KOJIC ACID

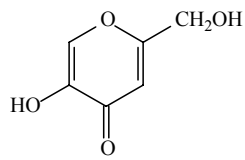
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 501-30-4
Deleted CAS Reg. No.: 123712-78-7
Chem. Abstr. Name: 5-Hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one
IUPAC Systematic Name: Kojic acid
Synonym: 5-Hydroxy-2-(hydroxymethyl)-4-pyrone; 2-hydroxymethyl-5-hydroxy-γ-pyrone

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_6H_6O_4$ Relative molecular mass: 142.11

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Prismatic needles from acetone (Lide & Milne, 1996; Budavari, 2000)
(*b*) *Melting-point*: 153.5 °C (Lide & Milne, 1996)
(*c*) *Spectroscopy data*: Infrared [prism (6381), grating (18126)], ultraviolet (1761), nuclear magnetic resonance [proton (10454)] and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996).

(*d*) *Solubility*: Soluble in water (43.85 g/L; Dialog Corp., 2000), acetone, chloroform, diethyl ether, ethanol, ethyl acetate and pyridine; slightly soluble in benzene (Lide & Milne, 1996; Budavari, 2000)
(*e*) *Dissociation constants*: pK_a, 7.90, 8.03 (Budavari, 2000)

1.1.4 *Technical products and impurities*

Kojic acid is commercially available at a purity greater than 98.0% and as a solution for spraying (TCI America, 2000; Tokyo Kasei Kogyo Co., 2000). Impurities may include heavy metals (10 mg/kg max.) and arsenic (4 mg/kg max.) (Jarchem Industries, 2000).

1.1.5 *Analysis*

Methods for the analysis of kojic acid in commercial foods, flavouring compounds, cosmetic products and microorganisms have been reported. These methods include voltammetry, spectrophotometry, column chromatography with ultraviolet detection, thin-layer chromatography, gas chromatography with or without flame ionization, electron capture or mass spectrometry detection, and high-performance liquid chromatography with photodiode-array or ultraviolet detection (Owens *et al*., 1970; Scott *et al*., 1970; Kawate *et al*., 1972; Qureshi *et al*., 1979; Tanigaki *et al*., 1980; Yang *et al.*, 1980; Manabe *et al.*, 1984; Dobias *et al.*, 1985; Frisvad, 1987; Frisvad & Thrane, 1987; Manabe *et al*., 1988; Goto *et al*., 1990; Karita *et al*., 1991; Shih & Zen, 1999; Kimura *et al*., 2000).

1.2 Production

Kojic acid is a natural antibiotic agent obtained from koji malt (*Aspergillus oryzae*). Koji malt has been used for the production of miso, soya sauce and sake in Japan for a long time (Budavari, 2000; Jarchem Industries, 2000).

Information available in 2000 indicated that kojic acid was manufactured by two companies in China and one company each in Japan, Switzerland and the USA (CIS Information Services, 2000).

1.3 Use

Kojic acid can act as a tyrosinase inhibitor (to inhibit melanin formation), an antioxidant, a bacteriostat, a metal chelating agent and an intermediate in synthesis. Applications of kojic acid include the prevention of discolouration of crustacea, meat and fresh vegetables, as a preservative, as an antioxidant for fats and oils, in cosmetics (skin whitening or depigmenting agent), in the preparation of derivative esters (i.e. kojic oleate, kojic stearate), in adhesives, in chelate-forming resins and as a plant growth-

regulating agent to increase production, early maturing and increase sweetness (Cabanes *et al.*, 1994; Chemos Group, 2000; Jarchem Industries, 2000).

Kojic acid has been used in flavourings at 0.2% to add luster, to prevent discolouration on vegetables at 1.0%, in flour production at 0.1%, in meat production at 0.2%, in syrup at 0.05% and as a whitening agent in cosmetics at 0.5–1.0% (Chemos Group, 2000).

1.4 Occurrence

1.4.1 *Occupational exposure*

No data were available to the Working Group.

1.4.2 *Environmental occurrence*

Kojic acid is a natural product that has been isolated from various strains of micro-organisms such as *Penicillium*, *Aspergillus* and *Gluconoacetobacter* (Novotny *et al.*, 1999).

1.5 Regulations and guidelines

No data were available to the Working Group.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Mouse: Groups of 65 male and 65 female B6C3F_1 mice, 6 weeks of age, were fed diets containing 0 (control), 1.5 or 3.0% kojic acid [purity unspecified] for 20 months. The survival rates at 18 months were 67% in control males, 56% in males given 1.5% and 76% in males given 3.0% kojic acid in the diet; 91% in female controls, 87% in females given 1.5% and 91% in females given 3.0% kojic acid in the diet. Thyroid follicular-cell adenomas were found in 34/52 (65%) and 46/53 (87%) males given 1.5 and 3.0% kojic acid, respectively, which were significantly higher than the control value of 1/48 (2%). In females, the incidences were 1/52 (2%), 4/51 (8%) and 39/49 (80%) at 0, 1.5 and 3.0% kojic acid, respectively. The increased incidences were statistically

significant ($p < 0.01$) in males at both concentrations and in females at the higher dietary concentration. In groups of 10–14 mice that were given normal diet 30 days before termination of the study, the incidence of adenomas was significantly decreased in the males at both the low and high concentration (Fujimoto *et al*., 1998). [The Working Group noted the rapid and substantial reduction in tumour incidence, at least in male mice, after only 1 month of withdrawal of the test compound.]

3.2 Administration with known carcinogens

Rat: In a study of the time course of thyroid proliferative lesions, male Fischer 344 rats, 6 weeks of age, were initiated with a subcutaneous injection of 2800 mg/kg bw *N*-nitrosobis(2-hydroxypropyl)amine (NBHPA) and 1 week later were promoted with kojic acid in the diet at a concentration of 0%, 2% or 4%. The animals were examined after 1, 2, 4, 8 and 12 weeks of treatment. Increased thyroid gland weights and diffuse follicular-cell hypertrophy (apparent from week 1) were observed in the kojic acid-treated rats. The incidences of thyroid follicular-cell adenomas were 0 with NBHPA alone, 60% with NBHPA plus 2% kojic acid and 20% with NBHPA plus 4% kojic acid at 4 weeks; 0 with NBHPA alone, 100% with NBHPA plus 2% kojic acid and 40% with NBHPA plus 4% kojic acid at 8 weeks; and 0 with NBHPA alone, 80% with NBHPA plus 2% kojic acid and 75% with NBHPA plus 4% kojic acid at 12 weeks. The multiplicity of thyroid tumours in rats treated with 4% kojic acid (0.2 ± 0.5 after 4 weeks, 0.4 ± 0.6 after 8 weeks and 1.0 ± 0.8 after 12 weeks) was lower than that of rats treated with 2% kojic acid (1.2 ± 1.3 after 4 weeks, 2.0 ± 0.7 after 8 weeks and 1.8 ± 0.8 after 12 weeks), perhaps owing to the marked decrease in dietary intake at the higher concentration (Tamura *et al.*, 1999a).

Two groups of 8–10 male Fischer 344 rats, 6 weeks of age, were given a single subcutaneous injection of 2800 mg/kg bw NBHPA, followed 1 week later by basal diet alone or basal diet containing 2% kojic acid. Half the rats were killed after 4 weeks and the remainder after 12 weeks. Thyroid follicular-cell hyperplasia and adenomas were observed in 4/5 and 3/5 rats given NBHPA plus kojic acid at week 4, respectively. At week 12, these lesions were observed in all rats given the two compounds. Animals given kojic acid alone showed marked diffuse hypertrophy of follicular epithelial cells at weeks 4 and 20 (Mitsumori *et al*., 1999).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

No data were available to the Working Group.

4.2 Toxic effects

4.2.1 *Humans*

The skin-whitening effect of kojic acid involves the formation of an enzyme complex that inhibits tyrosine hydroxylase and blocks the synthesis of 3,4-dihydroxyphenylalanine. The commonest adverse effect after topical application of skin depigmenting agents is skin irritation and contact allergy. Patch testing of 220 female patients with suspected cosmetic-related contact dermatitis showed five who reacted to kojic acid (Nakagawa *et al.*, 1995). Another case of contact sensitization was reported by Serra-Baldrich *et al*. (1998).

4.2.2 *Experimental systems*

In the study described in section 3.1 (Fujimoto *et al.*, 1998), B6C3F_1 mice, aged 6 weeks at the start of the experiment, were given diets containing kojic acid at a concentration of 0, 1.5 or 3.0% for 20 months. At sacrifice, the thyroid gland weights were found to be increased, and diffuse hyperplasia was found, the effects being more severe in males than in females. Serum was collected from five animals per group at 6, 12 and 20 months for measurement of triiodothyronine (T3) and thyroid-stimulating hormone (TSH). At 6 months, the T3 concentration was significantly decreased in males and females at the higher dietary concentrations and in females also at the lower concentration, whereas the serum concentration of TSH was increased. Thereafter, the T3 concentration remained low, but there was no consistent change in TSH.

In the study described in section 3.2 (Mitsumori *et al.*, 1999), male Fischer 344 rats were initiated with NBHPA and 1 week later were given a diet containing kojic acid at a concentration of 0 or 2% for 12 weeks. Serum T3 and thyroxine (T4) concentrations were decreased and those of TSH markedly increased in kojic acid-treated rats at weeks 4 and 12. The weights of the thyroid gland of these animals were increased, and marked diffuse follicular-cell hypertrophy was observed at 4 weeks in four of five rats. No changes were seen in thyroid-related hormone concentrations or in the thyroid glands of rats that received NBHPA alone or no treatment.

In the study described in section 3.2 (Tamura *et al*., 1999a), changes in serum thyroid hormone concentrations were studied in male Fischer 344 rats initiated with NBHPA and promoted with kojic acid. The serum concentrations of T3 and T4 were significantly reduced and those of TSH were increased, and increased thyroid gland weights were observed in the kojic acid-treated rats.

In a further study on the effect of kojic acid on thyroid iodine uptake and iodine organification, male Fischer 344 rats were given diets containing kojic acid at a concentration of 0.008, 0.03, 0.125, 0.5 or 2% for 4 weeks. ^{125}I uptake was significantly decreased in the groups receiving 0.03% or more, and organification was significantly reduced at 2% kojic acid. Thyroid gland weights were increased at concentrations ≥ 0.5%, and decreased colloid and follicular-cell hypertrophy were observed at concen-

trations ≥ 0.03%. The serum concentrations of T3 and T4 were significantly reduced and those of TSH markedly increased, but only in the group at 2% kojic acid. The finding that TSH concentrations were not significantly increased at lower concentrations was attributed to a possible role of TSH receptor autoregulation under conditions of low iodine or inhibition of iodine organification (Tamura *et al.*, 1999b).

In order to study the effect of kojic acid on thyroid gland function during development of thyroid hyperplasia, Fischer 344 rats were given a diet containing 2% kojic acid for 4 weeks. The serum concentrations of T3 and T4 were decreased, with a marked increase in TSH concentration, and iodine uptake into the thyroid gland was markedly decreased. The authors concluded that kojic acid interrupts thyroid gland function primarily by inhibiting iodine uptake (Fujimoto *et al.*, 1999).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Seven mated female Sprague-Dawley rats, weighing 140–160g, were dosed orally with 50 μg/rat per day kojic acid dissolved in 0.1 mL propylene glycol on days 1–5 of gestation (positive vaginal smear = day 1) and compared with a similar group of vehicle-treated controls. Laparotomy to count the number of corpora lutea and implants was performed on day 8, and the animals were allowed to litter. One dam treated with kojic acid died before term. There was no effect on corpora lutea count, but a 50% reduction in the number of implantation sites ($p < 0.02$) was seen, and the litter size was reduced to a mean of 2.71 pups ($p < 0.001$), of which only 0.71 ($p < 0.001$) were alive at birth, compared with 6.57 (all alive) in the controls (Choudhary *et al*., 1992).

Eight proven fertile male Sprague-Dawley rats weighing 150–200 g were given orally 50 μg/rat per day kojic acid dissolved in 0.1 mL propylene glycol orally for 21 days and compared with vehicle-treated controls. Each male was mated with two proven fertile females on days 16–21, and vaginal smears were examined for sperm to confirm the day of mating. Laparotomy to count the number of corpora lutea and implants was performed on day 8, and the animals were allowed to litter. The males were killed on day 22, epididymal spermatozoa were examined for number, morphology and viability, and the testes were examined histologically. The testis and epididymal weights were slightly ($p < 0.05$) reduced, but no interference with spermatogenesis was seen. Six of the males mated successfully with a total of eight females. There was a reduction in the number of implantation sites in the females mated with kojic acid-treated males, to a mean of 4.62 compared with 7.87 ($p < 0.05$) in controls. The litter size was also reduced, to 3.64 (only 1.79 viable) compared with 5.94 (all viable) in controls. Cannibalism 2–3 days after littering was also observed (Choudhary *et al*., 1994).

4.4 Effects on enzyme induction or inhibition and gene expression

Kojic acid does not appear to induce hepatic microsomal enzymes. The activity of T4-UDP glucuronosyltransferase was not significantly increased in Fischer 344 rats treated for 4 weeks with kojic acid at 2% in the diet (Mitsumori *et al*., 1999).

4.5 Genetic and related effects

4.5.1 *Humans*

No data were available to the Working Group.

4.5.2 *Experimental systems* (see Table 1 for references)

In most of the experiments reported, but not all, kojic acid induced mutations in *Salmonella typhimurium* TA100, TA1535 and TA98 both without and with an exogenous metabolic system; it was not mutagenic to TA1537. It did not induce a response in the *Escherichia coli* SOS-repair test. Kojic acid did not induce gene mutations in Chinese hamster lung V79 cells, but did induce sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells *in vitro*, both in the presence and absence of an exogenous metabolic system. Kojic acid did not induce dominant lethal mutations in mice.

4.6 Mechanistic considerations

Kojic acid is a directly acting genotoxin. It is also a potent goitrogen in rodents, causing decreased serum thyroid hormone concentrations, increased thyroid-stimulating hormone concentrations, increased thyroid gland weights and diffuse follicular-cell hypertrophy and/or hyperplasia. Kojic acid inhibits iodine uptake by the thyroid and inhibits iodine organification at high doses. The antithyroid effects of kojic acid are therefore the probable mechanism by which it produces thyroid gland tumours; however, a role of genotoxicity cannot be excluded in the light of the positive findings.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Kojic acid is a natural product, which is used as a food additive and preservative, in cosmetics as a skin-whitening agent, as a plant growth regulator and as a chemical intermediate.

Table 1. Genetic and related effects of kojic acid

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli K12, SOS repair, forward mutation	–	NT	NR	Auffray & Boutibonnes (1986)
Salmonella typhimurium TA100, reverse mutation	+	+	1000 µg/plate	Bjeldanes & Chew (1979)
Salmonella typhimurium TA100, TA1535, TA98, reverse mutation	+	+	2000 µg/plate	Shibuya *et al.* (1982)
Salmonella typhimurium TA100, reverse mutation	+	(+)	1000 µg/plate	Wei *et al.* (1991)
Salmonella typhimurium TA98, reverse mutation	+	+[c]	100 µg/plate	Wei *et al.* (1991)
Salmonella typhimurium TA98, reverse mutation	–	+	0.5 µg/plate	Wehner *et al.* (1978)
Salmonella typhimurium TA100, TA1535, TA1537, reverse mutation	–	–	500 µg/plate	Wehner *et al.* (1978)
Salmonella typhimurium TA1537, reverse mutation	–	–	4000 µg/plate	Shibuya *et al.* (1982)
Salmonella typhimurium TA98, reverse mutation	–	–	10 000 µg/plate	Bjeldanes & Chew (1979)
Gene mutation, Chinese hamster lung V79 cells, 6-TG resistance *in vitro*	–	NT	3000	Shibuya *et al.* (1982)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	3000	Wei *et al.* (1991)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	+	3000	Wei *et al.* (1991)
Dominant lethal mutation, C57BL/6×DBA/2 mice *in vivo*	–		700 po × 5	Shibuya *et al.* (1982)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw per day; po, orally; NR, not reported

[c] With metabolic activation, a positive response was seen only at a ≥ 20-fold higher dose.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Kojic acid was tested by oral administration in one study in mice. It produced thyroid follicular-cell adenomas in both males and females. In two initiation–promotion studies in rats, kojic acid promoted thyroid follicular-cell carcinogenesis initiated by *N*-nitrosobis(2-hydroxypropyl)amine.

5.4 Other relevant data

No data were available on the absorption, distribution, metabolism or excretion of kojic acid.

Kojic acid is a potent goitrogen in rodents, in which treatment results in decreased serum thyroid hormone concentrations, increased thyroid-stimulating hormone secretion, increased thyroid gland weights and diffuse follicular-cell hypertrophy and/or hyperplasia.

Kojic acid inhibited iodine uptake by the thyroid and inhibited iodine organification at high doses.

No data were available on the genetic and related effects of kojic acid in humans. Kojic acid did not induce dominant lethal mutations in mice. In the presence and absence of metabolic activation, it induced sister chromatid exchange and chromosomal aberrations, but not mutations, in hamster cells in culture. Kojic acid was mutagenic in bacteria in the presence and absence of metabolic activation. The overall data indicate that kojic acid is genotoxic *in vitro*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of kojic acid.

There is *limited evidence* in experimental animals for the carcinogenicity of kojic acid.

Overall evaluation

Kojic acid is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

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