2.07%), and wogonin (0.48%)) was classified as a non-irritant in 6 rabbits. This test substance was also classified as a non-sensitizer in a test involving 10 guinea pigs.

Results from a human patch test on a 10% Scutellaria Baicalensis trade name mixture (butylene glycol extract; dose per cm^2 not stated) involving 12 subjects were negative for skin irritation. Furthermore, results from an HRIPT on the same 10% Scutellaria Baicalensis trade name mixture (butylene glycol extract; dose per cm^2 not stated) involving 49 subjects were negative for skin sensitization. In another HRIPT involving 54 subjects patch tested with an undiluted Scutellaria Baicalensis trade name mixture (30% ethanol extract; dose per cm^2 not stated), test results were also negative for skin sensitization.

Skin sensitization was observed in a patient after patch testing with 0.5% aqueous Scutellaria Baicalensis Extract. The individual developed facial eczema after using a product that contained the extract. The extract is an ingredient of a skin cream that had been used over a period of several weeks. Positive reactions were not observed when 15 control patients were patch tested with Scutellaria Baicalensis Extract.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions and functions of the ingredients in this safety assessment.[1]

Ingredient CAS No.	Definition	Function(s)
Scutellaria Baicalensis Extract 94279-99-9	Scutellaria Baicalensis Extract is the extract of the whole plant, *Scutellaria baicalensis.*	Antimicrobial Agents
Scutellaria Baicalensis Root Extract 94279-99-9	Scutellaria Baicalensis Root Extract is the extract of the roots of *Scutellaria baicalensis*.	Skin-Conditioning Agents – Humectant
Scutellaria Baicalensis Root Powder 94279-99-9	Scutellaria Baicalensis Root Powder is the powder obtained from the dried, ground roots of *Scutellaria baicalensis*.	Abrasives; Fragrance Ingredients; Skin Protectants
Scutellaria Baicalensis Sprout Extract 94279-99-9	Scutellaria Baicalensis Sprout Extract is the extract of the sprouts of *Scutellaria baicalensis*.	Antioxidants

Table 2. Components of Scutellaria Baicalensis Extract (ethanol extract).[9]

5,7,6′-trihydroxyflavone 2′-O-β-D-glucopyranoside
(2R,3R)-3,5,7,2′,6′-pentahydroxyflavanone
3,5,7,2′,6′-pentahydroxyflavone
Viscidulin III 6-O-β-D-glucopyranoside
Chrysin 6-C-α-L-arabinopyranoside-8-C-β-D-glucopyranoside
Acteoside
5,6′-dihydroxy-7,8-dimethoxyflavone 2′-O-β-D-glucopyranoside
Chrysin 6-C-β-D-glucopyranoside-8-C-α-L-arabinopyranoside
Chrysin 8-C-β-D-glucopyranoside
5,2′-dihrdroxy-6-methoxyflavone 7-O-β-D-glucuronopyranoside
(2S)-5,7,2′,6′-tetrahydroxyflavanone
Baicalin
Baicalein 7- O-β-D-glucopyranoside
Norwogonin 7-O-β-D-glucuronopyranoside
Wogonin 5-O-β-D-glucopyranoside
Cistanoside D
Chrysin 7-O-β-D-glucuronopyranoside
Oroxylin A 7-O-β-D-glucuronopyranoside
Oroxylin A 7-O-β-D-glucopyranoside
Wogonoside
5,7,6′-trihydroxy-8,2′-dimethoxyflavone
Baicalein
Wogonin
Chrysin
5,6′-dihydroxy-6,7,8,2′-tetramethoxyflavone
Oroxylin A
(2S)-5,7,6′-trihydroxyflavanone 2′-O-β-D-glucopyranoside
(2S)-5-hydroxy-6-methoxyflavanone 7-O-β-D-glucuronopyranoside
Aschrysin 6-C-β-L-arabinopyranosyl-8-C-β-D-glucopyranoside
Chrysin 6-C-β-D-glucopyranosyl-8-C-β-L-arabinopyranoside

Table 3. Frequency (2019) and Concentration (2018-2019) of Use According to Duration and Type of Exposure.[13-15]

	Scutellaria Baicalensis Extract		**Scutellaria Baicalensis Root Extract**		**Scutellaria Baicalensis Sprout Extract**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	**102**	**0.000027-0.03**	**419**	**0.00001-0.5**	**NR**	**0.0002-0.0005**
Duration of Use						
Leave-On	*88*	*0.000027-0.03*	*338*	*0.0002-0.5*	*NR*	*0.00025-0.0005*
Rinse off	*14*	*NR*	*81*	*0.00001-0.002*	*NR*	*0.0002*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	9	NR	28	0.07	NR	NR
Incidental Ingestion	NR	NR	1	0.0045	NR	NR
Incidental Inhalation- Sprays	31[a];37[b]	0.03[a]	115[a];116[b]	0.002[a]	NR	NR
Incidental Inhalation- Powders	37[b]	NR	116[b]	0.0002-0.35[c]	NR	0.00025-0.0005[c]
Dermal Contact	101	0.000027	394	0.00001-0.5	NR	0.0002-0.0005
Deodorant (underarm)	NR	NR	2[a]	NR	NR	NR
Hair - Non-Coloring	1	0.03	22	0.002	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	16	0.0002-0.0045	NR	0.0002
Baby Products	3	NR	10	NR	NR	NR

NR = Not Reported
Totals = Rinse-off + Leave-on + Diluted for Use Product Uses
[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays
[b]Not specified these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories
[c]It is possible that these products may be powders, but it is not specified whether the reported uses are powders

Table 4. *Scutellaria baicalensis* root extract Metabolites in the Rat.[6]

Metabolite Type*	**Formula**	**Source**	**Parent Compound****
glucuronide conjugation	$C_{27}H_{26}O_{17}$	urine and bile	baicalin
glucuronide conjugation	$C_{22}H_{28}O_{17}$	urine and bile	wogonoside
hydroxylation + sulfation	$C_{16}H_{12}O_9S$	urine	wogonin
sulfate conjugation	$C_{15}H_{10}O_8S$	urine	baicalein
sulfate conjugation	$C_{16}H_{12}O_8S$	urine	wogonin
2 x hydroxylation	$C_{22}H_{26}O_{19}$	urine	wogonoside
loss of oxygen	$C_{21}H_{18}O_{10}$	urine	baicalin
2 x hydroxylation	$C_{15}H_{10}O_7$	urine and feces	baicalein
acetylation	$C_{24}H_{22}O_{12}$	urine	wogonoside
reduction	$C_{16}H_{14}O_5$	urine	wogonin
hydroxylation + methylation	$C_{22}H_{20}O_{12}$	urine	baicalin
loss of oxygen	$C_{15}H_{10}O_4$	urine and feces	baicalein
hydroxylation	$C_{16}H_{12}O_6$	feces	wogonin
deglucuronide	$C_{15}H_{10}O_5$	feces	baicalin
deglucuronide	$C_{16}H_{20}O_5$	feces	wogonoside

*Metabolite of parent compound
**Component of *Scutellaria baicalensis* root

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2019 FDA VCRP Data

Scutellaria Baicalensis Extract

01A - Baby Shampoos	1
01C - Other Baby Products	2
03D - Eye Lotion	5
03G - Other Eye Makeup Preparations	4
07C - Foundations	1
07F - Makeup Bases	1
07I - Other Makeup Preparations	1
12A - Cleansing	9
12C - Face and Neck (exc shave)	27
12D - Body and Hand (exc shave)	10
12F - Moisturizing	24
12G - Night	3
12H - Paste Masks (mud packs)	4
12I - Skin Fresheners	1
12J - Other Skin Care Preps	6
13A - Suntan Gels, Creams, and Liquids	3
Total	**102**

Scutellaria Baicalensis Root Extract

01B - Baby Lotions, Oils, Powders, and Creams	8
01C - Other Baby Products	2
03A - Eyebrow Pencil	1
03B - Eyeliner	2
03D - Eye Lotion	12
03E - Eye Makeup Remover	1
03G - Other Eye Makeup Preparations	12
05A - Hair Conditioner	3
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	8
05G - Tonics, Dressings, and Other Hair Grooming Aids	7
05I - Other Hair Preparations	3
07B - Face Powders	2
07C - Foundations	11
07F - Makeup Bases	3
07I - Other Makeup Preparations	5
09A - Dentifrices	1
10A - Bath Soaps and Detergents	4
10B - Deodorants (underarm)	2
10C - Douches	2
10E - Other Personal Cleanliness Products	9
11A - Aftershave Lotion	2
11E - Shaving Cream	1
12A - Cleansing	32
12C - Face and Neck (exc shave)	98
12D - Body and Hand (exc shave)	18

12F - Moisturizing	84
12G - Night	15
12H - Paste Masks (mud packs)	19
12I - Skin Fresheners	6
12J - Other Skin Care Preps	42
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	2
Total	**419**

Scutellaria Baicalensis Root Powder - No FDA Data

Scutellaria Baicalensis Sprout Extract - No FDA Data

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: October 25, 2018

SUBJECT: Council Concentration of Use Survey: *Scutellaria baicalensis*-Derived Ingredients

Concentration of Use by FDA Product Category – *Scutellaria baicalensis*-Derived Ingredients*

Scutellaria Baicalensis Root Extract
Scutellaria Baicalensis Extract
Scutellaria Baicalensis Root Powder
Scutellaria Baicalensis Sprout Extract

Ingredient	Product Category	Maximum Concentration of Use
Scutellaria Baicalensis Root Extract	Eye shadows (3C)	0.07%
Scutellaria Baicalensis Root Extract	Hair conditioners (5A)	0.002%
Scutellaria Baicalensis Root Extract	Shampoos (noncoloring) (5E)	0.002%
Scutellaria Baicalensis Root Extract	Tonics, dressings and other hair grooming aids (5G)	0.002%
Scutellaria Baicalensis Root Extract	Foundations (7C)	0.015%
Scutellaria Baicalensis Root Extract	Lipstick (7E)	0.0045%
Scutellaria Baicalensis Root Extract	Bath soaps and detergents (10A)	0.0002%
Scutellaria Baicalensis Root Extract	Aftershave lotions (11A)	0.01%
Scutellaria Baicalensis Root Extract	Shaving cream (11E)	0.002%
Scutellaria Baicalensis Root Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	0.00001%
Scutellaria Baicalensis Root Extract	Face and neck products (12C) Not spray	0.0002-0.35%
Scutellaria Baicalensis Root Extract	Body and hand products (12D) Not spray	0.0024--0.18%
Scutellaria Baicalensis Root Extract	Moisturizing products (12F) Not spray	0.003-0.5%
Scutellaria Baicalensis Root Extract	Paste masks and mud packs (12H)	0.0015%
Scutellaria Baicalensis Root Extract	Other skin care preparations (12J)	0.015-0.05%
Scutellaria Baicalensis Root Extract	Suntan products (13A) Not spray	0.01%
Scutellaria Baicalensis Extract	Tonics, dressings and other hair grooming aids (5G)	0.03%
Scutellaria Baicalensis Extract	Moisturizing products (12F) Not spray	0.000027%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2018
Table prepared October 24, 2018

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: April 11, 2019

SUBJECT: Concentration of Use by FDA Product Category: Scutellaria Baicalensis Sprout Extract

Concentration of Use by FDA Product Category – Scutellaria Baicalensis Sprout Extract

Product Category	Maximum Concentration of Use
Bath soaps and detergents (10A)	0.0002%
Face and neck products (12C) Not spray	0.0005%
Body and hand products (12D) Hand cream - Not spray	0.00025%

Information collected in 2019

Table prepared April 10, 2019

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: July 22, 2019

SUBJECT: Scutellaria Baicalensis Root Extract

Anonymous. 2019. Summary information Scutellaria Baicalensis Root Extract.

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July 2019

Summary Information Scutellaria Baicalensis Root Extract

Method of manufacture data

	Method of manufacture
Scutellaria Baicalensis Root Extract (90% ethanol extract)	Dried raw material ⇒extract with 90vol% ethanolic solution ⇒filtrate ⇒ concentration ⇒ concentration adjustment (50vol% ethanolic solution) ⇒sedimentation⇒filtrate ⇒packaging
Scutellaria Baicalensis Root Extract (butylene glycol extract)	Dried raw material ⇒ extract with 50vol% 1,3-butylene glycolic solution ⇒filtrate ⇒sedimentation ⇒filtrate ⇒packaging
Scutellaria Baicalensis Root Extract (30% ethanol extract)	Dried raw material ⇒extract with 30vol% ethanolic solution ⇒filtrate ⇒ concentration ⇒ add squalene ⇒ sedimentation ⇒ filtrate ⇒ packaging

Chemical characterization data

Trade name	Chemical characterization
Scutellaria Baicalensis Root Extract (90% ethanol and butylene glycol extracts)	Tannin and flavonoid
Scutellaria Baicalensis Root Extract (30% ethanol extract)	Flavonoid

Impurities data

Trade name	Impurities
Scutellaria Baicalensis Root Extract (ethanol and buthylene glycol extracts)	Heavy metals: not more than 20 ppm Arsenic: not more than 2 ppm

Human skin irritation and sensitization data

Trade name	Human skin irritation and sensitization
Scutellaria Baicalensis Root Extract (butylene glycol extract)	Human patch test : Negative (10%, 12 participants) HRIPT : Negative (10%, 49 participants)
Scutellaria Baicalensis Root Extract (30% ethanol extract)	HRIPT : Negative (100%, 54 participants)

Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: July 22, 2019

SUBJECT: Scientific Literature Review: Safety Assessment of *Scutellaria baicalensis*-Derived Ingredients as Used in Cosmetics (release date June 20, 2019)

The Council respectfully submits the following comments on the scientific literature review, Safety Assessment of *Scutellaria baicalensis*-Derived Ingredients as Used in Cosmetics.

Key Issue

Introduction - By stating: "may be consumed in food", the Introduction implies that *Scutellaria baicalensis* is used in food. There is no other information in the CIR report that suggests that this plant is used in food. If there is evidence that this plant is used as food, it should be added to the CIR report, or the Introduction should be revised so that it does not imply that this plant is used in food.

Additional Considerations

Method of Manufacture - If available, please state the final concentration of the root extract described in reference 6.

ADME - Please state the plant part used to prepare the ethanol extract used in reference 16.

Effect on Melanogenesis - If reference 22 identified the flavonoids in the root extract that inhibited melanogenesis, they should be stated in the CIR report.

Summary - Please correct "form" to "from"

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