Amended Safety Assessment of Kojic Acid as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date (i.e., by **December 19, 2026**) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.*

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ABBREVIATIONS

2-AAF	2-acetylaminofluorene
8-OxodG	8-oxodeoxyguanosine
ALP	alkaline phosphatase
AUC	area under the curve
BrdU	bromodeoxyuridine
CAR	constitutive androstane receptor
C_{max}	peak concentration
CHO	Chinese hamster ovary
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
DART	developmental and reproductive toxicity
Dictionary	*International Cosmetic Ingredient Dictionary*
DHPN	*N*-bis(2-hydroxypropyl)nitrosamine
DMBA	9,10-dimethyl-1,2-benzanthracene
EC	European Commission
ECHA	European Chemicals Agency
EPA	US Environmental Protection Agency
EU	European Union
FDA	US Food and Drug Administration
GEDIAC	Grupo Español de Investigación Dermatitis de Contacto y Alergia Cutánea
GLP	good laboratory practice
GOT	glutamic-oxaloacetic transaminase
GPT	glutamic-pyruvic transaminase
GST-P	glutathione S-transferase-placental form
HRIPT	human repeated insult patch test
IARC	International Agency for Research on Cancer
iDMM	iPS cell-derived melanocyte medium
IL	interleukin
iPS	induced pluripotent stem
LDH	lactate dehydrogenase
LI	labeling indices
MDA	malondialdehyde
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MOE	margin of exposure
MOS	margin of safety
MTT	methyl thiazol tetrazolium
NOAEL	no-observable-adverse-effect level
NOEL	no-observable-effect level
NR	not reported
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PCNA	proliferating cell nuclear antigen
POD	point of departure
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RLD	Registration and Listing Data
SCCP	EC Scientific Committee on Consumer Products
SCCS	EC Scientific Committee on Consumer Safety
SDM	sulfadimethoxine
SED	systemic exposure dose
SPB	phenobarbital sodium salt
T3	triiodothyronine
T4	thyroxine
TG	test guideline
TPA	phorbol-12-myristate-13 acetate
TSH	thyroid-stimulating hormone
UDP-GT	diphosphate glucuronosyltransferase
US	United States
USDA	US Department of Agriculture

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of Kojic Acid, which is reported to function as an antioxidant in cosmetic products. The Panel reviewed the available data to determine the safety of this ingredient. Accordingly, the Panel issued an amended report with a revised conclusion stating that the available data are insufficient to make a determination of safety for Kojic Acid for use in anogenital wipes, douches, and baby products. Additionally, the Panel concluded that Kojic Acid is safe in the present practices of use and concentration for all other uses described in this safety assessment.

INTRODUCTION

This assessment reviews the safety of Kojic Acid as used in cosmetic formulations. According to the *International Cosmetic Ingredient Dictionary* (*Dictionary*), Kojic Acid functions as an antioxidant in cosmetic formulations.[1] While Kojic Acid is purported to have skin-lightening properties, whitening of the skin is considered to be a drug effect in the US.

The Panel first reviewed the safety of Kojic Acid in a report published in 2010, with the conclusion "Kojic Acid is safe for use in cosmetic products up to a concentration of 1%."[2] In June 2022, the Panel determined that this safety assessment should be re-opened for re-evaluation due to reported restrictions by the European Commission (EC) on the use of Kojic Acid.[3] Excerpts from the summaries of the 2010 report are disseminated throughout this document, as appropriate, and are identified by *italicized* text. (This information is not included in the Summary section.)

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last performed in September 2026. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Some of the new data included in this safety assessment were found in the opinions by the EC Scientific Committee on Consumer Products (SCCP)[4] and Scientific Committee on Consumer Safety (SCCS)[3,5] Please note that these sources provide summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when the SCCP and SCCS are cited.

CHEMISTRY

Definition and Structure

According to the *Dictionary*, Kojic Acid (CAS No. 501-30-4) is the heterocyclic compound that conforms to the structure in Figure 1.[1]

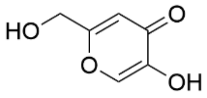


Figure 1. Kojic Acid

Chemical Properties

UV absorption appears to vary as a function of the pH.[2] *The enolic hydroxyl group at C5 gives Kojic Acid its weakly acidic property and allows it to form salts with a number of metals.*

Chemical properties for Kojic Acid are summarized in Table 1. Kojic Acid is a white to light yellow crystalline powder with a molecular weight of 142.11 g/mol.[2,3] The log K_{ow} is reported to be -0.64.[3]

Method of Manufacture

The method of manufacturing of Kojic Acid for cosmetic use is not clearly described in the published literature. However, Kojic Acid is a hydrophilic metabolite mainly derived from various species of *Aspergillus* and *Penicillium* by using glucose and yeast extract as carbon and nitrogen sources, respectively.[6] It also can be produced by using a variety of sugars (e.g., sucrose, lactose, galactose, arabinose, ribose, and starch) or using different organic wastes via microbial fermentation. Different fermentation procedures have been reported for large scale Kojic Acid production, including submerged batch fermentation.

Kojic Acid may also be synthesized by acetylation of tetraacetyl-galactosone hydrate by action of acetic anhydride and pyridine to yield diacetylkojic acid.[7] This is followed by deacetylation in the presence of ammonia in methanol or methoxide.

Impurities

The purity of Kojic Acid was reported to be greater than 97%.[3] Impurities may include heavy metals (10 mg/kg maximum) and arsenic (4 mg/kg). One sample was reported to contain ≤ 2 ppm arsenic, ≤ 50 ppm chloride, ≤ 10 ppm heavy metals, ≤ 120 ppm sulfate, and < 1.08 ppb aflatoxins.

Natural Occurrence

Kojic Acid is naturally produced as a secondary metabolite in the following Aspergillus strains: A. albus, A. alliaceus, A. awamori, A. arachidicola, A. bombycis, A. caelatus, A. candidus, A. clavatus, A. effusus, A. flavus, A. fumigatus, A. giganteus, A. glaucus, A. gymnosardae, A. leporis, A. luteovirescens, A. lutescens, A. minisclerotigenes, A. nidulans, A. nomius, A. parasiticus, A. parvisclerotigenus, A. pseudotamarii, A. tamarii, and A. wentii.[2] *Kojic Acid is also a secondary metabolite of several strains of Penicillium and Acetobacter fungi and several species of acetic acid bacilli.*

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of Kojic Acid in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[8] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

According to RLD obtained from the FDA in 2025, Kojic Acid is reported to be used in 3726 formulations, with the majority of the uses reported in personal cleanliness products (867 in bath soaps and body washes) and skin care preparations (822 in face and neck products; Table 2).[9,10] The results of the concentration of use survey conducted by the Council in 2024 indicate Kojic Acid is used at up to 1% in leave-on skin care preparations.[11]

RLD and the results of the concentration of use survey indicate that Kojic Acid is used in products that may come into contact with mucous membranes (0.001% in bath oils, tablets, and salts; 0.05% in bath soaps and body washes; anogenital wipes and douches (concentrations not reported).[9,10] Uses have also been reported in baby products, and eye makeup preparations (no concentrations reported for either category). Additionally, Kojic Acid is used in cosmetic sprays and powders and could possibly be inhaled; for example, Kojic Acid is used in hair sprays and face powders (concentrations not reported).[9,10] In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Following the passage of MoCRA, the FDA created a number of new product categories, including "(17) Other preparations (i.e., those preparations that do not fit another category)" (Category 17). However, citation of Category 17, alone, as the product use category is uninformative. When a product is co-categorized with both Category 17 and one or more common product use categories (e.g., eye makeup preparations), then those uses are accounted for and may be considered to be part of the "the present practices of use" for those products; as such, the Panel's safety conclusion may be inclusive thereon. Conversely, for instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17, the present practices of use for these products remain unknown and the Panel's safety assessment conclusion does not apply to these preparations.

It is possible that some products containing Kojic Acid may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined therein, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. None of the reported product categories for this ingredient as listed in the RLD include a designation indicating airbrush application, so it is possible that this ingredient is used with airbrush delivery systems, but not reported as such. Additionally, concentration of use surveys are conducted based on product categories as stated in the RLD, but airbrush use was not reported in response to the survey. No consumer habits and practices data or particle size data are

publicly available to evaluate the exposure associated with airbrush technology, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. If this ingredient was to be used in airbrush formulations, the data are insufficient to evaluate the exposure resulting from cosmetics applied in such a manner.

In the European Union (EU), the SCCS concluded in 2022 that Kojic Acid is safe when used as a skin lightening agent in cosmetic products at concentrations of up to 1%.[3] (It should be noted that in Europe, products that whiten the skin are considered to be cosmetics; however, in the US, skin lightening is considered to be a drug effect.) The EC has categorized Kojic Acid in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down.[12] For this ingredient, the regulation states that Kojic Acid may only be used in face and hand products at a maximum concentration of 1%. This restriction is based on the overall safety assessment performed by the SCCS, which incorporated margin of exposure (MOE) evaluations that indicate higher exposure levels, such as those resulting from use on larger body areas, may pose a health risk.[13]

Non-Cosmetic

Non-cosmetic uses reported for Kojic Acid include therapeutic uses for melasma, antioxidant and preservative in foods, antibiotic, chemical intermediate, metal chelate, pesticide, and antimicrobial agents.[2]

Numerous studies have identified Kojic Acid as a topical treatment for hyperpigmentation.[6,14-16] Research has also been conducted on Kojic Acid for use as treatment for neurodegenerative diseases, including Alzheimer's disease,[17,18] and corneal injuries.[19] Kojic Acid is used in the production of a number of foods, including soybean paste (miso), shoyu (soy sauce), or sake.[5]

While Kojic Acid is purported to have skin lightening properties, it is currently not approved by the US FDA for such use in over-the counter pharmaceutical products. However, a study that quantified several known skin-lightening agents in commercial skin lightening products found Kojic Acid at concentrations as high as 3.9% (in a cream formulation).[20]

TOXICOKINETIC STUDIES

Dermal Penetration

Absorption of radiolabeled Kojic Acid at 1.045% in a formulation through human dermatomed skin resulted in 17% of the applied dose being absorbed.[2] *The in vivo percutaneous absorption of 1% Kojic Acid in a cream formulation (500 mg) was studied in 6 human volunteers. [This study was used in the 2022 SCCS opinion to calculate the margin of exposure (MOE).] The test material was applied to the entire surface of the facial skin (left and right cheeks). Kojic Acid was detected in the plasma of all the participants at one or more blood collection times (up to 24 h after application). All the concentrations in plasma were only slightly above the quantitation limit of 1 ng/ml. The mean peak concentration (C_{max}) was 1.54 ng/ml and the mean area under the curve ($AUC_{0-24\,h}$) was 19.4 h·ng/ml. There were no adverse effects observed in the participants. Based on pharmacokinetic studies in rat (described below under Absorption, Distribution, Metabolism, and Excretion) and in vitro percutaneous absorption values in human skin, the systemic exposure dose (SED) range was determined to be 0.03 to 0.06 mg/kg/d. The SED range was calculated using the application area of the hands and face (400 and 590 cm^2, respectively), a maximum application rate of 1.0 g of 1% Kojic Acid cream at 1 mg/cm^2 (total application of 10 mg Kojic Acid/d), and percutaneous absorption of 17% of the applied dose (3.6 µg/cm^2) in humans.*

In Vitro

The percutaneous absorption of ^{14}C-Kojic Acid was studied in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 428 with human dermatomed skin.[5] A leave-on skin care formulation containing 1% Kojic Acid was applied to 12 intact skin membranes on static diffusion cells at a rate of 2 mg/cm^2 (equivalent to 20 µg Kojic Acid/cm^2) for 24 h. The skin surface was then washed with 2% sodium dodecyl sulfate in water, followed by rinsing with water. The stratum corneum was then removed by tape-stripping. The 24-h penetration profile was determined by collecting receptor fluid (phosphate buffered saline) samples at 0.5, 1,2, 4, 8, 12, 16, 20 and 24 h following application. Mean recovery of the applied test material was 95.48 ± 3.33% (19.44 ± 0.68 µg/cm^2). The average penetration rate was 0.006 µg/cm^2/h. The mean amount of Kojic Acid that penetrated over the 24-h exposure period was 0.698% of the applied dose (0.142 ± 0.265 µg/cm^2). The mean total systemically available dose of Kojic Acid (remaining epidermis + dermis and receptor fluid) was 3.68% of the applied dose (0.749 µg/cm^2). The SCCS noted that there were several issues with the study, including a discrepancy in the reported concentration of Kojic Acid tested (0.88% instead of 1%) and the potential that the formulation may not be representative of the majority of the Kojic Acid-containing formulations on the market due to the high amount of silicones, polyols and nylon in the test material.[3,5]

Absorption, Distribution, Metabolism, and Excretion

In rats, Kojic Acid is rapidly absorbed and distributed to all organs in oral treatments.[2] *Kojic Acid is not as rapidly absorbed or distributed in subcutaneous treatments, is slowly absorbed in dermal treatments, and can be transferred at low levels to milk. Kojic Acid is mainly excreted in the urine; metabolites are sulfate and glucuronide conjugates of Kojic Acid.*

The toxicokinetics of ^{14}C-Kojic Acid was studied in male Wistar rats (number not reported) in a non-good laboratory practice (GLP) study.[21] The rats received a single oral (33 mg/kg in water/propylene glycol (2:1)), subcutaneous (same dose as oral), or dermal (1% in cream formulation at 33 mg/kg on 9 cm^2 area; 24-h application under occlusion) dose. With the oral and subcutaneous doses, Kojic Acid was rapidly absorbed and metabolized, with approximately 70% of the dose excreted in urine, 5% in feces, and 1.4% in expired radiolabeled carbon dioxide. The order of magnitude of plasma levels (C_{max} > 20 µg eq/ml following a single dose of 1.72 mg/kg) suggest a relatively high bioavailability after oral or subcutaneous administration. Appearance of radiolabel in expired air indicated that a minor portion of the administered Kojic Acid was metabolized completely. Topical administration resulted in lower plasma values, indicating a lower bioavailability, as compared with those following oral or subcutaneous administration. The calculated $AUC_{0\text{-}6\ h}$ values were 71.8, 63.9, and 13.3 µg ^{14}C eq · h/ml for oral, subcutaneous, and topical administration, respectively. It was determined that the bioavailability after topical application in rats under occluded conditions may be estimated to be in the order of 18% of a respective oral administration.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

In acute mouse studies with Kojic Acid, oral, subcutaneous, and intraperitoneal LD_{50} values were 5.1, 2.7, and 2.6 g/kg bw, respectively.[2] *In rats, the LD_{50} values were greater than 2 g/kg bw in oral and dermal studies, and 2.6 and 2.4 g/kg bw in subcutaneous and intraperitoneal studies, respectively.*

Short-Term Toxicity Studies

Dermal

A 4-wk dermal study in rats found that exposure at up to 1000 mg/kg/d Kojic Acid lowered lymphocyte counts at 300 and 1000 mg/kg/d and decreased absolute and relative spleen weights at 1000 mg/kg/d.[2] *The no-observable-effect level (NOEL) for this study was 100 mg/kg/d.*

The dermal toxicity of Kojic Acid was assessed in a 30-d study in New Zealand White rabbits.[3,4] Groups of 5 males and 5 females received 0, 13, 130, or 1300 mg/kg bw/d (0, 0.65, 6.5, or 65% w/v) Kojic Acid in 1% aqueous methylcellulose on abraded skin daily (2 ml/kg/d). Treatment sites were covered for 6 h each day with gauze before being washed with warm water. Animals were observed daily for clinical signs and mortality, and body weight and feed consumption were recorded weekly. Blood samples for hematological and biochemical parameters were taken prior to the start of treatment and in the control and in the highest dose group prior to study end. The rabbits were killed after the end of the treatment and underwent necropsy and histopathology.

All rabbits had slight dermal reactions, but effects were more persistent in the animals that were treated with Kojic Acid. Erythematous papules and abscesses were observed in several rabbits (no further details provided). Two animals had an infection of *Staphylococcus aureus*. One female of the 13 mg/kg bw/d group and 1 male of the 130 mg/kg bw/d group were found dead and 1 male of the control group was killed *in extremis*. Necropsy of these animals revealed lesions of the lung, liver, kidney, and brain that may have been contributing factors. In the 1300 mg/kg bw/d dose group, statistically significant changes were observed in the mean corpuscle hemoglobin concentration, the mean cell volume, and A/G ratio when compared to controls. In the 13 mg/kg bw/d dose group, the pituitary weight was significantly increased. Ophthalmoscopic examination revealed changes in the eyes in 1 control animal, 1 animal in the 13 mg/kg bw/d dose group, 3 animals in the 130 mg/kg bw/d dose group, and 3 animals in the 1300 mg/kg bw/d dose group. Plaques in the aorta were reported in 1 control male, 3 males and 1 female in the 13 mg/kg bw/d dose group, 1 male and 1 female in the 130 mg/kg bw/d dose group, and 4 males in the 1300 mg/kg bw/d dose group. Pale kidneys were reported in all treated groups. The SCCP noted that effects on skin and eyes could not be evaluated due to the bacterial infection in the animals. Because hematological and biochemical parameters after the treatment period were only studied in the 1300 mg/kg bw/d dose group, a conclusion on dose-dependency of statistically significant changes could not be made.[3,4]

Subchronic Toxicity Studies

Oral

In a 13-wk oral toxicity study, male rats received up to 3000 mg/kg/d Kojic Acid in 1.0% carboxymethycellulose.[2] *Rats that received 250 mg/kg or more of Kojic Acid had significant suppression of body weight gain when compared to the control group. The 1000 mg/kg dose group also had a slight decrease in erythrocyte counts and decreases of hematocrit value and hemoglobin concentration. Increases of glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) were observed in dose groups receiving 250, 500, and 1000 mg/kg. The 500 and 1000 mg/kg dose groups had increased alkaline phosphatase (ALP), and slight increases of total cholesterol, bilirubin, and calcium were observed in the 1000 mg/kg dose group. At necropsy, the absolute and relative weights of the adrenal glands were increased in the dose groups receiving 500 and 1000 mg/kg Kojic Acid. The NOEL was determined to be 125 mg/kg/d.*

Chronic Toxicity Studies

Oral

In a 26-wk study, groups of 10 male SLC-SD rats received 0, 125, 250, 500, or 1000 mg/kg bw/d Kojic Acid in 1% aqueous solution of carboxymethylcellulose (0.5 ml/100 g bw) via gavage.[3] A 5-wk recovery period occurred in the 250, 500, and 1000 mg/kg bw/d dose groups. The animals were observed for abnormalities daily, and body weight, feed consumption, and water intake were measured twice a week until 13 wk after the initial administration, then once a week thereafter. Urine was analyzed prior to necropsy at the end of the dosing period and at the end of the 5-wk recovery. Hematological and serobiochemical tests were performed before necropsy. Blood levels for triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) were not measured. Animals were killed and subjected to macroscopic and microscopic examinations.

In the groups receiving 250 mg/kg bw/d and more, excitation and subsequent sedation were observed for 2 and 3 h after administration of Kojic Acid. In the groups receiving 500 mg/kg and more, there were also some cases accompanied by exophthalmos and salivation. Suppression of body weight gain was reported in groups receiving 250 mg/kg bw/d and above. A temporary decrease in feed consumption and increase in water intake were observed in the groups treated with 500 mg/kg and above. A decrease in urine volume was observed in the 2 highest dose groups, and at 1000 mg/kg bw/d a decrease of urinary pH was reported. Statistically significant hematological and biochemical differences reported included an increase in creatinine in the 250 and 500 mg/kg bw/d groups; an increase in ALP values in the 500 and 1000 mg/kg bw/d groups; increases in GOT, GPT, bilirubin, and relative amounts of monocytes; and decreases in the number of erythrocytes, hematocrit and hemoglobin in the highest dose group. These changes were not observed at the end of recovery period. Relative weights for several organs were statistically different from controls in the 250 mg/kg bw/d dose group and above. Decreases in absolute organ weights were reported for the heart (500 mg/kg bw/d and above dose groups) and for the spleen (500 mg/kg bw/d group only). Absolute organ weight increased in the adrenals in the 500 mg/kg bw/d and above dose groups. Thyroid weights were increased significantly at 500 and 1000 mg/kg bw/d. The NOEL for Kojic Acid was determined to be 125 mg/kg bw/d in this oral study.[3]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

The no-observable-adverse-effect level (NOAEL) for maternal toxicity and embryotoxicity was 150 mg/kg/d in an oral two-generation developmental and reproductive toxicity (DART) study in female mice that received 0, 25, 150, or 900 mg/kg/d Kojic Acid in 1% methylcellulose on gestation days 6 - 15.[2] Fetuses of the 900 mg/kg dose group had a slight but significant decrease in the body weights (males), a slight but significant retardation of ossification (males and females), and a significant decrease in ossified calcaneus (males and females). In another two-generation oral study, female mice received 0, 30, 160, or 800 mg/kg on gestation day 15 to postpartum day 21. The dams in the 800 mg/kg/d does group, which had a significant decrease in feed consumption and water intake accompanied by a significant decrease in body weight at the end of gestation through the lactation period had a significantly decreased number of live female pups and total number of live pups at birth compared to controls, and a significant decrease in body weight gain was observed in female weanlings of this dose group. The F_1 mice had decreased relative organ weights and significant retardation of incisor eruption.

Female rats that received 50 µg/d Kojic Acid in propylene glycol on days 1 - 5 post-coitum had significant decreases in implantation sites, a significant increase in litter mortality, and a significant decrease in litter sizes. Cannibalistic behavior towards pups in treated dams was also observed. Significant decreases in the number of implantations occurred, but no decline in the number of corpora lutea were observed. No teratogenic effects were observed in the treated group. In an oral DART study in male and female rats that received 0, 25, 150, or 900 mg/kg/d Kojic Acid in methylcellulose prior to mating (9 wk prior in males and 2 wk prior in females) and through gestation day 7 in females, clinical signs of toxicity were observed in both sexes in the 900 mg/kg/d dose group. In the 900 mg/kg/d dose group, slightly delayed mating and lower values of mean litter size and number of implantations per litter were observed when compared to controls. No treatment-related effects were observed in any treatment group with regard to post-implantation loss, mean fetal weight, or embryonic or fetal development. In an oral developmental study in female rats that received 0, 100, 300, or 1000 mg/kg/d Kojic Acid in 0.5% methylcellulose on gestation days 6 - 17, no clinical signs of toxicity, abnormal macroscopic findings, abortions/resorptions, or death were observed in the dams at any dose level. There were no treatment-related effects on litter parameters, external malformations, or anomalies in fetuses in any dose group. In a fertility study of male rats that received 50 µg/d Kojic Acid in propylene glycol for up to 21 d (rats were mated on days 16 - 21), body weights were significantly decreased in treated males, and weights of the testis and epididymis were also significantly decreased when compared to controls. Implantations and litter sizes were significantly decreased in the treated group, and a loss of litter viability was observed on the second or third day after delivery. Cannibalism of the litter occurred in the dams mated with treated males 2 days after delivery that was not observed in the controls.

Female rabbits were given 0, 20, 100, or 500 mg/kg/d Kojic Acid in 1% methylcellulose via gavage on days 6 - 18 of gestation. No treatment-related effects on litter size, post-implantation loss, litter and mean fetal weights, or embryonic and fetal development were observed.

GENOTOXICITY STUDIES

Some genotoxicity assays are no longer considered appropriate as standard methods for evaluating genotoxic potential under current OECD guidance. (See https://www.cir-safety.org/sites/default/files/Genotoxicity_ResourceDocument_062026.pdf for the identification of such study types.) Although these assays may be reported in the published literature, unpublished reports, or data submissions, the results from these assays (as identified in the guidance) are of limited interpretability and therefore, the studies are not summarized herein.[2,22]

Kojic Acid (tested at up to 10,000 µg/plate) was genotoxic in Salmonella typhimurium and Escherichia coli in several Ames studies performed with and without metabolic activation.[2] *Genotoxicity was observed to Kojic Acid in Chinese hamster ovary (CHO) assays for chromosomal aberrations (up to 6 mg/ml, with or without metabolic activation) assay, but genotoxicity was not observed in cell mutation assays in mouse lymphoma L5178 TK$^{+/-}$ cells (up to 1421 µg/ml, with or without metabolic activation) or in Chinese hamster V79 cells (up to 3000 µg/ml). Kojic Acid was a weak clastogen without metabolic activation in a chromosome aberration assay in Chinese hamster V79 cells when tested at up to1420 µg/ml, with and without metabolic activation, but the effects observed may have been related to cytotoxicity. In in vivo mammalian tests, Kojic Acid was not genotoxic in micronucleus tests in mice that received up to 4000 mg/kg bw intraperitoneally, a dominant lethal test in mice (up to 700 mg/kg orally), a comet assay in rats (up to 2000 mg/kg orally), or DNA adduct assays (up to 2% in diet). In an oral micronucleus study in both mice (3- and 9-wk old) and rats (9-wk old) with up to 1000 mg/kg Kojic Acid, mean values of micronucleated hepatocytes in 9-wk old mice were increased in a dose-dependent manner, with a significant increase over the negative control at 1000 mg/kg; however, this effect was not observed in 3-wk old mice or in the rats. Kojic Acid was a weak photo-mutagen in a photo-reverse mutation assay in S. typhimurium and E. coli when tested at up to 5000 µg/ml, and in a chromosomal aberration study with light irradiation in Chinese hamster lung cells when tested at up to 1.4 mg/ml. Irradiation of Kojic Acid, both in a gene mutation assay with E. coli at up to 5000 µg/plate and in a micronucleus study in mice that were treated dermally with a cream containing up to 3% Kojic Acid, did not result in genotoxicity.*

Additional in vitro and in vivo genotoxicity studies on Kojic Acid are summarized in Table 3. Chromosomal damage was not observed in an in vitro micronucleus assay, with or without metabolic activation, in SVK14 human keratinocyte cells at 500 - 8000 µg/ml Kojic Acid.[3] Genotoxicity results were not clear in another in vitro micronucleus assay using HepG2 human liver cancer cells at 1000 - 8000 µg/ml Kojic Acid.[3] In an in vivo chromosomal damage study, no induction of micronuclei were observed in a micronucleus assay in male rats at up to 1000 mg/kg/d Kojic Acid.[23] Additionally, no DNA strand breaks were observed in a comet assay performed in male rats at up to 1000 mg/kg/d Kojic Acid.

CARCINOGENICITY STUDIES

The International Agency for Research on Cancer (IARC) concluded that Kojic Acid is in group 3—not classifiable to human carcinogenicity.[2] *Tumorigenic potential of Kojic Acid was observed in the liver, but not in the thyroid follicular epithelial cells in mice that were fed a diet containing up to 3% Kojic Acid for 26 wk; however, up to 1% Kojic Acid was not tumorigenic to mice in a 78-wk dietary study. In a 55-wk rat dietary study of 0.5 or 2% Kojic Acid, the no-observable-adverse-effect level (NOAEL) was determined to be below 0.5%. Changes in the liver, thyroid glands, and adrenal glands, including diffuse follicular cell hyperplasia in the thyroid glands in both treatment groups and adenomas and/or carcinomas in the 2% group, were observed.*

Liver tumors observed in rodents often arise through a mode of action involving activation of the constitutive androstane receptor (CAR), leading to hepatocellular proliferation via enzyme induction.[24] However, this mechanism is not considered relevant to humans, as CAR activators do not induce the same proliferative response in human hepatocytes. Adrenal pheochromocytomas reported in rat studies are also generally considered not relevant to human cancer risk.[25] These tumors are frequently induced via secondary, non-genotoxic mechanisms such as sustained endocrine stimulation or mitochondrial dysfunction, which are not reflective of processes in humans.

Tumor Promotion and/or Tumor Initiation

Kojic Acid did not possess initiation or promotion potential for skin carcinogenesis in mice.[2] *Several studies on mice and rat liver found Kojic Acid to have carcinogenesis-promoting potential but not an initiation potential. While data from previous reports are usually not presented in tables in amended safety assessments, data from the previous report are found in Table 4 in order to adequately capture the details of these numerous studies.*

Thyroid Effects

Studies on the effect of Kojic Acid on rodent thyroids found the chemical inhibits iodine uptake and organification in the thyroid, which causes a proliferative effect.[2] *More robust summaries of these data may be found in Table 5. The SCCS utilized the results of the 4-wk oral studies in rats (up to 2% or 1387.3 mg/kg bw/d) for MOE calculations.*

In a 4-wk dietary study, groups of 8 male F344 rats received Kojic Acid at 0, 0.008, 0.03, 0.125, 0.5, 2.0% (0, 5.85, 23.8, 95.3, 393.6, 1387.3 mg/kg bw/d, respectively).[26] Blood samples were taken from 5 rats at the end of treatment period for hormone analysis and animals were necropsied. Histopathological examination of thyroid and pituitary tissues was performed. The remaining animals injected intraperitoneally with 0.4 ml of 0.1 M $Na^{125}I$ in saline 24 h prior to being killed

for measurement of ^{125}I uptake and organification in the thyroid. There were no significant intergroup differences in the final body weights. Absolute and relative thyroid weights were increased in a dose-dependent manner in all treatment groups, with statistical significance at 0.5 and 2% Kojic Acid. Pituitary and liver relative weights also significantly increased compared to the control. ^{125}I uptake decreased in a dose-dependent manner, with statistical significance starting at 0.03% and higher. In addition, a significant reduction of organic formation of iodine and serum T3 and T4 levels were observed in the 2% Kojic Acid group along with a significant increase of TSH. Histopathologically, decreased colloid in the thyroid follicles and follicular cell hypertrophy in the thyroid were apparent at high incidences in the groups that received 0.03% Kojic Acid or more. In addition, thyroid capsular fibrosis was evident in all rats of the 2% Kojic Acid group. In quantitative morphometric analysis the ratio of the area of follicular epithelial cells to the area of the colloids in a unit area was significantly increased in groups treated with 0.03% Kojic Acid and above.

Kojic Acid has been considered to have no genotoxic potential in vivo; evidence indicates that humans are less sensitive than rodents with regard to perturbation of thyroid hormone homeostasis.[3] Rodent thyroid follicular cell tumors are often associated with sustained elevations in thyroid-stimulating hormone (TSH), leading to hypertrophy and tumor formation.[27] However, these effects are species-specific, as rodents exhibit a shorter half-life of thyroxine (T4) and heightened TSH responsiveness compared to humans. There are currently no compound-specific quantitative data available to substantiate the assertion that Kojic Acid could interfere with thyroid hormone homeostasis in humans. Reflecting these differences, both the IARC and the US Environmental Protection Agency (EPA) have emphasized that rodent thyroid tumorigenesis should be interpreted with caution when extrapolating to humans, as the underlying mechanisms are not predictive of human thyroid cancer risk. The US EPA concluded that elevated TSH in rodents leads to thyroid hypertrophy and potential thyroid cancer, an adverse outcome that has limited relevance to human thyroid cancer due to species differences in sensitivity.[28]

The effects of Kojic Acid on thyroid function were studied in cultured rat FRTL-5 thyroid cells and by a single-dose oral administration in rats.[29] In the thyroid cells, Kojic Acid inhibited iodine organification dose-dependently, but did not inhibit iodine uptake. In rats receiving a single dose of 1000 mg/kg Kojic Acid, the ^{125}I uptake from blood into the thyroid gland was significantly lower than that of the control group from 30 min to 24 h after administration. The ^{125}I organification activity of the Kojic Acid groups was significantly lower than controls from 30 min to 6 h after administration; however, this activity 24 or 48 h after administration recovered enough to be nearly comparable with the control group. These results suggest that the observed lower iodine uptake activity in the single-dose administration study in rats was due to the inhibition of iodine organification caused by Kojic Acid, which decreased iodine in the entire thyroid gland. Although serum T4 showed a tendency to decrease from 2 to 48 h after oral administration of Kojic Acid, serum TSH did not show any evident change associated with the administration of Kojic Acid in rats.

ANTI-CARCINOGENICITY STUDIES

The anti-carcinogenic effects of Kojic Acid were studied in human A375 and A2058t melanoma cells and in a mouse xenograft model established using A375 cells.[30] In vitro, A375 and A2058t cells were treated with 0, 0.25, 0.5, 1, 2, or 4 mM Kojic Acid in sterile water. After 48 h, Kojic Acid reduced cell viability and induced apoptosis, with the greatest effects observed at 2 and 4 mM. Colony formation was also significantly reduced after 14 d, with nearly complete suppression at 4 mM. No detectable cytotoxicity was observed in WS1 human dermal fibroblasts.

Transcriptomic and mechanistic analysis indicated dose-dependent repression of MYC target genes, including CCNA2 and KPNA2. Kojic Acid did not affect MYC expression but reduced MYC binding to the *CCNA2* and *KPNA2* promoters, thereby reducing their transcriptional activation. In the xenograft model, male BALB/c-nude mice were injected subcutaneously with A375 cells into the right flank. When tumors were approximately 100 mm^3, mice were randomized into vehicle-control and treatment groups (6/group). Kojic Acid (4 mM or 0.568 mg/ml; in sterile water) or an equal volume of vehicle was applied directly onto the tumor surface once daily for 21 d. At study termination, the tumors were excised for histopathological and immunohistochemical analyses. Compared to control mice, topical application of Kojic Acid led to significant reductions in tumor volume and weight in the mice. Histopathological examination revealed extensive necrosis in Kojic Acid-treated tumors. Immunohistochemical analysis showed decreased expression of the proinflammatory chemokine Cxcl1, the proliferation marker Ki-67, and the angiogenesis-related factor VEGFA, suggesting suppression of tumor cell proliferation, inflammation, and vascularization.[30]

OTHER RELEVANT STUDIES

Cytotoxicity

The effect of Kojic Acid (4.22, 8.02, or 12.67 mM) on human liver HepG2 cells was assessed using the methyl thiazol tetrazolium (MTT) and crystal violet cell viability assays.[31] Kojic Acid significantly reduced cell viability in a dose-dependent manner following treatment up to 48 h, with an IC_{50} of 8.02 mM. A significant loss in cell viability was seen at 4.22 and 12.67 mM. After 24 h treatment, caspase - 3/7, -8, and -9 activities were all increased in HepG2 cells at 4.22 mM and 8.02 mM. The effect of Kojic Acid on the integrity of cell membrane was assessed by lactate dehydrogenase (LDH) assay, with LDH leakage observed at 12.67 mM.

The study further examined the impact of Kojic Acid on oxidative stress and antioxidant responses. Kojic Acid significantly increased the production of extracellular malondialdehyde (MDA), a by-product of lipid peroxidation, while significantly reducing protein carbonyl levels. However, 8-OHdG levels remain unchanged. The expression of antioxidant response proteins, Nrf2 and p-Nrf2, and catalase, a component in the detoxification of peroxides, were significantly downregulated. The gene expression of glutathione peroxidase was increased at 4.22 mM (1.51-fold) and 8.02 mM (1.07-fold), but unchanged at 12.67 mM. *NFκB* gene expression was decreased at 8.02 mM (0.24-fold), indicating a significant suppression of the NFκB inflammatory pathway. Mitogen-activated protein kinases including JNK 1/2 and p38 were also evaluated by Western blot: Kojic Acid significantly decreased JNK 1/2 expression but increased p38 expression at 4.22 and 8.02 mM. At the treated doses, no DNA or protein damage were detected. The researchers concluded that Kojic Acid exhibited minimal toxicity to HepG2 cells.[23]

Hepatic Effects

The effect of Kojic Acid on the expression of cytochrome P450 isozymes was studied in 4 groups of 4 male F344 rats.[32] The rats received 0.6, 3, or 1875 mg/kg bw Kojic Acid for 14 d. Kojic Acid at 1875 mg/kg bw significantly decreased body weight and serum T4 levels, but increased liver and thyroid gland weights. Protein expression of CYP2B1, CYP2E1, and CYP2C11 in liver tissues were analyzed by Western blotting. The pattern of CYP2B1 protein expression in the livers of Kojic Acid-treated rats showed that low-dose Kojic Acid significantly decreased the level of expression, but medium and high doses of Kojic Acid significantly increased CYP2B1 expression. Kojic Acid also decreased CYP2E1 expression in rat livers, and CYP2C11 was significantly decreased in livers of the rats that received the high dose of Kojic Acid.

Effects on Keratinocytes

Primary human melanocyte and keratinocyte co-culture systems were used to evaluate whether Kojic Acid induced changes in keratinocytes were associated with anti-melanogenic activities in melanocytes.[33] The cytokine secretion profiles in response to Kojic Acid (0.2 mM) were analyzed. Kojic Acid was found to have increased interleukin (IL)-6 and IL-8 production in melanocyte/keratinocyte co-cultures; however, only IL-6 directly suppressed melanogenesis while IL-8 did not. Kojic Acid did not increase IL-6 production in melanocyte monocultures; whereas in keratinocyte monoculture it significantly up-regulated IL-6 gene and protein expression. Anti-IL-6 antibody treatment antagonized the anti-melanogenic effect of Kojic Acid on the co-cultures. The authors concluded that anti-melanogenic activity of Kojic Acid on hyper-pigmented skin was associated with the Kojic Acid-induced IL-6 production in keratinocytes.

Tyrosinase Effects

Because of its well-documented ability to inhibit tyrosinase activity, Kojic Acid has been used in numerous studies as a positive control.[2]

The effects of Kojic Acid on melasma were studied using human induced pluripotent stem (iPS) cell-derived melanocytes.[34] The melanocytes were cultured in human iPS cell-derived melanocyte medium (iDMM). Kojic Acid (70 µg/ml) was directly added to iDMM. Microscopic analysis did not show any differences between human iPS cell-derived melanocytes treated with Kojic Acid when compared to untreated controls. The effects of Kojic Acid on tyrosinase activity were then investigated in human iPS cell-derived melanocytes. The addition of 70 µg/ml Kojic Acid for 2 wk had no effect on tyrosinase activity when compared to untreated controls.

Dermal Depigmentation

The depigmenting effects of Kojic Acid were studied in a black guinea pig study.[2] *Kojic Acid at 0.1 ml was applied at concentrations of 1 and 4% (w/v) in a 1:4 mixture of dimethyl sulfoxide and ethanol to the shaved dorsal area (4 x 4 cm^2 or 4 x 3 cm^2) of 4 JY-4 black guinea pigs. The vehicle alone was also tested. The test substance was applied once a day, 6 d/wk, for 5 successive weeks. After the application period had ended, the animals were killed and skin samples were prepared for examination. The depigmentation action was evaluated by macroscopic observation and spectrophotometric colorimetry. Optical and electron microscopy of epidermal melanocytes were also performed for morphological examination. The mechanism for which skin whitening occurs was also investigated by measuring oxygen consumption and the relation of free radicals to melanin synthesizing enzyme tyrosinase.*

The skin whitening action of Kojic Acid was very weak when compared to phenylhydroquinone: the results of the macroscopic evaluation of phenylhydroquinone at 1 and 4% were "+" and "++", respectively, while these results were "-" and "+ ~ ±" in the 1 and 4% Kojic Acid, respectively. The 4% Kojic Acid test group, however, showed no statistically significant difference from the vehicle group in the colorimetric value. A white substance that was thought to be crystals of the applied Kojic Acid may have been causing the whitening rather than an actual depigmenting action. With repeated application, the white substance on the skin surface of the 4% Kojic Acid group turned light brown. There was no difference in the melanocyte count nor were there any morphological differences between the Kojic Acid groups and the vehicle group. The number of melanocytes in the 1 and 4% Kojic Acid groups was comparable to the vehicle group. Kojic Acid did not show oxygen consumption and free radical production, which indicated melanocytes were not damaged. The researchers concluded that Kojic Acid showed almost no depigmenting action in black guinea pigs.

Toxicogenomics

In a gene expression study, human skin A375 malignant melanoma cells were cultured with 0. 0.32, 1.6, 8, 40, 200, or 1000 µg/ml Kojic Acid for 72 h to evaluate cell-growth inhibition.[35] Cell growth was observed to be inhibited in a dose-dependent manner by Kojic Acid (20% for 0.32 - 40 µg/ml and ~ 40% for 1000 µg/ml). For the gene expression analysis, total RNA was isolated from cells exposed to 8 µg/ml Kojic Acid for 24 h. A total of 361 differently expressed genes were identified, including 136 up-regulated and 225 down-regulated genes. Category classification of differentially expressed genes was conducted. Seven of the downregulated genes (APOBEC1, ARHGEF16, CD22, FGFR3, GALNT1, UNC5C and ZNF146) were identified as tumor suppressor genes in melanoma cancer cells.

Immunomodulatory Effects

The effects of Kojic Acid (50 µg/ml) on functional properties related to macrophage activation were assessed in an in vitro study.[36] Macrophages incubated for 1 h with Kojic Acid had enhanced cell spreading and an increase in cell surface exposure, associated with a rearrangement of microtubules, actin filaments, and intermediate filaments. Kojic Acid also potentiated phagocytosis by macrophages, as seen by the increase in phagocytic activity towards yeast, when compared to untreated cells. Reactive oxygen species production was increased in the presence of Kojic Acid, but not nitric oxide production. Cell viability of macrophages was furthermore not affected following Kojic Acid treatment.

The ability of Kojic Acid (50 µg/ml) to influence innate immune responses was studied in vitro using human peripheral blood monocytes.[37] Following a 48-h exposure, Kojic Acid induced morphological alterations in monocytes, such as increased cell size, as well as numerous cellular projections. Increased labeling of cell surface EMR1-F4/80 was detected using a flow cytometer, but labeling of CD11b and CD14 was decreased. Kojic Acid exposure was found to increase IL-6 cytokine production, but did not cause cytotoxic effects in monocytes. It was concluded that Kojic Acid promotes the differentiation of monocytes into macrophages, and thus has the ability to act as an immunomodulatory agent.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Kojic Acid at 1 and 3% was a mild dermal irritant in rabbits.[2] *In guinea pigs, 30% Kojic Acid was not a dermal sensitizer.*

In a human repeated insult patch test (HRIPT), subjects received 24-h occlusive induction applications of a cream product containing 1% Kojic Acid (amount sufficient to cover ¾ in^2 pad) on the same previously untreated site on the back 3 times/wk for 3 wk. Following a 2-wk non-treatment period, the challenge application was applied to a previously untreated site for 24 h, and the site was scored 24 and 72 h after patch removal. No responses were observed during either the induction or challenge tests. In another HRIPT study, the potential of a formula containing 2% Kojic Acid (0.2 mg on a 2 cm^2 pad) to induce sensitization was evaluated using 218 subjects. The test sites were semi-occluded. The patches were removed after 24 h, and the test sites were evaluated after 48 or 72 h. After a 2-wk non-treatment period, the subjects received challenge applications on previously untreated sites for 24 h, and the test sites were evaluated after 48 or 72 h. During the induction phase, 11 minimal or doubtful ("?") responses and 4 definite erythema ("+") responses were observed. Only one minimal or doubtful response was observed at 48 h, but was resolved at 72 h.

Phototoxicity

Slight skin reactions with 5 consecutive daily exposures of 15 or 30 min to UV light (5 Blacklite tubes of 15 W each; 350 nm) were observed in guinea pigs that received 5% Kojic Acid dermally.[2] *No phototoxicity was observed in guinea pigs that received 5 consecutive daily exposures of 38 min to UV light (10 Blacklite tubes; 320 nm) following topical treatments of 1 or 3% Kojic Acid.*

OCULAR IRRITATION STUDIES

Kojic Acid in a 3% aqueous solution was not an ocular irritant in rabbit eyes.[2]

CLINICAL STUDIES

Kojic Acid is reportedly used to treat melasma.[2] *In an efficacy test of formulations containing 2% Kojic Acid and glycolic acid (with or without hydroquinone) for the treatment of melasma in 39 patients for a month, burning and desquamation were reported in all patients. In another efficacy study in 40 Chinese women with a formulation containing 2% Kojic Acid, 10% glycolic acid, and 2% hydroquinone, patients experienced redness, itchiness, and exfoliation on the treatment sites, although these results were also observed on skin that was not treated with Kojic Acid. Another therapeutic study reported that the side effect of the treatment of melasma with 1% Kojic Acid was contact allergy.*

The efficacy of a topical therapy for the treatment of dyschromia was evaluated in a 12-wk clinical study in 55 healthy female patients with Fitzpatrick skin types I-IV.[15] At least 50% of the subjects had self-perceived sensitive skin. The topical therapy contained 1% Kojic Acid, 3% transexamic acid, 5% niacinamide, and 5% hydroxyethylpiperazineethane sulfonic acid. The test material was applied to clean facial skin twice daily. In addition to the efficacy parameters tested, the subjects were assessed for irritation. Minor transient effects such as erythema (2/55), itching (1/55), pruritis (1/55), redness (1/55) or stinging (1/55) were observed during the study. These effects quickly resolved after application of the test material.

Retrospective and Multicenter Studies

Of 220 female patients patch tested for suspected cosmetic-related contact dermatitis, 5 had reactions to Kojic Acid as well as products they owned that contained 1% Kojic Acid.[2] *The 5 patients had developed facial dermatitis within 1 to 12 mo of using Kojic Acid-containing cosmetic products. Reactions to 1 and 5% Kojic Acid in these patients were + and ++, respectively. The remaining 215 patients in the patch test group, including 3 that had previous exposures to Kojic Acid, did not have any reactions to Kojic Acid.*

Case Reports

A 30-yr-old woman was prescribed a cream containing 3% Kojic Acid, urea, hydroquinone, lactic acid, witch hazel, castor oil, citric acid, cellulose, and propylene glycol to treat hyperpigmentation.[2] *More than 4 mo later and a few weeks after a second medication was prescribed to use in conjunction with the cream, the patient presented with eczematous eruption on and around the hyperpigmentation. Patch tests with the Grupo Español de Investigación Dermatitis de Contacto y Alergia Cutánea (GEIDAC) series were negative, but a patch test of the cream was ++ after 4 d. Patching with 0.1, 0.5, 1, and 5% Kojic Acid resulted in positive results after 2 and 4 d, with a ++ reaction to 1 and 5% Kojic Acid. Patch tests of other components were negative. In another case report, a 54-yr-old woman with actinic lentigines on her arms and forearms developed pigmented contact dermatitis. The patient had been using a formulation similar to the one described above with 3% Kojic Acid. One year prior to presentation, the patient experienced progressive, asymptomatic erythematous and hyperpigmented area on her arms, but continued to use the formulation. A biopsy showed pigmentary incontinence, melanophagia, and moderate lymphohistiocytic infiltrate without a spongiotic epidermis. Patch tests with GEIDAC series, disperse dyes, and photopatch tests were negative. Patch tests with 1% Kojic Acid (aq.) and the compound "as is' were negative on day 2, but hyperpigmentation was present at both sites on day 4 and 7. These lesions persisted for 1 mo.*

A 40-yr-old woman developed acute dermatitis on the face and neck following application of a makeup product containing Kojic Acid on pigmented areas of her skin for 3 d.[38] The patient was patch tested with the European standard series, the makeup product, and individual components of the product, including 0.5, 1, and 3% Kojic Acid (pet.). Positive reactions were obtained for the makeup product (+++), Kojic Acid (0.5% ++, 1% +++, and 3% +++), lactic acid (++), and to polysorbate 80 (++) after 2 and 4 d. No reactions were observed to the other ingredients of the makeup product. Negative results were observed in 10 control patients tested. Further patch testing after 3 wk with lactic acid and polysorbate 80 were negative.

In another case report, a 54-yr-old woman presented with facial erythema associated with itching and a burning sensation.[39] The patient had been applying a serum to her face for approximately 1 mo prior. The patient was patch tested with the standard series recommended by GEIDAC and the serum. The 48- and 96-h readings were positive (+++) for the serum only. The patient was later tested with the individual ingredients of the serum, including 1% Kojic Acid in a water solution. No reactions were observed at 48 h, but a strong positive reaction (++) to Kojic Acid was observed at 96 h. The reaction persisted for 7 d. No reactions were observed to the other ingredients. No reactions were observed to 1% Kojic Acid solution in 12 control patients.

RISK ASSESSMENT

MOE is a quantitative ratio calculated for cosmetic ingredients by dividing the point of departure (POD) obtained for an ingredient in an animal experiment by the estimated SED for the ingredient in humans, generally according to US EPA and EC SCCS guidelines. An MOE value greater than 100 has traditionally been considered an indication of safety. The basis for this MOE value of 100 comes from two multiplication factors: a 10-fold factor for extrapolating data from test animals to human beings (interspecies extrapolation), and an additional 10-fold for differences among the human population (intraspecies extrapolation). Notably, the MOE value is sometimes referred to as the margin of safety (MOS) despite the parameters being definitionally different.

The SCCS calculated MOE values for Kojic Acid at 1% in a cream product for application scenarios involving the face and neck, the hands, and an aggregate of these applications (face + neck + hands).[3] The MOE values were 267, 199, and 141, respectively (the value for the hands appears to be a typographical error in the SCCS opinion and should be 299[40, CIR Staff]). When the same approach was applied to the whole-body exposure scenarios, the resulting MOE values were 83 for body exposure and 36 for total body area exposure, which may include body, face, and hands exposure.[3,40-42]

In these calculations, the SED was derived from a human percutaneous absorption study in which 500 mg of a cream containing 1% Kojic Acid, corresponding to 5 mg Kojic Acid, was applied to the entire face.[43] The internal exposure was estimated from the 95th percentile of the $AUC_{0\text{-}24\ h}$ of 32.4 ng/ml·h, which corresponded to an AUC-derived systemic estimate of 0.093 mg/d. This value was then scaled according to the amount of Kojic Acid applied in each adult exposure scenario presented in Table 6. The SCCS used an adjusted NOAEL of 2 mg/kg bw/d in its MOE calculations. This value was derived from a 28-d oral repeated dose study in rats, which identified histological changes in the thyroid and altered iodine uptake, with a reported NOAEL of 6 mg/kg bw/d.[26,44] An assessment factor of 3 was further applied to account for extrapolation from a subacute study duration to a subchronic exposure scenario.

The Panel considered that the iodine uptake endpoint was not the most appropriate POD for evaluating adult cosmetic exposure to Kojic Acid. Thyroid iodine uptake changes in rats may reflect species-specific thyroid physiology and homeostatic responses that are not directly predictive of adverse thyroid effects in adult humans. Because species differences in thyroid hormone binding, metabolism, clearance, and compensatory regulation may affect extrapolation of rodent thyroid endpoints to humans, use of this endpoint may overestimate adult human risk.

The Panel reviewed the other available NOEL/NOAEL values for Kojic Acid and selected the NOEL of 125 mg/kg bw/d from the 26-wk oral rat study as the POD for adult MOE calculation, which represents a repeated-dose systemic toxicity endpoint. However, because thyroid iodine uptake is an essential upstream step in thyroid hormone biosynthesis and thyroid hormone homeostasis is critical for growth and neurodevelopment during early life,[45-47] the Panel retained the iodine uptake endpoint as a conservative basis for a separate infant MOE calculation.

Exposure parameter details for the MOE calculations are presented in Table 6. For adult use of leave-on cream products containing 1% Kojic Acid, the calculated MOEs were 16,667 for face and neck, 18,657 for hands, 8803 for aggregate face, neck, and hands exposure, 5156 for body exposure, and 2240 for total body area exposure. For adult use of rinse-off shower gel containing 0.05% Kojic Acid, the resulting MOE was 4,325,260.

SUMMARY

Kojic Acid is reported to function as an antioxidant in cosmetics, according to the *Dictionary*. The Panel first reviewed the safety of Kojic Acid in a report published in 2010 with the conclusion "Kojic Acid is safe for use in cosmetic products up to a concentration of 1%."[2] In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In June 2022, the Panel determined that this safety assessment should be re-opened for re-evaluation due to reported restrictions by the European Commission on the use of Kojic Acid.

According to RLD obtained from the FDA in 2025, Kojic Acid is reported to be used in 3726 formulations. The results of the concentration of use survey conducted by the Council in 2024 indicate Kojic Acid is used at up to 1% in leave-on skin care preparations.

In the EU, the SCCS concluded in 2022 that Kojic Acid is safe when used as a skin lightening agent in cosmetic products at concentrations of up to 1%. (It should be noted that in Europe, products that whiten the skin are considered to be cosmetics; however, in the US, skin lightening is considered to be a drug effect.) The EC has categorized Kojic Acid in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down. For this ingredient, the regulation states that Kojic Acid may only be used in face and hand products at a maximum concentration of 1%. Based on the SCCS opinion and MOE calculations, the EC determined that high exposure to Kojic Acid (when the concentration exceeds certain levels form applications beyond those to the face and hands), may increase health risk.

The percutaneous absorption of a leave-on skin care formulation containing radiolabeled ^{14}C-Kojic Acid at 1% was studied using human dermatomed skin. Mean recovery of the applied test material was 95.48 ± 3.33% (19.44 ± 0.68 μg/cm^2). The average penetration rate was 0.006 μg/cm^2/h. The mean amount of Kojic Acid that penetrated over the 24 h exposure period was 0.698% of the applied dose (0.142 ± 0.265 μg/cm^2). The mean total systemically available dose of Kojic Acid (remaining epidermis + dermis and receptor fluid) was 3.68% of the applied dose (0.749 μg/cm^2).

In a 30-d dermal toxicity study in rabbits, 0, 13, 130, or 1300 mg/kg bw/d (0, 0.65, 6.5, or 65% w/v) Kojic Acid in 1% aqueous methylcellulose was applied to abraded skin daily. Effects on the skin and eyes could not be accurately evaluated due to a bacterial infection in the animals. Necropsy of 3 animals that died during the course of the study (1 female in the 13 mg/kg group, 1 male in the 130 mg/kg group, and 1 male control) revealed lesions of the lung, liver, kidney, and brain that may have been contributing factors. In the 1300 mg/kg bw/d dose group, statistically significant changes were observed in the mean corpuscle hemoglobin concentration, the mean cell volume, and A/G ratio when compared to controls. In the 13 mg/kg bw/d dose group, the pituitary weight was significantly increased. A conclusion of dose-dependent statistical changes for hematology and biochemistry could not be made because parameters were only measured in the controls and the 1300 mg/kg dose groups. Plaques in the aorta were reported in 1 control male, 3 males and 1 female in the 13 mg/kg bw/d dose group, 1 male and 1 female in the 130 mg/kg bw/d dose group, and 4 males in the 1300 mg/kg bw/d dose group. Pale kidneys were reported in all treated groups.

The NOEL for Kojic Acid in a 26-wk oral toxicity study in rats was 125 mg/kg bw/d. Male rats received 0, 125, 250, 500 or 1000 mg/kg bw/d Kojic Acid in 1% aqueous solution of carboxymethylcellulose and a 5 wk-recovery occurred in the 3 highest does groups. Statistically significant hematological and biochemical differences reported included an increase in creatinine in the 250 and 500 mg/kg bw/d groups; an increase in ALP values in the 500 and 1000 mg/kg bw/d groups; increases in GOT, GPT, bilirubin, and relative amount of monocyte; and decreases in number of erythrocytes, hematocrit and hemoglobin in the highest dose group. These changes were not observed at the end of recovery period. Relative weights for several organs were statistically different from controls in the 250 mg/kg bw/d dose group and above. Decrease in absolute organ weights were reported for the heart (500 mg/kg bw/d and above dose groups) and for the spleen (500 mg/kg bw/d

group only). Absolute organ weight increased in the adrenals in the 500 mg/kg bw/d and above dose groups. Thyroid weights increased significantly at 500 and 1000 mg/kg bw/d.

Chromosomal damage was not observed in an in vitro micronucleus assay, with and without metabolic activation, in SVK14 human keratinocyte cells at 500 - 8000 µg/ml Kojic Acid. Genotoxicity results were not clear in another in vitro micronucleus assay using HepG2 human liver cancer cells at 1000 - 8000 µg/ml Kojic Acid. In an in vivo chromosomal damage study, no induction of micronuclei were observed in a micronucleus assay in male rats at up to 1000 mg/kg/d Kojic Acid. Additionally, no DNA strand breaks were observed in a comet assay performed in male rats at up to 1000 mg/kg/d Kojic Acid.

The effects of Kojic Acid on thyroid function in cultured rat thyroid cells found that Kojic Acid inhibited iodine organification dose-dependently, but did not inhibit iodine uptake. In rats receiving a single dose of 1000 mg/kg Kojic Acid, the ^{125}I uptake from blood into the thyroid gland was significantly lower than that of the control group from 30 min to 24 h after administration, and the ^{125}I organification activity of the Kojic Acid groups was significantly lower than controls from 30 min to 6 h after administration. This activity 24 or 48 h after administration recovered enough to be nearly comparable with the control group.

Kojic Acid (4.11, 8.02, or 12.67 mM) significantly reduced cell viability in human liver HepG2 cells in a dose-dependent manner following treatment up to 48 h, with an IC_{50} of 8.02 mM. Further examination of the impact of Kojic Acid on oxidative stress and antioxidant responses found that this ingredient exhibited minimal toxicity to HepG2 cells.

In rats, Kojic Acid at 1875 mg/kg bw significantly decreased body weight and serum T4 levels, but increased liver and thyroid gland weights. The pattern of CYP2B1 protein expression in the livers of Kojic Acid-treated rats showed that 0.6 mg/kg bw Kojic Acid significantly decreased the level of expression, but 3 and 1975 mg/kg bw of Kojic Acid significantly increased CYP2B1 expression. Kojic Acid also decreased CYP2E1 expression in rat livers, and CYP2C11 was significantly decreased in livers of the rats that received 1875 mg/kg bw Kojic Acid.

Kojic Acid (0.2 mM) was found to have increased IL-6 and IL-8 production in melanocyte/keratinocyte co-cultures; however, only IL-6 directly suppressed melanogenesis while IL-8 did not. Kojic Acid did not increase IL-6 production in melanocyte monocultures; whereas in keratinocyte monoculture it significantly up-regulated IL-6 gene and protein expression. Anti-IL-6 antibody treatment antagonized the anti-melanogenic effect of Kojic Acid on the co-cultures.

In a study using human iPS cell-derived melanocytes, microscopic analysis did not show any differences between human iPS cell-derived melanocytes treated with Kojic Acid when compared to untreated controls. The addition of 70 µg/ml Kojic Acid to the melanocytes for 2 wk had no effect on tyrosinase activity when compared to untreated controls.

In a gene expression study with human skin A375 malignant melanoma cells cultured with 0. 0.32, 1.6, 8. 40, 200, or 1000 µg/ml Kojic Acid, cell growth was observed to be inhibited in a dose-dependent manner. A total of 361 differently expressed genes were distinctively changed with 136 up-regulated and 225 down-regulated. Seven of the downregulated genes were identified as tumor suppressor genes in melanoma cancer cells.

Macrophages incubated for 1 h with Kojic Acid (50 µg/ml) had enhanced cell spreading and an increase in cell surface exposure, associated with a rearrangement of microtubules, actin filaments, and intermediate filaments. Kojic Acid also potentiated phagocytosis by macrophages, as seen by the increase in phagocytic activity towards yeast, when compared to untreated cells. Reactive oxygen species production increased in the presence of Kojic Acid, but not nitric oxide production. Cell viability of macrophages was furthermore not affected following Kojic Acid treatment. Following a 48-h exposure, Kojic Acid (50 µg/ml) induced morphological alterations in human peripheral blood monocytes, such as increased cell size, as well as numerous cellular projections. Kojic Acid exposure was found to increase IL-6 cytokine production but did not cause cytotoxic effects in monocytes.

In an efficacy study evaluating a topical therapy containing 1% Kojic Acid for the treatment of dyschromia, minor transient irritation effects were observed. Case studies in 2 women reported acute dermatitis to the face following application of skin products that contained Kojic Acid; patch testing yielded positive results to 0.5 to 3% Kojic Acid.

The SCCS calculated MOE values for Kojic Acid at 1% in a cream product for application scenarios on the face and neck, the hands, and an aggregate of these applications (face + neck + hands). The MOE values were 267, 299, and 141, respectively. The Panel reviewed the other available NOEL/NOAEL values for Kojic Acid and selected the NOEL of 125 mg/kg bw/d from the 26-wk oral rat study as the POD for adult MOE calculation, and the Panel retained the iodine uptake endpoint as a conservative basis for a separate infant MOE calculation. For adult use of leave-on cream products containing 1% Kojic Acid, the calculated MOEs were 16,667 for face and neck, 18,657 for hands, 8803 for aggregate face, neck, and hands exposure, 5156 for body exposure, and 2240 for total body area exposure. For adult use of rinse-off shower gel containing 0.05% Kojic Acid, the resulting MOE was 4,325,260. For infant exposure, the NOAEL of 2 mg/kg bw/d was used, the resulting MOE was 32,786; after application of the additional 10-fold safety factor, the adjusted MOE was 3279. All of the calculated MOE values for adults were greater than 100 and were considered protective.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusions of previously-issued reports approximately every 15 years. In 2010, the Panel published a final report on Kojic Acid and concluded that Kojic Acid is safe for use in cosmetic products up to a concentration of 1%. This report was reopened for re-evaluation due to reported restrictions by the EC on the use of Kojic Acid, and this amended report reviews the safety of Kojic Acid as used in cosmetic formulations, in accordance with the product categories and concentrations of use identified in the Use section and Use table. The Panel concluded that the available data are insufficient to make a determination of safety of Kojic Acid for use in anogenital wipes, douches, and baby products. Additionally, the Panel concluded that Kojic Acid is safe in the present practices of use and concentration for all other uses described in this safety assessment.

The Panel noted that uses were reported in anogenital applications and in baby products. The Panel was concerned about the potential for irritation and sensitization and increased absorption in baby skin and mucosal skin that may be occluded. Concentrations of use are needed to determine the MOE for these types of use.

The Panel observed that liver, thyroid, and adrenal tumors were reported in rodent studies. However, these effects are considered not relevant to human cancer risk due to well-characterized species differences in modes of action. Liver tumors are associated with CAR-mediated enzyme induction, which is a rodent-specific mechanism not operative in humans. Thyroid effects are linked to disruption of hormone homeostasis, to which rodents are particularly sensitive due to differences in thyroid hormone metabolism and regulation. Adrenal tumors observed in rats also involve mechanisms not predictive of human risk. Given these species-specific responses, the Panel stated that the observed tumorigenic effects do not indicate a significant carcinogenic risk to humans under cosmetic use conditions.

The Panel also discussed the human relevance of rodent findings on thyroid iodine uptake, a functional endpoint related to thyroid hormone synthesis, and the use of thyroid findings to derive PODs for MOE calculations. The Panel considered species differences in thyroid hormone binding, metabolism, and regulation when interpreting the rodent thyroid findings for adult human risk assessment. Based on their evaluation of the available toxicity data, the Panel selected an adult repeated-dose systemic toxicity POD for MOE calculations. For baby exposure, the Panel considered the lower POD based on thyroid iodine uptake findings to be an appropriate conservative basis for MOE calculations, given the importance of thyroid hormone homeostasis for growth and neurodevelopment during early life. However, concentration of use data for the relevant baby product categories are unavailable, and these data are needed to estimate baby systemic exposure and calculate MOEs for these uses. Therefore, the data are insufficient to determine safe use in baby products.

Data included in this report indicate that Kojic Acid may have a skin lightening effect. The Panel noted that skin lightening is considered a drug effect in the US and should not occur during the use of cosmetic products. Because of that caveat, the Panel's knowledge of the mechanism of action (i.e., inhibition of tyrosinase activity), and clinical experience, concern for this effect in cosmetics was mitigated. Nevertheless, cosmetic formulators should only use this ingredient in products in a manner that does not cause depigmentation.

The Panel expressed concern regarding heavy metals that may be present in this ingredient. They stressed that the cosmetics industry should continue to use the necessary procedures to minimize impurities in cosmetic formulations according to limits set by the US FDA and EPA. Certain *Aspergillus* species used in the production of Kojic Acid are capable of producing aflatoxins. The Panel believes that aflatoxins should not be present in Kojic Acid and has adopted the limits set by the US Department of Agriculture (USDA) corresponding to "negative" aflatoxin content.

Additionally, at least 1 use for the ingredient reviewed in this assessment is reported in the RLD under Category 17, "other preparations." For instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17, and other information in the RLD is not indicative of use type, the present practices of use for such products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply to these preparations.

The Panel discussed the issue of incidental inhalation exposure resulting from this ingredient. Inhalation toxicity data were not available. However, the Panel noted that the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the low concentrations at which this ingredient is used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery

systems cannot be determined by the Panel. Accordingly, the Panel has concluded that if this ingredient is used in airbrush formulations, the data are insufficient to support safe use when applied with such delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination of safety for Kojic Acid as used in anogenital wipes, douches, and baby products. Additionally, the Panel concluded that Kojic Acid is safe in the present practices of use and concentration for all other uses described in this safety assessment.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	Prismatic needles from acetone, ethanol + ether, or methanol + ethyl acetate White to light yellow crystalline powder	2 3
Molecular Weight (g/mol)	142.11	2
Density (g/ml)	1.542	3
Melting Point (ºC)	152-154	2
Water Solubility (g/l)	43.85 Soluble in water	3 2
Other Solubility	Soluble in ethanol, acetone; sparingly soluble in ether, ethyl acetate, chloroform, pyridine; insoluble in benzene	2
log K_{ow}	-0.64 -1.25	3 2
Disassociation constants (pKa @ 25 ºC) (pKa)	7.66 7.90, 8.03	3 2
UV Absorption (λ nm)	270 in water 215-216 and 268-269 in acidic or neutral solutions; 226-227 and 309-312 in alkaline solution 280 (pH of solution not reported)	3 2 2

Table 2. Frequency and concentration of use of Kojic Acid according to likely duration and exposure and by product category

	# of Uses RLD (2025)[9,10]	Max Conc of Use % (2024)[11]
Totals*	**3726**	**0.001-1**
summarized by likely duration and exposure**		
Duration of Use		
Leave-On	*2142*	*0.005-1*
Rinse-Off	*1973*	*0.05*
Diluted for (Bath) Use	*190*	*0.001*
Unknown	*107*	*0.66*
Exposure Type		
Baby Products	7	NR
Children's Makeup	NR	NR
Eye Area	51	NR
Incidental Ingestion	1	NR
Mucous Membrane	1274	0.001-0.05
Incidental Inhalation-Spray	7; 1149[a], 1098[b]	NR
Incidental Inhalation-Airbrush	NR	NR
Incidental Inhalation-Powder	6; 1098[b]; 5[c]	0.005-1[c]
Dermal Contact	4274	0.001-1
Deodorant (underarm)	4	NR
Hair - Non-Coloring	23	NR
Hair-Coloring	NR	NR
Nail	4	NR
Other Preparations (Unknown Exposure Type)	107	0.66[d]
as reported by product category		
Baby Products		
Baby Shampoos	1	NR
Baby Lotions/Oils/Powders/Creams	5	NR
Baby Wipes	1	NR
Bath Preparations		
Bath Oils, Tablets, and Salts	32	0.001
Bubble Baths	2	NR
Bath Capsules	1	NR
Other Bath Preparations	155	NR
Eye Makeup Preparations (other than children's eye makeup preparations)		
Eyebrow Pencil	1	NR
Eye Lotion	27	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	5	NR
Other Eye Makeup Preparations	18	NR
Fragrance Preparations		
Other Fragrance Preparation	5	NR
Hair Preparations (non-coloring)		
Hair Conditioners	6 r.o.	NR
Hair Sprays (aerosol fixatives)	2	NR

Table 2. Frequency and concentration of use of Kojic Acid according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use
	RLD (2025)[9,10]	% (2024)[11]
Shampoos (non-coloring)	5 r.o.	NR
Tonics, Dressings, and Other Hair Grooming Aids	8	NR
Other Hair Preparations	1 r.o.	NR
Makeup Preparations (not eye; not children's)		
Blushers and Rouges (all types)	1	NR
Face Powders	6	NR
Lipsticks and Lip Glosses	1	NR
Other Makeup Preparations	15	NR
Manicuring Preparations		
Other Manicuring Preparations	4	NR
Personal Cleanliness		
Bath Soaps and Body Washes	867	0.05
Deodorants (underarm)	4	NR
Douches	3	NR
Disposable Wipes	43	NR
Other Personal Cleanliness Products	22 l.o.; 147 r.o.	NR
Shaving Preparations		
Aftershave Lotions	1	NR
Shaving Creams (aerosol, brushless, and lather)	1	NR
Shaving Soaps (cakes, sticks, etc.)	7	NR
Other Shaving Preparation Products	1	NR
Skin Care Preparations (creams, lotions, powder, and sprays)		
Cleansing (cold creams, cleansing lotions, liquids, and pads)	620	NR
Depilatories	2	NR
Face and Neck (excluding shaving preparations)	822 l.o.; 174 r.o.	0.01-1 (l.o.; not spray)
Body and Hand (excluding shaving preparations)	128 l.o.; 37 r.o.	0.005-1 (l.o.; not spray)
Foot Powders and Sprays	2	NR
Moisturizing	720	0.01 (not spray)
Night	32	NR
Paste Masks (mud packs)	48	NR
Skin Fresheners	126	NR
Other Skin Care Preparations	137 l.o.; 53 r.o.	NR
Suntan Preparations		
Suntan Gels, Creams, and Liquids	5	NR
Other Suntan Preparations	1	NR
Other Preparations (i.e., those preparations that do not fit another category)	107	0.66[d]

NR – not reported

l.o. – leave-on; r.o. – rinse-off

*The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.

**Likely duration and exposure are derived from survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[d] Facial toner used before applying facial peel

Table 3. Genotoxicity studies of Kojic Acid

Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO					
Chromosomal Damage					
500 – 8000 µg/ml	Not reported	SVK14 human keratinocyte cells	Micronucleus assay, with and without metabolic activity; no further details provided	Not genotoxic, no further details provided	[3]
1000 – 8000 µg/ml	Not reported	HepG2 human liver cancer cells	Micronucleus assay, without metabolic activity; no further details provided	Results uncertain; positive at concentration that are above the OECD required level of the top concentration, which are cytotoxic concentrations; no further details provided	[3]
IN VIVO					
Chromosomal Damage					
250, 500, or 1000 mg/kg/d for 14 d, or, 125, 250, or 500 mg/kg/d for 28 d	0.5% sodium carboxymethylcellulose	Groups of 5 male Crl:CD (SD) rats	Mammalian micronucleus assay; oral administration via gavage for 14- or 28-d; cells from the liver, bone marrow, and peripheral blood were assessed for genotoxic effects	No induction of micronuclei; an increase of relative liver weight was observed in the 14-d 1000 mg/kg dose group, minimal hypertrophy of hepatocytes was also observed in this group	[23]
DNA Strand Breaks					
250, 500, or 1000 mg/kg/d for 14 d	0.5% sodium carboxymethylcellulose	Groups of 5 male Crl:CD (SD) rats	Comet assay in accordance with OECD TG 489; assay was performed in concert with the micronucleus assay described above; assay performed 21 h after last oral administration and cells from the liver and peripheral blood were assessed for genotoxic effects	No induction of strand breaks	[23]

Table 4. Tumor promotion and/or tumor initiation studies from the original safety assessment on Kojic Acid [2]

Concentration/Dose	*Vehicle*	*Test System*	*Procedure*	*Results*
			DERMAL	
up to 3%	*cream formulation*	*groups of 10 or 15 female CD-1 mice*	*The study utilized 9,10-dimethyl-1,2-benzanthracene (DMBA) as the tumor initiator and phorbol-12-myristate-13 acetate (TPA) as the promoter. Groups of mice were treated in the following manner: DMBA + vehicle, DMBA + 0.3% Kojic Acid, DMBA + 3% Kojic Acid, DMBA + TPA, acetone + 0.3% Kojic Acid, acetone + 3% Kojic Acid, vehicle + TPA, or 3% Kojic Acid + TPA. The control or test substances were applied to shaved backs (4 cm^2). The mice receiving DMBA or acetone were treated once at the beginning of the experiment while the mice treated with vehicle + TPA or 3% Kojic Acid + TPA received 50 mg of the test substances daily for 1 wk. A week after the study commenced, the treatment groups with DMBA or acetone received 50 mg of the test substances 5 x weekly for 19 wk. The remaining groups received TPA twice weekly for 19 wk at 1 or 2 wk after study commencement.*	*Kojic Acid in a cream formulation did not possess promotion potential for skin carcinogenesis. The positive controls (DMBA + TPA) yielded expected results that included skin nodules that were squamous cell hyperplasia, papilloma, or carcinoma, significantly increased body weight gain, and significantly increased absolute and relative liver weights. Body weight gain was significantly decreased in week 2 or weeks 3 and 4 in the DMBA + 0.3% Kojic Acid and acetone +3% Kojic Acid dose groups, respectively. Squamous cell papilloma was observed in 1 mouse from the DMBA + 3% Kojic Acid group.*
			ORAL	
0 or 3%	*diet*	*male ICR mice*	*A dietary study on the tumor-initiating potential of Kojic Acid The mice received the test material in the diet for 4 wk. The mice then received distilled water containing 0 or 500 ppm phenobarbital for 14 wk. A partial hepatectomy was performed on all mice 2 wk after the treatment with phenobarbital.*	*No proliferative lesions were observed in any dose groups during microscopic examinations. The authors concluded that Kojic Acid has no tumor-initiating activity in mouse liver; however, the SCCP concluded that the Kojic Acid effect on proliferation of liver cells cannot be excluded since Kojic Acid + distilled water PCNA values were increased compared to basal diet + distilled water.*
0, 0.125, 0.5, or 2%	*diet*	*male F344 rats (60 total)*	*20-wk dietary study; rats received a single subcutaneous injection of N-bis(2-hydroxypropyl)nitrosamine (DHPN) or the vehicle prior to receiving a diet containing test material*	*Kojic Acid was found to have carcinogenesis-promoting potential; rats that received 2% Kojic Acid with DHPN had a significantly increased ($p < 0.01$) relative liver weights. Histopathology revealed an increased incidence of microgranuloma and vacuolation of centrilobular hepatocytes. A significant increase ($p < 0.01$) in the number and area of glutathione S-transferase-placental form (GST-P) positive foci per unit area of liver in the DHPN and 2% Kojic Acid group was observed when compared to the DHPN only treated group. A similar increase was also observed in the 2% Kojic Acid group that did not receive DHPN. No treatment-related effects were observed in the other test groups that received Kojic Acid, with or without DHPN.*
0, 0.125, 0.5, or 2%	*diet*	*groups of 20 male F344 rats*	*20-wk dietary study of Kojic Acid were performed without DHPN initiation. The researchers also performed a medium-term liver bioassay to determine the promoting influence of Kojic Acid.*	*2% Kojic Acid was tumor-promoting and had weak hepatocarcinogenic potential. Dose-related increases in absolute and relative liver weights were observed in both treatment groups. Numbers and areas of GST-P positive foci were significantly increased ($p < 0.01$) in the 2 % Kojic Acid group when compared to the control group. Additionally, increased incidences of microgranuloma and vacuolation of hepatocytes were observed in the 2% Kojic Acid group. PCNA expression was significantly increased ($p < 0.05$) in the 2% Kojic Acid group, with proliferating cell nuclear antigen (PCNA)-positive hepatocytes mainly localized around the vacuolated and granulomatous regions. A dose-related decrease in body weight gains and an increase in relative liver weights were observed, with statistical significance ($p < 0.01$) observed in the 2% dose group. Significant increases ($p < 0.01$) in number and areas of GST-P positive foci were observed in the 2% dose group when compared to the control.*

Table 4. Tumor promotion and/or tumor initiation studies from the original safety assessment on Kojic Acid [2]

Concentration/Dose	Vehicle	Test System	Procedure	Results
0 or 2%	*diet*	*groups of 5 male F344 rats*	*A 2-part study investigated the initiation potential of Kojic Acid. In the first part of the study, the rats received Kojic Acid in the diet for 3, 7, or 28 d. All rats were injected with 100 mg/kg bw bromodeoxyuridine (BrdU) intraperitoneally once a day for the last 2 d of exposure and 2 h prior to termination. Labeling indices (LIs) were calculated as percentages of cells positive for BrdU incorporation divided by the total number of cells counted. In addition, 8-oxo¬deoxy¬guanosine (8-OxodG) was measured in nuclear DNA to examine the formation of oxidative DNA adduct.* *In the second part of this study, the rats were subjected to a two-third partial hepatectomy on day 0. At 12-h post-surgery, the rats were treated once orally with carboxymethylcellulose vehicle, or 1000 or 2000 mg/kg Kojic Acid. The rats were then fed basal diet for 2 wk and then diet containing 0.015% 2-acetylaminofluorene (2-AAF) for another 2 wk. At 3 wk post-Kojic Acid administration, rats received a single 0.8 ml/kg bw dose of carbon tetrachloride.*	*In the first part of the study on day 28, body weight gains in the 2% Kojic Acid group were significantly decreased compared to the control group. In the 2% Kojic Acid dose group, absolute liver weights were significantly increased on day 7 but decreased on day 28. Relative liver weights were significantly increased at all time points. The LI values of hepatocytes of the 2% dose group were significantly increased as compared to the controls on days 3 and 7. All 8-OxodG levels in the liver DNA in the 2% dose group were slightly higher than the control values but were not statistically significant.* *In the second part, slight decreases were observed in the mean area and numbers of GST-P positive foci, but these differences were not statistically significant. The researchers concluded that Kojic Acid has neither liver initiation activity nor the capability of 8-OxodG formation; however, the findings suggest that Kojic Acid has liver tumor-promoting effects.*
0, 0.5, 1 or 2%	*diet*	*groups of 15 male F344 rats*	*Liver carcinogenesis bioassay; rats received Kojic Acid or the positive control 2-AAF at concentrations of 0.001 or 0.01% for 4 wk. After the treatment period, all rats received basal diet for 1 wk, and then a diet containing 0.5% phenobarbital sodium salt (SPB) for 6 wk. In another portion of the study, groups of 9 rats received 0 or 2% Kojic Acid or 0.001 or 0.01% 2-AAF in feed for 4 wk, and then all rats received basal diet for 7 wk. At 6 wk after the beginning of the study, all animals from both portions of the study underwent a two-third partial hepatectomy.*	*No treatment-related effects or deaths were observed during the study. Rats that received 2% Kojic Acid in both portions of the study had significant decreases in body weights during initiation period of the study, but body weights returned to control levels during the SPB or basal diet treatments. Decreases in feed consumption during the initiation period occurred in the 1 and 2% Kojic Acid groups, but increases in feed consumption during the SPB or basal diet treatment were marked with increases in body weight change. No treatment-related differences were observed in final body or liver weights, with or without SPB. Numbers of GST-P-positive foci in Kojic Acid-treated groups were similar to the control values, with or without SPB. No other treatment-related effects were observed. The positive control groups yielded expected results. This study concluded that Kojic Acid did not possess initiation potential in the rat liver.*

Table 5. Thyroid effects studies from the original safety assessment of Kojic Acid [2]

Concentration/Dose	Vehicle	Test System	Procedure	Results
0, 1.5, or 3%	*diet*	*groups of 65 male and female B6C3F1 mice*	*20-mo study of the tumorigenicity of Kojic Acid*	*Thyroid weights were increased significantly in the Kojic Acid-treated groups of both genders, especially in the male groups; there were no significant differences in other major organ or tissue weights or hematological values or serum biochemical parameters in any of the treatment groups. Incidences of thyroid gland hyperplasia and follicular adenomas were significantly increased in all treatment groups. In mice that received normal feed 30 d prior to termination, incidences of thyroid gland adenomas were significantly decreased, although average thyroid weights were unchanged. The serum-free T3 levels in the 3.0% dose groups of both genders were significantly lower than the control at month 6, while the TSH levels were increased. The decreases in the free T3 levels continued at the later measurements, but changes in the TSH levels disappeared. It was concluded that chronic high doses of Kojic Acid induced thyroid adenomas in mice.*

Table 5. Thyroid effects studies from the original safety assessment of Kojic Acid [2]

Concentration/Dose	***Vehicle***	***Test System***	***Procedure***	***Results***
0, 0.008, 0.03, 0.125, 0.5, or 2.% (doses equivalent to 0, 5.85, 23.8, 95.3, 393.6, and 1387.3 mg/kg bw/d)	*diet*	*groups of 8 male F344 rats*	*4 wk study to determine the mechanisms of serum thyroid hormone reduce and thyroid tumor-promotion effects of Kojic Acid exposure on rats*	*Absolute and relative thyroid gland weights were increased in all groups treated with Kojic Acid in a dose-dependent manner, with significant increases occurring at 0.5% or more. A statistically significant decrease in serum T3 and T4 levels was observed in the 2% group when compared with the control group. The serum TSH in the 2% group was significantly increased when compared to controls. There were no other significant differences in these parameters in the other dose groups. Thyroid 125I uptake was significantly decreased in a dose-dependent manner starting at 0.03% Kojic Acid. A significant reduction in organic formation of iodine was observed in the 2% group. Histopathologic examination revealed decreased colloid in the thyroid follicles and follicular cell hypertrophy in the thyroid in high incidences in groups that received 0.03% Kojic Acid or more. All rats in the 2% group had thyroid capsular fibrosis. In a quantitative morphometric analysis, the ratio of the area of follicular epithelial cells to the area of colloids was significantly increased in the 0.03% dose group and higher.* *This study was utilized in MOE calculations performed by the SCCS.*
0, 0.008, 0.03, 0.125, 0.5, or 2% (doses equivalent to 0, 5.85, 23.8, 95.3, 393.6, and 1387.3 mg/kg bw/d)	*diet*	*groups of 9 male F344 rats in the 1st experiment; groups of 8 male and 8 female F344 rats in the 2nd experiment; groups of 8 male F344 rats in the 3rd experiment*	*The mechanism of thyroid tumorigenesis from Kojic Acid was studied in a 3-part experiment. In the first experiment, rats received Kojic Acid in their diets for 4 wk. In the second experiment, male and female rats received diet containing 0 or 2% Kojic Acid; male groups were killed at weeks 1, 2, 3, or 4 and female groups were killed at weeks 2 and 4. For the final experiment in this study, groups of male rats received 0 and 2% Kojic Acid in diet for 4 wk. At the end of the treatment, Kojic Acid was replaced with basal diet for 0, 6, 12, 24, or 48 h.*	*In the first experiment, thyroid gland weights were increased in a dose-dependent manner in rats receiving 0.125% or more Kojic Acid, with the thyroid gland weights from the 2% dose group 9 times that of the controls. Uptake of ^{125}I into the thyroid gland was more sensitive to Kojic Acid treatment, with significant suppression at 0.03%. Organic ^{125}I formation was interrupted only in the 2% dose group. Serum T3, T4, and TSH levels were affected only in the 2% group.* *In the second experiment, thyroid gland weights of male rats increased linearly in the 4 wk of treatment with 2% Kojic Acid. A less prominent, but still significant, increase in thyroid gland weights was observed in females. The suppression of ^{125}I uptake was also time-dependent and in males, the decrease started at 1 wk after Kojic Acid treatment and reached about 2% of control values by wk 3, with organic ^{125}I formation significantly decreased by 50% compared to the controls. These effects were not as significant in females, with only 20% suppression of ^{125}I uptake at wk 4. Serum T3 and T4 levels were decreased to minimum levels after 2 wk of Kojic Acid treatment, but recovered thereafter although at lower than control values in both genders. Serum TSH started to increase at wk 1 and reached a maximum at weeks 2 and 3.* *In the third experiment, organic ^{125}I formation returned to normal limits after 6 h and ^{125}I uptake per unit of thyroid weight increased to 70% of the control values within 24 h. Serum T3 and T4 were 47% and 34% of the control values, respectively, after 4 wk of the Kojic Acid diet. The levels increased to normal limits within 48 h after returning to basal diet and high levels of TSH decreased to normal within 24 h. The histopathological investigation on thyroid glands in these 3 experiments found a diffuse type of hyperplasia. After 2 wk of returning to basal diet, normal thyroid follicular structure was apparent in enlarged thyroid glands.* *This study was utilized in MOE calculations performed by the SCCS.*
0 or 2%	*diet*	*Groups of 10 male F344 rats*	*In a study to determine whether Kojic Acid causes a promoting effect on thyroid carcinogenesis, rats were initiated with DHPN. One week later, the rats received basal diet containing Kojic Acid for 12 wk. A control group received no DHPN initiation or Kojic Acid and were fed basal diet for 13 wk. Another 2 groups of rats not initiated with DHPN received diet containing Kojic Acid for 20 wk.*	*Body weights were decreased in the rats that received Kojic Acid at both week 4 and 12. Rats exposed to Kojic Acid also had increased absolute and relative thyroid weights up to 25-fold greater than the control group, as well as increased relative liver weights at each time point. Absolute liver weights were significantly increased in rats exposed to Kojic Acid for 20 wk. Serum T3 and T4 levels were significantly decreased (approximately one half to one third the values of the DHPN alone group) and serum TSH was significantly increased (13-19 times higher than the DHPN alone group) in the DHPN + Kojic Acid group at both time periods. Similar changes in other serum thyroid-related hormones were observed in the 2% Kojic Acid alone group at wk 4 but not at week 20. At wk 4, 4 of the 5 rats in the DHPN + Kojic Acid group had focal thyroid follicular hyperplasias, while 3 of the 5 rats had focal thyroid follicular adenomas. These lesions were observed in all rats in the DHPN + Kojic Acid group by wk 12. Rats that only received Kojic Acid had marked diffuse hypertrophy of follicular epithelial cells at wk 4 and 20. The DHPN alone and the untreated control groups had no changes in thyroid-related hormone levels or histopathological lesions. There were no significant intergroup changes of the liver T4-uridine diphosphate glucuronosyltransferase (UDP-GT) activity*

Table 5. Thyroid effects studies from the original safety assessment of Kojic Acid [2]

Concentration/Dose	***Vehicle***	***Test System***	***Procedure***	***Results***
0, 0.02, 0.2, or 2%	*diet*	*groups of 20 male F344 rats*	*The potential thyroid tumor initiation activity of Kojic Acid was evaluated in a 2-part study on rats. Rats received a diet containing 0, 0.02, 0.2, or 2% Kojic Acid for 8 wk that was followed by treatment with 0.1% sulfadimethoxine (SDM) in drinking water for 23 wk. A 13-wk recovery period followed the SDM treatment. Controls included a group that received 4 subcutaneous injections of DHPN during the initiation period followed by an administration of 0.1% SDM, a group that received diet containing 2% Kojic Acid for the initial 8 wk alone, a group that received 2% Kojic Acid for the entire 31 wk, and a group that received only basal diet.*	*During the treatment and recovery periods, deaths from tracheal obstruction from extremely hypertrophied thyroids were observed in the DHPN control group (5 in total), the 31-wk administration of Kojic Acid control group (3 in total), the 8-wk Kojic Acid control group (1 in total), and the 2% Kojic Acid + SDM treatment group (1 in total). Significant suppression of body weight gain was observed in the DHPN and 31-wk Kojic Acid control groups during administration that continued until the end of the recovery period. All treated groups had significantly increased absolute and relative thyroid gland weights when compared to the basal diet control group at the end of the administration period. These values, however, were decreased at the end of the recovery period, except in the DHPN control group. When compared to the untreated controls, serum T3 levels in the 0% Kojic Acid + SDM, 2% Kojic Acid + SDM, and DHPN control group were significantly decreased at the end of the administration period, as were the serum T4 levels in all treatment groups except the 8-wk Kojic Acid control. The serum T3 and T4 levels in the 8-wk Kojic Acid control were significantly increased compared to the untreated controls. Dose-dependent significant increases in the serum TSH levels occurred in all treatment groups, except the 8-wk Kojic Acid control. These increases were also dependent on treatment duration in the groups that received Kojic Acid. Thyroid carcinomas and adenomas were observed in all rats of the DHPN control group, while no histopathological lesions were observed in the untreated control group. One adenoma was observed in the 31-wk Kojic Acid control group, but no other carcinomas or adenomas were observed in the remaining treatment groups. At the end of administration, focal follicular cell hyperplasia was significantly higher in rats in the 2% Kojic Acid + SDM, DHPN control, and 31wk Kojic Acid control groups. This effect was observed in the latter 2 groups until the end of the recovery period. The mean percentage of PCNA positive cells to follicular cells counted per proliferative lesion was significantly increased in the DHPN control and the 31-wk Kojic Acid control group.*
received 0, 4, 15, 62.5, 250, or 1000 mg/kg	*0.5% carboxy-methyl-cellulose*	*groups of 10 male F344/Du Crj rats*	*In a study on the effect of Kojic Acid on thyroid function, groups of male rats received Kojic Acid via gavage daily for 4 wk.*	*No abnormalities were observed in rats in the 0 to 250 mg/kg dose groups during treatment. Several rats in the 1000 mg/kg dose group had transient and slight decreases in motility 30 min to 1 h after dosing on days 18 to 28 of treatment. Body weights and feed consumption in the 1000 mg/kg dose group were significantly inhibited when compared to the control group. The absolute and relative weights of the thyroid glands were nearly comparable to the controls in the 4 to 250 mg/kg dose groups throughout the treatment period. Absolute and relative weights of the thyroid gland in the 1000 mg/kg dose groups were 1.2-fold and 1.3-fold greater than the control group, respectively. Serum T3 concentration in the 250 mg/kg dose group had a significant decrease only at week 1 when compared to the control group, but the other dose groups showed no significant differences compared to the control at weeks 2 to 4. The serum T4 concentration in the 1000 mg/kg dose group was significantly decreased at week 4, but no dosage of Kojic Acid affected the serum TSH concentration significantly. The 1000 mg/kg dose group had hypertrophy of epithelial cells in the thyroid gland at week 1 to 4; this was not observed in the 250 mg/kg dose group. Radioactive iodine uptake in the 4 to 250 mg/kg dose groups was comparable to the control group at week 1 to 4. In the 1000 mg/kg dose group, the iodine uptake was about 2-fold greater than the control group in week 1; the uptake in this group continued to be constant and high through wk 4. The TCA-precipitable radioactive iodine in the thyroid gland was also increased in the 1000 mg/kg dose group. The absorption of Kojic Acid was rapid as manifested by the Tmax of blood concentration of radioactivity, which was as short as 1.0 + 0.0 h and the t1/2 was 4.8 + 0.3 h. Blood concentrations of radioactivity had nearly disappeared by 24 h after treatment.*

Table 6. MOE calculations for cosmetic product use in adults

	Area of Application	Surface Area (cm^2)[3,48]	Retention Factor[48]	Conc. of Kojic Acid (%)[9,10]	Estimated Daily Amount Applied (g/d)[3,48]	Calculated Systemic Amount of Applied Kojic Acid (mg/d) [3,40,41]	SED* (mg/kg bw/d)[3,40-42]	NOEL† (mg/kg bw/d)[3]	MOE
Leave-on (Cream)	Face + Neck	565+320=885	1	1	2.41	0.448	0.0075	125	16,667
	Hands	860	1	1	2.16	0.402	0.0067	125	18,657
	Aggregate (Face + Neck + Hands)	1745	1	1	4.57	0.850	0.0142	125	8803
	Body	15,670	1	1	7.82	1.455	0.0242	125	5156
	Total body area	17,500	1	1	18.0	3.348	0.0558	125	2240
Rinse-off (shower gel)	Total body area	17,500	0.01	0.05	18.67	0.00174	0.0000289	125	4,325,260

*SED was calculated based on the 95th percentile of AUC values (0 – 24 h) obtained from a clinical study[43] in which a cream containing 1% of Kojic Acid was applied dermally.

†NOEL = 26-wk oral rat study; identified systemic toxicity, including clinical signs, reduced body-weight gain, hematological/clinical chemistry changes, and organ-weight changes

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