SCIENTIFIC ADVISORY GROUP ON CHEMICAL SAFETY OF NON-FOOD AND NON-MEDICINAL CONSUMER PRODUCTS (SAG-CS)

Final Opinion on Kojic Acid in Cosmetic Products

1. Introduction

1.1. Kojic acid (5-hydroxy-2-(hydroxymethyl)pyran-4-one; CAS 501-30-4) is currently not regulated under the Cosmetic Products Regulation UK No 1223/2009 (as amended)[1].

1.2. Kojic acid is a natural product derived from fungi and is largely used as a skin lightening/whitening or depigmenting agent in cosmetic products through action as a tyrosinase inhibitor. Kojic acid may further function as an antioxidant, a bacteriostat (prevents the growth of bacteria), a metal chelating agent and an intermediate in chemical synthesis. Commercially, kojic acid is used in Japan as a food preservative, additive and flavouring agent.

1.3. Kojic acid has been reported to interfere with iodine uptake, resulting in altered thyroid function in rodents (Tamura *et al.,* 1999). Kojic acid is suspected to be a non-genotoxic carcinogen in rodents, although the human relevance of this is unknown. As a result, kojic acid is not classified as a human carcinogen (Group 3) (IARC, 1999).

1.4. Kojic acid was first reviewed by the SAG-CS in February 2022 (SAGCS-022201). The SAG-CS stated that there remained several areas of uncertainty in the risk assessment and that more time was needed to review the full data package to draw a conclusion on the risk to health of kojic acid in cosmetic products.

1.5. In April 2022, OPSS released a call for data on the safety of cosmetic ingredients with suspected endocrine disrupting properties in which kojic acid was included.

[1] The UK Regulation currently consists of the Regulation UK No 1223/2009 as amended by SI 696/2019 Product Safety and Metrology (EU Exit) Regulations. The full consolidated UK text will be available soon.

1.6. A response was submitted by an industry applicant to OPSS to support the safe use of kojic acid in cosmetic products up to a maximum concentration of 1%. In light of this new information, OPSS requested that the SAG-CS assess the safety of kojic acid intended to be used within cosmetic products.

1.7. Derivatives of kojic acid, such as esters (kojic dipalmitate, kojic isopalmitate) and halogenated compounds (chlorokojic acid), are registered within the CosIng database. However, they were not assessed and hence not considered within this opinion.

2. Background

Intended function and uses of kojic acid in cosmetic products

2.1. Kojic acid primarily serves as a skin lightening/whitening or depigmenting agent in cosmetic products through action as a tyrosinase inhibitor. Such products are predominantly leave-on hand and face creams with concentrations of kojic acid in such products generally in the range of 1-4%. Pure form '100% kojic acid' is also available from online retailers.

Mode of action of kojic acid as a skin lightening or depigmenting agent

2.2. Kojic acid acts as a competitive and reversible inhibitor of animal and plant polyphenol oxidases, such as tyrosinase.

2.3. The inhibition of tyrosinase prevents this catalytic conversion of tyrosine to melanin *via* 3,4-dihydroxyphenylalanine and dopaquinone. Kojic acid inhibits melanosis (hyperpigmentation associated with elevated melanin in the skin) by interfering with the uptake of oxygen required for enzymatic browning Spectrophotometric and chromatographic methods demonstrated that kojic acid is capable of reducing *o*-quinones to diphenols to prevent the melanin from forming (SCCP, 2008).

3. Potential Endocrine Disrupting Properties

3.1. Kojic acid has been reported to interfere with iodine uptake by the thyroid, resulting in altered thyroid function (Tamura *et al.,* 1999).

3.2. Data suggests that kojic acid may disturb the synthesis of thyroid hormones by suppression of iodine uptake and subsequent organification (SCCS, 2022; Higa *et al*., 2002; Tamura *et al.*, 1999).

3.3. When kojic acid was administered to rodents it resulted in a dose dependent decrease in serum thyroid hormones, thyroxine (T4) and triiodothyronine (T3), alongside a compensatory increase in thyroid stimulating hormone (TSH) release (SCCS, 2022).

3.4. Histopathological examination of the thyroid of rodents exposed to kojic acid generally show significantly increased thyroid weight (SCCS, 2022).

3.5. In male rats the uptakes of ^{125}I, as well as the numbers of colloid in thyroid follicles and follicular cell hypertrophy were significantly changed when kojic acid was administered in the diet over 28 days. A No Observed Adverse Effect Level (NOAEL) of approximately 23.8 mg/kg bw/day was derived with respect to thyroid weight, and a NOAEL of approximately 5.85 mg/kg bw/day was derived with respect to iodine uptake (Fujimoto *et al.*, 1999; SCCS, 2012). A further 28-day oral toxicity study in rats study shows that a NOAEL of 6 mg/kg bw/day can be derived for altered ^{125}I uptake when kojic acid is administered in the diet (Tamura *et al.*, 1999).

4. Previous Expert Group Opinions

4.1. The use of kojic acid in cosmetic products has been assessed several times by the Scientific Committee on Consumer Safety (SCCS) and its predecessor the Scientific Committee on Consumer Products (SCCP).

4.2. In the initial opinion of the SCCP in 2008 (SCCP, 2008), it was concluded that the use of kojic acid at a maximum concentration of 1.0% in skin care formulations poses a risk to the health of the consumer due to an insufficiently protective Margin of Safety (MoS) based upon a NOAEL of 6 mg/kg bw/day from a 28-day oral toxicity study in rats (Tamura *et al.*, 1999).

4.3. In a subsequent 2012 opinion (SCCS, 2012), the SCCS concluded that, upon re-examination of the available data and consideration of a reduced interspecies assessment factor of 1, *'kojic acid, used as a skin whitening agent at a concentration of 1.0% in leave-on creams, which are generally applied to the face and/or hands leads to the conclusion that it is safe for the consumers*'. This reduced interspecies factor was applied as the SCCS stated that '*it is generally known that humans are much less susceptible to HPT-axis disturbances than rats*,' citing RIVM report 601516009/2002 Part II (RIVM, 2002). The SCCS noted in their most recent opinion (SCCS, 2022) that: *'As kojic acid is sometimes added to peeling agents, a weakened skin barrier may be of additional concern because of greater dermal absorption'*. In this opinion (SCCS, 2022), the SCCS concluded that a concentration of 1% kojic acid is safe for the intended use in cosmetic products. A sufficiently protective Margin of Safety (MoS) of greater than 100 was calculated. This was based on a NOAEL of 6 mg/kg bw/day from a 28-day oral toxicity study in rats (Tamura *et al.*, 1999), adjusted by an additional safety factor of 3 to extrapolate from a 28- to 90-day timeframe, resulting in an adjusted NOAEL of 2 mg/kg bw/day.

5. Discussion by the Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS)

5.1. At their September and November 2022 meetings, the SAG-CS discussed the safety of kojic acid within cosmetic products up to a maximum concentration of 1%.

5.2. Members discussed the regulatory background of kojic acid and relevant opinions from other risk assessment bodies (SCCP, 2008; SCCS, 2012 and 2022). In particular noting the comment made by the SCCS in their 2022 opinion regarding the use of kojic acid in skin peeling agents (see 4.3 above) and concerns relating to increased dermal absorption for users of skin peeling agents. Members noted the lack of data with respect to the use of kojic acid in skin peeling agents; such cosmetic products have the potential to weaken the skin's protective barrier function and increase dermal absorption.

5.3. Members were content with new data provided in response to the call for data, which sufficiently address their previous comments and concerns.

5.4. With respect to endocrine effects, members discussed the following aspect in detail:

The choice of Point of Departure (PoD) used in the safety assessment: A wide range of *in vivo* repeated dose toxicity studies were available. This included 28-day dermal studies in rabbits and rats, 28-day oral studies in rats, a 90-day oral study in rats, a 6-month oral study in rats and a range of reproductive and developmental studies in rats, mice and rabbits. Treatment-related adverse effects were observed in these repeated dose studies, with NOAELs in the range of 6 to 150 mg/kg bw/day. Members agreed the NOAEL of 6 mg/kg bw/day, from two 28-day oral repeated dose rat studies (Fujimoto *et al*., 1999; Tamura *et al*., 1999), was the most suitable starting point to derive the PoD. This NOAEL was the lowest (critical) NOAEL from the available database. The effects observed at the LOAEL (iodine uptake) are relevant to humans. The NOAEL is protective of the potential for endocrine disruption and developmental neurotoxicity in humans. However, as this NOAEL is from a 28-day rather than a 90-day study (the 90-day exposure period being more appropriate than 28 days for cosmetic products), an additional uncertainty factor of 3 was applied, when extrapolating to account for study duration. This additional uncertainty factor of 3 was selected considering the relevance and reliability of the data. This resulted in an adjusted NOAEL of 2 mg/kg bw/day.

The choice of dermal absorption value used in the safety assessment: A range of *in vitro* and *in vivo* dermal absorption studies are available, including an *in vivo* study in humans (Fukase, 2005). The unpublished Japanese study evaluated the use of cosmetic products containing kojic acid applied to the face of six women. This study was considered the pivotal study on which to base the dermal absorption value given the human subjects. Results were used to

estimate the amount of kojic acid in plasma over 24 hours (0.093 mg/day). This was then adjusted (assuming linearity) to take into account the difference between estimated daily exposure to kojic acid from face (including neck) or hand cream, and the amount of kojic acid applied in the study. The safety assessment relates to the use of kojic acid in normal, healthy skin.

The key inputs used to calculate the systemic exposure dose (SED) and MoS for kojic acid are presented below (Table 1).

5.5. In addition, the following points were noted:

- The rodent specificity of observed effects, which were not observed in a dermal repeated dose rabbit study.
- Effects on the liver-thyroid axis.
- Potential reversibility of secondary endocrine effects on hormone levels.

However, these observations did not change the NOAEL and PoD identified from the database (point 5.4 above).

5.6. Members concluded that, according to the WHO/IPCS definition of an endocrine disruptor[2] (WHO/IPCS, 2002), kojic acid exhibits endocrine activity but the evidence from the study data is not sufficient to conclude that kojic acid is an endocrine disruptor that causes adverse outcomes *in vivo*. It is unlikely that kojic acid is endocrine disrupting *in vivo* and causes adverse outcomes at the exposure levels that are likely to be experienced by the majority of the population through cosmetic use at the specified levels.

5.7. Members commented on the lack of validated analytical methods for determination of kojic acid within the regulatory community.

[2] *'An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.'*

Table 1. Key inputs used in the calculation of the SED and MoS for kojic acid.

Product	**Face cream**	**Hand cream**	**Aggregated**
Calculated daily exposure to product (g/day)	2.41	2.16	4.57
Concentration kojic acid (%)	1.0	1.0	1.0
Calculated daily exposure to kojic acid (mg/day)	24.1	21.6	45.7
Amount kojic acid applied in the dermal absorption study (mg)	5	5	5
Calculated daily exposure to kojic acid divided by amount applied in dermal absorption study	4.82	4.32	9.14
Amount kojic acid measured in plasma over 24hr (mg/day)	0.093	0.093	0.093
Estimate for kojic acid in plasma (mg/day)	0.448	0.402	0.850
Body weight[1] (kg)	60	60	60
SED (mg/kg bw/d)	**0.0075**	**0.0067**	**0.0142**
PoD (mg/kg bw/d)	6	6	6
Additional safety/uncertainty factor	3	3	3
Adjusted PoD	2	2	2
Oral absorption (%)	100	100	100
PoDsystemic (mg/kg bw/day)	2	2	2
MoS	**268**	**299**	**141**
Conclusion	**MoS>100 Safe for use[2]**	**MoS>100 Safe for use[2]**	**MoS>100 Safe for use[2]**

SED – systemic exposure dose. PoD – point of departure. MoS – margin of safety
1 - the default value stated in the SCCS NoG (2021) was used, which at the time of calculation applies in GB.
2 – Where the MoS>100 a chemical is demonstrably safe according to the MoS principles and metric; conversely, where MoS<100 a chemical is not demonstrably safe according to the MoS principles and metric.
NOTE: SED values stated are rounded. Calculation of the MoS used unrounded numbers and therefore sometimes resulted in different final MoS values compared to those the rounded figures would lead to.

6. Conclusions

Members were satisfied that there was sufficient evidence to form an opinion at this stage.

Members agreed that kojic acid is safe for use at a maximum concentration of up to 1% in the following cosmetic products: 1) face cream (including application to neck) and 2) hand cream.

Members did not consider kojic acid to be an endocrine disrupting chemical in vivo *according to the WHO/IPCS (2002) definition, and at the exposure levels that are likely to be experienced by the majority of the population through cosmetic use at the specified level.*

Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products

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References

Fujimoto N, Onodera H, Mitsumori K, Tamura T, Maruyama S, Ito A (1999), Changes in thyroid function during development of thyroid hyperplasia induced by kojic acid in F344 rats, Carcinogenesis, Volume 20, Issue 8, 1 August 1999, Pages 1567–1572, https://doi.org/10.1093/carcin/20.8.1567 .

Fukase, H. (2005). Percutaneous absorption study of kojic acid in humans. CPC Clinic, Medical facility, Kagoshima, Japan, April 28, unpublished report. Cited in SCCS (2022).

Higa, Y., Ohkubo, A., Kitajima, S., Moriyasu, M., Kariya, K. (2002), Effects of Kojic Acid on Thyroidal Functions in Rats by Single-Dose Administration and in Cultured Rat Thyroid Cells (FRTL-5 Cells), *J. Toxicol. Sci.*, 2002, Volume 27, Issue 5, Pages 423-431, Released on J-STAGE January 31, 2003, Online ISSN 1880-3989, Print ISSN 0388-1350, https://doi.org/10.2131/jts.27.423, https://www.jstage.jst.go.jp/article/jts/27/5/27_5_423/_article

IARC (International Agency for Research on Cancer) (1999), Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis, IARC Scientific Publication No. 147, https://publications.iarc.fr/Book-And-Report-Series/Iarc-Scientific-Publications/Species-Differences-In-Thyroid-Kidney-And-Urinary-Bladder-Carcinogenesis-1999

RIVM (2002), Report 601516009/2002 Factsheets for the (eco)toxicological risk assessment strategy of the National Institute for Public Health and the Environment (RIVM), Part II, Editors: R. Luttik and S.M.G.J. Pelgrom, https://www.rivm.nl/bibliotheek/rapporten/601516009.pdf

SCCP (Scientific Committee on Consumer Products), Scientific Opinion on Kojic Acid, 30 September 2008, SCCP/1182/08, https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_148.pdf

SCCS (Scientific Committee on Consumer Safety), Scientific Opinion on Kojic Acid, 26-27 June 2012, SCCS/1481/12, https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_098.pdf

SCCS (Scientific Committee on Consumer Safety), Scientific Opinion on Kojic Acid, preliminary version of 26-27 October 2021, final version of 15-16 March 2022, Corrigendum of 10 June 2022, SCCS/1637/21, https://health.ec.europa.eu/publications/kojic-acid_en

SCCS (Scientific Committee on Consumer Safety) (2021), SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 11th revision, 30-31 March 2021, SCCS/1628/21, https://health.ec.europa.eu/publications/sccs-notes-guidance-testing-cosmetic-ingredients-and-their-safety-evaluation-11th-revision_en

Tamura T, Mitsumori K, Onodera H, Fujimoto N, Yasuhara K, Takegawa K, Takahashi M. (1999), Inhibition of thyroid iodine uptake and organification in rats treated with kojic acid. *J Toxicol Sci*. 1999 Feb;47(2):170-175. https://doi.org/10.1093/toxsci/47.2.170

WHO/IPCS (International Programme on Chemical Safety). (2002). Global assessment on the state of the science of endocrine disruptors. World Health Organization. https://apps.who.int/iris/handle/10665/67357