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

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 4 *Scutellaria baicalensis*-derived ingredients in cosmetic products; these ingredients are reported to have the following functions in cosmetics: antimicrobial agent, skin conditioning agent, abrasives, fragrance ingredients, skin protectants, and antioxidants. The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations, and concluded that Scutellaria Baicalensis Root Extract and Scutellaria Baicalensis Root Powder are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the available data are insufficient to make a determination of safety for Scutellaria Baicalensis Extract and Scutellaria Baicalensis Sprout Extract under the reported conditions of use in cosmetic formulations.

Keywords

Cosmetic Ingredient Review, Expert Panel for Cosmetic Ingredient Safety, Cosmetics, Safety, *Scutellaria Baicalensis* Extract, *Scutellaria Baicalensis* Root Extract, *Scutellaria Baicalensis* Root Powder, *Scutellaria Baicalensis* Sprout Extract

Introduction

The safety of the following 4 *Scutellaria baicalensis*-derived ingredients, as used in cosmetics, is reviewed in this 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* (INCI; *Dictionary*), these ingredients, collectively, 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, the Panel is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex mixture. The Panel 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This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated.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 the Panel evaluates, is available 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.

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Table 1. Definitions and Reported 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

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 either the root or the sprout plant parts, or the whole plant. 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.[1] 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]

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 short-wavelength UV (UVC)) and an absorption peak between 250 and 300 nm (crossing both mid-wavelength UV (UVB) and UVC)) were observed.[4]

Method of Manufacture

Scutellaria Baicalensis Root Extract. Data on the methods of manufacture of Scutellaria Baicalensis Root Extract (using different extractants) were provided via the Personal Care Products Council (Council).[5,6] According to one method, the dried raw material (*Scutellaria baicalensis* root) is extracted with 90 vol% ethanolic solution.[5] Extraction is followed by filtration, concentration of the filtrate (and then concentration adjustment with 50 vol% ethanolic solution). The next steps include sedimentation, filtration, and then packaging. Another method uses a lower concentration of the extractant.[5] The first step in this production process is extraction of the dried raw material with 30 vol% ethanolic solution.[5] Extraction is followed by filtration and concentration of the filtrate. Squalene is then added, and this step is followed by sedimentation, filtration, and then packaging. A third production method involves extraction of the dried raw material with 50 vol% 1,3-butylene glycolic solution.[5] Extraction is followed by filtration and then sedimentation. This step is followed by additional filtration and then packaging. The production of Scutellaria Baicalensis Root Extract via aqueous extraction of *Scutellaria baicalensis* has also been described. The botanical raw material (*Scutellaria baicalensis* root) is cut and cleaned. This is followed by water extraction, a concentration phase, and then spray drying.[6]

A method of preparation of a *Scutellaria baicalensis* root extract (aqueous extract) from a published study is summarized as follows.[7] 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°C 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.[8] The extract was filtrated using analytical filter paper and evaporated to dryness using a rotary evaporator at 60°C 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*.[9] 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).[10]

Scutellaria Baicalensis Root Extract. *Scutellaria baicalensis* root extract contains flavonoid glucuronides (baicalin, wogonoside, and oroxylin A 7-*O*-β-d-glucuronide) and their aglycones (baicalein, wogonin, and oroxylin A).[7] The content of these major flavonoids in a *Scutellaria baicalensis* root extract (250 g, aqueous extract) has 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). 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.[5] Another Scutellaria Baicalensis Root Extract trade name mixture (90% ethanol and butylene glycol extract) 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.[7] 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.[7,11] 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.[12]

Table 2. Components of Scutellaria Baicalensis Extract (Ethanol Extract).[10]

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

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.[13] *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 extract) is reported to contain no more than 20 ppm heavy metals and no more than 2 ppm arsenic.[5]

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.[14] 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.[15,16]

According to 2020 VCRP data, Scutellaria Baicalensis Root Extract is reported to be used in 514 cosmetic products (419 leave-on products, 95 rinse-off products).[14] 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).[15,16] This is the highest use concentrations in leave-on products that is reported for the *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment. According to VCRP and

Council survey data, Scutellaria Baicalensis Root Powder is not currently in use in cosmetic products. Further use data are presented in Table 3.

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.

The *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[17]

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.[7] *Scutellaria baicalensis* Georgi is one of the 50 fundamental herbs of traditional Chinese medicine, and pharmacological effects of *Scutellaria baicalensis* have been described.[7,12,18]

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.[19] *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 glucuronidated flavone) 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 (the aglycone) 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.[8] 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)).[7] Blood samples (250 µl) were obtained from the jugular veins and collected at the following times after dosing: 0.083, 0.167, 0.25, 0.33, 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 36, 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

Table 3. Frequency (2020) and Concentration (2018–2019) of Use According to Duration and Type of Exposure.[14–16]

	Scutellaria Baicalensis Extract		Scutellaria Baicalensis Root Extract		Scutellaria Baicalensis Sprout Extract	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals*/Conc. Range	**109**	**0.000027-0.03**	**514**	**0.00001-0.5**	**NR**	**0.0002-0.0005**
Duration of Use						
Leave-On	*93*	*0.000027-0.03*	*419*	*0.0002-0.5*	*NR*	*0.00025-0.0005*
Rinse off	*16*	*NR*	*95*	*0.00001-0.002*	*NR*	*0.0002*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	9	NR	30	0.07	NR	NR
Incidental Ingestion	NR	NR	1	0.0045	NR	NR
Incidental Inhalation- Sprays	32[a];31[b]	0.03[a]	163[a];151[b]	0.002[a]	NR	NR
Incidental Inhalation - Powders	31[b]	NR	151[b];8[c]	0.0002-0.35[c]	NR	0.00025-0.0005[c]
Dermal Contact	106	0.000027	473	0.00001-0.5	NR	0.0002-0.0005
Deodorant (underarm)	NR	NR	2[a]	NR	NR	NR
Hair - Non-Coloring	1	0.03	25	0.002	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	15	0.0002-0.0045	NR	0.0002
Baby Products	3	NR	10	NR	NR	NR

NR = Not Reported.
*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[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.[8]

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.

of oroxylin A, one would expect that the systemic exposure of baicalein would have been greater, but it was comparable to that of oroxylin A. Therefore, the potential for systemic exposure per unit time would be greater for oroxylin 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).[20] 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.[21] The test substance was administered by gavage to 3 groups, at doses of 0.25, 12.49, and 24.98 g/kg/d, on gestation days 7 to 17 (11 d). 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/d 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/d 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 Sprague-Dawley rats.[22] The extract, in saline (15 g in 750 ml), was administered slowly (186 mg/kg bw/d), 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 at 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 ± 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 ± 0.01%) was decreased on postnatal day 50 when compared to the fetuses that were delivered by cesarean section on day 20. 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 gestational 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 induction 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, 8, or 32 g/kg/d.[23] 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/d 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/d during organogenesis did not cause statistically significant fetal external or skeletal malformations. However, dosing with 32 g/kg/d presented potential maternal toxicity.

Genotoxicity Studies

In Vitro

Scutellaria Baicalensis Root Extract. The genotoxicity of a trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract) was evaluated in the Ames test using the following *Salmonella typhimurium* strains with and without metabolic activation: TA97a, TA98, TA100, TA102, and TA1535.[6] The tradename mixture was evaluated at doses up to 5 µl/dish, and testing was performed in accordance with Organization for Economic Co-Operation and Development (OECD) Test Guideline (TG) 471. The test procedure included a negative/solvent control (positive control not stated). The trade name mixture did not cause significant cytotoxicity and was non-genotoxic over the range of doses tested in all bacterial strains.

The Ames test was also used to evaluate the genotoxicity of *Scutellaria baicalensis* root extracts (methanol extract and aqueous extract), using *S. typhimurium* strains TA98 and TA100, with and without metabolic activation.[24] The bacterial suspension + extract (0.1 ml) was incubated for 2 d, 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.

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.[24] 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.

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.[25] B16F10 cells were cultured for 24 h with a *Scutellaria baicalensis* root extract at concentrations of 7, 35, 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 *Scutellaria baicalensis* root extract (methanol 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.[26] 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 DNPin saline containing 4% Evans blue. A *Scutellaria baicalensis* extract (28 mg/100 g bw) 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. RPMCs 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 (all 3 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 a topically applied *Scutellaria baicalensis* root extract (aqueous extract) in suppressing 2,4-dinitrochlorobenzene (DNCB)-induced allergic contact dermatitis was studied.[27] This *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%). *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 (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 (DNCB +0.5% *Scutellaria baicalensis* root extract (aqueous extract) cream). Each gram of cream 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. The mice received topical applications (on dorsal skin) of ~20 mg dexamethasone cream, a *Scutellaria baicalensis* root extract (aqueous extract) cream, 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-d 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 (obtained from Leibniz Institute DSMZ—German Collection of Microorganisms and Cell Cultures), peripheral blood (obtained from all patients) leukocytes, and bone marrow cells (obtained from all patients).[28] 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 × 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 was reportedly 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 from 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.[29] 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 = 8.77×10^{-5}). This *Scutellaria baicalensis* root extract was classified as negative for estrogenic activity.

Dermal Irritation and Sensitization 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 OECD TG 404, using 6 New Zealand white rabbits.[30] 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, 48, 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 not stated) involving 12 subjects were negative for skin irritation.[5] 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.[30] The dried powder (spray dried extract), applied to the skin using an occlusive patch, was defined as a *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. The skin sensitization potential of an undiluted leave-on product containing 0.001%

Scutellaria Baicalensis Root Extract was evaluated in a human repeated insult patch test (HRIPT) involving 220 subjects.[31] The product (0.2 g, under semi-occlusive patch) was applied undiluted to the skin for 24 h. The location and area of the application site were not stated. Nine induction patch applications were made during a 3-wk induction period, followed by a 2-wk non-treatment period. A challenge patch was then applied to a new test site (location not stated), and reactions were scored at 24, 48, 72, and 96 h according to the International Contact Dermatitis Research Group (ICDRG) reading scale: 0 (no visible reaction) to 4 (severe reaction with erythema, induration, vesicles, and pustules (may be weeping)). A low-level reaction was associated with a score of 0 or 1, and a high-level reaction was associated with a score of 2 and above. Three subjects had a low-level reaction during induction. A low-level reaction was also observed in 1 subject during the challenge phase. Whether or not the subject with the low-level reaction during challenge was among the 3 with a low-level induction reaction was not stated. None of the subjects had a high-level reaction. The product did not induce an allergic response, and the authors commented that the product did not induce dermal sensitization in any of the subjects tested.

Results from an 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.[5] 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.

Phototoxicity

In Vitro

Scutellaria Baicalensis Root Extract. The phototoxicity of a trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract) was evaluated in the 3T3 neutral red uptake in vitro phototoxicity assay (equivalent to OECD Guideline for Testing Chemicals – In Vitro 3T3 NRU phototoxicity test) using Balb/c 3T3 cells at a density of 1×10^4 cells per well.[6] The maximum test concentration of the trade name mixture was 1000 µg/ml. Untreated cells served as the negative control, and the positive control was chlorpromazine. An appropriate continuous dose-response curve (model, *x*-axis = cell concentration and *y*-axis = cell viability) was used. This model was consistent with the European Union instructions (EU 67/548/EEC Appendix VB.41 3T3 Neutral Red Uptake (NRU) in Vitro Phototoxicity Test Methods). A photo-irritation factor (PIF) was calculated. A PIF of 1 was calculated for the trade name mixture, and was interpreted as a prediction of no phototoxicity.

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 female developed facial eczema after using a resveratrol skin cream containing Scutellaria Baicalensis Extract (concentration not stated) for several weeks.[32] Repeated open application testing of the product twice daily on the antecubital flexures yielded a positive reaction within 2 d. 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.

Another case report involves a male lupus patient with facial eczema who had applied a sunscreen containing Scutellaria Baicalensis Extract several times per day while on a 10-d vacation and afterward.[33] The eczema occurred only after he returned home and he noted that the more the sunscreen was applied, the eczema became progressively worse. The results of a photopatch test on the sunscreen product were positive at the irradiated site (+reaction) and non-irradiated site (+++) on day 2. Subsequent photopatch tests on ingredients of the sunscreen product yielded a positive reaction on only one of the ingredients, Scutellaria Baicalensis Extract. This ingredient was tested at a concentration of 0.2% in 50/50 water/ alcohol, and a ++ reaction was observed at the non-irradiated site on day 2. A reaction at the irradiated site was not observed.

Scutellaria Baicalensis Root Extract. A female non-atopic patient had a 2-yr history of pruritic, erythematous scaly plaques involving both eyelids and periorbital skin.[34] The patient was patch tested, according to European Society of Cosmetic Dermatitis guidelines, with a sunscreen containing Scutellaria Baicalensis Root Extract that was being used. Reactions were scored on days 2, 4, and 7. Positive reactions to the sunscreen (−/+/++) and 0.2% 50/50 Scutellaria Baicalensis Root Extract (?+/+/++) were reported.

In a second case report, a female patient with a history of mild atopic dermatitis (antecubital flexures and face) presented with facial eczema that she had experienced for 1 yr.[35] She had slowly developed recalcitrant facial eczema, and, during the 1-yr period, a retinoic acid-containing cream and

sunscreens had been applied to treat both the acne and solar brown spots. Both patch test and photopatch test results for one of the sunscreens (contained Scutellaria Baicalensis Root Extract) used were positive on day 2 (+reaction) and day 3 (++ reaction). The reaction to the sunscreen was not photo aggravated, and was identical at UV-exposed and non-exposed sites. Furthermore, reaction to the sunscreen was confirmed by a positive repeated open application test result after 2 d of application. Patch and photopatch tests on ingredients of the sunscreen were also performed. In both tests, a positive reaction to Scutellaria Baicalensis Root Extract (0.2% aqueous/ethanol) was reported on day 2 (+reaction) and day 3 (++ reaction), with no photo aggravation. The patch testing of 10 control subjects with Scutellaria Baicalensis Root Extract (0.2% aqueous/ethanol) yielded negative results.

Summary

The safety of the following 4 *Scutellaria baicalensis*-derived ingredients, as used in cosmetics, is reviewed in this 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 (root extracted with ethanol, butylene glycol extract, or water) 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 (root) that is extracted, 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 same methodology is used when butylene glycol (50% 1,3-butylene glycolic solution) is the extractant; squalene is not added. Regarding the method of manufacture of Scutellaria Baicalensis Root Extract (aqueous extract), the starting botanical raw material (root) is extracted and then concentrated and spray-dried.

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 (90% ethanol and butylene glycol extracts) is reported to contain not more than 20 ppm heavy metals and not more than 2 ppm arsenic. 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.* Additionally, a *Scutellaria baicalensis* root (dried root) contains a variety of flavones, phenylethanoids, amino acids, sterols, and essential oils.

According to 2020 VCRP data, Scutellaria Baicalensis Root Extract is reported to be used in 514 cosmetic products (419 leave-on products, 95 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 (suspended in an aqueous 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/d, 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, 8, or 32 g/kg/d 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/d 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 trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract) was evaluated in the Ames test using the following *S. typhimurium* strains with and without metabolic activation: TA97a, TA98, TA100, TA102, and TA1535. Doses up to 5 µl/dish were tested, and results were classified as negative in all strains tested. 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.

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.

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.

The skin sensitization potential of an undiluted leave-on product containing 0.001% Scutellaria Baicalensis Root Extract was evaluated in an HRIPT involving 220 subjects. The product (0.2 g, under semi-occlusive patch) was applied (24 h) repeatedly to the skin. A low-level reaction was observed in 3 subjects during induction and in 1 subject during challenge. The authors commented that the product did not induce dermal sensitization in any of the subjects tested. A 10% Scutellaria Baicalensis trade name mixture (butylene glycol extract) was not irritating in a patch test involving 12 subjects and was not a sensitizer in an HRIPT (dose per cm^2 not stated) involving 49 subjects. 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.

The phototoxicity of a trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract) was evaluated in the 3T3 neutral red uptake in vitro phototoxicity assay. The maximum test concentration of the trade name mixture was 1000 µg/ml. A PIF of 1 was calculated for the trade name mixture, and was interpreted as a prediction of no phototoxicity.

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. Another eczema patient photo-patch tested with 0.2% Scutellaria Baicalensis Extract (in 50/50 water/alcohol) had a positive reaction at the non-irradiated site and no reaction at the irradiated site. A patient with pruritic erythematous plaques was patch tested with 0.2% Scutellaria Baicalensis Root Extract (in 50/50 water/alcohol). Reactions classified as ?+, +, and ++ were observed on days 2, 4, and 7, respectively. In another case report, an eczema patient was patch tested and photo-patch tested with Scutellaria Baicalensis Root Extract (0.2% aqueous/ethanol). In both tests, a positive reaction was reported on day 2 (+reaction) and day 3 (++ reaction). The patch testing of 10 control subjects in this case report yielded negative results.

Discussion

All of these ingredients are derived from the same species, i.e., *Scutellaria baicalensis*. The toxicities and composition of these plant extracts are dependent, in part, upon which solvent is used to prepare the extract.

The Panel initially expressed concern over the increased incidence or a statistically significant, dose-dependent increase in the incidence of skeletal variations (presence of lumbar ribs) in developmental and reproductive toxicity studies on *Scutellaria baicalensis* root extract (aqueous extract) involving Sprague-Dawley rats. However, after further review of the data, the Panel agreed that the study results suggest that the appearance of lumbar ribs induced by the test material was a transient fetal variation rather than teratogenicity or maternal toxicity.

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. Results were positive for the methanol extract and negative for the aqueous extract. However, in Ames tests, results were positive for the aqueous extract and negative for the methanol extract. The Panel noted that, given these mixed results, a repeat of these assays and the addition of another assay (mammalian system) would be needed in order to develop a weight of evidence approach for evaluating the genotoxicity of *Scutellaria baicalensis* root extract. Subsequently, negative Ames test results on a trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract; constituent analysis not available) were received, and the Panel agreed that these data support the safety of Scutellaria Baicalensis Root Extract in cosmetic products.

In vitro studies indicated that ethanol and methanol extracts (but not n-hexane, ethyl acetate, and water extracts) could have an inhibitory effect on melanogenesis. However, the Panel noted that skin lightening is considered to be a drug effect and should not occur during the use of cosmetic products. Because of that caveat, and based on the low concentrations of use of Scutellaria Baicalensis Root Extract in cosmetic products, the results of these in vitro experiments on *Scutellaria baicalensis* root extract, and clinical experience, concern for this effect in cosmetics was mitigated. Nevertheless, the Panel noted that cosmetic formulators should only use Scutellaria Baicalensis Root Extract in products in a manner that does not cause depigmentation.

The Panel noted that Scutellaria Baicalensis Root Extract is being used in suntan products and the in vitro data on the potential inhibitory effect of *Scutellaria baicalensis* root extract on melanogenesis; however, this concern was mitigated by negative in vitro phototoxicity data on a trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract) were received.

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

Finally, although the Panel found the available data sufficient to support the safety of Scutellaria Baicalensis Root Extract and Scutellaria Baicalensis Root Powder, the Panel determined that available data are insufficient to conclude on the safety of Scutellaria Baicalensis Extract and Scutellaria Baicalensis Sprout Extract. The following data are needed to determine safety of these 2 *Scutellaria baicalensis* ingredients:

Scutellaria Baicalensis Extract and Scutellaria Baicalensis Sprout Extract

- genotoxicity (in vitro and mammalian); for ingredient extracts, methanol and aqueous extracts should be tested
- phototoxicity
- skin irritation and sensitization

Scutellaria Baicalensis Extract

- 28-d dermal toxicity; if dermal absorption occurs, additional data may be needed

Scutellaria Baicalensis Sprout Extract

- method of manufacture
- composition
- impurities
- dermal absorption; if dermal absorption occurs, additional data may be needed

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that Scutellaria Baicalensis Root Extract and Scutellaria Baicalensis Root Powder* are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the available data are insufficient to make a determination of safety for Scutellaria Baicalensis Extract and Scutellaria Baicalensis Sprout Extract under the intended conditions of use in cosmetic formulations.

**Not reported to be in current use. Were this ingredient not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to the root extract.*

Author's Note

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