
Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics

Status: Scientific Literature Review for Public Comment
Release Date: October 4, 2017
Panel Meeting Date: December 4-5, 2017

All interested persons are provided 60 days from the above release date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, 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 safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

INTRODUCTION

The *Ginkgo biloba*-derived ingredients detailed in this report function mainly as skin conditioning agents and antioxidants in cosmetic products according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*).¹ This report assesses the safety of the following 10 *Ginkgo biloba*-derived ingredients:

Ginkgo Biloba Leaf Extract	Ginkgo Biloba Leaf Water
Ginkgo Biflavones	Ginkgo Biloba Meristem Cell
Ginkgo Biloba Leaf	Ginkgo Biloba Nut Extract
Ginkgo Biloba Leaf Cell Extract	Ginkgo Biloba Root Extract
Ginkgo Biloba Leaf Powder	Ginkgo Leaf Terpenoids

Ginkgo biloba leaves and nuts (also called seeds) have been used as a source of traditional Chinese medicines.² More recently, extracts of the leaves of *Ginkgo biloba* have been used as herbal medicines or dietary supplements for treatment of heart disease, eye ailments, tinnitus, cerebral and peripheral vascular insufficiency, injuries involving brain trauma, dementias, short-term memory improvement, cognitive disorders secondary to depression, vertigo, and various cognitive disorders.^{2,3} Investigations into the efficacy of the leaf extract for these uses are numerous and are mainly based on oral administration. There are no publically available toxicity data that corresponds to any one of these cosmetic ingredients, specifically. For all of the endpoint results summarized in this report, the test article is a vaguely and variably described extract of *Ginkgo biloba* leaves, or some other non-cosmetic-ingredient source, such as “fruit pulp.” The focus of this safety assessment will be on data relevant to the use of *Ginkgo biloba*-derived ingredients in cosmetics, with specific focus on dermal application when available.

Often in the published literature, the information provided is not sufficient to determine how well the tested substance represents the cosmetic ingredient; therefore, the taxonomic name is used unless it is clear that the test substance is similar to a cosmetic ingredient. However, in the case of data on the extract of *Ginkgo biloba* leaves, the abbreviation GBE will be used, unless the data specifically are related to the cosmetic use of Ginkgo Biloba Leaf Extract.

Botanicals, such as *Ginkgo biloba*-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 *Ginkgo biloba*-derived ingredient as a whole, complex mixture. CIR is not reviewing the potential toxicity of the individual constituents, except wherein such constituents are also ingredients under review.

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

CHEMISTRY

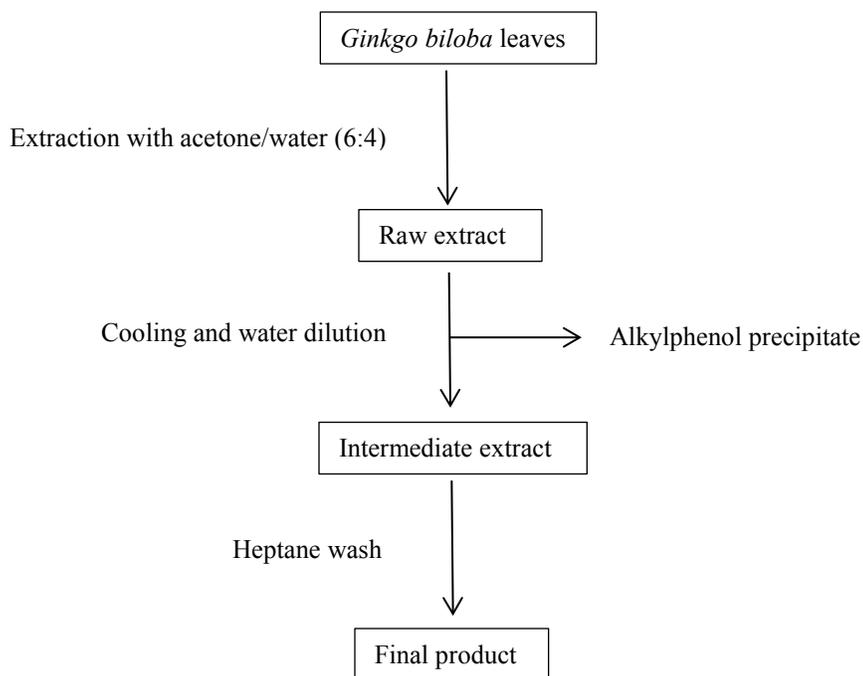
Definition and Plant Identification

The definitions and functions of the *Ginkgo biloba*-derived ingredients included in this report are provided in Table 1. The raw materials for the ingredients in this report are obtained from the deciduous tree, *Ginkgo biloba*, which has fan-shaped leaves that turn golden yellow in autumn and which can grow to 40 m (~131 ft) tall.² The female trees bear offensive-smelling, inedible fruit that contain a single thin-shelled semi-edible nut. Ginkgo trees are planted widely as ornamental trees via cultivation. Few naturally-occurring specimens grow in Zhejiang province China. Trees grown commercially for the leaves are found in China, France, and in the United States.

Methods of Manufacturing

A general description of manufacturing for “medicinal” GBE reported that the leaves of the *Ginkgo biloba* tree are harvested either mechanically or by hand from plantations or in the wild.³ The leaves are then dried and pressed into balls. A dry extract from the dried leaf of *Ginkgo biloba* can be manufactured using acetone/water and subsequent purification steps without addition of concentrates or isolated ingredients.

GBE may be full extracts or standardized extracts.⁴ Full extracts are prepared with alcohol and contain all constituents soluble in alcohol. Standardized extracts (referred to as EGb 761 in published literature) are more common, especially in herbal supplements, and are prepared in a manufacturer-dependent multi-step process in which some compounds, such as flavonoids and lactones, are enriched while others, such as ginkgolic acids, are removed (Scheme 1). According to one manufacturer, standardized extracts contain 6% terpene trilactones, 24% flavonol glycosides, and less than 5 ppm ginkgolic acids.



Scheme 1. General manufacturing process of standardized *Ginkgo biloba* extract⁵

Composition/Impurities

Table 2 summarizes the composition ranges of the major constituents of various extracts (standardized and non-standardized) of *Ginkgo biloba* leaves.

General *Ginkgo biloba* composition was reported in the *Physician's Desk Reference for Herbal Medicines* to be the following: flavonoids (0.5% to 1.8%) including monosides, biosides and triosides of quercetin, isorhamnetins, 3-*O*-methylmyricitins, and kaempferol (may be esterified with *p*-coumaric acid); biflavonoids (0.4% to 1.9%) including amentoflavone, bilobetin, 5-methoxybilobetin, ginkgetin, and isoginkgetin; proanthocyanidins (8% to 12%); trilactonic diterpenes (0.06% to 0.23%) including ginkgolide A, B, and C; and trilactonic sesquiterpene bilabolids (0.04% to 0.2%).³

An extraction of 60% w/w ethanol of dried green *Ginkgo biloba* leaves yielded an extract comprised of 3.4% flavone glycosides, 0.7% terpene lactones, and 5.5% ginkgolic acids.⁶ Further fractionation by liquid-liquid partition between water and heptane yielded a fraction comprised of 0.3% flavone glycosides, 0.1% terpene lactones, and 24.6% ginkgolic acids.

For use as an herbal medicine in Germany, GBE must be extracted with acetone/water and contain 22%-27% flavone glycosides (quercetin and kaempferol) with a molar mass of 756.7 (quercetin glycoside) and 740.7 (kaempferol glycoside); 5%-7% terpene lactones of which 2.8%-3.4% consists of ginkgolides A, B, and C and 2.6%-3.2% bilobalide; and less than 5 ppm ginkgolic acids.⁷ An example of standardized GBE specifications is the following: brown powder with characteristic smell containing not more than 20 ppm heavy metals; not more than 2 ppm arsenic; not more than 5 ppm ginkgolic acid; not less than 24.0% total flavonoid content; and not less than 6.0% total terpene trilactone content.⁴

Ginkgolic acid is a salicylic acid derivative with a C₁₅ side chain that is related to the pentadecylcatechols (i.e. urushiol) found in poison ivy.⁸ One analysis found crude aqueous extracts of GBE contained up to a total of 30 ppm urushiols while the process to produce standardized GBE removed long chain alkylphenols to below detection levels.⁵

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2017 VCRP survey data, *Ginkgo Biloba* Leaf Extract has the most reported uses in cosmetic products, with a total of 726; the majority of the uses are in leave-on eye makeup preparations and skin care products (Table 3).⁹ Two other *Ginkgo*-derived ingredients are reported to be in use, with 24 or less uses reported in the VCRP. The results of the

concentration of use survey conducted in 2014 by the Council only had results for Ginkgo Biloba Leaf Extract, which is reported to be used at a maximum of 1%, as reported in face and neck skin preparations.¹⁰ Ingredients with no reported uses in the VCRP or by the Council are listed in Table 4.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, Ginkgo Biloba Nut Extract is reported to be used in 24 formulations, but no use concentration data were provided.

Some of these ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes; for example, Ginkgo Biloba Leaf Extract is used in lipstick at up to 0.2%. Additionally, some of these ingredients are used in formulations that are used near the eyes; for example, Ginkgo Biloba Leaf Extract is used in eye shadows and eye lotions at up to 0.01%.^{9,10} Moreover, some of these ingredients were reported to be used in sprayed products that could possibly be inhaled. For example, Ginkgo Biloba Leaf Extract was reported to be used in pump spray suntan products at a maximum concentration of 0.05%.¹⁰ In practice, 95% to 99% of the droplets/ particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump spray.¹¹⁻¹⁴ Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{11,13} Ginkgo Biloba Leaf Extract is also used in powders, and these products could possibly be inhaled; for example, it is used in face powders at a maximum concentration of 0.05%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.¹⁵⁻¹⁷

The *Ginkgo biloba*-derived ingredients described in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.¹⁸

Non-Cosmetic

GBE is used extensively as an herbal supplement for anti-inflammatory, cognitive-promoting, antioxidant, and vascular effects.^{2,3} In Germany, GBE is an approved herbal medicine for use for treatment of memory deficits, dementia, and other organic brain syndromes when extracted with acetone/water.⁷ It is not approved when extract with other solvents due to lack of supporting safety data.

Standardized GBE and/or constituents of the extract, such as bilobalide, kaempferol and ginkgetin, have also been studied for potential neuroprotective effects against Huntington's disease, anti-inflammatory and analgesic effects on post-surgical incisions and diseases such as osteoarthritis and atopic dermatitis, protective effects (antioxidant) against radiation and chemotherapy-induced toxicity, anticancer effects, and therapy for vitiligo.¹⁹⁻²⁷

GBE as an herbal supplement may interact with pharmaceutical drugs and act as or enhance anticoagulants, anti-inflammatory agents, antihypertensives, and/or anesthetics which may lead to hemorrhage, apraxia, hematoma, hyphema, permanent neurological deficit, and death.^{28,29} The *Physician's Desk Reference for Herbal Medicines* reports major drug interaction risks with anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), and trazodone and moderate drug interaction risks with low molecular weight heparins and thrombolytic agents.³ GBE may also interact with anticonvulsants, buspirone, insulin, monoamine oxidase (MAO) inhibitors, nifedipine, nifedipine, omeprazole, papaverine, St. John's wort, selective serotonin reuptake inhibitors, and thiazide diuretics.

The nuts of *Ginkgo biloba* are a delicacy in Japan and China, but must be removed completely from the pulp, boiled or roasted, and eaten sparingly (limit 8-10 per day).² In traditional Chinese medicine, the nut is dried and used to treat such ailments as asthma, cough, bronchitis, scabies, and sores.

TOXICOKINETICS

In general, toxicokinetics data are not expected to be found on botanical ingredient because each botanical ingredient is a complex mixture of hundreds of constituents. However, there have been many pharmacokinetics studies on GBE, specifically on some of the key constituents, which indicate GBE may be well absorbed after oral administration.³⁰

Dermal Penetration

The ability of the GBE constituent, quercetin, to penetrate the skin while in a cosmetic formulations was studied in vitro with human dermatomed skin.³¹ The cosmetic formulation used in the study was an emulsion containing trilaureth-4 phosphate, ammonium acryloyldimethyltaurate/VP copolymer and emollients, sclerotium gum, humectants, preservatives and water that was prepared and supplemented with 6.0% (w/w) *Ginkgo biloba* glycolic leaf extract (Titrami Ginkgo biloba). An analysis of the GBE used in this study showed it contained 0.12% quercetin. The test formulation (10 mg/cm²) was applied to the skin samples (n=6) that were mounted on Franz diffusion cells for 24 h. Samples of the receptor fluid were taken after 6 h and 24 h exposures and quantified with high performance liquid chromatography (HPLC). The skin cells were washed at the end of the exposure time and the stratum corneum was removed by tape stripping. The stratum corneum and viable epidermis contained 0.17 ± 0.002 µg/cm² (24% of the applied dose) and 0.23 ± 0.04 µg/cm² (33% of the applied dose) quercetin, respectively. Quercetin in the dermis and the receptor fluid was below limits of quantification or below limits of

detection. Approximately 40% quercetin was measured in the washing solution. The total recovery of quercetin was approximately 97%.

Absorption, Distribution, Metabolism, and Excretion (ADME)

The absorption, distribution, and elimination of radiolabeled GBE were studied in male and female Sprague-Dawley rats.^{30,32} The rats received a single oral suspended dose (20 μ Ci; 380 mg/kg) of the radiolabeled GBE. The test material was obtained from *Ginkgo biloba* grown under a supply of [¹⁴C]-acetate. The pharmacokinetic results, based on blood specific activity data versus time course, were characteristic of a two-compartment model with an apparent first order phase and a half-life of approximately 4.5 h. Expired [¹⁴C]-CO₂ represented 16% of the administered dose 3 h post-treatment. After 72 h, 38% of the radioactivity was excreted via exhalation, while 21% was determined to be excreted in the urine and 29% was excreted in the feces. The researchers of this study concluded that at least 60% of the radiolabeled GBE was absorbed

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Animal

Oral

The LD₅₀ of standardized GBE administered orally to mice was reported to be 7.73 g/kg.³⁰

Intravenous

The LD₅₀ after intravenous administration of standardized GBE was 1.1 g/kg for both rats and mice.³⁰

Human

Oral

In anecdotal accounts from Chinese medicine, consumption of fresh *Ginkgo biloba* nuts may cause stomachache, nausea, diarrhea, convulsions, weak pulse, restlessness, difficulty breathing, and shock.² Death has been reported in children following consumption of fresh nuts.

Short-Term Studies

The results of a combined liver comet assay (see Genotoxicity section) using male and female C3H-derived constitutive androstane receptor knockout (CARKO) and wild-type mice found no abnormal clinical signs and no treatment-related effects on body weight following oral exposure of up to 2000 mg/kg body weight/day GBE for 3 days in either mouse genotype.³³ Relative liver weights were significantly increased in male and female wild-type mice at all doses of GBE in a dose-dependent manner. The liver weights in the CARKO mice were similar to the negative control group. The wild-type mice in all GBE-treated groups had dose-dependent slight-to-moderate hepatocellular hypertrophy in the centrilobular area: this effect was only observed in a single mouse in the highest dose group. No histopathological findings suggesting cytotoxicity in the liver was observed in any GBE-treated groups.

Subchronic Toxicity Studies

Animal

Oral

The toxicity of GBE was investigated in a 3-month mouse study performed by the National Toxicology Program (NTP).³⁰ Groups of 10 male and 10 female B6C3F1/N mice received 0, 125, 250, 500, 1000, or 2000 mg/kg body weight GBE in corn oil via gavage, 5 days per week for 14 weeks. Control groups received corn oil (5 ml/kg). Clinical findings and body weights were recorded initially, then weekly, and at the end of the study. Blood was collected at the end of the study from all animals for hematology analyses. Sperm motility and vaginal cytology evaluations were made on the mice in the 0, 500, 1000, and 2000 mg/kg dose groups. At the end of the study period, tissues from over 40 sites were examined for every animal, including ovaries and uteri in females and prostate gland and testes with epididymis and seminal vesicles in males.

One female mouse in the 1000 mg/kg group died of a dosing accident during week 11. Mean body weights of 2000 mg/kg females were significantly less than those of the vehicle control group. Ruffled fur was observed in two 1000 mg/kg males between weeks 7 and 8 and all 2000 mg/kg males between weeks 5 and 9. No treatment-related differences in sperm parameters in males or in the estrous cycle of females were observed when compared to controls. Liver weights of males of the 250 mg/kg or greater dose groups and females of all dose groups were significantly greater than those of the vehicle control groups. Kidney weights of males of the 2000 mg/kg group were significantly less than those of the vehicle control group. Female mice in the 2000 mg/kg group had a significantly higher probability of extended estrus than did the vehicle control females. Incidences of hepatocytic hypertrophy were significantly increased in males and females dosed with 250 mg/kg or greater. Significantly increased incidences of focal hepatocytic necrosis occurred in males of the 1000 and 2000

mg/kg dose groups. The incidences of hyaline droplet accumulation in the respiratory epithelium of the nose were significantly increased in males of the 500 mg/kg and females of the 1000 and 2000 mg/kg dose groups. In the olfactory epithelium of the nose, the incidences of hyaline droplet accumulation were significantly increased in the 125 (female only), 500, and 1000 mg/kg groups. Incidences of atrophy of the olfactory epithelium were significantly increased in the 1000 mg/kg groups. The incidences of pigment accumulation in macrophages in the olfactory epithelium were significantly increased in males in the 500 mg/kg or greater groups and in females in the 1000 and 2000 mg/kg dose groups.³⁰

The NTP also performed a 3-month study of GBE in rats.³⁰ Groups of 10 male and 10 female F344/N rats received 0, 62.5, 125, 250, 500, or 1000 mg/kg body weight GBE in corn oil via gavage, 5 days per week for 14 weeks. Additional groups of 10 male and 10 female rats received the same doses for a clinical pathology study, 5 days per week for 23 days. Control groups received corn oil (2.5 ml/kg). The same methods that were followed in the mouse study described above were used in the main study animals, while animals in the clinical pathology study had blood samples collected on days 4 and 23.

All rats survived to the end of the study. Mean body weights of all dosed groups were similar to those of the vehicle control groups. No treatment-related clinical findings were observed. Liver weights of all dosed groups of males and females were significantly greater than those of the vehicle control groups. Incidences of hepatocyte hypertrophy in all dosed groups of males and in 500 and 1000 mg/kg females were significantly greater than those in the vehicle control groups; there was a dose-related increase in severity of this lesion in males. Hepatocyte fatty change occurred in all dosed males. The incidences of thyroid gland follicular cell hypertrophy were significantly increased in 500 and 1000 mg/kg males and in 1000 mg/kg females. The incidences of pigmentation in the olfactory epithelium of the nose were significantly increased in 500 and 1000 mg/kg males and in females administered 125 mg/kg or greater.³⁰

Chronic Toxicity Studies

There was no evidence of organ damage or impairment of hepatic or renal function when GBE was administered orally over 27 weeks to rats and mice at doses ranging from 100 to 1600 mg/kg.³⁰

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

The reproductive and developmental toxicity of standardized GBE was studied in mice. In one study, groups of 25 mated female CD-1 mice received 0, 100, 350, or 1225 mg/kg/day GBE in tap water via gavage (20 ml/kg) on days 6 through 15 of gestation.³⁴ The dams were observed daily for clinical signs of toxicity. Feed and water consumption were monitored during the study. Body weight was measured daily. On day 17 of gestation, the dams were killed and the ovaries, uteri, and the fetuses were removed. The internal organs and the placentae of the dams were examined macroscopically. The fetuses were examined for several parameters, including external and internal damages (malformations), sex, viability, and weight. The skeletal systems and soft tissues of the fetuses were also examined.

No clinical signs of toxicity were observed in the dams and there were no unscheduled deaths. No treatment related effects were observed in body weight gains or feed and water consumption. There were no pathological findings observed during necropsy. No embryotoxic effects were observed during external and internal examinations of the fetuses nor were any observed in skeletal or soft tissues. There were no increased incidences of malformation, variations, or retardations. The authors concluded the no-observed-effect-level (NOEL) was greater than 1225 mg/kg/day for both the dams and the fetuses in this study of standardized GBE.³⁴

Another study examined the effects of oral administration of standardized GBE in saline on the mouse reproductive and developmental toxicity.³⁵ Female Swiss albino mice received 0, 3.7, 7.4, or 14.8 mg/kg body weight/day for 28 days prior to mating, from day 1 to day 7 of gestation, or from day 10 to day 18 of gestation. There were 10 animals per dose group to study the anti-implantation and abortifacient activities for GBE, while there were 10 mice per dose group to study the reproductive cycle and 20 mice per dose group to study the developmental cycle (12 test groups total). Blood hormones were measured in the pre-mating group on day 28. Vaginal smears were performed daily. The mice were observed daily for clinical signs of toxicity and premature deaths. Body weights were recorded weekly. On day 20 of gestation, the remaining mice were killed and their kidneys, liver, brain, placenta, spleen and ovaries were removed and weighed. The ovaries were prepared for histological examinations, and then ovarian follicles were counted. Maternal toxicity, estrous cycle, reproductive hormones, ovarian follicle counts, resorption index, implantation index, fetal viability and fetuses, and placenta mean weights were evaluated.

No clinical signs of toxicity were observed in the dams during treatment and there were no unscheduled deaths. Statistically significant decreases in body weight gains were observed in the 14.8 mg/kg/day dose group when compared to the controls. There were no treatment-related differences in the relative weights of the liver, kidney, brain, spleen, ovary, and placenta, but there was a significant dose-dependent decrease in the relative weight of the gravid uterus in the 14.8 mg/kg/day dose group for 28 days when compared to controls. Ovarian follicle counts, resorption index, implantation index, fetal viability were significantly reduced in 14.8 mg/kg/day dose group. Treatment with 14.8 mg/kg bw/day GBE induced disruption of estrous cycle and caused maternal toxicity, in addition to fetal toxicity. No adverse effects were observed in the

3.7 or 7.4 mg/kg bodyweight/day dose groups. The authors concluded that 14.8 mg/kg body weight/day GBE produced adverse effects on the estrous cycle, fertility, abortifacient, reproductive performance, and hormone levels of female mice and may cause adverse effects on ovarian function as an antifertility agent.³⁵

GENOTOXICITY

In Vitro

GBE at up to 10,000 µg/plate was mutagenic in an Ames test using *Salmonella typhimurium* strains TA98 and TA100 and in *Escherichia coli* strain WP2 *uvrA*/pKM101, with and without metabolic activation.³⁰

The genotoxicity of GBE and eight of its constituents (quercetin; quercetin-3-β-D-glucoside; kaempferol; isorhamnetin; ginkgolide A; ginkgolide B; ginkgolide C; and bilobalide) were evaluated in mouse L5178Y cells using a lymphoma assay and a Comet assay.³⁶ The GBE (0.2-1.2 mg/ml) and the eight constituents were tested in a DMSO solution. A dose-dependent increase in mutant frequency was observed in GBE, quercetin (10-100 µM), quercetin-3-β-D-glucoside (200-1000 µM), and kaempferol (10-200 µM) without metabolic activation. DNA double-strand breaks were also observed in dose-dependent increases in GBE, quercetin, and kaempferol. Negative results were observed in the other constituents. A Western blot analysis confirmed that GBE, quercetin, and kaempferol activated the DNA damage signaling pathway. Additionally, GBE produced reactive oxygen species and decreased glutathione levels in L5178Y cells. Loss of heterozygosity analysis of mutants indicated that GBE, quercetin, and kaempferol resulted in extensive chromosomal damage. The authors concluded that GBE, quercetin, and kaempferol are mutagenic in mouse L5178Y cells.

In Vivo

In a micronucleus test in male and female B6C3F1/N mice, no increase in the frequency of micronucleated erythrocytes was observed in peripheral blood of male mice administered 125 to 2000 mg/kg/day GBE orally for 3 months.³⁰ Female mice that received the same doses had results that were deemed equivocal based on a significant trend test and due to no individual dose group being significantly elevated over the vehicle control group. A significant ($P < 0.001$) dose-related decrease in the percentage of circulating polychromatic erythrocytes (PCEs) was observed in male mice, which may indicate GBE induced bone marrow toxicity. In the female mice, a significant ($P = 0.001$) decrease in the percentage of circulating PCEs was also observed, but the response was not as correlated with dose as it was in the males.

In a reporter gene mutation assay using male B6C3F1 *gpt* delta mice, oral dosing of GBE in corn oil at up to 2000 mg/kg body weight/day for 90 days did not produce remarkable increases in *gpt* or *Sp*⁻ mutation frequencies in DNA extracted from the liver.³³ No treatment-related clinical signs or deaths were observed during the treatment period. Relative liver weights were significantly increased in the 2000 mg/kg group. Hepatocellular hypertrophy in the centrilobular area and slight focal necrosis were observed in the 2000 mg/kg group.

This assay was performed in conjunction with a combined liver comet assay and bone marrow micronucleus assay using male and female CARKO and wild-type mice. The short-term toxicity effects were described in the Toxicological Studies section. In the micronucleus study, no significant alterations in the percentages of PCEs were observed in females of either genotype; however, a significant decrease in the percentage of PCEs were observed in both genotypes in males, indicating GBE induced bone marrow toxicity in male mice. In the comet assay, there was no significant difference in the percent tail DNA in any of the GBE-treated groups in either mouse genotype. Heavily damaged cells called “hedgehogs” indicating cytotoxic effects were not detected in any animals. The researchers performing these 3 assays concluded that GBE is not genotoxic.³³

CARCINOGENICITY

Oral

The carcinogenic potential of GBE administered orally was studied by the NTP in male and female rats and mice.³⁰ In the study on mice, groups of 50 male and 50 female B6C3F1/N mice received 200, 600, or 2000 mg/kg GBE in corn oil 5 day per week for 104 weeks via gavage. In the study on rats, groups of 50 F344/N male and 50 female rats received 100, 300, or 1000 mg/kg body weight GBE for 104 (males) or 105 (females) weeks via gavage. Control groups received corn oil (5 ml/kg in mice and 2.5 ml/kg in rats). In rats involved in what was deemed a “special study,” groups of 10 male and female rats received the same doses as in the main study; blood was collected from these rats on day 22 and at week 14 for thyroid hormone analyses and other analyses of the liver and thyroid gland. All animals were observed twice daily. Body weights were evaluated at study beginning and ending and at different intervals during the course of the study. At the end of the study period, tissues from over 40 sites were examined for every animal, including ovaries and uteri in females and prostate gland and testes with epididymis and seminal vesicles in males.

In mice, mortality was significantly higher in the 600 and 2000 mg/kg males than in the vehicle controls, with the most frequent cause of death being liver tumors. Survival in the 600 mg/kg females was significantly greater than that of the vehicle controls. Mean body weights in the mid- and high-dose group male mice were less than those of the vehicle controls after weeks 85 and 77, respectively. The mean body weights of the high-dose females were generally less than the vehicle controls between weeks 17 and 69 and after week 93.

In rats, mortality in the 1000 mg/kg males was significantly higher than that of the vehicle controls, with the most frequent cause of death being mononuclear cell leukemia. The survival of the treated female rats was comparable to the vehicle control. In week 14, all dose group males and females of the 1000 mg/kg group in the special study had increased levels of thyroid stimulating hormone compared to the vehicle controls; the increase was dose-related in the male rats. Mean body weights in the mid- and high-dose male and female rats were less than the vehicle controls after weeks 93 and 89, respectively.

Lesions in the liver, thyroid gland, and nose were observed in all GBE dose groups in mice and rats. These lesions included hypertrophy in the liver and thyroid gland in rats and mice, liver hyperplasia in male and female rats, and hyperplasia and atrophy of the epithelium in the nose of male and female rats. Inflammation, hyperplasia, hyperkeratosis, and ulcers were also observed in the forestomach of male and female mice. Additionally, increased incidences of cancers of the thyroid gland were observed in male and female rats and male mice and of liver cancers in male and female mice. The study concluded that GBE caused cancers of the thyroid gland in male and female rats and male mice, and cancers of the liver in male and female mice.³⁰

The International Agency for Research on Cancer (IARC) has determined that GBE is possibly carcinogenic to humans (group 2B) based on inadequate human carcinogenicity evidence and sufficient evidence in experimental animals.³⁷

OTHER RELEVANT STUDIES

Immunotoxicity

In a popliteal lymph node assay (PLNA), the sensitization potential of GBE was evaluated.⁶ Groups of male C57BL/6 mice received subplantar injections of 10 µl DMSO (induction) followed by another injection of DMSO (negative control group), crude ethanolic-aqueous GBE, heptane fraction of the crude GBE, or diphenylhydantoin (positive control group) at doses of 2 mg each. The negative control yielded small enlargement of the lymph nodes, while the crude ethanolic-aqueous GBE resulted in statistically significant lymphoproliferative reaction (LPR) in the ipsilateral popliteal lymph node. A massive lymph node hyperplasia that was almost comparable to the positive control was observed in the heptane solution fraction of the crude GBE. Chemical analyses of the crude extract and the heptane fraction found ginkgolic acid at 5.5% and 24.6%, respectively, which were theorized to be responsible for the LPR observed in this study.

DERMAL IRRITATION AND SENSITIZATION STUDIES

No dermal irritation or sensitization studies were found in the published literature.

OCULAR IRRITATION STUDIES

No ocular irritation studies were found in the published literature.

CLINICAL STUDIES

Case Studies

The fruit pulp of the *Ginkgo biloba* tree has been reported to cause contact dermatitis, with several cases reported after patients handled the fruit pulp during extraction of the edible nut center.^{3,8,38} Symptoms include intense itching, edema, papules, and pustules that usually resolve in 7-10 days.

A 66-year-old woman presented with progressive erythematous eruption over the face, neck, trunk, and extremities that started approximately one week after the patient had ingested two 60 mg doses of a GBE supplement.³⁹ No other new medications or changes in behavior were reported. A physical examination, complete blood cell count, and chemistry panel were unremarkable. The authors of the report did not disclose if patch or skin prick tests were performed.

A 45-year-old man developed acute generalized exanthematous pustulosis on his limbs and face 48 h after starting oral GBE treatment for tinnitus.⁴⁰ The patient had not previously taken GBE before and was taking any other medication. The patient had no history of adverse drug reactions or psoriasis. The rash cleared within 10 days of stopping GBE treatment. The patient refused a follow-up cutaneous patch test.

Other Clinical Reports

No adverse effects were reported in clinical studies of an anti-aging cosmetic formulation containing 1.5% GBE and other antioxidants in 45 volunteers⁴¹ and of an anti-wrinkle cosmetic formulation containing 0.30% GBE in 20 volunteers.⁴²

SUMMARY

The *Ginkgo biloba*-derived ingredients detailed in this report function mainly as skin conditioning agents and antioxidants in cosmetic products. Investigations into the efficacy of the leaf extract for these uses are numerous and are mainly based on oral administration. There are no publically available toxicity data that corresponds to any one of these ingredients specifically. For all of the endpoint results summarized in this report, the test article is a vaguely and variably described extract of *Ginkgo biloba* leaves, or some other non-cosmetic-ingredient source, such as "fruit pulp." The focus of

this safety assessment has been on data relevant to the use of *Ginkgo biloba*-derived ingredients in cosmetics, with specific focus on dermal application when available.

According to 2017 VCRP survey data, Ginkgo Biloba Leaf Extract has the most reported uses in cosmetic products, with a total of 726; the majority of the uses are in leave-on eye makeup preparations and skin care products. Two other *Ginkgo*-derived ingredients are reported to be in use, with 24 or less uses reported in the VCRP. The results of the concentration of use survey conducted in 2014 by the Council only had results for Ginkgo Biloba Leaf Extract, which is reported to be used at up to 1% in face and neck skin preparations.

GBE is used extensively as an herbal supplement for anti-inflammatory, cognitive-promoting, antioxidant, and vascular effects and is an approved herbal medicine in Germany for use for treatment of memory deficits, dementia, and other organic brain syndromes when extracted with acetone/water. GBE may interact with pharmaceutical drugs. Nuts from *Ginkgo biloba* are consumed as a delicacy in Japan and China and are used in traditional Chinese medicine. Anecdotal accounts report that consumption of the nuts may have acute adverse effects.

In general, toxicokinetics data are not expected to be found on botanical ingredient because each botanical ingredient is a complex mixture of hundreds of constituents. However, there have been many pharmacokinetics studies on GBE, specifically on some of the key constituents, which indicate GBE may be well absorbed after oral administration. The GBE constituent, quercetin, was found to penetrate human dermatomed skin. In an oral ADME study in rats, at least 60% of radiolabeled GBE absorbed. Radioactivity was measured in exhalation and elimination products.

The LD₅₀ of standardized GBE administered orally to mice was reported to be 7.73 g/kg, and the LD₅₀ after intravenous administration of standardized GBE was 1.1 g/kg for both rats and mice.

In anecdotal accounts from Chinese medicine, consumption of fresh *Ginkgo biloba* nuts may cause stomachache, nausea, diarrhea, convulsions, weak pulse, restlessness, difficulty breathing, and shock. Death has been reported in children following consumption of fresh nuts.

In 3-month studies of GBE at up to 2000 mg/kg/day, increased liver weights, decreased kidney weights, increased incidences of hepatocytic hypertrophy and focal hepatocytic necrosis, and increased incidences hyaline droplet accumulation, atrophy and pigment accumulation in macrophages in the olfactory epithelium were observed in mice. In a similar study of GBE in rats, increased liver weights, increased incidences of hepatocyte hypertrophy, increased incidences of thyroid gland follicular cell hypertrophy, and increased incidences of pigmentation in the olfactory epithelium of the nose were observed. There was no evidence of organ damage or impairment of hepatic or renal function when GBE was administered orally over 27 weeks to rats and mice at doses ranging from 100 to 1600 mg/kg.

In an oral DART study of standardized GBE in mice, the NOEL for dam and fetuses was greater than 1225 mg/kg/day. No clinical signs of toxicity were observed in the dams and no embryotoxic effects were observed in the fetuses. In another oral DART study in mice, standardized GBE at 14.8 mg/kg/day produced adverse effects on the estrous cycle, fertility, abortifacient, reproductive performance, and hormone level in female mice and may cause adverse effects on ovarian function as an antifertility agent.

GBE at up to 10,000 µg/plate was mutagenic in an Ames test. GBE (0.2 - 1.2 mg/ml) was mutagenic in mouse L5178Y cells. In a mouse micronucleus test of GBE up to 2000 mg/kg/day, no increase in the frequency of micronucleated erythrocytes was observed in male mice, but the results were deemed equivocal in female mice. GBE at up to 2000 mg/kg/day was not genotoxic in a reporter gene mutation assay, a combined liver comet assay, and bone marrow micronucleus assay in mice.

In carcinogenicity studies of rats and mice conducted by the NTP, lesions in the liver, thyroid gland and nose were observed in all GBE dose groups (200 - 2000 mg/kg/day). Lesions included hypertrophy in the liver and thyroid gland in rats and mice, liver hyperplasia in male and female rats, and hyperplasia and atrophy of the epithelium in the nose of male and female rats. Inflammation, hyperplasia, hyperkeratosis, and ulcer were also observed in the forestomach of male and female mice. Additionally, increased incidences of cancers of the thyroid gland were observed in male and female rats and male mice, as were liver cancers in male and female mice. IARC has determined that GBE is possibly carcinogenic to humans (group 2B).

In a PLNA validation study, GBE exposure yielded statistically significant lymphoproliferative reactions in the ipsilateral popliteal lymph node, which may have been caused by ginkgolic acid.

Reports of contact dermatitis have been reported following exposure to the fruit pulp of *Ginkgo biloba*. Patients have reported erythematous reactions and generalized exanthematous pustulosis following ingestion of GBE supplements. No adverse effects were reported in clinical studies of cosmetic formulations containing up to 1.5% GBE.

No dermal or ocular irritation and no dermal sensitization studies were found in the published literature.

DATA NEEDS

CIR is seeking additional data on the extraction methods and composition and impurities of the *Ginkgo biloba*-derived ingredients described in this report that are used in cosmetic formulations, as there may be a difference in constituent levels of different extracts. Additional toxicological data, specifically dermal and ocular irritation and sensitization data on these cosmetic ingredients at use concentrations, are also being sought in order to help the CIR Expert Panel assess the safety of the use of these ingredients in cosmetics.

TABLES

Table 1. Definitions, Structures, and functions of the ingredients in this safety assessment.⁴³

Ingredient/CAS No.	Definition & Structure	Function
Ginkgo Biloba Leaf Extract 90045-36-6	Ginkgo biloba leaf extract is the extract of the leaf of <i>Ginkgo biloba</i> .	skin-conditioning agent – misc.
Ginkgo Biflavones	Ginkgo biflavones is a mixture of biflavones derived from the leaves of <i>Ginkgo biloba</i> . It consists predominantly of sciadopitysin, bilobetin, ginkgetin, and isoginkgetin.	antioxidant
Ginkgo Biloba Leaf 90045-36-6	Ginkgo biloba leaf is the leaf of <i>Ginkgo biloba</i> .	skin-conditioning agent – misc.
Ginkgo Biloba Leaf Cell Extract 90045-36-6	Ginkgo biloba leaf cell extract is the extract of a culture of the leaf cells of <i>Ginkgo biloba</i> .	flavoring agents; skin protectant
Ginkgo Biloba Leaf Powder 90045-36-6	Ginkgo biloba leaf powder is the powder obtained from the dried, ground leaves of <i>Ginkgo biloba</i> .	skin-conditioning agent – misc.
Ginkgo Biloba Leaf Water 90045-36-6	Ginkgo biloba leaf water is the aqueous solution of the steam distillate obtained from the leaves of <i>Ginkgo biloba</i> .	fragrance ingredient; skin-conditioning agent – misc.
Ginkgo Biloba Meristem Cell	Ginkgo biloba meristem cell are the cultured meristem cells isolated from <i>Ginkgo biloba</i> .	antimicrobial agent; antioxidant; skin-conditioning agent – misc.
Ginkgo Biloba Nut Extract 90045-36-6	Ginkgo biloba nut extract is the extract of the seeds of <i>Ginkgo biloba</i> .	cosmetic astringent; hair conditioning agent; nail conditioning agent; skin-conditioning agent – misc.
Ginkgo Biloba Root Extract 90045-36-6	Ginkgo biloba root extract is the extract of the roots of <i>Ginkgo biloba</i> .	skin-conditioning agent – misc.
Ginkgo Leaf Terpenoids 107438-79-9 15291-75-5 15291-76-6 15291-77-7 33570-04-6	Ginkgo leaf terpenoids is a mixture of terpenoids isolated from the leaves of <i>Ginkgo biloba</i> consisting chiefly of ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J, and bilobalide.	antiacne agent; antifungal agent; antimicrobial agent; antioxidant; external analgesics; hair conditioning agent

Table 2. Major GBE constituents (% unless otherwise indicated).^{30,44-46}

Class	Identified	Range
Terpene trilactones	Total	0.07-15.4
	Bilobalide	0.03-8.64
	Ginkgolide A	0.01-3.82
	Ginkgolide B	<0.005-2.00
	Ginkgolide C	<0.005-3.06
	Ginkgolide J	0.03-0.78
Flavonol glycosides	Total	0.18-35.54
	Quercetin	<0.01-16.71
	Kaempferol	0.02-12.20
	Isorhamnetin	0.04-2.37
Alkylphenols	Ginkgolic acids, cardanols	10.45; <500-89,576 ppm

Table 3. Frequency (2017) and concentration of use (2014) according to duration and type of exposure for *Ginkgo biloba*-derived ingredients^{9,10}

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Ginkgo Biloba Leaf Powder		Ginkgo Biloba Leaf Extract*		Ginkgo Biloba Nut Extract	
Totals†	4	NR	726	0.000002-1	24	NR
Duration of Use						
Leave-On	3	NR	637	0.000002-1	14	NR
Rinse Off	1	NR	87	0.00002-0.25	10	NR
Diluted for (Bath) Use	NR	NR	2	NR	NR	NR
Exposure Type						
Eye Area	1	NR	222	0.00001-0.01	NR	NR
Incidental Ingestion	NR	NR	5	0.00002-0.2	NR	NR
Incidental Inhalation-Spray	1 ^a ; 1 ^b	NR	7; 165 ^a ; 101 ^b	0.05; 0.00005-0.0041 ^a	2 ^a ; 6 ^b	NR
Incidental Inhalation-Powder	1 ^b	NR	47; 101 ^b	0.00001-0.05; 0.00038-1 ^c	6 ^b	NR
Dermal Contact	2	NR	664	0.00001-1	23	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	48	0.00005-0.001	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	5	0.00002-0.24	NR	NR
Mucous Membrane	NR	NR	21	0.00002-0.2	1	NR
Baby Products	NR	NR	NR	0.005	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.

*Combined with the generic entry “Ginkgo Extract” in the VCRP database, which is not an INCI name.

^a. It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

^b Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^c It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 4. Ingredients not reported in use.^{9,10}

Ginkgo Biloba Leaf Extract
Ginkgo Biflavones
Ginkgo Biloba Leaf
Ginkgo Biloba Leaf Water
Ginkgo Biloba Meristem Cell
Ginkgo Biloba Root Extract
Ginkgo Leaf Terpenoids

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